Safety and Efficacy of $^{90}$Y Selective Internal Radiation Therapy Using Glass Microspheres in Hepatocellular Carcinoma: A Southeast Asian Single-Institution Initial Experience

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Our objective was to demonstrate primarily the safety and secondarily the efficacy of $^{90}$Y glass microspheres in selective internal radiation therapy (SIRT) for hepatocellular carcinoma (HCC) in a local Southeast Asian hospital. Methods: Eleven consecutive patients with small, unresectable, nonmetastatic HCC and referred for locoregional therapy with SIRT with a curative intention were followed up for 6 mo after the procedure by way of interviews, blood tests, and anatomic scans. Results: Although 5 patients had deranged liver function tests after the procedure, in only 1 patient did this constitute a grade 1 toxicity (in alkaline phosphatase) by the Common Terminology Criteria for Adverse Events. Half the patients showed a reduction in serum alpha-fetoprotein measurements, and 6 of 11 patients demonstrated an objective response (complete or partial) on imaging. Conclusion: SIRT with $^{90}$Y glass microspheres is a safe and efficacious locoregional therapy for unresectable HCC. There are similar articles published in the West; however, the patient population there comprises far fewer Asians and the underlying cause for HCC is different from that in the Asian population. Despite these differences, SIRT is an equally effective and safe option for such patients.

Key Words: hepatocellular carcinoma; selective internal radiation therapy; $^{90}$Y

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Selective internal radiation therapy (SIRT) with $^{90}$Y-impregnated microspheres is an efficacious locoregional modality for unresectable hepatocellular carcinoma (HCC). To date, the procedure is showing maturing data, with a multitude of publications showing good treatment efficacy (improved objective response rates, prolonged time to tumor progression, and improved overall survival) either as a stand-alone procedure (1,2) or in combination with stereotactic body radiation therapy or systemic therapies such as kinase inhibitors or immunotherapy (3).

Although most published data have shown safety and efficacy in the Western population, there are limited data on the safety and efficacy of $^{90}$Y SIRT using glass microspheres (TheraSphere; Boston Scientific) in the Asian population and whether the data for Western patients can be extrapolated to Asians given differences in disease biology, underlying pathology, prevalence of liver cirrhosis, normal liver, and lung masses (4–6). For example, the incidence of primary HCC is higher in East Asia and Southeast Asia than in North America and Europe. Additionally, the causal agent in Asia is predominantly hepatitis B virus infection, whereas hepatitis C virus infection and metabolic syndrome appear the be the main causes in the Western population. In this case series, we highlight the initial safety of performing $^{90}$Y SIRT using glass microspheres to deliver high tumor-absorbed doses in our local patient population within a single institution in Southeast Asia.

MATERIALS AND METHODS

Patient Selection

This report on our single-center retrospective study describes our initial 11 consecutive patients with unresectable HCC referred for radiation segmentectomy from December 2021 to December 2022. The study protocol was approved by the SingHealth institutional review board, and all patients gave written informed consent to be included in the study. All patients had pathologically proven HCC or met the diagnostic imaging criteria for HCC (Liver Imaging Reporting and Data System category 5) (7). None of the patients had metastatic disease at the time of $^{90}$Y SIRT treatment.

The decision on whether to use $^{90}$Y SIRT in each patient was made by way of multidisciplinary team discussion (Fig. 1). However, the final decision about the type of microsphere used (glass or resin) was determined by the treating nuclear medicine physician, taking into consideration patient baseline characteristics (e.g., Eastern Cooperative Oncology Group status, Child–Pugh score, and nontumorous liver volumes), treatment intent, findings during hepatic angiography, and $[^{99m}$Tc$]Te$-macroaggregated albumin (MAA) SPECT/CT imaging findings. Post-SIRT $^{90}$Y bremsstrahlung SPECT/CT or $^{90}$Y PET/CT imaging was used to confirm microsphere deposition.
Radioembolization
All patients were deemed to benefit more from unicompartiment \(^{99m}\text{Tc}\)Tc-MAA–predicted dosimetry and dose activity calculation (using MIRD dosimetry) than from the multicompartment partition model dose activity calculation. Thus, the final decision was made to use \(^{90}\text{Y}\) glass microspheres for SIRT in these patients. The perfused liver volume was calculated from OsiriX (Pixmeo SARL) applying both intraprocedural catheter-directed CT angiography using cone beam CT or hybrid CT/angiography and \(^{99m}\text{Tc}\)Tc-MAA SPECT/CT. To ensure no extrahepatic deposition of \(^{90}\text{Y}\) microspheres, appropriate measures were taken as necessary, including coil embolization of vessels supplying extrahepatic structures. No deviation in catheter position between \(^{99m}\text{Tc}\)Tc-MAA and \(^{90}\text{Y}\) microsphere administrations was encountered. The time between the \(^{99m}\text{Tc}\)Tc-MAA planning procedure and the \(^{90}\text{Y}\) SIRT was kept to within 1–2 wk.

Dose activity was determined using the TheraSphere Treatment Window Illustrator (Boston Scientific). The mean absorbed radiation dose to the perfused liver volume was 369 Gy (range, 200–595 Gy), with 9 patients receiving at least 300 Gy, 1 patient receiving 200 Gy, and 1 patient receiving 230 Gy.

Residual activity after \(^{90}\text{Y}\) microsphere administrations was routinely measured and recorded to ensure that more than 90% of the planned activity had been delivered.

Follow-up
All patients received their planned \(^{90}\text{Y}\) microsphere treatment without alterations to dose activity. Patients were followed up for at least 6 mo after SIRT to assess for adverse effects and complications. Treatment tolerability, including immediate post-SIRT toxicity, was assessed by means of patient interview and review of serum blood tests and relevant imaging. Interval anatomic imaging, if available, had been performed at least 2 mo after SIRT.

Response evaluation using modified RECIST was performed on interim CT scans at 3 and 6 mo after SIRT.

RESULTS
In total, 11 patients were included in this series. The patient population parameters are included in Table 1. There were 10 men and 1 woman, with a mean age of 70 y (age range, 55–87 y). All patients had histologically confirmed HCC or fulfilled the diagnostic imaging criteria for HCC according to the American Association for the Study of Liver Disease. Patients were Eastern Cooperative Oncology Group 2 or lower, had either background hepatitis B or nonalcoholic fatty liver disease, had liver cirrhosis, had a Child–Pugh score of A5/6, and had 1 or 2 liver tumors, of which the larger was selected for \(^{90}\text{Y}\) SIRT whereas the smaller was treated with other locoregional modalities such as radiofrequency ablation or transcatheter chemoembolization. The \(^{99m}\text{Tc}\)Tc-MAA lung shunt

![FIGURE 1. Decision algorithm for choice of \(^{90}\text{Y}\) microsphere product and treatment dosimetry model. MDT = multidisciplinary team.](image)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Tumor size (cm)</th>
<th>Perfused treatment volume (mL)</th>
<th>Perfused-volume absorbed radiation dose (Gy)</th>
<th>Tumor response (modified RECIST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>64</td>
<td>2.5 and 3.0</td>
<td>495.0</td>
<td>300</td>
<td>PD</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>87</td>
<td>3.8</td>
<td>106.0</td>
<td>410</td>
<td>CR</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>82</td>
<td>3.3</td>
<td>93.8</td>
<td>230</td>
<td>SD</td>
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<tr>
<td>4</td>
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<td>72</td>
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<td>170.0</td>
<td>385</td>
<td>PD</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>55</td>
<td>3.9</td>
<td>430.0</td>
<td>309</td>
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<tr>
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<td>M</td>
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<td>4.1</td>
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</tr>
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<td>4.5</td>
<td>93.0</td>
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<td>74</td>
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<td>132.0</td>
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<td>4.6</td>
<td>88.0</td>
<td>595</td>
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</tr>
<tr>
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<td>M</td>
<td>65</td>
<td>2.7</td>
<td>90.2</td>
<td>432</td>
<td>PR</td>
</tr>
</tbody>
</table>

PD = progressive disease; CR = complete response; SD = stable disease; PR = partial response.

![TABLE 1](table)
fraction was less than 5% in all patients. The intended treatment was complete ablative therapy by means of segmental 90Y microsphere administration, which in 1 patient was used as a bridge to liver transplantation. Since the dominant tumor would receive 90Y SIRT, any toxicity effects were attributed to 90Y SIRT alone. All tumor-perfused liver volumes were no more than 30% of the total liver volume.

Toxicity
Five of 11 patients had deranged liver enzymes after 90Y SIRT (bilirubin, alanine transferase, aspartate transferase, or alkaline phosphatase). Of these, in only 1 patient did they qualify as Common Terminology Criteria for Adverse Events grade 1 toxicity (in alkaline phosphatase). Patient 5 was noted incidentally on routine postprocedural CT imaging to have a ground glass opacity in the adjacent lung parenchyma, which was attributed to near-field irradiation and localized radiation pneumonitis. He was asymptomatic, and serial CT scan showed resolution. Patient 6 developed melena secondary to variceal bleeding. None of the patients required hospitalization after the procedure for complications due directly to 90Y SIRT.

Treatment Response
Patients were followed up for at least 6 mo after 90Y SIRT. Treatment responses were tabulated according to biochemical (serum α-fetoprotein [AFP] if available) and anatomic responses. A reduction in AFP level was seen in half the patients who had available baseline AFP before 90Y SIRT (between 33% and 94%). One patient showed residual tumor after 90Y SIRT on an interval CT scan (patient 1) and underwent transarterial chemoembolization, and 1 patient died 5 mo after treatment (patient 4) because of progression to metastatic HCC. In these 2 patients, AFP levels rose compared with baseline levels. In interval CT scans performed up to the 6-mo review period, there were 4 showing a complete response, 2 showing a partial response, 3 showing stable disease, and 2 showing progressive disease when analyzed according to modified RECIST. An example of a patient with complete response is seen in Figures 2 and 3.

DISCUSSION
We report our initial experience, in a Southeast Asian hospital, of using segmental injections of 90Y glass microspheres in 11 consecutive patients with unresectable HCC, with a treatment intention of complete ablation, emphasizing the safety aspects of this procedure. 90Y SIRT with glass microspheres is generally well tolerated even for older patients and has a low complication rate in our selected local Asian patient population. The study was not powered to assess treatment efficacy, and the follow-up period of only 6 mo after the last 90Y SIRT patient is likely too short to observe the full effects of deposited radiation on tumor tissue or size. At the latest review, half the treated patients with available baseline serum AFP showed a reduction in these levels, and 6 patients demonstrated an objective response (complete or partial) to treatment. 90Y SIRT with glass microspheres is a promising locoregional option for Asian patients with unresectable HCC. Further large-scale studies should be undertaken to demonstrate the efficacy and responses in Asian patients in the DOSISPHERE-01 (8) and LEGACY studies.

CONCLUSION
This small case series of 90Y SIRT using glass microspheres performed in our cohort of middle-age to elderly Asian patients with unresectable hepatocellular carcinoma highlights the safety aspects of this locoregional therapy. It is fairly well tolerated and a safe and promising therapeutic option. Most treated patients demonstrated objective anatomic responses and reduction in serum AFP levels despite potential differences in patient cohort and disease pathophysiology compared with studies published in the West.

DISCLOSURE
No potential conflict of interest relevant to this article was reported.
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KEY POINTS

QUESTION: Is $^{90}$Y SIRT using glass microspheres safe and effective in Asian patients with HCC?

PERTINENT FINDINGS: In our series of 11 consecutive local patients with HCC treated with $^{90}$Y glass microspheres with the intention of radiation segmentectomy, this procedure was effective and had minimal complications.

IMPLICATIONS FOR PATIENT CARE: SIRT using $^{90}$Y glass microspheres can be a safe and effective option for Asian patients with HCC despite differences from Western populations in disease pathophysiology.

REFERENCES