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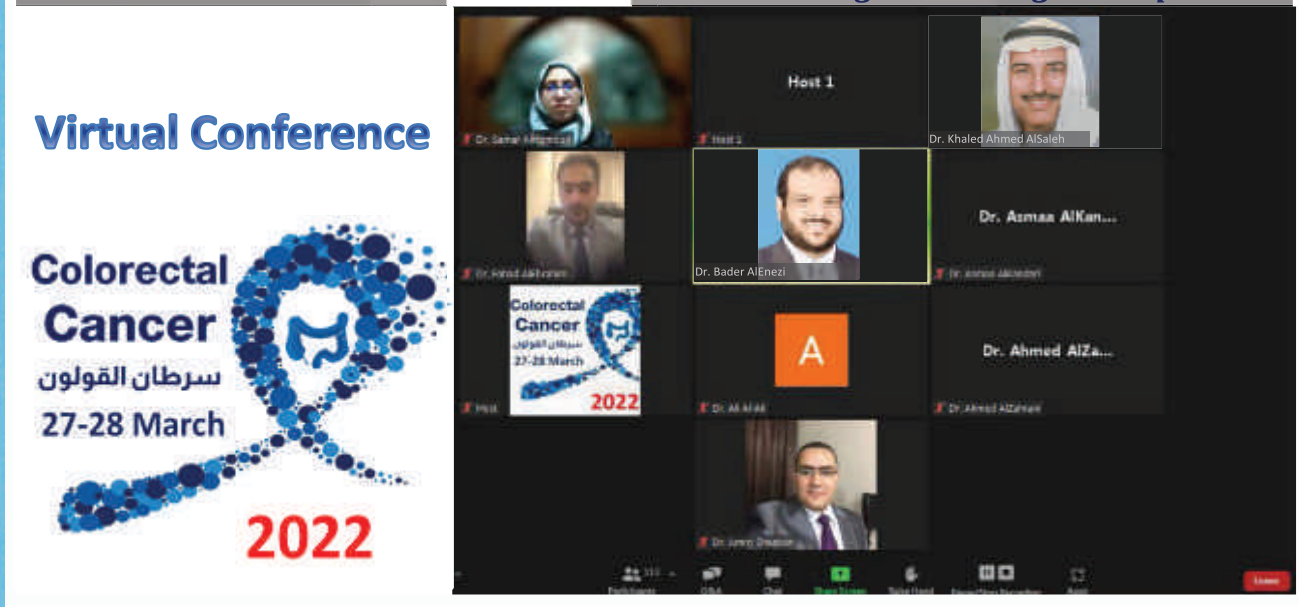

The Official Journal of the Gulf Federation For Cancer Control

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Clinical Outcomes of Radiological Treatment Modalities of Hepatocellular Carcinoma: A Single–Center Experience from Saudi Arabia

Yaser M. Dahlan[1,2,3], Bader H. Shirah[2,3], Abdullah S. Alghamdi[2,3], Abdulkader A. Al Kenawi[1,2,3], Faisal M. Sanai[1,2,3]

[1] King Abdulaziz Medical City, Jeddah, Saudi Arabia.
[2] King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia.
[3] King Abdullah International Medical Research Center, Jeddah, Saudi Arabia.

Abstract

Background: Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. Most patients with HCC are unsuitable for surgical therapies. Therefore, nonsurgical therapies play a central role in the management of this disease. Several percutaneous treatment modalities are available for HCC including radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE). In this study, we aim to evaluate the clinical outcomes, morbidity and mortality rates, and survival rates of four treatment modalities for HCC (RFA, TACE, TARE, and Sorafenib) and compare the success rate of each modality.

Methods: A retrospective observational study was conducted at King Abdulaziz Medical City in Jeddah, Saudi Arabia. The inclusion criteria were composed of patients diagnosed with HCC who received RFA, TACE, TARE, or Sorafenib treatments between 2008 and 2017. The primary outcome of this study was recurrence–free patients at the last follow–up.

Results: A total of 108 patients were included in this study. The mean age of the patients was 68.01±9.98 years. Eighty–Two patients (75.9%) underwent interventions with the intention to cure or stabilize HCC, while twenty–six patients (24.1%) were started on Sorafenib as a palliative treatment. The five years recurrence–free rates were 41.2% with RFA, 40% with the combination of TACE and RFA, 23.3% with TACE, and 0% with TARE. All patients on Sorafenib died from advanced–stage HCC.

Conclusion: This study provides further evidence for the efficacy of several treatment modalities for the management of HCC. RFA and the combination of TACE and RFA showed better outcomes with a recurrence–free rate reaching up to 40%. TACE had a moderate survival benefit up to 23.3%. TARE showed negative survival benefits. Sorafenib continues to be an important palliative treatment but does not offer curative potential.

Keywords: Hepatocellular Carcinoma; Radiofrequency Ablation; Transarterial Chemoembolization; Transarterial Radio embolization; Sorafenib; Saudi Arabia.

Introduction:

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It represents the sixth most common cancer and the third most common cause of cancer–related death among men and the sixth among women worldwide[1]. Annually, more than 560,000 people are diagnosed with HCC, and approximately the same number die with it. It has a variable geographical distribution. The incidence in developing countries is two to three times higher than in Western countries[2]. HCC has a significant prevalence in Saudi Arabia, and difficulties are often faced in early and accurate diagnoses, evidence–based management, and appropriate referral of HCC patients[3]. In early–stage HCC, liver transplantation, surgical resection, and percutaneous techniques are classified as radical treatments and may be offered to about 25% of all patients with HCC evaluated in referral centres[4].

Most patients with HCC are unsuitable for surgical therapies due to the extension of the disease, poor hepatic

Corresponding Author: Yaser M. Dahlan, Assistant Professor of Gastroenterology and Consultant in Hepatology, King Abdulaziz Medical City/ King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia. Contact No.: 00966558822133. Address: Saudi Arabia, Jeddah. P.O. Box: 9515, Jeddah 21423. Email: yaserdahlan@hotmail.com,

reserve, or coexistent morbidity. Therefore, nonsurgical therapies play a central role in the management of this disease. Several percutaneous treatment modalities are available for HCC including radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE). The rationale for these therapies is supported by appropriate outcome–based studies. Ablation of HCC has been carried out for many years now. This can be done by either chemical means (absolute alcohol or trichloracetic acid) or by physical means (cryoablation, RFA, microwave coagulation, or injection of hot saline). In general, percutaneous treatments are best offered to patients with early–stage HCC and relatively small size tumors[5].

A thorough literature search showed a limited number of local articles studying the clinical outcomes of the newly introduced treatment modalities for HCC (RFA, TACE, and TARE). In this study, we aim to evaluate the clinical outcomes, morbidity and mortality rates, and survival rates of four treatment modalities for HCC (RFA, TACE, TARE, and Sorafenib) and compare the success rate of each modality.

Methods:

A retrospective observational study was conducted at King Abdulaziz Medical City in Jeddah, Saudi Arabia. The process of collecting data started in June 2018 and was completed in December 2018. The inclusion criteria were composed of patients diagnosed with HCC who are currently receiving or received RFA, TACE, TARE, or Sorafenib treatments in the past between 2008 and 2017. Patients with HCC who received other treatment modalities such as resection or transplant and those with incomplete data were excluded.

Barcelona clinic liver cancer (BCLC) staging criteria were used for the selection of the appropriate treatment modality for our HCC patients. Data collected from HCC patients included the demographic profile (i.e. age and gender), clinical features (onset, duration, etiology, comorbidities, Child–Pugh score, functional status, and Milan criteria), tumor features (distribution, size, the presence of cirrhosis), biochemical characteristics (alpha–fetoprotein, liver enzymes, blood group), and treatment parameters (the type of procedure, complications, prognosis, and cure rate). Patients had regular visits to the hepatology clinic every three months for clinical assessment, blood tests, and evaluation of response and complications. Unscheduled patient visits to the clinic were allowed if there were any new symptoms or if they experienced side effects or complications.

The primary outcome of this study was the proportion of recurrence–free patients at the last follow–up. Secondary outcomes were stabilization of the tumor, improvement of the functional status, and presence of metastasis.

The numerical values from each variable of the data collection sheet including the demographic profile were calculated by simple descriptive statistical tests (i.e. mean and standard deviation), frequency, and percentage. The program used for data analysis was the Statistical Package for Social Sciences (SPSS) version 21.0. The anonymity of all data collection sheets was ensured, and confidentiality of information was maintained. This study was approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC).

Results:

A total of 108 patients were included in this study. The mean age of the patients was 68.01±9.98 years, with a mean age of the females being 65.9±9.323 years and a mean age of the males 68.56±11.45 years. Females represented 30.6% of the study population (33 patients), while males represented 69.4% (75 patients), with a male to female ratio of 2.27:1.

The mean age at onset of the disease was 65.7±10.6 years old. The mean duration of the disease was 24.12±26.49 months (range 0.5–108 months). Ninety–three patients (86.1%) had liver cirrhosis as the primary cause of HCC, 38 patients of them (40.8%) were diagnosed with HCV, 41 patients of them (44.1%) were diagnosed with HBV, and 14 patients of them (15.1%) had mixed HBV and HCV. Other causes of HCC in our patients included unknown etiology and HBV or HCV without cirrhosis.

The main Child–Pugh score was (A) accounting for 66.6% (72 patients) (Table 1). Fifty–two patients (48.1%) had a functional status of two (Table 2). The majority of the patients (74.1%) were not applicable for liver transplant based on Milan criteria.

The mean tumor size was 52±29 mm with 25 patients (23.1%) showing evidence of vascularity. 46.3% of the cases had a single localized tumor, followed by 18.5% with two tumors, and the rest were multifocal. Thirteen patients (12.0%) showed evidence of distant metastasis at the time of diagnosis. The main localized tumor sites were in segments six, seven, and eight accounting for 42.5%.

Child–Pugh Classification	Number	Percentage (%)
A	72	66.6%
B	21	19.4%
C	15	14.0%

Table 1: Child–Pugh Classification of the Study Population

Functional Status	Number	Percentage (%)
0	9	8.3%
1	29	26.9%
2	52	48.1%
3	13	12.0%
4	5	4.6%

Table 2: Functional Status of the Study Population

Eighty–Two patients (75.9%) underwent interventions with the intention to cure or stabilize HCC, while twenty–six patients (24.1%) were started on Sorafenib as a palliative treatment based on BCLC.

Seventeen patients (15.7%) underwent RFA. The recurrence–free rate was 41.2% (7 patients), while the death rate was 58.8% (10 patients). The mean survival time was 37.7±10.91 months, and the survival rates at 1, 3, and 5 years were 76.47%, 64.7%, and 17.67%, respectively. No significant postoperative complications were noted.

Thirty patients (27.8%) underwent TACE. Seven patients (23.3%) were recurrence–free, while 23 patients (76.7%) died from advanced–stage HCC. The mean survival time was 20.5±2.69 months, and the survival rates at 1 and 3 years were 70% and 30%, respectively. Two patients developed postoperative complications, which include significant fatigue, fever, and worsening performance status.

Twenty–five patients (23.1%) underwent TARE. The recurrence–free rate was 0%. The median survival time was 24±19.5 months, and the survival rates at 1 and 3 years were 56% and 16%, respectively. Three patients had postoperative complications, which include bile leak and hematoma.

Ten patients (9.3%) underwent combination therapy. Five patients had TACE and RFA with a recurrence–free rate of 40%, and the survival rates at 1, 3, and 5 years were 100%, 60%, and 20%, respectively. The remaining five patients, three of them received a combination of TARE and RFA, and the last two had TACE and TARE. These two treatment modalities showed no survival benefit.

Sorafenib was given to 26 patients (24.1%). All patients died from advanced–stage HCC. The median survival time was 3±10 months, and the survival rates at 1 and 3 years were 11.5% and 0%, respectively (Figure 1–3).

Five patients (4.6%) developed complications following the intervention as mentioned. The mean duration of follow–up was 72.9441.7±. Fifty–one patients (54.6%) showed radiological improvement observed on CT at follow–up studies when compared to the baseline. Seventeen patients (15.7%) were cured, while ninety–one patients (84.3%) died from advanced–stage HCC.

Discussion:

Many patients present with HCC that is beyond potentially curative options[6]. In advanced HCC, palliative treatment with Sorafenib has been shown to extend survival[7–8]. Small tumors (< 2 cm) are potentially curable with RFA[9]. In tumors that are non–abatable, palliative chemoembolization in selected patients improves survival compared with best supportive care[10–11]. Therefore, the standard of care for unresectable HCC patients is TACE[12].

In RFA, an electrode tip, through which an electric current passes, is inserted percutaneously into the tumor

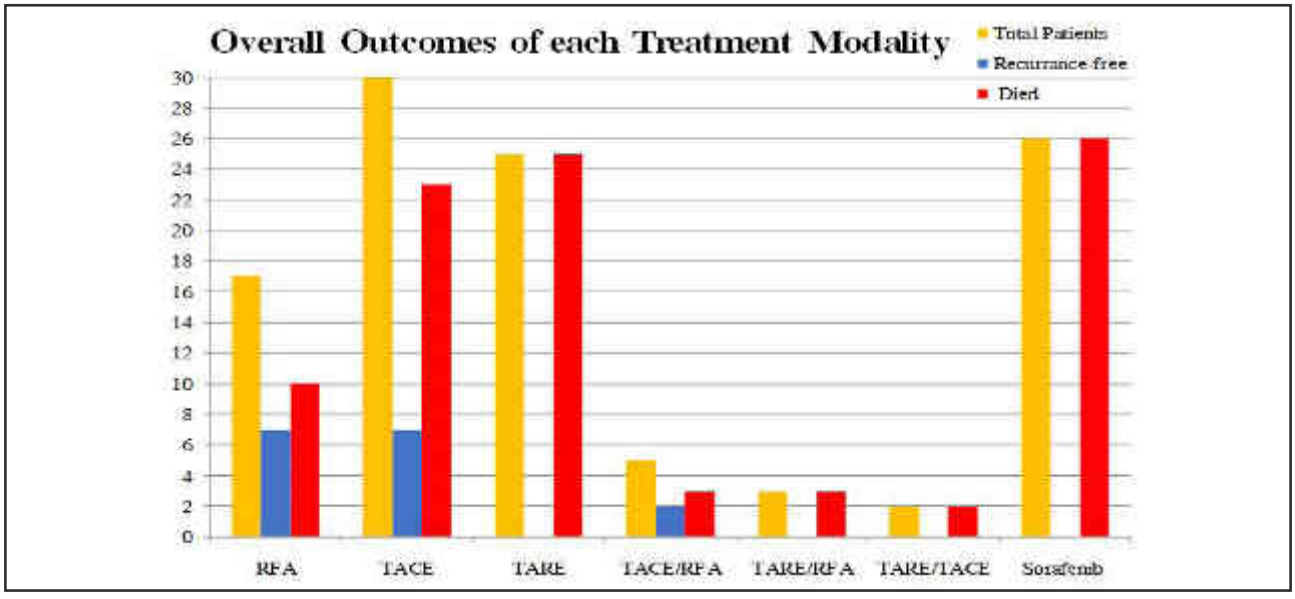

Figure 1: Overall Outcomes of Each Treatment Modality.

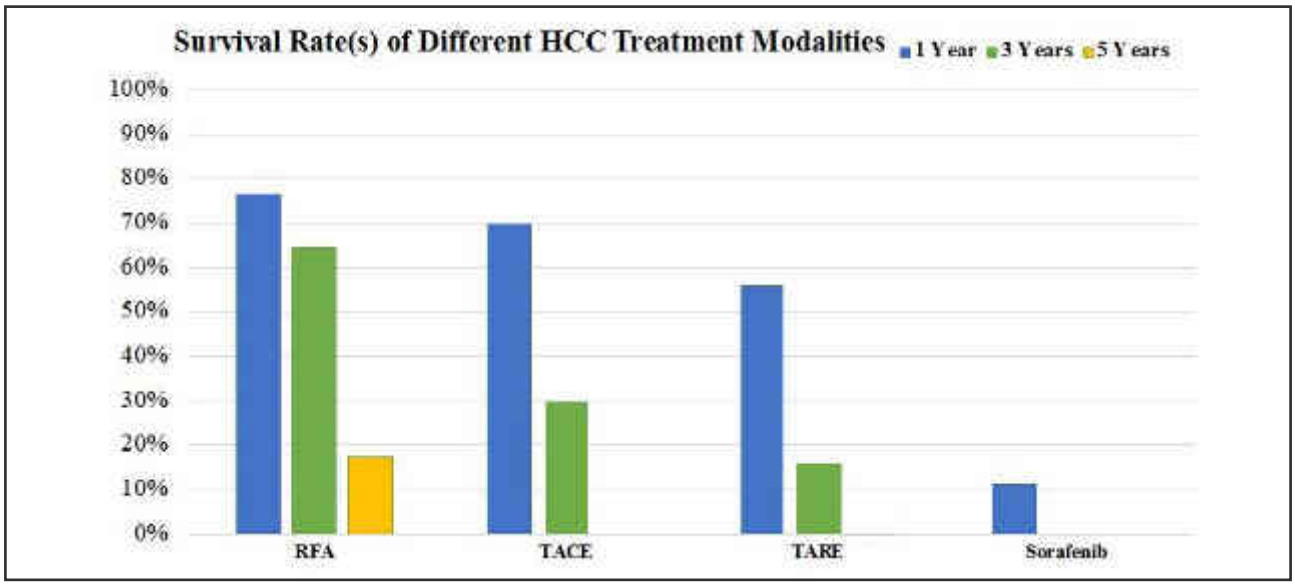

Figure 2: Survival Rate(s) of Different HCC Treatment Modalities.

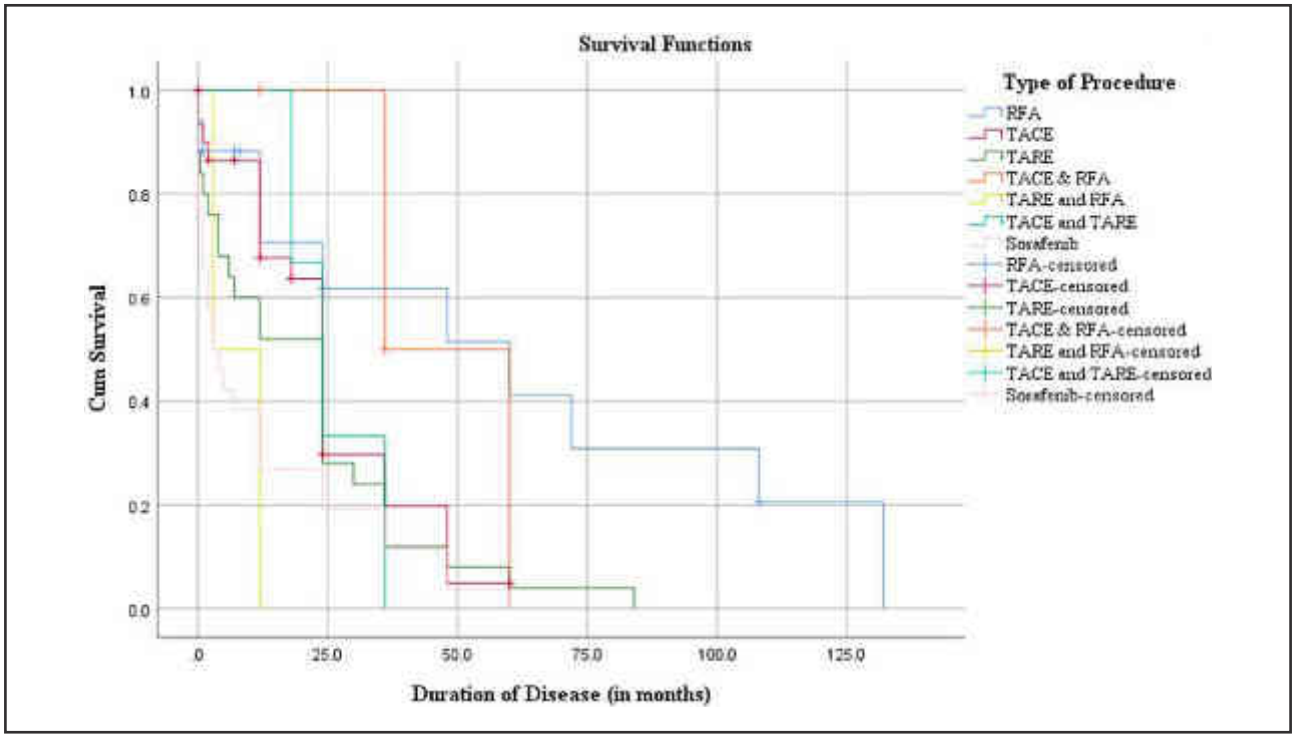

Figure 3: Kaplan–Meier Curves of the Survival of HCC Patients with Different Treatment Modalities.

under imaging guidance. Heat is generated, resulting in thermal destruction and coagulation necrosis. This technique seems to be very effective with low recurrence rates[13]. In previous research on very early HCC tumors (< 2 cm) and early HCC (3 cm), RFA was the most effective treatment modality achieving complete necrosis rates of 90%[14]. Since the initial use of RFA, the outcomes have improved in HCC tumors ≤ 3 cm in diameter. In a randomized controlled trial conducted by Peng et al., seventy patients received RFA with a recurrence–free rate reaching 18% and survival rates at 1, 3, and 5 years of 82%, 47%, and 36%, respectively[15]. A systematic review and meta–analysis for 4,295 patients concluded that RFA had a 38% recurrence–free rate and 1, 3, and 5 years survival rates of 49%, 34%, and 22%, respectively[16]. In our study, the recurrence–free rate with RFA was 41.2%, and the survival rates at 1, 3, and 5 years were 76.47%, 64.7%, and 17.67%, respectively, which are higher than the previously published data.

TACE is the most commonly used treatment modality for patients with stage B (intermediate) HCC defined by BCLC classification[17–18]. In TACE, the segmental hepatic

artery supplying the tumor is catheterized. The formation of an emulsion is achieved by mixing chemotherapeutic agents (commonly cisplatinum or doxorubicin) with a water–soluble contrast or lipiodol (known as ethiodized oil which can be concentrated in the tumor tissue for several weeks). This mixture is then injected into the desired segmental artery, followed by occlusion of the artery, causing obstruction of the flow, which is achieved by Gelfoam. This technique helps to lower systemic side effects and increase the concentration of the drug delivered to the tumor, which subsequently results in the induction of tumor necrosis. TACE is effective 80% of the time in causing significant necrosis of the tumor[19]. In patients with the intermediate stage (stage B in BCLC), more than three tumors regardless of size, or multifocal two to three tumors >3 cm in maximal diameter HCCs, single large tumor >5 cm, Child–Pugh A and B liver function, asymptomatic without evidence of vascular invasion or extrahepatic metastasis, TACE is the recommended treatment modality[12]. In a study done by Liu et al., 195 patients were involved, and the recurrence–free rate following TACE was 16.7 % and 1, 3, and 5 years survival rates were 80.7%, 26.4%, and 16.7%, respectively[20]. In our study, the recurrence–free rate with TACE was 23.3%, and the survival rates at 1 and 3 years were 70% and 30%, respectively, which are close to the previously published data.

In TARE, radioembolization with yttrium–90 (Y90) microspheres is a new concept in radiation therapy for HCC. Here, radiolabeled particles are injected through the hepatic artery, become trapped at the precapillary level, and emit lethal internal radiation[21]. This method limits exposure to the surrounding normal parenchyma, thus allowing higher dose delivery compared to an external beam. Radioembolization has shown promising outcomes in primary and secondary liver malignancies in several studies. There are currently two types of radioembolization using Y90 microspheres. TheraSphere (MDS Nordion, Ottawa, Ontario, Canada) is made of glass, and SIR–Spheres (Sirtex Medical, Sydney, Australia) is made of resin. Treatment response is the same despite differences in physical characteristics[21]. In a previous study done by Salem et al., they found that HCC patients treated either by TARE (Yttrium–90 microspheres) or TACE had no statistical significance in survival times with 20.5 months vs. 17.4 months, respectively, P= 0.232)[22]. In our study, the median survival time with TARE was 24±19.5 months, and the survival rates at 1 and 3 years were 56% and 16%, respectively, which is higher than the previous studies.

Sorafenib, an oral multi–kinase with antiproliferative and antiangiogenic properties, is the treatment of choice in BCLC C patients. It inhibits the vascular endothelial growth factor receptor (VEGFRs), the platelet–derived growth factor receptor β (PDGFR–β) [23–24]. In a study done by Llovet et al., the use of Sorafenib in advanced HCC has been shown to prolong the median survival and the time to progression by nearly three months[7]. Another study done in Kuwait included 111 patients receiving Sorafenib found an overall survival of only 3 months[25]. In advanced HCC, Sorafenib is considered a palliative treatment to extend survival with no curative potentials[7–8]. In our study, the median survival time with Sorafenib was 3±10 months, and the survival rates at 1 and 3 years were 11.5% and 0%, respectively, which is in agreement with previous publications.

RFA is better than TACE in controlling local HCC with a higher potential in achieving complete necrosis for small lesions. Unfortunately, RFA has unsatisfactory results in patients with intermediate or large HCC, with tumor necrosis rate that ranges from 29% to 70%[26]. A combination of TACE and RFA was studied by Kim et al., on a population of 67 patients with 29.7% recurrence–free and survival rates at 1, 3, and 5 years of 100%, 93.4%, and 83.5%, respectively[27]. The combination of TACE and RFA in intermediate HCC compared to supportive care alone had overall survival rates at 1, 3, and 5 years of the combination therapy group of 91%, 53%, and 27%, respectively with a statistically significant difference ($P < 0.0001$), while supportive care group had 42%, 8%, 8% and 0%, respectively[28]. In our study, the combination of TACE and RFA had a recurrence–free rate of 40%, and the survival rates at 1, 3, and 5 years were 100%, 60%, and 20%, respectively, which is close to the previously published studies.

The present study had several limitations including the relatively small sample size, being a single–center study, and the retrospective nature of the research. Future studies with larger sample sizes are warranted to validate our results. There is a need for a randomized trial comparing the curative potentials of TACE and TARE in patients with intermediate stage, apart from an ongoing prospective study comparing Sorafenib and TACE in advanced HCC. Combining thermal ablation with systemic chemotherapy, including immunotherapy, is an area of future development.

Conclusion:

This study provides further evidence for the efficacy of several treatment modalities for the management of HCC. RFA and the combination of TACE and RFA showed better outcomes with a recurrence–free rate reaching up to 40%. TACE had a moderate survival benefit up to

23.3%. TARE showed negative survival benefits. Sorafenib continues to be an important palliative treatment but does not offer curative potential.

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Conflict of Interest: The authors declare that they have no conflicts of interest.

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