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ORIGINAL ARTICLE

^{90}Yttrium Selective Internal Radiation Therapy in Unresectable or Otherwise High-Risk Hepatocellular Carcinoma: Single-Centre Experience

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ABSTRACT

Objectives: *We reviewed prognostic factors and clinical outcomes of selective internal radiation therapy (SIRT) with ^{90}Yttrium (^{90}Y) microsphere using transarterial embolisation in unresectable hepatocellular carcinoma (HCC).*

Methods: *All cases of hepatocellular carcinoma patients who underwent ^{90}Y SIRT at Princess Margaret Hospital between July 2017 and September 2021 were retrospectively reviewed. Overall survival (OS), progression-free survival (PFS), and prognostic factors, as well as tumour response according to modified Response Evaluation Criteria in Solid Tumors criteria and safety, were evaluated.*

Results: *Thirty HCC patients were treated with ^{90}Y SIRT , of whom 26 (87%) were male. The median age of patients was 66.5 years (range, 40-93). Fifty-seven percent were chronic hepatitis B carriers and the majority (93%) had Child–Pugh class A liver disease. Patients had portal vein thrombosis, or tumour size >8 cm. After a median follow-up of 14.6 months, the objective response rate was 26.9% and the local control rate was 76.9%, including three complete responses, four partial responses and 13 cases of stable disease. The median PFS was 6.3 months and the 1-year PFS was 40.2%. Median OS was not yet reached and the 1-year OS was 57.5%. In multivariable analysis, alpha-fetoprotein level was a significant prognostic factor for OS (p = 0.045) and PFS (p = 0.011). Most side-effects were grades 1-2 only.*

Conclusion: *^{90}Y SIRT via transarterial embolisation is an effective and safe treatment for intermediate- to advanced-stage HCC patients which provides satisfactory local control with minimal toxicity. Longer survival was observed in patients with alpha-fetoprotein level <400 μg/L at baseline.*

Key Words: *Carcinoma, hepatocellular; Radiotherapy; Survival; Yttrium radioisotopes*

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Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

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中文摘要

不可切除或其他高危肝細胞癌的釔90選擇性內放射治療：單中心經驗

梁君豪、林美瑩

目的：本研究檢視在不可切除肝細胞癌使用經動脈栓塞術的釔90微粒選擇性內放射治療的預後因素及臨床結果。

方法：本研究回顧於2017年7月至2021年9月期間在瑪嘉烈醫院進行釔90選擇性內放射治療的所有肝細胞癌病人個案，評估了整體存活、疾病無惡化存活、預後因素及根據經修訂固體腫瘤反應評估標準的準則及安全程度評估的腫瘤反應。

結果：共30名病人接受了釔90選擇性內放射治療，當中26名（87%）為男性。病人年齡中位數為66.5歲（範圍，40-93）。57%病人為慢性乙型肝炎帶菌者，當中大部分（93%）為Child–Pugh分級A肝病病人。病人有肝門靜脈栓塞或腫瘤>8 cm。在覆診期中位數14.6個月後，客觀緩解率為26.9%，局部疾病控制率為76.9%，包括3個完全緩解、4個部分緩解及13個無變化個案。疾病無惡化存活中位數為6.3個月，一年疾病無惡化存活為40.2%。整體存活中位數尚未達到，一年整體存活為57.5%。在多變量分析中，甲型胎兒蛋白水平是整體存活（p = 0.045）及疾病無惡化存活（p = 0.011）的重要預後因素。大部分副作用只屬1-2級。

結論：對於中期至晚期肝細胞癌病人而言，使用經動脈栓塞術的釔90選擇性內放射治療是有效及安全的治療，能提供毒性最低而令人滿意的局部控制。本研究顯示，甲型胎兒蛋白基線水平<400 μg/L的病人的存活期較長。

INTRODUCTION

In Hong Kong, hepatocellular carcinoma (HCC) ranks fifth most common cancer and third among the most common causes of cancer death since 2014.[1] Transarterial embolisation or transarterial chemoembolisation (TACE) has been shown to improve the survival of patients with unresectable HCC.[2,3]

Selective internal radiation therapy (SIRT) is a directed liver therapy making use of the tumour vascularity in HCC in which the hepatic artery is usually the sole blood supply. SIRT involves the injection of beta emitters within resin or glass microspheres via the hepatic artery, where the spheres form microemboli, thus giving a very high radiation dose (100 to 1000+ Gy) to the tumour(s) while at the same time minimising the radiation exposure to normal liver tissue by not going through the hepatic veins or the portal system.

^{90}Yttrium (^{90}Y) is a pure beta-emitting isotope (maximum energy 2.28 MeV; mean energy 0.934 MeV), with a mean and maximum penetration range of 2.5 mm and 11 mm, respectively. It is commonly used to treat HCC.[4] ^{90}Y SIRT is effective, with one study showing an objective response rate up to 40.0% and a median overall survival (OS) of 16.4 months.[5] It has shown effectiveness in terms of survival, response rates, and safety profile similar to that with TACE in unresectable HCC in several studies and meta-analyses.[6-9] It was also shown to be an effective treatment to accomplish downstaging as a bridge to transplantation, surgical resection, or radiofrequency ablation.[10] Survival in patients receiving ^{90}Y SIRT for intermediate-advanced HCC can vary from 12-24 months (1-year pooled OS = 63%) to 6-12 months (1-year pooled OS = 37%), should portal vein thrombosis be present.[11,12]

Careful selection of suitable candidates for ^{90}Y SIRT is necessary. Several prognostic factors, including a low Child–Pugh score, percentage of liver replaced by tumour (≤50%) and alpha-fetoprotein (AFP) level (<400 μg/L) are associated with better survival.[13] Unilobar disease before SIRT and tumour response (complete response/partial response) have also been found to be significant predictors of survival.[14] It is believed that survival can be prolonged in unresectable HCC to a similar extent using TACE[15] with careful selection of candidates.

In our hospital (Princess Margaret Hospital), HCC patients are under the care of a multidisciplinary hepatoma team with oncologists, surgeons, and radiologists. Since 2012, ^{90}Y SIRT has been offered as a funded treatment by Hospital Authority, a statutory body managing the public healthcare services in Hong Kong, to high-risk HCC patients whose tumours are not resectable or ablatable, with portal vein thrombosis, or with tumour size >8 cm. Patients with infiltrative HCC, Child–Pugh class C disease, ascites, or inadequate liver reserve (with bilirubin level >34 μmol/L) are generally considered ineligible for SIRT. In this study, we report the outcome together with prognostic factors in the use of ^{90}Y in the treatment of these advanced cases of HCC in our centre.

METHODS

We retrospectively enrolled HCC patients who received ^{90}Y SIRT, either resin microspheres containing ^{90}Y (Sirtex, Australia) or ^{90}Y-impregnated glass microspheres (TheraSphere; MDS Nordion, Canada), at our hospital between July 2017 and September 2021. Before SIRT, patients underwent hepatic angiography, ^{99m}technetium-macroaggregated albumin scintigraphy, and computed tomography (CT) scans to estimate the potential doses to tumour, liver, and lung. A catheter was guided through the femoral artery and into the hepatic artery by an interventional radiologist. Blood vessels feeding the gastrointestinal tract and extrahepatic sites such as the pancreas were identified and prophylactically embolised if necessary. Patients were deemed ineligible when lung shunting was >20%. The dose activity calculation was based on a partition model.[16] The aim of the treatment was to administer a minimum dose of 120 Gy to the tumour while keeping the dose to normal liver at <40 Gy and to <50 Gy in patients with poor liver reserve. The lung dose was planned to be <20 Gy.

Treatment

Intrahepatic administration of radioactive ^{90}Y microspheres using either resin microspheres containing ^{90}Y or ^{90}Y-impregnated glass microspheres was performed. Understanding of radiation exposure of patients implanted with pure beta emitters is very limited. Patients were kept in a radiation isolation room to wait for assessment by physicists and considered safe if radiation activity was <1.5 GBq according to Radiation Ordinance of Hong Kong and Hospital Authority Code of Practice on Radiation Safety and Protection. They were discharged with medications including pantoprazole, ursodeoxycholic acid, prednisolone, and entecavir if they were viral hepatitis B carriers. A bremsstrahlung scan was performed on day 2 or 3 to document any extrahepatic reflux of ^{90}Y microspheres.

Outcome Assessment

Patients were followed up by surgeons after ^{90}Y treatment with liver function tests and AFP tumour marker test. The first follow-up was within 4 weeks after discharge to assess for any treatment-related toxicities. All patients had reassessment with triphasic CT at approximately 3 months after ^{90}Y treatment for an objective evaluation of treatment outcome according to mRECIST (modified Response Evaluation Criteria in Solid Tumors) based on combined assessment of target lesions, non-target lesions, and new lesions. Appearance of one or more new lesions was counted as progression regardless of the response of treated target and non-target lesions classified according to mRECIST. Subsequent follow-up was performed at approximately 1- to 3-month intervals with laboratory tests and/or CT at the discretion of surgeons. Any toxicity or adverse events noted during the first 6 months after completion of ^{90}Y treatment were reviewed and graded according to CTCAE (Common Terminology Criteria for Adverse Events) version 5.0 criteria.

Statistical Measures

Treatment responses were assessed radiologically according to mRECIST. Local control rate was defined as the proportion of patients with at least stable disease of an irradiated target lesion. Objective response rate was defined as the proportion of patients with partial or complete response in target lesions and at least stable disease in non-target lesions to ^{90}Y SIRT. Progression-free survival (PFS) was defined from the date of SIRT to the date of a radiological sign of progression or death from any cause. OS was calculated from the date of SIRT to the date of death from any cause. Survival curves were determined by the Kaplan-Meier method and comparison between different Barcelona Clinic Liver Cancer (BCLC) stages[17] and AFP levels was done by the log-rank test. Statistical significance was defined at $p < 0.05$. Univariate and multivariable analyses of different prognostic factors of survival outcomes, including patient and tumour factors, were performed using the Cox proportional hazards analysis. Only factors with p values < 0.05 were considered significant and included in the multivariable analysis. Commercial software SPSS (Windows version 28.0; IBM Corp, Armonk [NY], United States) was used to perform the statistical analyses.

Table 1. Baseline characteristics of the patients treated with ^{90}Yttrium (n = 29)*.

Characteristics	No. of patients (%)
Median age, y	66.5 (40-93)
Male	25 (86%)
Aetiology of cirrhosis	
Hepatitis B viral infection	16 (55%)
Hepatitis C viral infection	3 (10%)
Alcoholic cirrhosis	1 (3%)
Cryptogenic cirrhosis	6 (21%)
Non-B, non-C	3 (10%)
Child–Pugh class	
A5	9 (31%)
A6	19 (66%)
B8	1 (3%)
BCLC stage	
B	12 (41%)
C	17 (59%)
ECOG performance status score	
0	16 (55%)
1	11 (38%)
2	2 (7%)
Liver function	
Median total bilirubin, μmol/L	10 (6-29)
AFP level	
<400 μg/L	19 (66%)
≥400 μg/L	10 (34%)
Distribution of liver tumours	
Unilobar	19 (66%)
Bilobar	10 (34%)
Number of lesions	
Single	19 (66%)
Multifocal	10 (34%)
2-5	7 (24%)
5-10	2 (7%)
>10	1 (3%)
Median tumour size, cm	11.7 (4-19.7)
Tumour size	
<5 cm	1 (3%)
5-10 cm	10 (34%)
>10 cm	18 (62%)
Treatment lines	
First	26 (90%)
Second‡	1 (3%)
Third or beyond§	2 (7%)
Prior treatments received	
TACE	3 (10%)
Surgery	2 (7%)
Targeted therapy	1 (3%)
Post-SIRT surgery done	8 (28%)
Subsequent treatments received	
TACE	14 (48%)
Microwave or radiofrequency ablation	3 (10%)
Targeted therapy	9 (31%)
Immunotherapy	1 (3%)
Portal vein thrombosis	
Absent	19 (66%)
Present	10 (34%)
Site of portal vein thrombosis	
Main	4 (40%)
Left or right only	6 (60%)
Median prescribed dose, GBq	2.98 (1.1-6.09)
Median dose to tumour, Gy	174 (100-300)
Dose to tumour	
≤120 Gy	6 (21%)
>120 Gy	23 (79%)
Median dose to liver, Gy	22.94 (3.72-40.35)
Median tumour/normal liver ratio	7.96 (3.1-67.19)
Median lung shunting, %	5.8 (2.6-13.9)
Median lung dose, Gy	9.34 (2.44-31.23)

Abbreviations: AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; SIRT = selective internal radiation therapy; TACE = transarterial chemoembolisation.

* One patient who had an ECOG performance status score of 3 and was classified as BCLC stage D (wheelchair bound with history of old haemorrhagic stroke) was excluded from analysis.

‡ Patient received prior TACE.

§ One patient received surgery and TACE while the other had prior surgery, TACE and targeted therapy.

RESULTS

Baseline Characteristics

From July 2017 to September 2021, 30 HCC patients were treated with ^{90}Y, of whom 26 (86.7%) were male. The median age was 66.5 years (range, 40-93). The majority of them (n = 17, 56.7%) were chronic hepatitis B carriers. Liver tumour sizes ranged from 4 cm to 19.7 cm, with a median size of 11.7 cm. Most of them had Child–Pugh class A liver disease (n = 28, 93.3%) and about one-third (n = 11, 36.7%) had AFP level ≥400 μg/L. Eleven (36.7%) patients had portal vein thrombosis with four (13.3%) having thrombosis involving the main portal vein. Half of the patients received TACE with cisplatin and one-third of them received targeted therapy (either sorafenib or lenvatinib) as subsequent treatment. Other characteristics and laboratory investigations are listed in Table 1.

Outcomes

Median follow-up time was 14.6 months. One patient with ECOG performance status score of 3 and BCLC stage D was excluded from the analysis. Of the 29 patients, 26 had assessable responses on CT (median time = 2.76 months after ^{90}Y treatment). Three patients had complete responses (11.5%), four with partial responses (15.4%), 13 with stable disease (50%), and six with progressive disease (23.1%). The objective response rate (defined as the sum of complete and partial responses) was 26.9% while the local control rate

(defined as the sum of complete and partial responses and stable disease) was 76.9%. Three patients were lost to follow-up. The median PFS was 6.3 months and 1-year PFS was 40.2% (Figure 1). Median OS was not yet reached and 1-year OS was 57.5% (Figure 2).

Eight out of 29 patients (27.6%) had surgery done after downstaging of disease (Table 2). Median time from ^{90}Y treatment to surgery was 6.1 months. One achieved a pathological complete response (Figure 3). Six of them had residual HCC completely resected and one resected with focally involved margin. Length of hospital stay was 5-24 days. One had significant intra-operative blood loss requiring massive blood transfusions. One had postoperative ileus and pulmonary embolism which resolved with anticoagulation. One died early postoperatively due to aspiration pneumonia.

Univariate and Multivariable Analyses

In univariate analysis (Table 3), BCLC stage C or above (hazard ratio [HR] = 5.733, p = 0.024), and AFP level ≥400 μg/L (HR = 4.270, p = 0.012) were significant prognostic factors for OS whereas BCLC stage C or above (HR = 3.652, p = 0.010), post-SIRT surgery (HR = 0.134, p = 0.008), AFP level ≥400 μg/L (HR = 3.527, p = 0.007), and treatment responder (defined as those with complete response or partial response) [HR = 0.203, p = 0.034; Figure 4] were significant prognostic factors for PFS. In multivariable analysis (Table 4), AFP level ≥400 μg/L remained as a significant

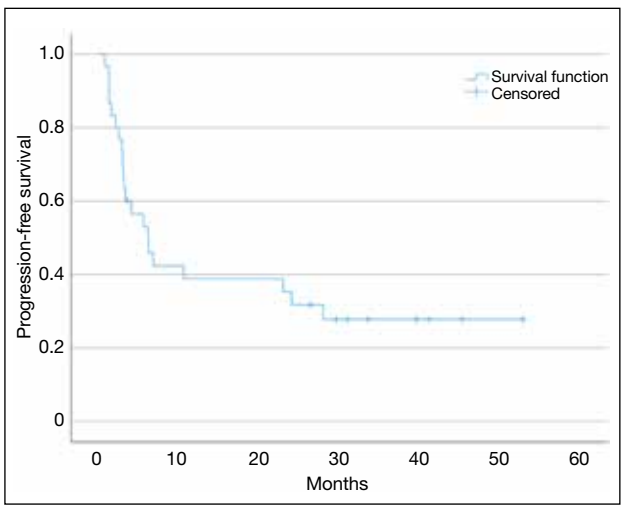

Figure 1. Kaplan-Meier curves showing progression-free survival (PFS) after ^{90}Yttrium selective internal radiation therapy. In all, 20 patients out of 29 had disease progression. Median PFS was 6.3 months. PFSs at 6, 12 and 24 months were 54.8%, 40.2% and 36.5%, respectively.

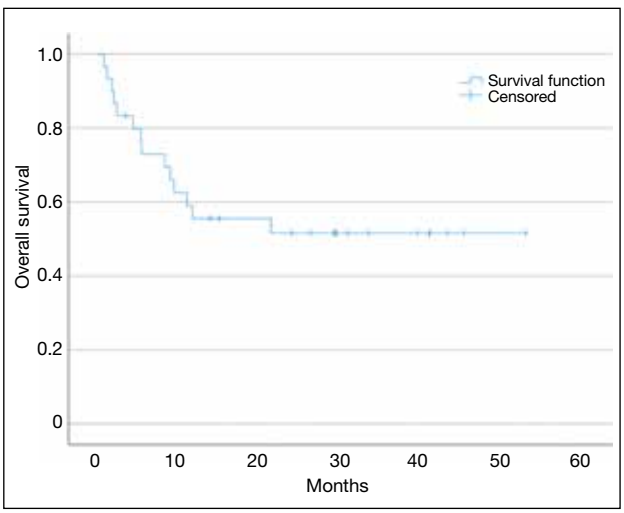

Figure 2. Kaplan-Meier curves showing overall survival (OS) after ^{90}Yttrium selective internal radiation therapy. In all, 13 died out of 29 patients. Median OS was not reached. OSs at 6 and 12 months were 75.4% and 57.5%, respectively.

Table 2. Demographics of patients amenable to surgery.

Patient No.	Sex/age	BCLC stage	Any PVT	No. of nodules	Size of target lesion, cm	AFP level, μg/L	Local response	Overall survival, mo
1	M/64	B	No	1	15.6	4.8	CR	29.63
2	M/66	B	No	2	10.2	9.5	PR	33.54
3	M/61	B	No	>10	13	1.6	PR	24.08
4	M/67	B	No	1	15	2.9	CR	52.87
5	M/64	C	Yes	1	4	87	CR	39.56
6	M/63	B	No	1	9	4.2	SD	41.11
7	F/53	B	No	1	8	7425	SD	31.01
8	M/61	B	No	1	9.2	13	SD	5.64*

Abbreviations: AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; CR = complete response; F = female; M = male; PR = partial response; PVT = portal vein thrombosis; SD = stable disease.
* Patient died of early postoperative complication.

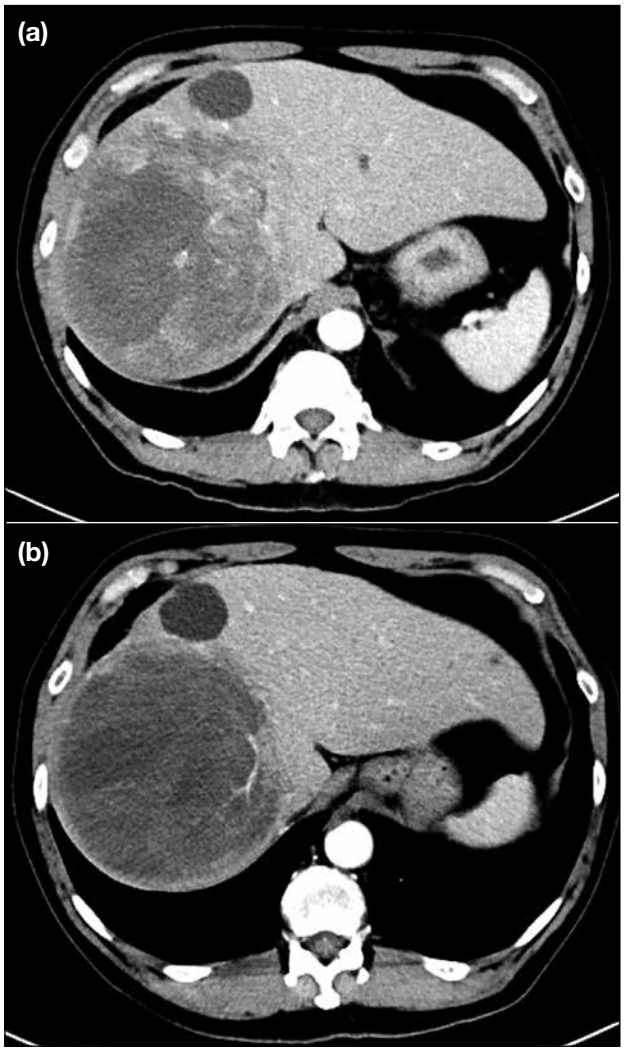

Figure 3. Computed tomography images of pre-^{90}Yttrium selective internal radiation therapy (^{90}Y SIRT) [a] and post-^{90}Y SIRT (b) in a 67-year-old patient. The known right lobe tumour showed mild reduction in size with no abnormal arterial enhancement. It suggested complete response according to modified Response Evaluation Criteria in Solid Tumors guideline.

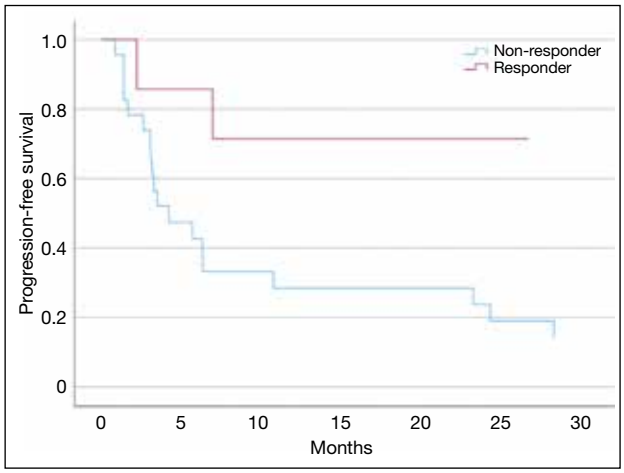

Figure 4. Kaplan-Meier curves showing progression-free survival (PFS) after ^{90}Yttrium selective internal radiation therapy in patients with responders and non-responders (median PFS not reached vs. 4.2 months, p = 0.034).

prognostic factor for OS (HR = 3.240, p = 0.045; Figure 5) as well as for PFS (HR = 3.930, p = 0.011; Figure 6).

In this series, there were four long-term survivors and three complete responders. Those with complete response achieved long survivals ranging from 29.6 to 52.9 months compared to a median of 11.2 months in non-responders. All of them had post-SIRT surgery done with clear resection margins. The median dose of ^{90}Y SIRT was higher in responders (200 Gy) than in non-responders (170 Gy). However, OS did not differ significantly with dose (lower dose: p = 0.268, 95% confidence interval = 0.983-1.005; higher dose: p = 0.456, 95% confidence interval = 0.201-2.056). Patient

Table 3. Univariate analysis.

Parameter	Overall survival		Progression-free survival	
	Hazard ratio (95% confidence interval)	p Value	Hazard ratio (95% confidence interval)	p Value
Prescribed dose >120 Gy	0.870 (0.239-3.171)	0.833	0.997 (0.333-2.985)	0.995
BCLC stage C or above	5.733 (1.262-26.042)	0.024	3.652 (1.369-9.748)	0.010
Presence of portal vein thrombosis	2.753 (0.918-8.255)	0.071	2.107 (0.836-5.307)	0.114
Post-SIRT surgery done	0.151 (0.020-1.169)	0.070	0.134 (0.030-0.591)	0.008
AFP level ≥400 μg/L	4.270 (1.379-13.217)	0.012	3.527 (1.406-8.845)	0.007
Multifocal tumour	2.610 (0.862-7.903)	0.090	1.647 (0.661-4.100)	0.284
Bilobed tumour	1.082 (0.353-3.314)	0.890	1.205 (0.492-2.953)	0.683
Treatment responder	0.197 (0.026-1.526)	0.120	0.203 (0.047-0.886)	0.034

Abbreviations: AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; SIRT = selective internal radiation therapy.

Table 4. Multivariable analysis.

Parameter	Overall survival		Progression-free survival	
	Hazard ratio (95% confidence interval)	p Value	Hazard ratio (95% confidence interval)	p Value
BCLC stage C or above	4.471 (0.958-20.873)	0.057	2.106 (0.704-6.298)	0.183
Post-SIRT surgery done	N/A	N/A	0.289 (0.042-1.999)	0.208
AFP level ≥400 μg/L	3.240 (1.025-10.246)	0.045	3.930 (1.378-11.212)	0.011
Treatment responder	N/A	N/A	0.463 (0.074-2.910)	0.412

Abbreviations: AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; SIRT = selective internal radiation therapy.

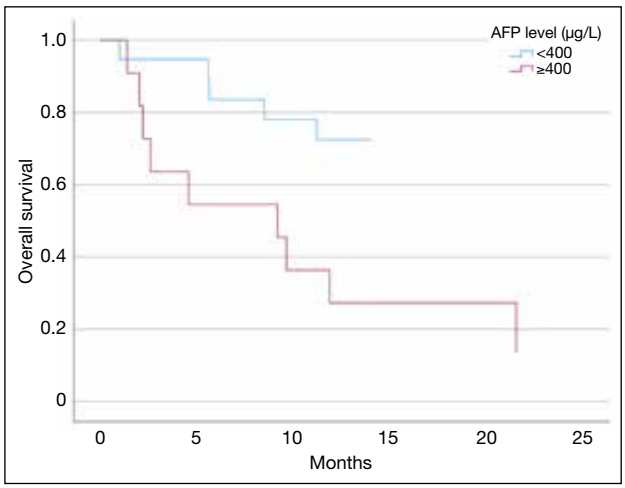

Figure 5. Kaplan-Meier curves showing overall survival (OS) after ^{90}Yttrium selective internal radiation therapy in patients with alpha-fetoprotein (AFP) level ≥400 μg/L and <400 μg/L (median OS = 9.2 months vs. not reached, p = 0.045).

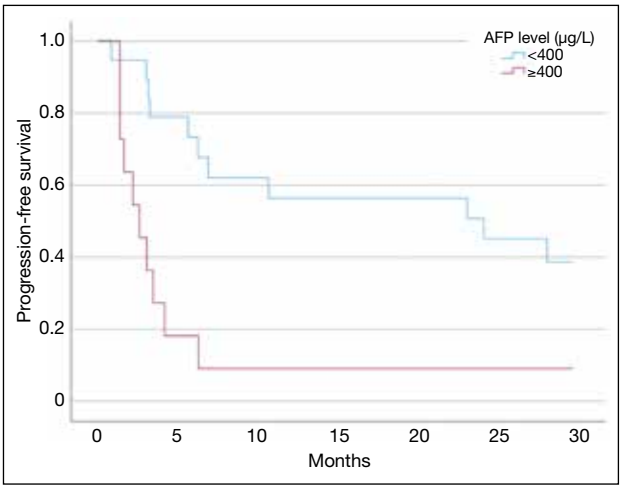

Figure 6. Kaplan-Meier curves showing progression-free survival (PFS) after ^{90}Yttrium selective internal radiation therapy in patients with alpha-fetoprotein AFP level ≥400 μg/L and <400 μg/L (median PFS = 2.2 months vs. 24.1 months, p = 0.011).

demographics and liver tumour baseline characteristics were investigated in treatment responders and non-responders together with those amenable to post-SIRT surgery and were compared to those that were not. The treatment responder group had better Eastern Cooperative Oncology Group (ECOG) performance status score (p = 0.039) and the group amenable to surgery had significantly more patients with BCLC stage B (p = 0.002) and better ECOG performance status score (p = 0.011).

Table 5. Radioembolisation-related toxicities (n = 29).*

Toxicities	All grades	Grade ≥3
Nausea	2 (6.9%)	0
Abdominal pain	7 (24.1%)	1 (3.4%)
Anorexia	3 (10.3%)	0
Fever	5 (17.2%)	0
Dyspepsia	1 (3.4%)	0
Deranged liver function	1 (3.4%)	0
Malaise	1 (3.4%)	0

* Data are shown as No. (%).

Toxicity

The median postoperative hospital stay was 6.5 days (range, 2-16). Twelve patients (41.4%) had some forms of post-^{90}Y treatment complications, in total 29 different kinds of toxicities experienced by them (Table 5). Most side-effects were mild with abdominal pain and fever being the most common. Only one patient had grade 3 abdominal pain requiring hospital admission 6 weeks after ^{90}Y SIRT. There was no identifiable cause found in work-up and the patient was discharged the next day after symptom subsided with analgesics. Abnormal liver function with grade 1 hyperbilirubinemia occurred in one patient and was self-limited.

There was one case of suspected radiation pneumonitis occurring approximately 7 weeks post-SIRT. The patient was a non-smoker and presented with fever and shortness of breath. The lung dose by the ^{90}Y SIRT was 24.4 Gy. Chest CT showed extensive ground-glass opacities and patchy consolidation, which may have represented oedema or infection. Multiple antibiotics and systemic steroids were administered but patient succumbed due to respiratory failure. Since the diagnosis was doubtful, it was not regarded as post-SIRT toxicity.

DISCUSSION

In this study, it was demonstrated that ^{90}Y SIRT was a feasible and effective treatment option in our local population who had intermediate- and advanced-stage HCC without serious adverse events. The response rate to ^{90}Y SIRT was high and the results were comparable to other Asian series that reported OS and PFS of patients receiving ^{90}Y SIRT ranging from 11 to 16.4 months and 2.4 to 11 months, respectively.[5,18-20] The wide range of survivals represents heterogeneity of patients' demographics and disease status, thus making direct comparison of survivals across different studies difficult. In our study, 59% and 34% of patients belong to BCLC stage C and had AFP level ≥400 μg/L, respectively. Both were found to be poor prognostic factors, which is consistent with the findings in a European multicentre analysis.[21] Despite this, the results of our cohort were impressive with encouraging results of local control, PFS, and OS.

TACE is commonly used in intermediate-stage HCC but is contraindicated in presence of portal vein thrombosis due to the potential risk of precipitating liver necrosis and failure by its effects on the already compromised hepatic vascular supply. This limitation can be overcome by ^{90}Y SIRT due to the small size of the ^{90}Y particles which exert microembolic effects on hepatic vascular dynamics.[22] Also, easy application in the left or right hepatic arteries of ^{90}Y SIRT makes it attractive for patients compared to superselective TACE with longer intervention times and repeated hospital admissions.[23] Yet, presence of portal vein thrombosis was shown to be associated with worse survival in treatment of ^{90}Y SIRT.[24] This was reconfirmed in our study in which the OS after SIRT was shorter in those with portal vein thrombosis compared to those without (median OS = 9.2 months vs. 26.4 months, $p = 0.045$).

In advanced HCC, targeted therapies are the mainstay of treatment with a median survival of approximately 13.6 months with lenvatinib and 12.3 months with sorafenib.[25] Although ^{90}Y SIRT failed to demonstrate a statistically significant difference in OS compared with sorafenib in two recent phase III trials, SARAH[26] and SIRveNIB[27], it had significantly fewer severe adverse events and better health-related quality of life. Most of the patients were classified as BCLC stage C in SARAH study, 68% in the ^{90}Y group and 67% in the sorafenib group, whereas respective rates were 48.4% and 44.9% in SIRveNIB study. Targeted therapy is associated with numerous side-effects, namely hypertension, diarrhoea, and hand-foot syndrome, and are known to lead to treatment discontinuation permanently in approximately 11% of patients.[28] On the other hand, ^{90}Y SIRT has better toxicity profiles with most side-effects being only mild as grades 1 to 2. This is also consistent with the observation in our cohort with the most common side-effects being grades 1 to 2 abdominal pain (23.3%) followed by fever (16.7%). There was only one grade 3 abdominal pain in our study with no identifiable causes. Symptom subsided quickly with analgesics and the patient was discharged the next day with no further complaints noted.

^{90}Y SIRT is also effective in bridging to liver surgery through tumour shrinkage and inducing future liver remnant hypertrophy in initially unresectable HCC.[29] In our study, 90% of the subjects underwent SIRT as the initial treatment and eight (30%) of them had surgery afterwards. They enjoyed a significantly longer survival (ranging from 24 to 52 months, excluded one died of postoperative complications). One of them demonstrated radiological and pathological complete response in his initial 4-cm tumour in subsequent hepatectomy after SIRT. He remains well without any disease recurrence for over 3 years by now. One of the long survivors received ^{90}Y SIRT twice to the right lobe of liver. Radiological complete response was achieved. Right hepatectomy was performed 2 months after the second ^{90}Y treatment. Pathology showed residual pT1 grade III HCC with clear resection margins. He has enjoyed >4 years of survival by now without disease recurrence. The above finding illustrated the potential role of downstaging and facilitating curative resection. ^{90}Y SIRT outperforms TACE in the role of downstaging from T3 to T2 HCC[30] and patients enjoyed better quality of life with ^{90}Y treatment.[31] Our series also showed ^{90}Y SIRT is safe with very low rates of grade ≥3 adverse events. Based on our study results, those amenable to surgery mostly were with ECOG performance status score of 0, classified as BCLC stage B with low AFP level, and without portal vein thrombosis, which could further guide our selection

of ^{90}Y SIRT candidates aiming for surgical resection.

The retrospective nature and the small sample size in this cohort might affect survival analysis and determination of the significance of different prognostic factors. Also, the survival is not mature yet where longer follow-up of patients is necessary. Another limitation was the time of the reassessment of CT scans. The mean time to the first response assessment CT was 2.35 months after SIRT and not all patients had regular scans afterwards. Later response might then be underreported. Yet, the first CT was chosen to assess the treatment response to ^{90}Y SIRT as most of the patients had subsequent treatment which might confound the response solely due to ^{90}Y SIRT. In fact, most of the subjects only had one CT scan done within 6 months of ^{90}Y treatment. Furthermore, 23 out of 26 patients had ^{90}Y SIRT alone whereas only three cases had planned combination treatment with SIRT and TACE or systemic therapy. Two patients had concurrent TACE and one was taking sorafenib during radioembolisation. Hence, it is believed the CT could reflect the treatment response of ^{90}Y SIRT.

Our study confirmed the role of ^{90}Y SIRT in intermediate- to advance-stage HCC patients. However, careful patient selection is of utmost importance to optimise treatment benefits. There has been evidence suggesting that AFP level ≥400 μg/L predicts a higher rate of dual-tracer positron emission tomography/CT–detected metastasis.[32] Our study further confirms it as a negative prognostic factor, probably due to occult extrahepatic metastases. With discreet use of incorporating staging dual tracer positron emission tomography/CT scan in high-risk cases with AFP level ≥400 μg/L, we might screen out those with extensive distant metastases whom ^{90}Y SIRT is not advised as the initial therapy.

The result of the series further consolidated the role of ^{90}Y SIRT in our local practice. In locally advanced HCC, selection of appropriate treatment modalities has been challenging. The study reflects the importance of careful selection of candidates for ^{90}Y SIRT. Good ECOG performance status score and the classification as BCLC stage B HCC are shown to be favourable factors for this expensive radioisotope treatment and should be prioritised when it comes to selection of suitable candidates in multidisciplinary meetings. Other local ablative treatments such as radiofrequency ablation and stereotactic radiotherapy should be reserved for solitary or lower volume disease, whereas systemic therapy is for clearly disseminated disease.

CONCLUSION

^{90}Y SIRT is an effective and safe treatment for intermediate- to advanced-stage HCC which provides satisfactory local control with minimal toxicity. Longer survival was observed in patients with AFP level <400 μg/L.

REFERENCES

1. Hong Kong Cancer Registry. Top ten cancers. Available from: https://www3.ha.org.hk/cancereg/topten.html. Accessed 1 May 2022.
2. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37:429-42.
3. D'Avola D, Iñarrairaegui M, Pardo F, Rotellar F, Marti P, Bilbao JI, et al. Prognosis of hepatocellular carcinoma in relation to treatment across BCLC stages. Ann Surg Oncol. 2011;18:1964-71.
4. Levillain H, Bagni O, Deroose CM, Dieudonné A, Gnesin S, Grosser OS, et al. International recommendations for personalised selective internal radiation therapy of primary and metastatic liver diseases with yttrium-90 resin microspheres. Eur J Nucl Med Mol Imaging. 2021;48:1570-84.
5. Hilgard P, Hamami M, Fouly AE, Scherag A, Müller S, Ertle J, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology. 2010;52:1741-9.
6. Kooby DA, Egnatashvili V, Srinivasan S, Chamsuddin A, Delman KA, Kauh J, et al. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol. 2010;21:224-30.
7. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer. 2010;116:1305-14.
8. Pitton MB, Kloeckner R, Ruckes C, Wirth GM, Eichhorn W, Wörns MA, et al. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol. 2015;38:352-60.
9. Facciorusso A, Serviddio G, Muscatiello N. Transarterial radioembolization vs chemoembolization for hepatocarcinoma patients: a systematic review and meta-analysis. World J Hepatol. 2016;8:770-8.
10. Kulik LM, Atassi B, van Holsbeeck L, Souman T, Lewandowski RJ, Mulcahy MF, et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. J Surg Oncol. 2006;94:572-86.
11. Rognoni C, Ciani O, Sommariva S, Facciorusso A, Tarricone R, Bhoori S, et al. Trans-arterial radioembolization in intermediate-advanced hepatocellular carcinoma: systematic review and meta-analyses. Oncotarget. 2016;7:72343-55.
12. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010;138:52-64.
13. Geschwind JF, Salem R, Carr BI, Soulen MC, Thurston KG, Goin KA, et al. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma. Gastroenterology. 2004;127(5 Suppl 1):S194-205.

14. Van Thai N, Thinh NT, Ky TD, Bang MH, Giang DT, Ha LN, et al. Efficacy and safety of selective internal radiation therapy with yttrium-90 for the treatment of unresectable hepatocellular carcinoma. BMC Gastroenterol. 2021;21:216.
15. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359:1734-9.
16. Ho S, Lau WY, Leung TW, Chan M, Ngar YK, Johnson PJ, et al. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. Eur J Nucl Med. 1996;23:947-52.
17. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329-38.
18. Lee VH, Leung DK, Luk MY, Tong CC, Law MW, Ng SC, et al. Yttrium-90 radioembolization for advanced inoperable hepatocellular carcinoma. Onco Targets Ther. 2015;8:3457-64.
19. Chaikajornwat J, Tanasoontrarat W, Phathong C, Pinjaroen N, Chaiteerakij R. Clinical outcome of yttrium-90 selective internal radiation therapy (Y-90 SIRT) in unresectable hepatocellular carcinoma: experience from a tertiary care center. Liver Res. 2022;6:30-8.
20. Mazzaferro V, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology. 2013;57:1826-37.
21. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011;54:868-78.
22. Quirk M, Kim YH, Saab S, Lee EW. Management of hepatocellular carcinoma with portal vein thrombosis. World J Gastroenterol. 2015;21:3462-71.
23. Kloeckner R, Ruckes C, Kronfeld K, Wörns MA, Weinmann A, Galle PR, et al. Selective internal radiotherapy (SIRT) versus transarterial chemoembolization (TACE) for the treatment of intrahepatic cholangiocellular carcinoma (CCC): study protocol for a randomized controlled trial. Trials. 2014;15:311.
24. Floridi C, Pesapane F, Angileri SA, De Palma D, Fontana F, Caspani F, et al. Yttrium-90 radioembolization treatment for unresectable hepatocellular carcinoma: a single-centre prognostic factors analysis. Med Oncol. 2017;34:174.
25. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163-73.
26. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017;18:1624-36.
27. Chow PK, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. J Clin Oncol. 2018;36:1913-21.
28. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-90.
29. Bekki Y, Marti J, Toshima T, Lewis S, Kamath A, Argiriadi P, et al. A comparative study of portal vein embolization versus radiation lobectomy with yttrium-90 microspheres in preparation for liver resection for initially unresectable hepatocellular carcinoma. Surgery. 2021;169:1044-51.
30. Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant. 2009;9:1920-8.
31. Salem R, Gilbertsen M, Butt Z, Memon K, Vouche M, Hickey R, et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. Clin Gastroenterol Hepatol. 2013;11:1358-65.e1.
32. Chu KK, Chan AC, Ma KW, She WH, Dai WC, Chok KS, et al. Role of C11-FDG dual-tracer PET-CT scan in metastatic screening of hepatocellular carcinoma — a cost-effectiveness analysis. Hepatobiliary Surg Nutr. 2021;10:301-7.