SIR-Spheres® Y-90 resin microspheres in Hepatocellular Carcinoma

The following summarises the key data supporting the use of SIR-Spheres Y-90 resin microspheres in the treatment of primary liver cancer due to hepatocellular carcinoma (HCC):

Lead Author	n	Treatment	Cohort	ORR		SD		Median Survival	
First-Line, Advanced Disease; Western Europe									
D'Avola[1]	35†	SIR-Spheres§		nr		nr		16.0 months	*P* < 0.001
	43†	matched control: standard care		nr		nr		8.0 months	
de la Torre[2]	26†	SIR-Spheres§		nr		nr		8.8/22.8[cen] months	*P* = 0.047/ *P* = 0.007[cen]
	47†	*vs.* sorafenib		nr		nr		5.4/5.4[cen] months	
First- or Second-Line, Intermediate to Advanced Disease; Western Europe									
Sangro[3]	325†	SIR-Spheres§		nr		nr		12.8 months	
(ENRY)	52		BCLC A					24.4 months	*P* < 0.001
	87		BCLC B					16.9 months	
	183		BCLC C					10.0 months	
	3		BCLC D					5.2 months	
Carpanese[4]	60†	SIR-Spheres§		52.0%		nr			
			Child A					14.0 months	*P* < 0.0001
			Child B					8.0 months	
Iñarrairaegui[5]	72†	SIR-Spheres§		nr		nr		13.0 months	
	40		≤5 nodules					19.0 months	*P* = 0.001
	32		>5 nodules					8.0 months	
	32		AFP <52 UI/mL					24.0 months	*P* = 0.002
	34		AFP >52 UI/mL					11.0 months	
Gramenzi[6]	63†	SIR-Spheres§	BCLC B/C	73.0%	*P* < 0.0001	92.0%[DCR]	*P* < 0.0001	13.2 months	*P* = 0.96
	74†	*vs.* sorafenib	BCLC B/C	9.5%		51.4%[DCR]		14.4 months	
Kolligs[7]	13	SIR-Spheres§	BCLC A/B/C	30.8%[TI]		76.9%[DCR]		46% at 1 yr	
(SIRTACE)	15	*vs.* TACE	BCLC A/B/C	13.3%[TI]		73.3%[DCR]		67% at 1 yr	
Pitton[8]	12	SIR-Spheres§	BCLC B	nr		nr		19.5 months	*P* = 0.93
	12	*vs.* DEB-TACE	BCLC (A)/B	nr		nr		25.9 months	
Soydal[9]	40†	SIR-Spheres§	BCLC B/C	nr		nr		48.0 months	
	40†	*vs.* TACE	BCLC B/C	nr		nr		32.0 months	
Golfieri[10]	104†	SIR-Spheres§						11.9 months	
	4		BCLC A	nr		nr		41.2 months	*P* = 0.018
	37		BCLC B	nr		nr		19.6 months	
	71		BCLC C	nr		nr		9.2 months	
First- or Second-Line, Advanced Disease; Western Europe									
Sangro[3,11] (ENRY)	183†	SIR-Spheres§	BCLC C	8.0%		70.0%		10.0 months	
Iñarrairaegui[12]	25†	SIR-Spheres§	Branch/Main PVT	66.7%/94%[TI]				10.0 months	
Sangro[13]	24	SIR-Spheres§		24.0%		64.0%		7.0 months	
First- or Second-Line, Intermediate to Advanced Disease; Asia-Pacific/Australia									
Chow[14]	29	SIR-Spheres§ > sorafenib		25.0%		54.0%			
(AHCC-05)	11		BCLC B	45.0%		55.0%		20.3 months	
	18		BCLC C	12.0%		53.0%		8.6 months	
Lau[15]	71	SIR-Spheres§		26.7%		nr		9.4 months	
Lau[16]	18	SIR-Spheres§	>120 Gy	87.5%	*P* = 0.005	12.5%		55.9 weeks	*P* = 0.005
			<120 Gy	12.5%		87.5%		26.2 weeks	
Kim[17]	40	SIR-Spheres§		57.7%		37.5%		75% at 3 yr	
Khor[18]	103†	SIR-Spheres§		21.2%		38.5%		14.4 months	
	61		Child-Pugh A	19.4%		41.7%		21.7 months	*P* < 0.0001
	39		Child-Pugh B	20.0%		33.3%		7.1 months	
	28		BCLC B	31.6%		36.8%		23.8 months	*P* = 0.06
	71		BCLC C	12.5%		40.6%		11.8 months	
Saxena[19]	45†	SIR-Spheres§		48.0%		22.0%		27.7 months	
	30		Child-Pugh A					30.8 months	*P* = 0.006
	11		Child-Pugh B/C					3.3 months	
	30		ECOG 0					30.8 months	*P* = 0.003
	15		ECOG 1					4.8 months	
Cho[20]	47†	SIR-Spheres§		nr		nr		13.0 months	*P* < 0.01
	77†	*vs.* sorafenib		nr		nr		6.0 months	

Key: ORR: objective response rate (complete response + partial response); SD: stable disease; †: retrospective study; §: SIR-Spheres Y-90 resin microspheres; nr: not reported; [cen]: radioembolisation group censored at the time of receiving sorafenib; EHD: extra-hepatic disease; AFP: alpha-fetoprotein; PVT: portal vein thrombosis; [TI]: target lesions. [DCR]: disease control rate

Prognosis of HCC

The survival of patients with HCC is influenced by prognostic factors including the extent of disease spread (graded through scales such as BCLC, which reflects tumour burden as well as invasion i.e. portal vein thrombosis [PVT] or metastases) and the impact of concomitant disease on functional liver reserve (e.g. cirrhosis graded by Child-Pugh).[21–23]

Survival is also subject to the ability to deliver a hierarchy of treatment options:

- potentially curative surgery (resection or transplantation) or ablation (i.e. RFA) that aim to remove the tumour burden; while restricted to patients with BCLC stage A or that fit the extended Milan transplant criteria (~15% of the HCC population);[16]
- local-regional therapy (i.e. trans-arterial embolisation [TAE], chemoembolisation [TACE] and selective internal radiation therapy [SIRT, also known as radioembolisation]) that aim to reduce tumour burden, extend survival and can down-stage the disease sufficiently to enable potentially curative treatment to be performed; these options may be applied to patients with unresectable BCLC A, B or C;[16]
- systemic chemotherapy or biologic agents, such as sorafenib.[16]

HCC remains a clinical challenge with a poor prognosis for the majority of patients, and particularly in certain sub-groups that have few treatment options. For patients with unresectable HCC, due to tumour location, extent of the disease burden, performance status or co-morbidity, SIRT/radioembolisation is one of the local-regional therapy options listed in the guidelines by the US National Comprehensive Cancer Network (NCCN), the American Hepato-Pancreato-Biliary Association (AHPBA)/Society of Surgical Oncology (SSO)/Society for Surgery of the Alimentary Tract (SSAT), and the European Society of Medical Oncology (ESMO).[24–26]

Candidates for SIRT/Radioembolisation

Studies indicate that SIRT/radioembolisation using SIR-Spheres Y-90 resin microspheres can be used in the following sub-groups of patients with HCC with well-compensated liver function (i.e. Child-Pugh class A or B ≤7 points) that are:

- candidates for TACE i.e. unresectable BCLC stage A or B with unilobar disease or few (1–5) nodules;
- poor candidates for TACE i.e. BCLC stage B with bilobar disease and/or multiple (>5) nodules;
- patients that have previously failed TACE/TAE;
- patients contraindicated for TACE i.e. BCLC stage C, particularly those with PVT.

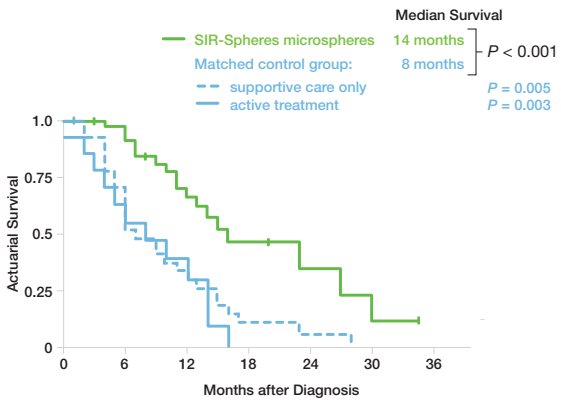
European Studies of SIR-Spheres Y-90 resin microspheres in HCC

Impact on survival of SIR-Spheres Y-90 resin microspheres compared to a matched control group in first-line HCC

A retrospective study conducted by D'Avola *et al.* in Pamplona, Spain in the first-line treatment of unresectable HCC compared survival in 35 consecutive patients using SIR-Spheres Y-90 resin microspheres against a matched control group of 43 patients who received standard care.[1] The study revealed:

- the control group received supportive care (32%), systemic chemotherapy with doxorubicin, taxanes, gemcitabine or platin-derivatives (28%), TAE or TACE (18%), sorafenib (14%), intra-arterial cisplatin and/or etoposide (9%), gene therapy (9%), tamoxifen (7%) or external beam radiotherapy (5%);[1]
- median overall survival was significantly higher in the SIR-Spheres Y-90 resin microspheres group compared with the control group (16.0 *vs.* 8.0 months; $P < 0.001$) and was maintained after adjusting for cirrhosis, vascular invasion, multinodular disease, bilobar involvement, or if patients that received sorafenib were censored from both cohorts (15.0 *vs.* 8.0 months; $P < 0.05$). 1-year and 2-year survival rates were 67% and 36% in the SIRT group, and 35% and 3% in the control group, respectively;[1]
- treatment using SIR-Spheres Y-90 resin microspheres was the only independent prognostic factor for survival in a multivariate analysis (hazard ratio [HR] 3.526; 95% CI 1.906–6.521; $P = 0.000$);[1]
- the investigators concluded that SIR-Spheres Y-90 resin microspheres are likely to improve survival in patients with unresectable, non-ablatable HCC with preserved liver function that are poor candidates for TACE or TAE.[1]

Comparison of Overall Survival in Advanced HCC[1]



Retrospective study comparing the outcome of HCC patients with portal vein invasion (PVI) treated with sorafenib or SIR-Spheres Y-90 resin microspheres

Survival among patients with HCC and PVI treated with sorafenib or SIR-Spheres Y-90 resin microspheres in four Spanish hospitals between 2005 and 2013 was analysed retrospectively by de la Torre *et al.*:[2]

- overall survival was compared using a methodology that minimises patient selection bias (treatment allocation depending on site and use of propensity score analysis);[2]
- in total 73 patients were analysed, 26 received SIR-Spheres Y-90 resin microspheres and 47 received sorafenib as first-line therapy;[2]
- patient characteristics were similar, only the diameter of the main lesion was higher in SIRT patients (106 mm *vs.* 60 mm, $P = 0.004$). Four patients in the SIRT group and 15 patients in the sorafenib group had extra-hepatic disease;[2]
- after a median follow-up of six months, 38 patients have died in the sorafenib and 22 patients in the SIRT group;[2]

- the median survival was 6.7 months (95% CI 5.2–8.1 months) for the entire cohort; in the SIRT group median survival was 8.8 months (95% CI 1.8–15.8) *vs*. 5.4 months (95% CI 2.7–8.1) in the sorafenib group ($P = 0.047$);[2]
- 13 patients in the SIRT group started sorafenib after a median time of eight months. Overall survival was calculated censoring these patients at the time they started sorafenib: median survival was then 22.8 months (95%CI 1–42.5) for SIRT patients and 5.4 months (95% CI 2.7–8.1) for patients treated with sorafenib ($P = 0.007$). This remarkable difference is likely due to the expected worse prognosis of patients showing early progression following SIRT;[2]
- independent predictors of survival were SIRT treatment, ECOG 0 or 1, and a total bilirubin <2mg/dl;[2]
- the investigators concluded that in a cohort of patients with HCC and PVI, treatment with SIR-Spheres Y-90 resin microspheres was associated with a more prolonged survival compared with sorafenib.[2]

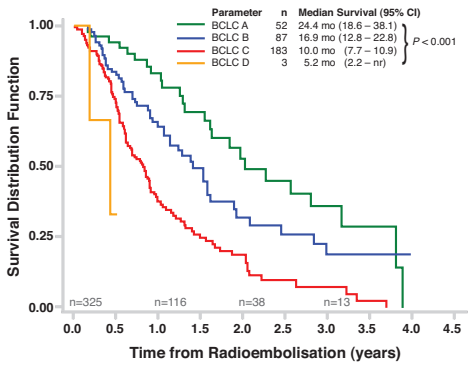
First large multi-centre evaluation of safety and survival of SIRT/radioembolisation across BCLC stages

A multi-centre collaboration by Sangro *et al.* on behalf of the European Network on Radioembolisation with Yttrium-90 Microspheres (ENRY) in eight European centres assessed survival and safety in 325 consecutive patients with unresectable HCC treated with SIR-Spheres Y-90 resin microspheres between September 2003 and December 2009.[3] The largest study of SIRT/radioembolisation to date reported:

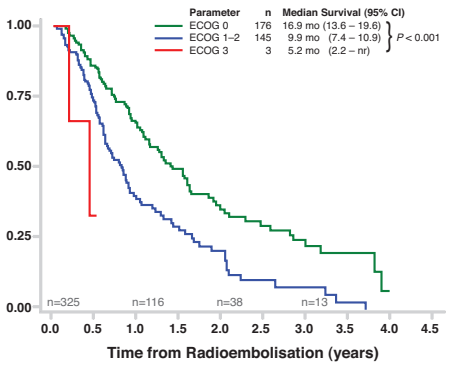
- most patients were male (81.5%), had Child-Pugh class A (82.5%), cirrhosis (78.5%), multi-nodular disease (75.9%; 38.6% with >5 nodules, typically an uncountable number) and bilobar disease (53.1%); 41.5% had ≥1 prior procedure (27.4% vascular i.e. TAE, TACE; 18.2% prior surgical i.e. resection, liver transplantation; 9.2% ablation i.e. RFA, PEI); 23.6% had PVT (13.5% branch, 9.8% main) and 9.2% had extra-hepatic disease (lymph, lung, bone, adrenal);[3]
- median activity administered was 1.6 GBq (range 0.3–4.0), predominantly by single-session, whole-liver (45.2%) and right-lobe (38.5%) infusions;[3]
- all-cause mortality was 0.6% and 6.8% (two and 22 patients) at 30 and 90 days, respectively;[3]
- common adverse events (primarily grade 1/2) included fatigue (typically in the first few weeks; all grades: 54.5%) with few (2.5%) grade 3 events, nausea/vomiting (all grades: 32.0%; grade 3: 0.3%) and abdominal pain (all grades: 27.1%; grade 3: 1.5%). GI ulceration (all grades) was 3.7%, with 1.8% having grade ≥3;[3]
- fatigue was most commonly reported in patients with advanced stage disease (all grades: 61.2%) compared to those with intermediate (41.4%) or early (50.0%) stage disease ($P = 0.021$);[3]
- elevated total bilirubin (all grades) was recorded in 22.6% of patients at baseline, increasing to 48.6% of patients up to day 90 ($P < 0.001$), with few grade ≥3 events (5.8% up to day 90). There were no significant changes from baseline to day 90 for albumin, ALT, INR, creatinine and platelets, and no significant differences in the transitions in CTCAE for laboratory values across BCLC stages;[3]
- median overall survival was 12.8 months (95% CI 10.9–15.7) at a median follow-up of 10.0 months (range 0.4–48);[3]
- survival varied significantly by ECOG performance status, hepatic function (Child-Pugh class, ascites, baseline total bilirubin and INR), tumour burden (number of nodules, alpha-fetoprotein), the presence of PVT or extra-hepatic disease, and BCLC stage (see table and figures for median survival);[3]

Kaplan-Meier survival analysis for SIR-Spheres Y-90 resin microspheres in unresectable HCC stratified by pre-treatment characteristics[3,11,28]

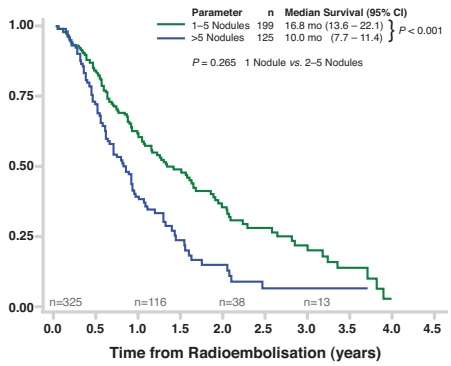
BCLC stage[3]



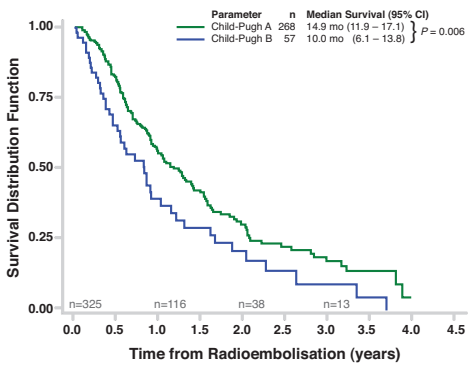
ECOG performance status[3]



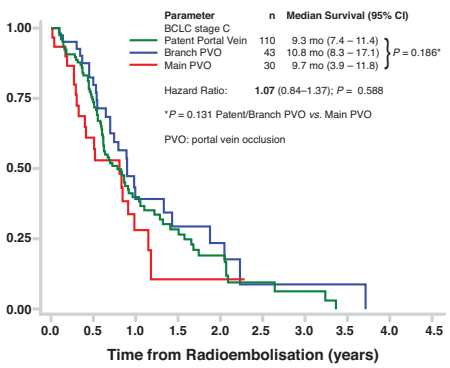
Tumour burden[3]



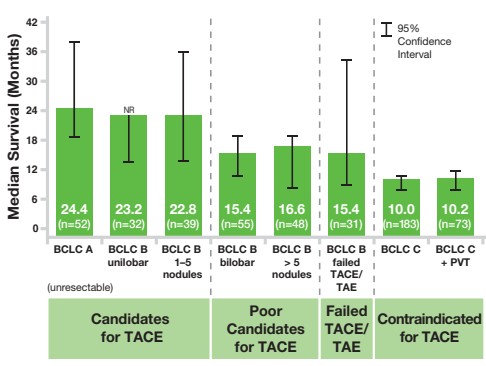
Child-Pugh class[28]



Portal vein involvement in BCLC stage C[11]



Typical candidates for treatment[3]



- the presence of cirrhosis did not significantly impact survival, and for patients receiving whole-liver or lobar treatment survival was similar although, unsurprisingly, segmental treatment was associated with increased survival ($P = 0.038$);[3]
- survival did not differ significantly between patients that had received any prior procedures and those with no prior procedure ($P = 0.533$);[3]
- in a comparison of elderly (≥70 years) and younger patients in the study, SIR-Spheres Y-90 resin microspheres were well-tolerated in both cohorts with no significant difference in survival (14.5 *vs.* 12.8 months, respectively; $P = 0.942$);[27]
- in a detailed analysis of patients with advanced, BCLC stage C disease, SIR-Spheres Y-90 resin microspheres were as effective and well-tolerated in patients with or without PVT, EHD or altered ECOG performance status, although fatigue and bilirubin dysfunction were significantly more common in patients with ECOG performance status 1 or 2 (see table and figures for median survival);[11]
- baseline ECOG performance status (HR 1.39; 95% CI 1.14–1.70; $P < 0.001$), tumour burden (>5 nodules) (HR 1.76; 95% CI 1.32–2.35; $P = 0.001$), extra-hepatic disease (HR 1.91; 95% CI 1.17–3.13; $P = 0.010$) and INR >1.2 (HR 1.47; 95% CI 1.04–2.09; $P = 0.028$) were found in a multivariate analysis to be the most significant independent prognostic factors for survival following treatment with SIR-Spheres Y-90 resin microspheres;[3]
- the authors noted that survival outcomes in specific cohorts:
  - compared favourably with TACE/TAE that would typically be considered for unresectable patients in BCLC A and B stages;
  - appeared particularly promising for the subset of patients with intermediate, BCLC stage B disease who are considered poor candidates for TACE (i.e. bilobar and/or multiple [>5] tumours), as well as for those who had failed prior TACE/TAE;
  - were also promising for patients with advanced stage (BCLC C) disease, particularly those with PVT, where SIRT/radioembolisation compares well to sorafenib, and is well tolerated;[3]
- the authors concluded that SIR-Spheres Y-90 resin microspheres were relatively well tolerated and that the results provide robust evidence of the survival in patients with HCC, including those with advanced disease and few treatment options.[3]

Study of SIR-Spheres Y-90 resin microspheres in intermediate & advanced HCC and identification of prognostic factors

A detailed analysis by Iñarrairaegui *et al.* of the influence of patient-, tumour- and treatment-related factors on tumour response and survival in 72 patients with unresectable intermediate to advanced HCC (BCLC B 46%, BCLC C 35%), mostly complicated by bulky disease (median tumour volume: 222 mL), cirrhosis (79%), ≥5 nodules (44%) and portal vein involvement (22%).[5] The study revealed:

- a decrease in target tumour size (partial response: 8%; stable disease: 70%) was seen in most of the 50 patients with evaluable disease;[5]
- the intensity of tumour response was not associated with any of the factors investigated, although the appearance of new lesions (in 20% of patients) was related to baseline characteristics denoting more aggressive disease including an uncountable number of tumour nodules, bilobar spread and AFP >52 UI/mL;[5]
- there was a significant correlation between the appearance of lesions in treated and untreated areas, suggesting that microscopic disease may not be efficiently targeted;[5]
- median survival was 13 months: univariate analysis showed a significant increase in survival for patients with ≤5 nodules (19.0 *vs.* 8.0 months in >5 nodules; $P = 0.001$) or AFP <52 UI/mL (24.0 *vs.* 11.0 months for >52 UI/mL; $P = 0.002$);[5]
- five patients were able to undergo radical procedures: two patients were resected at two and 12 months post-SIRT (one recurrence-free at 41 months; one died from recurrence at 35 months post-surgery); three patients were transplanted at seven, 10 and 36 months post-SIRT (recurrence-free at 12, 30 and 32 months).[5]

Retrospective study comparing sorafenib with SIR-Spheres Y-90 resin microspheres in patients with intermediate-locally advanced HCC

A single-centre retrospective study from the Bologna Liver Oncology Group (BLOG) compared outcomes achieved with sorafenib and SIR-Spheres Y-90 resin microspheres in HCC patients potentially amenable to either therapy:[6]

- 63 SIRT HCC patients (66 ± 9 years, male 79%, BCLC B/C 41%/59%) and 74 sorafenib HCC patients (71 ± 10 years, male 87%, BCLC B/C 53%/47%) were included;[6]
- sorafenib patients were significantly older, had a greater prevalence of comorbid illnesses and multinodular tumours; there was a trend towards a less favourable distribution of PS;[6]
- ORR by mRECIST was significantly higher in patients receiving SIRT: 73% (including 19% with a CR) *vs.* 9.5% ($P < 0.0001$); DCR was also significantly higher: 92% *vs.* 51% ($P < 0.0001$);[6]
- down-staging to liver transplantation was achieved in two patients receiving SIRT *vs.* none following sorafenib;[6]
- median survival was similar in both cohorts (13.2 *vs.* 14.4 months, respectively; $P = 0.959$);[6]
- survival was also similar across BCLC stages: median in stage B was 22.1 *vs.* 20.4 months, and stage C was 6.0 *vs.* 8.7 months, respectively ($P = 0.879$);[6]
- there were significantly more adverse events overall following sorafenib (91% *vs.* 59% of patients). However, the grade 3/4 rates were similar in the two cohorts and these were not statistically different (33% in SIRT arm and 30% in sorafenib arm; $P = 0.7$);[6]
- the authors conclude that SIRT is a valuable therapy for patients with locally advanced HCC or whenever previous therapies have failed to control the disease.[6]

The SIRTACE study: a prospective multi-centre randomised study comparing safety and health-related quality of life (HRQoL) following SIRT and TACE

This pilot randomised-controlled trial is the first to compare selective internal radiation therapy (SIRT) with transarterial chemoembolisation (TACE) for unresectable HCC:[7]

- 28 patients were randomised to receive either SIRT (13) or TACE (15);[7]
- in the SIRT arm patients had either BCLC stage A (38.5%), BCLC stage B (38.5%) or BCLC stage C (23%) HCC at baseline and in the sorafenib arm patients had either BCLC stage A (26.7%), BCLC stage B (53.3%) or BCLC stage C HCC (20.0%);[7]
- patients received a mean of 3.4 (median 2) TACE treatments, or one SIRT treatment;[7]
- median PFS were 3.6 months (95% CI: 2.3–6.2) and 3.7 months (95% CI: 1.6–11.0) with SIRT and TACE, respectively;[7]
- partial response rates (PR) for target lesions were 13.3% for TACE and 30.8% for SIRT; disease control rates were 73.3% for TACE and 76.9% for SIRT;[7]
- six TACE and three SIRT patients were treated for progression (outside the study);[7]
- nine (69.2%) and 13 (86.7%) patients in the SIRT and TACE study arms were alive at six months, and six (46.2%) and 10 (66.7%), respectively, at 12 months;[7]
- two patients in each group were down-staged for either liver transplantation (three patients) or radiofrequency ablation (one SIRT patient);[7]
- HRQoL was measured by Functional Assement of Cancer Therapy-Hepatobiliary and data were analysed for 18 patients (eight SIRT and 10 TACE); 10 patients with missing baseline data were excluded; despite SIRT patients having significantly worse physical functioning at baseline, at week-12, neither treatment had a significantly different impact on HRQoL;[7]
- seven patients in the SIRT group and five patients in the TACE group were hospitalized with SAEs ($P = 0.445$); two in each group were treatment-related, including two cases of grade 3 infection (one SIRT and one TACE), one case of grade 3 post-TACE syndrome accompanied by a grade 4 increase in AST, and one case of grade 3 hyperbilirubinemia with SIRT; all treatment-related SAEs resolved with active management with no procedure-related deaths;[7]
- the authors conclude that both SIRT and TACE appeared to be well tolerated without deleterious effect on HRQoL. However patients receiving TACE required a significantly greater number of procedures, while repeat SIRT is rarely deemed necessary or recommended for patients with HCC. Like TACE, SIRT was effective for the local control of liver disease and may have a role in rendering unresectable patients eligible for transplantation.[7]

Retrospective study comparing SIR-Spheres Y-90 resin microspheres to TACE in HCC BCLC B/C patients

The study by Soydal *et al.* included 80 BCLC B or BCLC C patients from a single centre in Turkey who received chemoembolisation (40) or SIR-Spheres Y-90 resin microspheres (40):[9]

- both groups were similar in respect of mean age, sex, and BCLC stages. However, the difference in the rates of chronic liver disease was statistically significant, with 34 cases (85%) in the TACE group and 22 (55%) in the SIRT group ($P = 0.003$);[9]
- the number of TACE sessions (mitomycin C and lipiodol administered superselectively every six weeks until complete response) varied between one and seven (mean: 2.8 ± 1.1), radioembolisation was administered to 37 patients in a single session;[9]
- the overall mean survival of the entire patient group was 37.31 ± 3.94 months (95% CI, 30.46– 44.1 months). During the follow-up period of 53 ± 15.7 months, 22 patients died in the SIRT group and 30 patients died in the TACE group;[9]
- mean OS in the TACE group was 30.63 ± 3.68 months (95% CI, 23.42–37.84 months) *vs.* 39.24 ± 4.62 months (95% CI, 30.18–48.29 months) in the SIRT group ($P = 0.014$);[9]
- median OS in the TACE group was 32 ± 3.98 months (95% CI, 24.16–39.83 months) *vs.* 48 ± 6.65 months (95% CI, 34.95–61.04 months) in the SIRT group;[9]
- the authors conclude that although chemoembolisation and radioembolisation for BCLC Stage B-C patients have similar levels of safety and efficacy, they differ in OS. Patients undergoing radioembolisation had a longer survival rate.[9]

Retrospective study of SIR-Spheres Y-90 resin microspheres in advanced HCC with portal vein thrombosis

A retrospective analysis by Iñarrairaegui *et al.* of SIR-Spheres Y-90 resin microspheres in 25 patients with unresectable advanced HCC and either branch (19; 76%) or main (six; 24%) PVT, most of whom (92%) also had cirrhosis, revealed:[12]

- disease control of target lesions by RECIST was achieved in all evaluable patients (100% at six months), with a global response in 66.7% at two months;[12]
- median overall survival was 10 months (95% CI: 6.6–13.3 months);[12]
- normal liver function was maintained in the majority of patients, with no significant changes observed in liver-related toxicities according to CTCAE v3.0 at one, two and six months post-treatment. Grade 1/2 hyperbilirubinaemia increased from 12 of 25 patients at baseline to 14 of 24 patients at two months, with one additional patient experiencing a grade 3 elevation. There was a statistically significant but clinically irrelevant increase in total bilirubin, from a mean of 1.15 mg/dL at baseline to 1.21 mg/dL and 1.4 mg/dL at one month ($P = 0.01$) and two months ($P = 0.007$), respectively;[12]
- the investigators concluded that treatment using SIR-Spheres Y-90 resin microspheres in unresectable HCC patients with branch or main PVT was associated with minimal toxicity, a favourable median survival time and that, unlike other embolic therapies such as TACE, SIRT appears to be an effective treatment for patients who otherwise have limited treatment options and present with a poor prognosis.[12]

Asian-Pacific Studies of SIR-Spheres Y-90 resin microspheres in HCC

Phase II study of SIR-Spheres Y-90 resin microspheres in sequence with sorafenib

A prospective multicentre phase II study conducted by Chow *et al.* and the Asia-Pacific Hepatocellular Carcinoma Trials Group in Singapore, South Korea, Myanmar and Malaysia, examined the safety and tumour response of SIR-Spheres Y-90 resin microspheres in sequence with sorafenib 400 mg twice daily.[14] The results showed:

- in total, 29 patients with unresectable HCC were recruited in the study, including 11 with BCLC stage B and 18 with BCLC C, including seven patients with ECOG 1 performance status, eight with major vascular invasion and 11 with extra-hepatic spread;[14]

- overall tumour response rate was 25%, with complete response in two patients (7%) and partial response in five (18%); 45% of the BCLC B patients had an ORR, with the remainder having stable disease (55%); 12% of the BCLC C patients had an ORR, with stable disease in 53%;[14]
- median TTP was 15.2 months for BCLC B patients and 9.0 months for BCLC C patients;[14]
- median overall survival was 20.3 months for BCLC B patients and 8.6 months for BCLC C patients;[14]
- the investigators concluded that the combination of SIR-Spheres Y-90 resin microspheres and sorafenib demonstrated good efficacy especially in patients without metastatic disease and exceeded the expected response rate. The survival compared well with sorafenib alone in patients with BCLC B (14.5 months) or BCLC C (9.7 months) in an Asia-Pacific randomised trial.[14]

Prospective study of SIR-Spheres Y-90 resin microspheres in HCC, including patients with relapsed resections

A prospective study conducted by Lau *et al.* in Hong Kong using SIR-Spheres Y-90 resin microspheres in 71 patients with unresectable HCC (median tumour size 8.5 cm; range 1–22.6 cm), including 28% who had relapsed after resection, showed:[15]

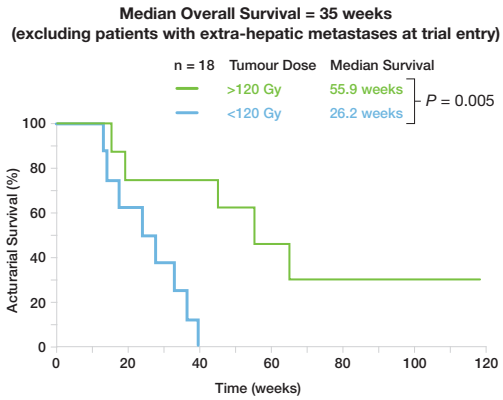
- partial response in 19 patients (27%) by CT imaging, minor response or stable disease in 46 (65%), and progressive disease in only six (8%), either due to new intra-hepatic lesions (three) or distant metastases (three);[15]
- down-staging to resection in four patients (6%), with two showing complete histological remission and confirmed CR and only occasional viable tumour cells in the necrotic centres of the other two resected tumours;[15]
- AFP dropped post-SIRT by a median of 94% (20–99+%) in all 46 patients (100%) who had an elevated AFP pre-SIRT, with a CR in 10 (22%) by normalisation of AFP levels, and a PR in 31 (67%) by >50% drop in AFP;[15]
- median overall survival of 9.4 months (1.8–46.4 months), with no significant difference in survival between the 20 patients with post-operative recurrence and 51 patients receiving SIRT first-line (8.6 *vs.* 9.4 months; $P = 0.941$);[15]
- 21% of patients received follow-up SIRT, which further extended disease control. The mean re-treatment interval was 5.2 (2.5–25.4) months;[15]
- 83% of patients had no side effects, 17% had post-embolisation symptoms and 14% had low-grade fever;[15]
- the majority of patients enjoyed a normal lifestyle with Karnofsky performance scores of 100 until very near the terminal stage of their disease;[15]
- the authors concluded that SIR-Spheres Y-90 resin microspheres are effective in selected cases of unresectable HCC, are well tolerated and can convert non-resectable tumours to resectable ones through down-staging.[15] They also noted that the rapid fall in tumour markers post-SIRT in most patients is not commonly observed with other treatment modalities, and that the median survival achieved by this group of patients was encouraging.[15]

Phase I/II dose optimisation study of SIR-Spheres Y-90 resin microspheres in HCC

A phase I/II study by Lau *et al.* of SIR-Spheres Y-90 resin microspheres in 18 patients with unresectable HCC (median tumour size 13 cm; range 4–20 cm), including some with recurrent disease (two; 11%) or cirrhosis (Child's B: two; 11%), demonstrated:[16]

- median survival of 55.9 weeks was significantly longer in those receiving an adequate tumour dose (>120 Gy), compared to 26.2 weeks in those receiving a lower dose (<120 Gy) to ≥1 tumours ($P = 0.005$);[16]
- objective response rate by CT for patients receiving a tumour dose >120 Gy was 87.5% with a further 12.5% of patients achieving static disease, equating to a disease control rate of 100%;[16]
- AFP levels dropped by >50% in all 10 patients (100%) who had an elevated AFP pre-SIRT (>300 mg/mL), and dropped by >80% in eight patients (80%);[16]
- tumour marker serum ferritin dropped by >50% in all eight patients (100%) who did not have an elevated AFP level pre-SIRT(<300 mg/mL);[16]
- the authors concluded that SIR-Spheres Y-90 resin microspheres are safe, with the treatment being well tolerated without major complications and that tumour response is dose related with a tumour recommended dose of >120 Gy.[16]

Phase I/II Study of SIR-Spheres Y-90 resin microspheres comparing dose to tumour[16]



Single centre study of SIR-Spheres Y-90 resin microspheres in unresectable hepatocellular carcinoma

The study evaluated the outcomes of 45 patients, of which 16 patients (36%) had ≥26% replacement of the liver by tumour and five patients (11%) had limited extra-hepatic disease:[19]

- ECOG performance was status zero in 30 patients (67%), one in 12 patients (27%) and two in three patients (7%);[19]
- Child-Pugh status was A in 30 patients (67%), B in 10 patients (22%), C in one patient (2%) and unknown in four patients (9%);[19]
- six patients (13%) had previously undergone a liver resection, 11 (24%) patients had previously undergone transarterial chemoembolisation or hepatic artery chemoinfusion, four patients (9%) had previously undergone ablative therapy, six patients (13%) had been previously treated with at least one line of systemic chemotherapy;[19]
- forty patients were followed-up beyond two months after initial radioembolisation therapy and underwent follow-up CT imaging from which hepatic response was assessed in accordance with RECIST criteria; complete response was observed in one patient (3%), partial response in 18 patients (45%), stable disease in 11 patients (22%), and progressive disease in 10 patients (25%);[19]
- the median survival after radioembolisation was 27.7 months and the 36-month survival was 26%. Univariate analysis identified six factors associated with overall survival: Extent of replacement of hepatic parenchyma by tumour, ECOG status, number of previous lines of chemotherapy, Child Pugh status, radiological response to treatment, and preoperative bilirubin;[19]

- a total of 13 (29%) patients developed clinical toxicity after treatment: nausea/vomiting in six patients (13%), fatigue in six patients (13%), non-specific self-limiting abdominal pain in four patients (9%), anorexia in three patients (7%), and shortness of breath in one patient (3%); the complications were minor (grade I/II) and resolved without active intervention;[19]
- the authors conclude that the study showed a high ORR (48%), with a low clinical toxicity rate (29%), and an excellent median OS at 27.7 months for patients with advanced disease.[19]

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