Outcome of locally advanced hepatocellular carcinoma treated with selective internal radiation therapy compared to sorafenib: a multicenter experience in the Philippines

Sawadjaan FLB
Ong JP

Section of Gastroenterology
Department of Medicine
The Medical City
Pasig, Philippines

Correspondence:
Dr. Fatimin Leila B. Sawadjaan
leilasawadjaan@gmail.com

Abstract

Significance: Sorafenib is the recommended first-line therapy for patients with advanced hepatocellular carcinoma (HCC). There is limited Philippine data comparing the benefit of selective internal radiation therapy with yttrium-90 resin microspheres to sorafenib in patients with locally advanced HCC. **Methodology:** This is a post hoc analysis involving Filipino patients included in the SIRveNIB trial. Primary end point was overall survival. Analysis of efficacy of treatment was performed in the intention-to-treat population. Patients who were ≥18 years old diagnosed with locally advanced HCC without extrahepatic disease, with or without portal vein thrombosis, and were not amenable to curative treatment options, were randomly assigned 1:1 and received assigned treatment. Survival rates up to 18 months were estimated and compared between the two groups. **Results:** A total of 57 patients were randomly assigned (SIRT 29; sorafenib 28). Males comprised 48%, mean age of 56. Chronic hepatitis B infection was present in 54.4% of patients. Most were Child A (91.2%), 58% had BCLC B, and 35% had portal vein thrombosis. Disease control rate was better with SIRT [86% (95% C.I., 64%, 97%) versus 32% (95% C.I., 14.9%, 53.5%)]. Median OS was 8.31 months with SIRT and 5.75 months with sorafenib (HR 0.75; 95% CI, 0.41 to 1.36; p = 0.34). Fewer patients receiving SIRT experienced treatment-related adverse events [SIRT, 9/21 (42.9%) versus sorafenib, 21/25 (84%)] or treatment-related serious adverse events [SIRT, 2/21 (9.5%)] versus sorafenib, 14/25 (56%)]. **Conclusion:** Difference in overall survival among locally advanced hepatocellular carcinoma treated with SIRT compared to sorafenib is not significant. Fewer adverse events were noted in patients treated with SIRT.

Keywords: sorafenib, hepatocellular carcinoma, Philippines, yttrium-90

According to the World Health Organization, hepatocellular carcinoma (HCC) is the second most common cause of death from cancer worldwide.[1] The incidence is high in Southeast Asia, particularly in China, Hong Kong, Thailand, Taiwan, South Korea and the Philippines. In the Philippines, the incidence rate is 13.4 (males) and 4.7 (females) per 100, 000 persons, and this is due to the increased incidence of Hepatitis B.[2] Based on a single serological detection of Hepatitis B virus marker, 68% of Filipinos are exposed, making the Philippines a hyperendemic region for Hepatitis B. Most Filipino patients with HCC are younger, with a mean age

of 54 years, and are diagnosed at an early stage of the disease. [3,4] And in a subgroup of patients diagnosed with advanced stage of HCC, treatment has been difficult.

Based on the 2017 Asia–Pacific clinical practice guidelines on the management of HCC, sorafenib is recommended as first-line treatment for advanced disease (macrovascular invasion or extrahepatic metastasis) that is not suitable for locoregional therapy and with Child–Pugh class A liver function.[5] Sorafenib is an oral multikinase inhibitor that has been shown to significantly increase overall survival compared with placebo in the SHARP Trial.[6] Sorafenib induces the apoptosis of tumor cells due to both its antiproliferative and antiangiogenic effects.[7] It has been approved for the treatment of unresectable HCC worldwide and listed in the Barcelona Clinic Liver Cancer (BCLC) staging system and the Asian Pacific Association for the Study of the Liver (APASL) as the treatment guideline for HCC.[5] Meanwhile, for Child- Pugh class B and C patients with advanced HCC, treatment has been limited to best supportive care.[5]

Selective internal radiotherapy (SIRT) with yttrium-90 (^{90}Y) is a therapeutic procedure that delivers high dose radiation to liver tumors and is applied via the hepatic artery. These microspheres are targeted and thus spares the liver parenchyma.[8] Tumor cell damage results from the high energy beta radiation that triggers DNA double strand breaks.[9]

In one randomized controlled trial comparing SIRT with ^{90}Y and sorafenib in patients with locally advanced non-metastatic HCC in France (SARAH Trial), there was no significant difference seen in the overall survival (OS).[10] In the Selective Internal Radiation Therapy Versus Sorafenib (SIRveNIB) study, which compared treatment with SIRT with ^{90}Y and sorafenib in an Asia-Pacific population with locally advanced HCC, it was also concluded that the overall survival did not differ significantly in both groups.[11]

In the Philippines, only a handful of centers offer SIRT with ^{90}Y, and the procedure is not covered by the national health insurance, making it an expensive option for the patient. We hypothesize that SIRT is superior than sorafenib as treatment in the overall survival of patients with locally advanced hepatocellular carcinoma. In this post hoc analysis, we aim to evaluate the outcome of Filipino patients with locally advanced hepatocellular carcinoma treated with SIRT compared to sorafenib included in the SIRveNIB trial.

Methods

Study Design and Interventions

This is a post hoc analysis involving the patient population from the Philippines included in the SIRveNIB trial (Clinical trial identifier: NCT01135056). The SIRveNIB trial was a prospective, randomized, investigator-driven, open-label, multi-center, phase III trial conducted at centers in the Asia-Pacific region that compared the efficacy and safety of a single delivery of radioembolization versus continuous sorafenib dosing in patients with locally advanced HCC.[10]

In this trial, patients were considered eligible if they were 18 years old and above, with an unequivocal diagnosis of HCC (on the basis of the American Association for the Study of the Liver imaging criteria or biopsy, had locally advanced cancer (Barcelona Clinic Liver Cancer [BCLC] stage B or C without extrahepatic disease, with or without portal vein thrombosis (PVT), and were not amenable to curative treatment modalities. Exclusion criteria were as follows: previous administrations of hepatic artery-directed therapy, hepatic artery-directed treatment within four weeks, previous treatment with sorafenib or vascular endothelial growth factor inhibitors, or previous radiotherapy. Eligible patients were then randomly assigned to 1:1 ratio to receive either radioembolization or sorafenib and stratified according to center and the presence or absence of PVT. Oral sorafenib (Nexavar®, Bayer HealthCare Pharmaceuticals, Berlin, Germany) was given at 400 mg twice daily, and was continued until there was evidence of treatment failure (tumor progression at any site), complete response, the initiation of other HCC therapies, unacceptable toxicity, patient request to stop treatment, or death. The subjects in the SIRT group received a single dose of ^{90}Y loaded resin microspheres [SIR-Spheres®; Sirtex Medical Limited, New South Wales, Australia]) that was calculated according to the body surface area model **(Figure 1)**.

This study was conducted in accordance with the principles in the Declaration of Helsinki on human research. A detailed description of the study methods, and inclusion and exclusion criteria, are available in the previously published report by Chow, et al.[11]

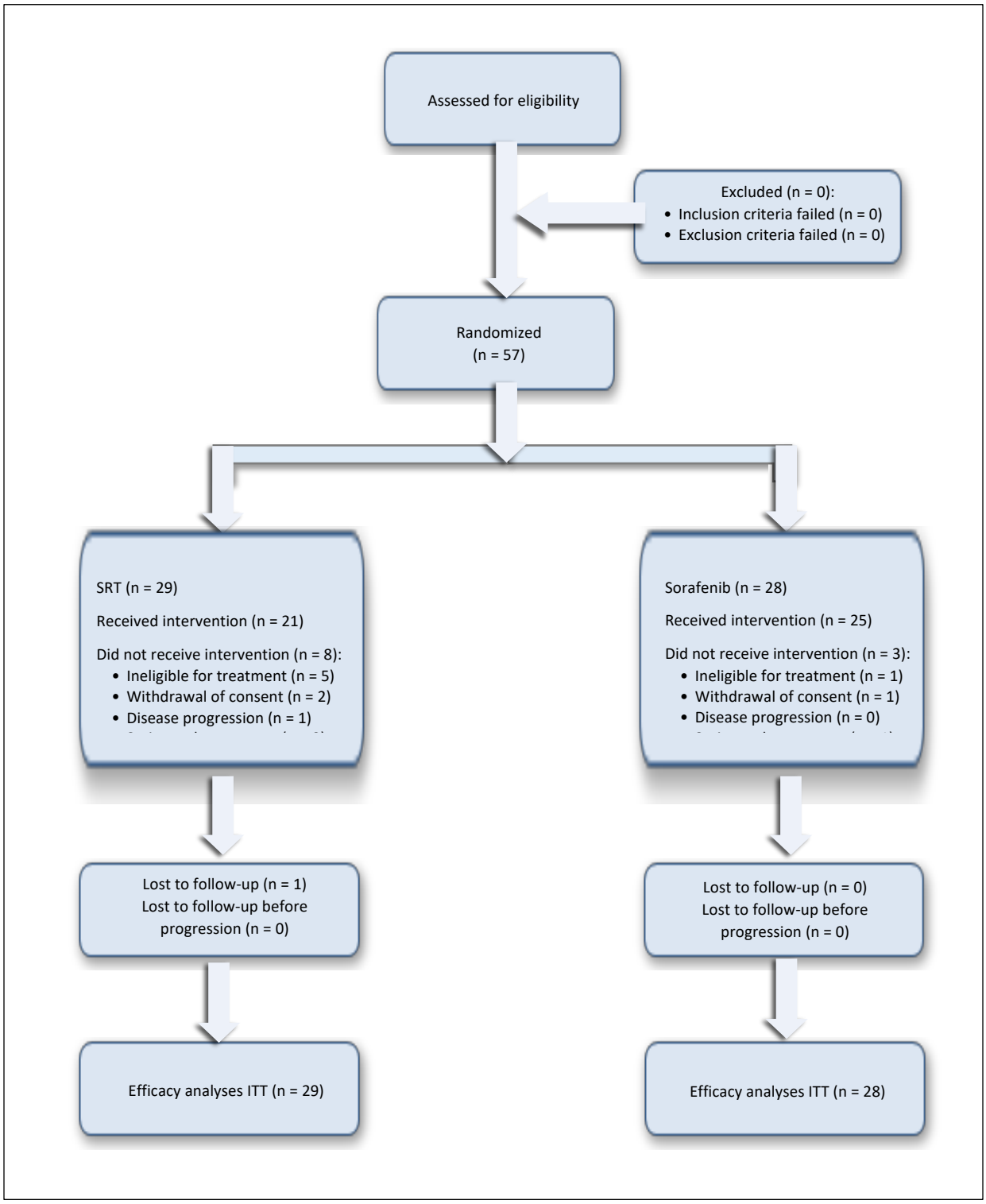

Figure 1. Consort diagram

Outcome Measures

The primary end point was overall survival (OS). Survival rate of up to 18 months were estimated using Kaplan-Meier plots and were compared between the two groups using the log-rank test. Secondary endpoints included tumor response rate, disease control rate, and adverse events by the treatment. Patients were clinically assessed for safety every four weeks for the first three months, and every three months thereafter, until the end of the study.[10] All adverse events were recorded from the time of signing the written informed consent until 30 days after the final sorafenib dose, or until 30 days post-SIRT regardless of cause of death.[10]

Statistical Analysis

The primary analysis was conducted on the intention-to-treat (ITT) population. Median overall survival was estimated using Kaplan-Meier plots with corresponding two-sided 95% CIs. Survival rates at 6, 12, and 18 months were estimated using Kaplan-Meier plots and compared between the two groups using the log-rank test (**Figure 2**). Tumor response rate and disease control rate were compared using the Fisher's exact test. Adverse event rates were compared between the two groups using the Fisher's exact test, on the basis of the treated population (n = 46). Categorical data were compared using a chi-square test. Continuous variables were summarized as means or medians with range. A *p* value of <0.05 was deemed to be statistically significant.

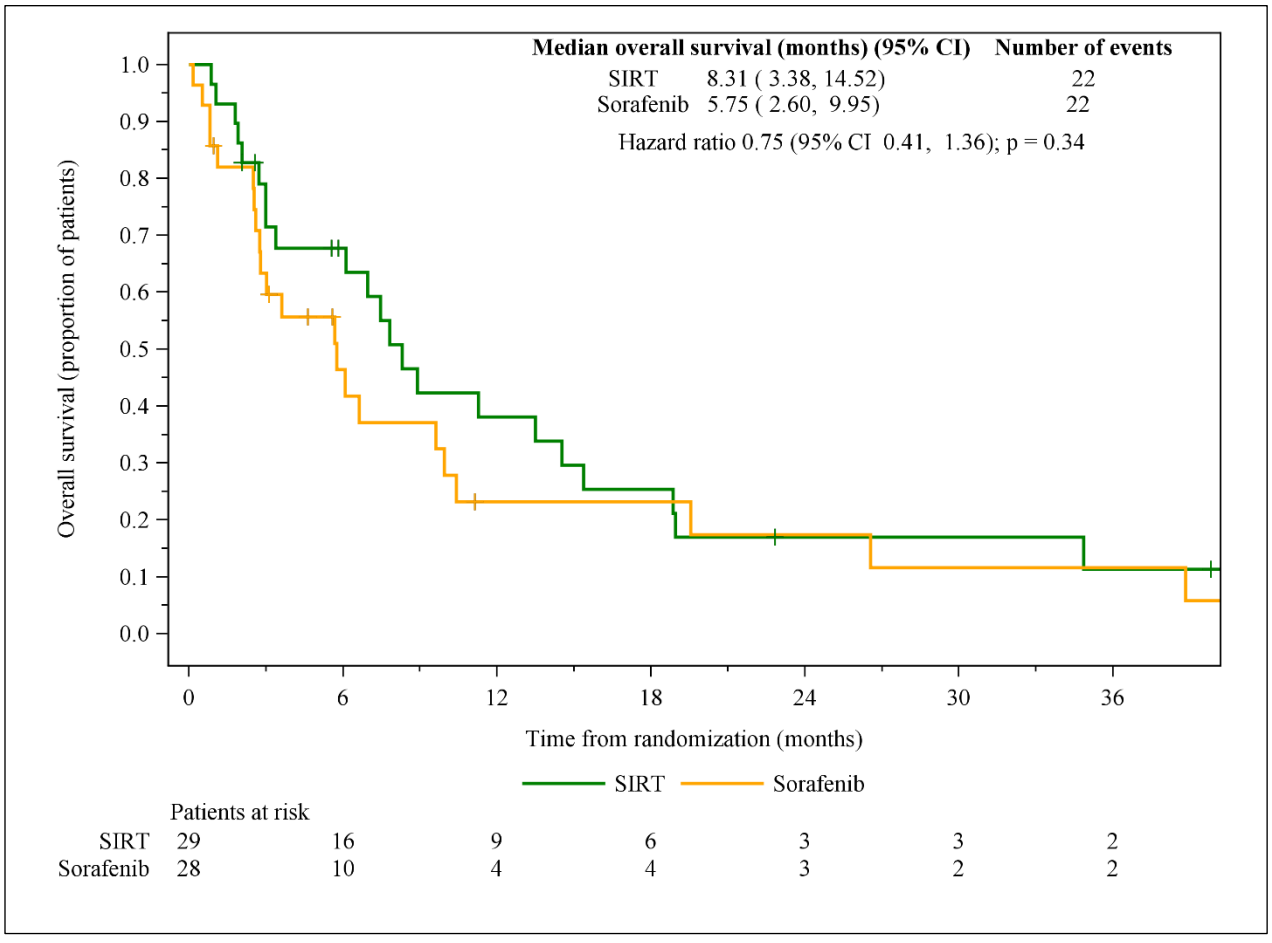

Figure 2. Kaplan-Meier for overall survival

Results

A total of 57 Filipino patients were randomly assigned in to two groups, SIRT group n = 29 and sorafenib group n = 28 from four tertiary centers in the Philippines.

The baseline characteristics of the enrolled patients are seen at **Table 1**. There were no statistically significant differences between both groups. Males comprised 48% and had a mean age of 56. Chronic hepatitis B infection was present in 54.4% of the patients. Most of the patients were Child-Pugh A status at 91.2%. Fifty-eight percent had BCLC B status, and 35% had portal vein thrombosis. Less than 1% of these patients had ascites, and none of them had encephalopathy. The size of the liver tumors was similar, comprising <50% of the liver in 76% of the enrolled patients. Fifty-four percent of the subjects had hepatitis B, and 5.3% had hepatitis C.

Twenty-one patients from the SIRT group and 25 patients from the Sorafenib group received the assigned treatment. Tumor response rate **(Table 2)** was not significant with SIRT 13.8% and Sorafenib at 0 ($p = 0.112$).

Table 1. Baseline characteristics of study population (N = 57)

Profile		**SIRT** (n = 29)	**Sorafenib** (n = 28)	**Total** (n = 57)	***p*-value**
Gender	Male	24	24	48	1.0000
	Female	5	4	9	
Age	n	29	28	57	0.9618
	mean	56.1	56.0	56.1	
	median	61.0	56.5	57.0	
PVT	Yes	10	11	21	0.7871
	No	19	17	36	
ECOG status	0	20	23	43	0.3578
	1	9	5	14	
Child-Pugh stage	A	27	25	52	0.6701
	B	2	3	5	
BCLC stage	B	15	18	33	0.4242
	C	14	10	24	
Hepatitis B	positive	15	16	31	0.9261
	negative	11	9	20	
	N/A	1	3	4	
Hepatitis C	positive	2	1	3	1.0000
	negative	21	21	42	
	N/A	6	6	12	
Both hepatitis B and C	positive	0	1	1	1.0000
	negative	9	9	18	
	N/A	3	3	6	

Table 2. Summary of outcomes

Outcome	**SIRT** (n = 29)	**Sorafenib** (n = 28)	**Total**	***p*-value**
Tumor response rate	4 (13.8)	0	4	0.1120
Disease control rate	18 (62.1)	9 (28.6)	27	0.0167
Overall survival (months)	8.31	5.75		0.3368
	SIRT (n = 21)	**Sorafenib** (n = 25)	**Total**	***p*-value**
No. of adverse events	149	299	448	0.6857
At least one adverse event	18	25	43	
At least one severe adverse event	7	20	27	
At least one serious adverse event	4	20	24	

Disease control rate was better with SIRT [86% (95% C.I., 64%, 97%) versus 32% (95% C.I., 14.9%, 53.5%)]. The median overall survival was 8.31 months with SIRT and 5.75 months with sorafenib (HR 0.75; 95% CI, 0.41 to 1.36; $p = 0.34$).

Fewer patients receiving SIRT experienced treatment-related adverse events [SIRT, 9/21 (42.9%) versus sorafenib, 21/25 (84%)] or treatment-related serious adverse events [SIRT, 2/21 (9.5%) versus sorafenib, 14/25 (56%)]. Reported significant adverse events among both groups included skin and subcutaneous disorders such as alopecia, palmar-plantar erythrodysaesthesia syndrome and rash, which occurred more often in the sorafenib group.

Discussion

In a developing country with limited health resources, the management of advanced diseases has proven to be difficult for the physicians. Hepatocellular carcinoma, in particular, is usually diagnosed at a later stage. And although guidelines have recommended sorafenib as the first line for patients with advanced HCC with Child Pugh A status, most patients are unable to afford and/or may not tolerate the medical treatment that is given for a prolonged time. SIRT, although also an expensive alternative for patients, is of shorter duration and has had promising results.

This study was conducted to evaluate the outcomes of the patients included in the SIRveNIB trial in the local setting in the Philippines. In the SIRveNIB trial, the authors have indicated that the results of the study may have been influenced by the unavailability of the SIRT in some of the countries that participated in the study. Those patients had to travel to Singapore for the treatment, and may have been the cause of delay for receiving the treatment, thus skewing the final results. The participants from the Philippines however, had the SIRT treatment done locally, and may have different results if analyzed independently.

In the SIRveNIB trial, radioembolization failed to demonstrate any statistical difference in overall survival compared with sorafenib in the treatment of locally advanced HCC. RE was neither superior nor detrimental compared with sorafenib in locally advanced HCC.

In this post hoc analysis, results show that the difference in overall survival among Filipino patients with locally advanced hepatocellular carcinoma treated with SIRT compared to sorafenib was also not significant. SIRT in the Philippines, as mentioned earlier, were conducted by overseas-trained interventional radiologists in only a few centers in the country. Hence, the effect of the treatment was not affected by the operator's expertise. Therefore, with regards to overall survival, it appears that a single dose of ^{90}Y through SIRT had a similar effect as sorafenib.

The limitations of this study arise primarily from the sample size, and thus may not give a robust inference.

Conclusion

In this post hoc analysis, we derive similar results with the study by Chow, et. al.[11] The difference in overall survival among Filipino patients with locally advanced hepatocellular carcinoma treated with SIRT compared to sorafenib is not significant. However, the disease control rate was significantly better with SIRT group. There were also fewer adverse events noted in patients treated with SIRT.

Conflict of Interest

The authors declare no conflict of interest.

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