Comparison of Transarterial Chemoembolization (TACE) vs Combination Transarterial chemoembolization plus Radiofrequency Ablation (TACE PLUS RFA) vs Selective Interventional Radiotherapy (SIRT) in the treatment of unresectable hepatocellular carcinoma (HCC): A Four-Year, Single Center Experience

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ABSTRACT

Significance. SIRT is an emerging locoregional therapy in the treatment of unresectable hepatocellular carcinoma. This study compared its treatment outcomes with TACE, the current standard of care and combination TACE with RFA.

Materials and methods. This is a retrospective, single center chart review which included eligible unresectable hepatocellular carcinoma patients who underwent either TACE, TACE plus RFA or SIRT in our center from 2012 to 2016.

Results. This study found that tumor response to treatment with SIRT was not significantly different from that of TACE or TACE with RFA at 3 months (p=1.000), 6 months (p=1.000) and 12 months (p=0.503). Likewise, tumor progression at 3 months (p=1.000), 6 months (p=0.758) and 12 months (p=0.279) were also not statistically significant.

Conclusion. SIRT may serve as a treatment option in patients with unresectable hepatocellular carcinoma as its outcomes are not significantly different from TACE or TACE plus RFA.

Keywords: TACE, SIRT, TACE vs SIRT

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BACKGROUND

Hepatocellular cancer (HCC) ranks only sixth among the most common cancers worldwide,[1] yet it remains the second leading cause of cancer death, only surpassed by lung cancer in its mortality rates.[2] In a global profile of the international incidence and mortality trends of the liver done by Wong et al[3], the number of deaths from hepatocellular cancer per year is almost the same as its incidence, with overall survival rates of 5-6%. [4]

The incidence of hepatocellular cancer is still increasing, due to the numbers of Hepatitis B and Hepatitis C infections. Due to its high case fatality rate and its increasing incidence, it remains an important public health issue worldwide.

The American Association for the Study of Liver Disease (AASLD) has published clinical guidelines for the management of hepatocellular carcinoma. The choice of treatment is dependent mainly on the extent of disease. In patients with tumors less than 2 cm in diameter, confinement to one lobe of the liver, absence of vascular invasion and Barcelona Clinic Liver Cancer Classification (BCLC) stage 0-A, surgical resection of the tumor remains the first line option. Surgery offers the best prognosis for long-term survival. Data from surgical centers achieved 5-year survival rates of 40% and 10 years at 26%. Unfortunately, most patients are diagnosed in advanced clinical stages, and only 5% of patients are eligible for resection.

Loco-regional therapies are recommended in early stage HCC patients precluding surgical options. This includes radiofrequency ablation (RFA), transarterial chemoembolization (TACE) and SIRT.

Transarterial chemoembolization (TACE) has been the standard of care since it was incorporated in the Barcelona clinic liver classification for HCC on 2003. This is sometimes combined with radiofrequency ablation, which is a localized treatment designed to induce tumor destruction by heating the tumor tissue.

TACE involves direct placement of chemotherapeutic agent into the hepatic artery through the tumor, with a macroembolic effect and arterial occlusion. In effect, tumor size is decreased. Treatment with TACE however, may lead to adverse events

through its mechanism, such as the post-embolization syndrome, which may require hospitalization and the possibility of hepatic artery occlusion.

Selective internal radiation therapy (SIRT) is a relatively new concept which involves intra-arterial injection of ^{90}Y microspheres which preferentially targets tumor tissues in the liver, thus, limiting exposure to the surrounding normal parenchyma. Injection of ^{90}Y microspheres does not lead to arterial occlusion. SIRT is increasingly used in intermediate and advanced stage HCC, but because of the lack of level 1 evidence, its use was not recommended in either the American Association or the study of Liver Disease guidelines (AASLD) or the European Association for the study of the Liver (EASL) treatment guidelines for HCC. However, the European Society for Medical Oncology (ESMO)/ European Society for Digestive Oncology (ESDO) and the recent National Comprehensive Cancer Network (NCCN) guidelines have included SIRT as treatment option in HCC.

In this study, we report our experience in our center regarding the use of SIRT in comparison to other locoregional therapies in patients with unresectable hepatocellular carcinoma.

RESEARCH QUESTION

Among patients with unresectable intermediate stage hepatocellular carcinoma, is SIRT comparable to the current standard of care, TACE or TACE with RFA when it comes to treatment outcomes?

OBJECTIVES

The main objective of this study is to determine if there is a significant difference in treatment outcomes among intermediate stage unresectable HCC patients who underwent TACE, TACE plus RFA or SIRT.

Specifically, it aims to:

1. determine and compare **rate of tumor progression** of unresectable HCC patients who undergo TACE, TACE plus RFA and SIRT over the first 3 months, 6 months and 12 months after initiation of treatment
2. determine and compare **response rate** of unresectable HCC patients who undergo TACE, TACE plus RFA and SIRT over the first 3 months, 6 months and 12 months after initiation of treatment

METHODOLOGY

Patient and data collection

This is a retrospective cohort study conducted in Makati Medical Center, a private tertiary urban 500-bed hospital in Makati City Philippines.

We studied the medical records of patients with hepatocellular carcinoma seen in our institution from the 1st of January 2012 to December 31, 2016 who received treatment with who underwent either of the three interventions: TACE, TACE plus RFA or SIRT.

Inclusion and Exclusion criteria

The following were the inclusion criteria for enrolment: (1) age 18 years old and above; (2) hepatocellular cancer (HCC) proven by histology or according to non-invasive methods by the AASLD; (3) unresectable according to BCLC); (4) Eastern Cooperative Oncology Group (ECOG) Performance status of 0 -1; (5) preserved liver function (Child Pugh A – B); (6) and at least one measurable lesion on contrast-enhanced CT or in MRI.

Patients were excluded from the study if they had (1) chemotherapy during the last 4 weeks; (2) Child Pugh stage C; (3) BCLC stage C; (4) ECOG performance status >0; (5) tumor involvement > 50% of the liver; and the (6) presence of a extrahepatic tumor.

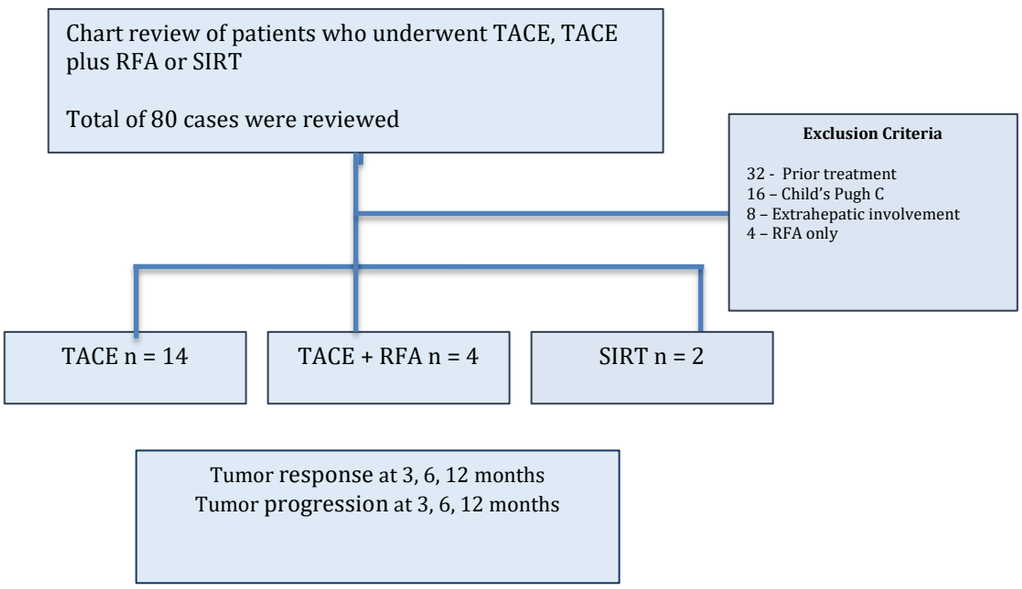

Figure 1. Flowchart representing the procedures for inclusion in the study

Measurement of outcomes

The charts of eligible patients were included in this study. The primary outcomes in this study are response to treatment at three months and tumor progression within 12 months of unresectable HCC patients who underwent TACE, TACE plus RFA and SIRT.

Charts of patients who underwent SIRT, TACE, and TACE with RFA were analyzed at three, six, nine and 12 months after initiation of treatment. At three, six , nine and twelve months, tumor response will be analyzed through the CT scan of the abdomen or MRI.

Sample size and data analysis

A total of 20 subjects were included in the study. However, a minimum of 149 subjects for this study is required to have a significance of 5% and a power of 90%. These values are based on the study by Kobby, 2010.

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion was used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. Independent sample t test, Mann-Whitney U test and Chi-square/Fisher's exact test were used to determine the difference of mean, median and frequency, respectively. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 12.0 was used for data analysis.

RESULTS

A total of 20 patients were included in our study, 14 were treated with TACE, 4 underwent TACE with RFA, and 2 underwent SIRT.

Table 1. Demographic profile of patients (n=20)

	SIRT (n=2)	TACE (n=14)	TACE with RFA (n=4)	P-value
	Frequency (%); Mean ± SD			
Age (years)	61 ± 2.8	62 ± 10.4	74 ± 10.6	0.130*
BMI (kg/m^2)	26.64	28.75 ± 5.4	25.6 ± 8.02	0.663*
GENDER				1.000@
Male: Female	1 (50): 1 (50)	8 (57.14) : 6 (42.86)	2 (50) : 2 (50)	
Etiology of liver disease				0.118@
HBV	1 (50)	8 (57.14)	0	
Cryptogenic	1 (50)	6 (42.86)	4 (100)	
Childs-Pugh class				1.000@
A	2 (100)	8 (57.14)	3 (75)	
B	0	6 (42.86)	1 (25)	
BCLC stage				0.830@
A	2 (100)	6 (42.86)	1 (25)	
B	0	8 (57.14)	3 (75)	
Multiple Tumors	1 (50)	6 (42.86)	3 (75)	0.777@

The demographic profile of these patients were summarized in table 1. There was no significant difference found among the three comparison groups when it comes to age, BMI, gender, etiology of liver cirrhosis, Child-pugh class, BCLC stage and multiplicity of tumor sites. It was noted that the etiology of cirrhosis was predominantly cryptogenic (n=11), while had 9 Hepatitis B infection.

When it comes to the severity of their cirrhosis, most of the patients who underwent intervention have a Child-Pugh classification A (n= 14). All of the patients who underwent SIRT (n=2/2) are under BCLC A while in the TACE group, 8 out of 14 are under this classification.

Table 2. Tumor characteristics and treatment strategy

	SIRT (n=2)	TACE (n=14)	TACE with RFA (n=4)	P-value
	Frequency (%); Mean ± SD; Median (Range)			
AFP (ng/ml)	151 (10 – 291)	21.47 (3.7 – 1986)	14.1 (3.09 – 9312)	0.720‡
-				
Portal vein involvement				0.561ê
Yes	1 (50)	4 (30)	2 (50)	
No	1 (50)	9 (70)	2 (50)	

Statistical tests used: ‡ - Kruskal Wallis test; ê - Fisher's exact test

Table 3 lists the imaging outcomes. In our study, among the 2 patients who underwent SIRT, both had an non-enhancing mass at 3 months, suggesting a good tumor response to the intervention. However, at 6 months, 1 had a new mass while the other 1 was lost to follow up at 6 months.

Table 3. Outcomes of CT scan (n=11)

	SIRT (n=2)	TACE (n=14)	TACE with RFA (n=4)	P-value
	Frequency (%); Mean ± SD; Median (Range)			
Underwent CT scan	2 (100)	12 (85.71)	2 (50)	0.192
At 3 months*				
Enhancing	0	4 (33.33)	0	0.853ê
Non enhancing	2 (100)	6 (50)	2 (100)	0.357ê
Decreased in size	0	4 (33.33)	1 (50)	1.000ê
Unchanged in size	0	2 (16.67)	0	1.000ê
New mass	0	1 (8.33)	0	1.000ê
At 6 months*				
Enhancing	0	2 (16.67)	1 (50)	0.607ê
Non enhancing	0	2 (16.67)	0	1.000ê
Decreased in size	0	1 (8.33)	0	1.000ê
Unchanged in size	0	1 (8.33)	0	1.000ê
New mass	1 (50)	2 (16.67)	0	0.607ê
No follow-up	1 (50)	5 (41.67)	1 (50)	1.000ê
Others (options for SIRT)	0	1 (8.33)	0	1.000ê
At 9 months				
Enhancing	1 (50)	1 (8.33)	1 (50)	0.136ê
Non enhancing	0	2 (16.67)	0	1.000ê
Decreased in size	0	1 (8.33)	0	1.000ê
Unchanged in size	0	0	0	-
New mass	0	2 (16.67)	0	1.000ê
No follow-up	1 (50)	8 (66.67)	1 (50)	1.000ê

Among the 14 patients who underwent TACE, at 3 months, 4 were found to have a decrease in tumor size, 6 were found to have a nonenhancing mass, while 3 either had a new mass or no change in tumor size. Among the 4 patients who underwent TACE plus RFA, with good tumor response at 3 months, presenting with either a non-enhancing mass or decrease in tumor size.

Table 4. Tumor response to treatment

	SIRT (n=2)	TACE (n=14)	TACE with RFA (n=4)	P-value
	Frequency (%); Mean ± SD; Median (Range)			
Number of treatments	[n=2]	[n=6]	[n=0]	1.000[ê]
1	1 (50)	4 (66.67)	-	
2	0	1 (16.67)	-	
3	1 (50)	1 (16.67)	-	
Tumor response at 3 months	[n=2]	[n=7]	[n=2]	0.818[ê]
Complete response	1 (50)	2 (28.57)	2 (100)	
Partial response	1 (50)	2 (28.57)	0	
Stable disease	0	1 (14.29)	0	
Progressive disease	0	2 (28.57)	0	
Any complications	0	0	0	-
Patient survival after treatment (months)				

At 3 months, 1 patient treated with SIRT had complete response to treatment, while the other one only had partial response. Two out of the 9 patients treated with TACE had complete response to treatment, 2 had partial response, 1 had stable disease and 1 had progressive disease. Despite this, the three groups of patients with HCC did not differ significantly when it comes to tumor response to treatment (p= 0.818) as summarized in Table 4.

The MRI or CT scans of the patients were recorded at 3 months, 6 months and 12 months for tumor progression. There was also no statistically significant difference among the three groups when it comes to tumor progression at 3 months (p=1.000), 6 months (p=1.000) and 12 months (p=0.503).

Table 5. Tumor recurrence rate

	SIRT	TACE	TACE with RFA	P-value
	Frequency (%); Mean ± SD; Median (Range)			
Tumor recurrence (n=14)	[n=2]	[n=10]	[n=2]	
3 months after initiation	0	2 (20)	0	1.000[ê]
6 months after initiation	1 (50)	3 (30)	1 (50)	1.000[ê]
12 months after initiation	1 (50)	2 (20)	1 (50)	0.503[ê]

Statistical test used: ê - Fisher's exact test

Tumor recurrence was noted in 2 out of 10 in the TACE group during the first 3 months after initiation, while none had tumor recurrence within 6 months from the

SIRT group. Although it was noted that only 50% of TACE patients (n-4/8) has recurrence within 12 months after initiation, compared to SIRT where recurrence was noted to be 100%, it was not statistically significant.

DISCUSSION

In patients with unresectable HCC, loco-regional therapies have demonstrated therapeutic efficacy for selected HCC patients. The main purpose of this study was to compare SIRT to trans-arterial chemoembolization (TACE), the current standard of care and the most widely used primary therapy for unresectable HCC and TACE with RFA. TACE has been shown by randomized clinical trials to delay tumor progression and macrovascular invasion and increase mean survival from 16 months to 20 months. SIRT on the other hand, is a new treatment modality and its role in unresectable liver disease still has to be defined.

The main finding of this study is that tumor response to treatment with SIRT was not significantly different from that of TACE or TACE + RFA.

Likewise, tumor progression at 3 months (p=1.000), 6 months (p=0.758) and 12 months (p=0.279) were also not statistically significant. This finding is the same the study of Salem et al, who reported a large prospective study wherein treatment with either SIRT or TACE resulted in similar outcomes.

SIRT may potentially serve as a treatment option, and is comparable to TACE or TACE plus RFA in the treatment of unresectable HCC. Since both exhibits almost the same survival, complications of treatment may be factored for the locoregional therapy of choice.

Our study should be interpreted in the light of its limitations. Our study is a single center study involving a limited sample size, which is not able to reach statistical significance. Hence, a continuation of this study to include more patients is recommended. Aside from this, its retrospective nature provides us with only limited data. But despite these limitations, however, our study was able to represent a current assessment of SIRT in comparison to TACE and TACE + RFA in our center.

CONCLUSION

In conclusion, this study showed that SIRT may potentially be comparable to TACE or TACE + RFA when it comes to tumor response and tumor progression in patients with unresectable hepatocellular carcinoma, and may serve as a treatment option.

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