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ORIGINAL ARTICLE

Selective Internal Radiation Therapy for Hepatocellular Carcinoma: Experience from a Hospital in Hong Kong

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ABSTRACT

Purpose: *To report the outcomes and prognostic factors of overall survival after selective internal radiation therapy (SIRT) for hepatocellular carcinoma (HCC).*

Methods: *Consecutive patients who underwent SIRT for HCC at Queen Elizabeth Hospital between December 2006 and February 2016 were retrospectively reviewed.*

Results: *51 male and 11 female patients aged 42 to 90 (median, 66) years were deemed suitable to receive SIRT. Most were hepatitis B carriers and had an Eastern Cooperative Oncology Group performance score of ≤1 and Child-Pugh class A cirrhosis. About half of the patients had portal vein thrombosis and an alpha-fetoprotein level of >200 ng/ml. 30.7% of patients were at Barcelona Clinic Liver Cancer stage B and 64.5% at stage C. 50% of tumours were ≥8 cm at the longest diameter. The median dose received by the tumour was 130 Gy. Three months after SIRT, 1.7% had a complete response, 43.3% had a partial response, 26.7% had stable disease, and 28.3% had progressive disease. The 1-year local control rate was 12.3%. The 1-year overall survival was 30.6%. The median time to tumour progression was 3 months and the median overall survival was 6 months. In multivariate analysis, Child-Pugh class, portal vein thrombosis, and post-SIRT intervention were significant prognostic factors for overall survival.*

Conclusion: *SIRT is an effective and safe treatment for intermediate- to advanced-stage HCC. It achieves good local control with minimal toxicity although the outcome is unsatisfactory in terms of new intrahepatic or distant recurrence. HCC patients with Child-Pugh class A cirrhosis, no portal vein thrombosis, and an ability to undergo subsequent treatments have longer survival.*

Key Words: *Brachytherapy; Carcinoma, hepatocellular; Radiotherapy*

中文摘要

選擇性內部放射治療肝細胞癌：香港一間醫院的經驗

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目的：報告選擇性內部放射治療（SIRT）肝細胞癌（HCC）的結果和總生存預後因素。

方法：回顧性分析2006年12月至2016年2月期間在伊利沙伯醫院接受SIRT的連續患者。

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結果：51名男性和11名女性患者，年齡42至90（中位數，66）歲的患者經評估適合接受SIRT。他們大多數是乙型肝炎帶菌者、東方合作腫瘤組評分為≤1和Child-Pugh A級肝硬化。大約一半的患者有門靜脈血栓和甲胎蛋白水平>200 ng/ml。30.7%的患者在巴塞羅那診所肝癌B期，64.5%在C期。50%的腫瘤最長直徑≥8厘米。腫瘤接受的中位劑量為130 Gy。SIRT後，1.7%有完全反應，43.3%有部分反應，26.7%腫瘤穩定和28.3%腫瘤惡化。一年局部控制率為12.3%。一年總生存率為30.6%。腫瘤惡化的中位時間為3個月，中位總生存期為6個月。在多變量分析中，Child-Pugh分級，門靜脈血栓和SIRT後干預是總體生存的重要預後因素。

結論：SIRT是治療中晚期HCC的有效和安全的方法。它具有良好的局部控制和較少毒性，但其在新的肝內或遠處復發中的效果不好。Child-Pugh A型肝硬化、沒有門靜脈血栓以及能接受後續治療的HCC患者有較好的生存結果。

INTRODUCTION

In Hong Kong in 2014, hepatocellular carcinoma (HCC) was the fourth most common cancer and the third most common cause of cancer mortality.[1] Transarterial chemoembolisation (TACE) and selective internal radiation therapy (SIRT) are locoregional treatment options for locally advanced tumours. SIRT is a form of brachytherapy that delivers a high dose of yttrium-90 intra-arterially to the tumour while minimising radiation to the surrounding normal liver. As opposed to TACE that results in macrovascular embolisation and is contraindicated in patients with portal vein thrombosis, SIRT exerts a micro-embolic effect and can be delivered to patients with portal vein thrombosis. SIRT is also indicated in patients refractory to TACE or experiencing tumour progression; it can be used as a bridging or down-staging therapy prior to liver transplantation.[2] It results in longer time-to-progression and reduced toxicity than TACE.[3] This study aimed to review outcomes and prognostic factors of overall survival after SIRT for HCC.

METHODS

This study was conducted in compliance with the Declaration of Helsinki. Consecutive patients who underwent SIRT at Queen Elizabeth Hospital between December 2006 and February 2016 were retrospectively reviewed. Data were retrieved from medical records and the Hospital Authority's Clinical Management System.

Decision for SIRT was made at the hospital's weekly multidisciplinary meeting. Between 2006 and early 2012, SIRT was offered as a self-financed alternative to TACE for patients with Barcelona Clinic Liver Cancer (BCLC) stage B or C tumours, some BCLC stage A tumours not responding well to TACE, and patients who refused repeated TACE. Since April 2012, it has been offered as a government-funded treatment only to patients with a tumour size of ≥8 cm or with portal vein thrombosis. SIRT as a self-financed treatment for wider indications is no longer permitted. Since July 2014, a multidisciplinary consensus guideline for eligibility for

Table 1. Eligibility criteria for selective internal radiation therapy for hepatocellular carcinoma (HCC).

Eligibility criteria
1. Unresectable HCC with liver-dominant or liver-only disease (Barcelona Clinic Liver Cancer stage B or C) not suitable for transarterial chemoembolisation
2. Liver tumour size of ≥8 cm or with presence of portal vein thrombosis (including side branches)
3. Eastern Cooperative Oncology Group performance score of 0-2
4. Life expectancy of >3 months
5. No prior radiation therapy to the liver or lungs
6. No contraindications for angiography (such as severe peripheral vascular disease or uncorrectable bleeding diathesis)
7. Child-Pugh class A or B (score of ≤8)
8. Bilirubin of <34 μmol/l, alanine aminotransferase of ≤5 x upper limit of normal, platelet count of >50 x 10^9/l
9. No ascites detectable on physical examination or clinically asymptomatic
10. ≥700 ml uninvolved liver volume or tumour involvement of <50% of liver
11. ≤20% lung shunting of the hepatic artery blood flow determined by technetium-99m macro-aggregated albumin scintigraphy

SIRT has been implemented (Table 1). Flexibility is allowed if the benefits of SIRT are deemed to outweigh the risks.

Before SIRT, hepatic vascular anatomy and microsphere distribution were assessed using hepatic angiography and technetium-99m macro-aggregated albumin (99mTc MAA) scintigraphy. Vessels feeding the extrahepatic sites were prophylactically embolised if necessary. The volume of the normal liver and tumour, and the simulated doses to the tumour, normal liver, and lungs were measured using computed tomography and single-photon emission computed tomography, respectively. Patients were deemed not eligible for SIRT when the tumour–normal liver uptake ratio was <4.0, lung shunting was >20%, or yttrium-90 microsphere reflux to extra-hepatic arteries could not be prevented. The activity of yttrium-90 was calculated with the partition model whenever possible, with reference to the body surface area model[4] after a consensus was reached among the radiologist, oncologist, and medical physicist. The aim was to give at least 120 Gy to the tumour while keeping the dose to the normal liver parenchyma to <50 Gy, or <40 Gy in patients with cirrhosis or previous chemoembolisation. The dose to the lungs should not exceed 25 Gy and preferably <20 Gy. Hepatitis B carriers were given antiviral treatment with the baseline hepatitis B viral DNA level measured. No patient received concurrent sorafenib with SIRT.

For SIRT, yttrium-90 was administered within 3 weeks according to the standard protocol. Patients were then transferred to the radiation isolation ward and discharged when the activity level was considered safe. Bremsstrahlung scan was performed 1 to 2 days later to document any extra-hepatic reflux of yttrium particles. Blood test was performed monthly for the first 3 months and ultrasonography of the abdomen was performed monthly for the first 2 months to detect any potential liver toxicity. Tri-phasic computed tomography or contrast-enhanced MRI was performed 3 monthly by radiologists to evaluate tumour response using the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[5] Biochemical response (defined as a >20% decrease in alpha-fetoprotein [AFP] level from the baseline[6]) and its duration were determined by serial AFP levels.

Local control rate of the lesions treated with SIRT was calculated. Intra-hepatic recurrence included all recurrences within or outside the treated volume in the liver. The median overall survival (from the date of SIRT commencement to the date of death from any cause) and time to progression (from the date of SIRT commencement to the date of recurrence or disease progression) were calculated using the Kaplan-Meier method. Survival curves between different BCLC stages, Child-Pugh classes, presence or absence of portal vein thrombosis, and levels of AFP were compared using the log-rank test. Prognostic factors of overall survival were determined using univariate analysis. Significant factors ($p < 0.1$) in univariate analysis were further analysed using multivariate analysis.

RESULTS

A total of 115 patients were assessed using 99mTc MAA scintigraphy. Of whom 62 (53.9%) aged 42 to 90 (median, 66) years were deemed suitable to receive SIRT and 53 (46.1%) were not owing to various reasons (Table 2). Two patients were lost to follow-up after SIRT.

Of the 62 patients who underwent SIRT, most were male and hepatitis B carriers and had an Eastern Cooperative Oncology Group (ECOG) performance score of ≤1 and Child-Pugh class A cirrhosis (Table 3). About half of the patients had portal vein thrombosis and a baseline AFP level of >200 ng/ml. 30.7% of patients were at BCLC stage B and 64.5% at stage C. 67.7% of patients had never received any treatment, and 29% had undergone TACE. 50% of tumours were ≥8 cm at the longest diameter. The median tumour volume was 447 ml. The median uninvolved liver volume was 1550 ml. The mean lung shunting was 7.05%.

Table 2. Reasons for patients not receiving selective internal radiation therapy after technetium-99m macro-aggregated albumin scintigraphy.

Reason	No. of patients
Excessive lung shunting	28
Major shunting to normal liver	6
Deteriorated liver function while awaiting yttrium-90	5
Unpreventable or high risk of reflux to extrahepatic arteries	3
Patient refusal	3
Poor tumour–normal liver uptake ratio	3
Subclinical tumour rupture	1
Common hepatic artery dissection during catheter insertion for yttrium-90	1
Multiple feeders with complex vascular anatomy	1
Intense uptake over gallbladder	1

Table 3. Baseline patient and tumour characteristics.

Characteristic	Value*
Patient age (years)	66 (42-90)
No. of males : females	51 : 11
Eastern Cooperative Oncology Group performance score	
≤1	61 (98.3)
2	1 (1.7)
Aetiology	
Hepatitis B virus	45 (72.6)
Hepatitis C virus	3 (4.8)
Hepatitis B virus + Hepatitis C virus	3 (4.8)
Non-hepatitis B or C virus	6 (9.7)
Alcoholic	4 (6.4)
Cryptogenic	1 (1.6)
Barcelona Clinic Liver Cancer stage	
A	3 (4.8)
B	19 (30.7)
C	40 (64.5)
Child-Pugh class	
A	51 (82.3)
B	11 (17.7)
Portal vein thrombosis	
Yes	30 (48.4)
No	32 (51.6)
No. of tumours	
Single	30 (48.4)
Multiple	32 (51.6)
Range of baseline alpha-fetoprotein (ng/ml)	1-746265
Baseline alpha-fetoprotein of >200 ng/ml	32 (51.6)
Prior treatment	
None	42 (67.7)
Resection	7 (11.3)
Transarterial chemoembolisation	18 (29)
Mean (range) lung shunting (%)	7.05 (1.9-19.6)
Tumour size (longest diameter) [cm]	8 (1-18.8)
Tumour size of ≥8 cm	31 (50)
Tumour volume (ml)	447 (2.85-2852.5)
Liver volume (ml)	1550 (691-4475.7)
Uninvolved liver volume (ml)	1131 (510-2111)
Activity administered (GBq)	2.28 (0.5064-5.58)
Dose to tumour (Gy)	130 (34.8-25476

* Data are presented as median (range) or No. (%) of patients unless otherwise stated.

Of the 62 patients who underwent SIRT, 60 received resin microspheres and two received glass spheres (available since December 2015). The median activity administered was 2.28 GBq. The median dose to the tumour was 130 Gy. 21 patients (34%) had yttrium injection into two separate arteries at the same session.

The median follow-up duration was 6 (range, 0-93) months for the 60 patients and 29 (range, 6-93) months for seven surviving patients. 60 patients were assessed radiologically for tumour response. One patient (1.7%) with a small tumour (2.6 cm) had a complete response; 26 patients (43.3%) had a partial response; 16 patients (26.7%) had stable disease; and 17 patients (28.3%) had progressive disease. The median duration of radiological response was 5 (range, 3-37) months. Of 41 patients with a raised baseline AFP level, 21 (51.2%) had a >20% decrease. The median duration of biochemical response was 3 (range, 1-8) months. Nine patients (14.5%) had improvement in Child-Pugh score by up to 4 points at 3 months.

Respectively at 3, 6, and 12 months, the local control rate of the lesions treated with SIRT was 76.3%, 74%, and 12.3%, but only 44.8%, 30%, and 12% of patients remained free of intra-hepatic recurrence. The median time to progression was 3 (range, 1-58) months. The median overall survival was 6 (range, 0-93) months, and the 1-year overall survival was 30.6%. The median overall survival was longer in patients without portal vein thrombosis than in those with portal vein thrombosis (15 months vs. 6 months, p = 0.002, Figure a), in patients with Child-Pugh class A cirrhosis than in those with Child-Pugh class B cirrhosis (12 months vs. 4 months, p = 0.031, Figure b), in patients with an ECOG score of 0 than in those with an ECOG score of 1 or 2 (11 months vs. 4 months vs. 2 months, p = 0.001), in patients with BCLC stage A than in those with BCLC stage B or stage C (24 months vs. 14 months vs. 5 months, p = 0.007), and in patients with an AFP level of <400 ng/ml than in those with an AFP level of >400 ng/ml (12 months vs. 4 months, p = 0.001).

Upon disease progression after SIRT, 24 patients (40%) underwent subsequent treatments. 16 patients underwent further TACE or liver resection and had a median overall survival of 25 (range, 4-93) months; three of them later received sorafenib and had a median overall survival of 36 months. Seven patients received sorafenib as the only subsequent treatment and had a median overall survival of 4 (range, 3-25) months. One patient received SIRT after failing six courses of TACE and achieved a partial response, but the tumour recurred in the contralateral lobe 12 months later. He subsequently underwent liver transplantation and was alive after 93 months. Overall, patients who had subsequent treatments after SIRT had longer median overall survival than those who did not (18 months vs. 4 months, p = 0.001, Figure c).

Four patients (6.5%) developed radio-embolisation–induced liver disease, defined as a raised serum total bilirubin of ≥3 mg/dl and ascites appearing

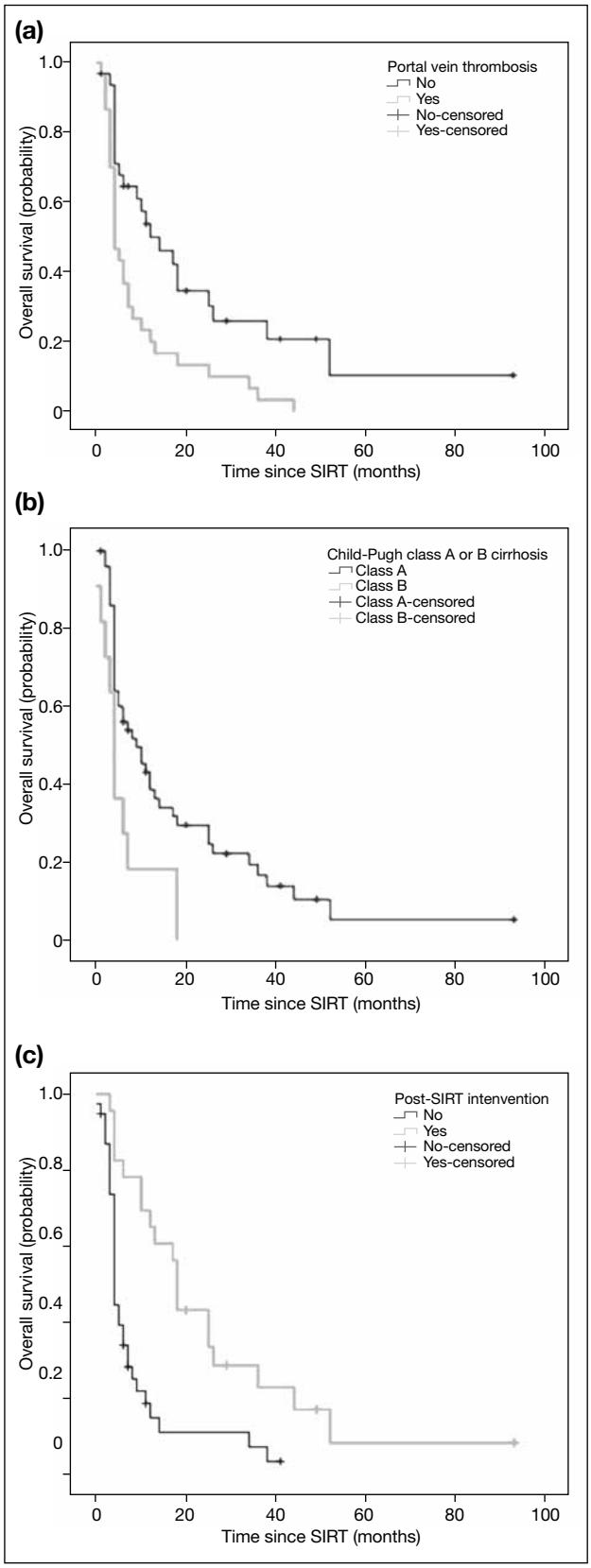

Figure. Kaplan-Meier curves showing overall survival after selective internal radiation therapy (SIRT) in patients (a) with or without portal vein thrombosis, (b) with Child-Pugh class A or B cirrhosis, and (c) with or without post-SIRT intervention.

within 3 months that could not be explained by tumour progression or bile duct obstruction.[7] Three patients (4.8%) developed radiation-induced peptic ulcer, with microsphere particles and / or irradiation changes identified in the gastric biopsies from oesophagogastroduodenoscopy. One patient (1.6%) developed radiation-induced oesophagitis and stricture requiring regular dilatation. Seven patients (11.2%) had grade 1 impaired liver transaminases. No patient developed grade 2 or above derangement in transaminases. Commonly reported side effects of SIRT such as nausea, vomiting, anorexia, fever, abdominal pain, and malaise were not routinely documented and thus were likely under-reported. No patient had SIRT-related mortality.

In univariate analysis, Child-Pugh class, ECOG score, BCLC stage, AFP level, and portal vein thrombosis were significant prognostic factors for both overall and progression-free survival (Table 4). Tumour multicentricity was significant for progression-free survival only, whereas post-SIRT intervention was significant for overall survival only. In multivariate analysis, Child-Pugh class, portal vein thrombosis, and post-SIRT intervention were significant prognostic factors for overall survival (Table 5).

DISCUSSION

SIRT is effective and tolerable in the treatment of HCC and has resulted in a median overall survival of 3.2 months to 41.6 months.[8] It is difficult to compare overall survival across different studies due to heterogeneity of patients. In our patients, 48.4% had portal vein thrombosis and 72.6% were hepatitis B carriers, both of which are poor prognostic factors. Less than 20% of the patients in the SHARP trial[9] and more than 70% of the patients in the Asia-Pacific trial for sorafenib[10] were hepatitis B carriers; patients in the Asia-Pacific trial had significantly shorter overall survival, despite a similar reduction of risk by sorafenib.[9,10]

The findings of our study are consistent with those of previous studies that Child-Pugh class and the presence of portal vein thrombosis are poor prognostic factors for survival.[11] The overall response rate of 45% in our study is also comparable with that in other Asian series.[12,13] Nonetheless, large tumour size was not predictive of survival in our patients. This may be due to the inclusion criteria that only patients with tumour size ≥8 cm and / or presence of portal vein thrombosis were considered for SIRT.

Table 4. Univariate analysis of prognostic factors affecting overall survival and progression-free survival.

Variable	Overall survival		Progression-free survival	
	Hazard ratio (95% confidence interval)	p Value	Hazard ratio (95% confidence interval)	p Value
Child-Pugh class B	2.249 (1.136-4.452)	0.02	1.11 (0.539-2.286)	0.777
Eastern Cooperative Oncology Group performance score of ≥2	1.845 (1.062-3.205)	0.001	2.087 (1.146-3.8)	0.016
Barcelona Clinic Liver Cancer stage C	2.271 (1.183-4.362)	0.007	2.56 (1.263-5.191)	0.009
Multiple tumours	1.686 (0.970-2.928)	0.064	2.583 (.1356-4.920)	0.004
Alpha-fetoprotein level of ≥400 ng/ml	2.584 (1.397-4.781)	0.002	2.364 (1.281-4.361)	0.006
Presence of portal vein thrombosis	2.243 (1.285-3.915)	0.004	1.874 (1.074-3.268)	0.027
Post–selective internal radiation therapy intervention	0.356 (0.193-0.657)	0.001	0.670 (0.382-1.173)	0.161
Tumour size of <8 cm	0.705 (0.410-1.215)	0.209	0.991 (0.935-1.050)	0.761
Tumour dose of <120 Gy	1.425 (0.778-2.611)	0.223	1.11 (0.612-2.016)	0.731
Uninvolved liver volume of ≥800 ml	0.827 (0.424-1.615)	0.555	0.974 (0.499-1.903)	0.938
Tumour volume of <700 ml	0.837 (0.479-1.463)	0.509	0.961 (0.557-1.656)	0.886
Positive alpha-fetoprotein response	0.553 (0.304-1.007)	0.053	0.571 (0.316-1.032)	0.064
Duration of alpha-fetoprotein response ≥3 months	0.544 (0.231-1.281)	0.137	1.126 (0.505-2.509)	0.772

Table 5. Multivariate analysis of prognostic factors affecting overall survival.

Variable	Hazard ratio (95% confidence interval)	p Value
Child-Pugh class B	3.103 (1.519-6.343)	0.002
Presence of portal vein thrombosis	3.836 (2.018-7.292)	<0.001
Post–selective internal radiation therapy intervention	0.230 (0.111-0.476)	<0.001

In our study, 14.5% of patients had an improvement in Child-Pugh score by up to 4 points at 3 months. This can be explained by yttrium-90–induced atrophy of the treated area with compensatory hypertrophy of the untreated liver. Indeed, for early-stage HCC, SIRT is useful as a bridging therapy to transplantation.[14] For intermediate-stage disease not amenable to liver transplantation based on the Milan criteria, SIRT resulted in more patients with a down-staging effect than chemo-embolisation (58% vs. 31%) as well as longer event-free survival (17.7 months vs. 7.1 months, p = 0.0017).[15]

For locally advanced HCC, SIRT is superior to sorafenib in terms of the response rate and toxicity profile. Sorafenib was reported to prolong survival by 2.3 to 2.8 months compared with placebo in the SHARP and Asia-Pacific trials.[9,10] In patients treated with sorafenib in the Asia-Pacific trial, none had a complete response and only 3.3% had a partial response, and 6% and 10.7% had grade 3 or above diarrhoea and hand-foot syndrome, respectively.[10] In the French SARAH study of 459 patients with advanced or inoperable HCC randomised to SIRT or sorafenib, SIRT resulted in a higher response rate (19.0% vs 11.6%, p = 0.042), more favourable side-effect profile and quality of life score (p = 0.005), and lower rates of treatment-related diarrhoea (13% vs. 68%, p < 0.001), hand-foot skin reaction (0.4% vs. 21%, p < 0.001), and alopecia (0% vs. 16%, p < 0.001).[16] Nonetheless, SIRT and sorafenib were comparable in terms of overall survival.[16] Similarly, the SIRveNIB study of >360 Asia-Pacific patients with HCC also reported comparable overall survival between the SIRT and sorafenib arms.[17] SIRT resulted in a better response rate (16.5% vs. 1.7%, p < 0.001), fewer severe (grade 3 or above) adverse events (27.7% vs. 50.6%, p < 0.0001), and fewer instances of diarrhoea, hand-foot syndrome, fatigue, alopecia, and hypertension.[17] In patients with unresectable HCC, SIRT is a good alternative to sorafenib.

Although local control of treated lesions after SIRT is satisfactory, recurrence or disease progression outside the treatment field is relatively common, as the short-range radiation is unable to reach the remaining cirrhotic liver, which is prone to developing metachronous multicentric malignant change. In our study, the local control rate of the treated lesions was 74% at

6 months, but only 30% of patients remained free of intra-hepatic recurrence at 6 months. It is unknown whether concurrent or sequential use of sorafenib would help prevent or eradicate new intrahepatic or distant metastases. The STOP-HCC trial (NCT01556490) that compares sorafenib and yttrium-90 radio-embolisation with sorafenib alone in patients with unresectable HCC may provide an answer.

In our study, patients who were able to receive subsequent treatments after SIRT had more than a four-fold increase in the median survival than those who were not. They were more likely to have more favourable prognostic factors (such as Child-Pugh class A cirrhosis, absence of portal vein thrombosis) and less aggressive tumour biology. Upon disease progression, they still retained a satisfactory liver function and performance status to receive subsequent treatments. In addition, SIRT could downsize a rather advanced disease to a small tumour suitable for liver transplantation. There is a role for SIRT in early-stage HCC in addition to intermediate- to advanced-stage HCC. In a bridging and down-staging study of patients with earlier-stage disease and smaller tumours (only 16% of patients had >8 cm tumour compared with 50% in our study),[15] the partial response rate after SIRT was higher (61% vs. 45%) and overall survival was longer (35.7 months vs. 6 months), compared with our study.

In view of the treatment efficacy and favourable toxicity profile, SIRT should also be considered in patients with less advanced disease. Stringent inclusion criteria are set to ensure delivery of SIRT to the most appropriate patients in the public sector despite resource implications and availability of alternative treatments. The criteria for government-funded SIRT are under review so that patients with a better prognosis can undergo SIRT.

CONCLUSION

SIRT is an effective and safe treatment for intermediate- to advanced-stage HCC. It achieves good local control with minimal toxicity although the outcome is unsatisfactory in terms of new intrahepatic or distant recurrence. HCC patients with Child-Pugh class A cirrhosis, absence of portal vein thrombosis, and an ability to undergo subsequent treatments have longer survival.

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