NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of selective internal radiation therapy for primary liver cancer

Selective internal radiation therapy using radioactive beads for primary liver cancer

Hepatocellular carcinoma is a type of primary liver cancer (a cancer that begins in the liver). Cholangiocarcinoma, or bile duct cancer, is a rare type of primary liver cancer. The bile ducts (tubes) carry bile from the liver to the small bowel. Bile helps digestion by breaking down fat in food.

Selective internal radiation therapy (known as SIRT) aims to kill cancer cells, causing as little damage to the surrounding tissues as possible. Tiny radioactive 'beads' are injected into branches of the artery that supplies blood to the liver. The beads then become trapped in the small blood vessels supplying the cancer, releasing radiation directly into the cancer cells and killing them.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2012 and updated November 2012.

Procedure name

- Selective internal radiation therapy for primary liver cancer
- Selective internal radiation therapy for primary hepatocellular carcinoma
- Selective internal radiation therapy for primary intrahepatic cholangiocarcinoma

Specialist societies

- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- British Society of Interventional Radiologists
- British Association of Surgical Oncology
- Faculty of Clinical Oncology

Description

Indications and current treatment

The most common primary liver cancer is hepatocellular carcinoma (also known as hepatoma). Cholangiocarcinoma is a rare type of primary liver cancer originating in the bile ducts.

The choice of treatment for primary liver cancer depends on a number of factors, including the exact location, stage of the cancer and the patient's liver function. The aim of treatment is normally to slow progression with a view to improving quality of life and prolonging survival. In some patients surgical removal with curative intent may be possible: this may sometimes be achieved by downstaging the tumour using other treatment modalities first. Treatment options include chemotherapy (intravenous or hepatic artery infusion), surgical excision, transarterial chemo-embolisation (TACE), and radiofrequency ablation.

Intrahepatic cholangiocarcinoma is not usually diagnosed before the symptoms of biliary obstruction occur, by which time the cancer may be too advanced for curative surgical resection. Occasionally, surgical removal with curative intent may be possible: this may sometimes be achieved by downstaging the tumour using other treatment modalities first. The standard options for palliative treatment include chemotherapy, surgical bypass of the bile duct or the insertion of a stent using surgical, endoscopic or percutaneous techniques.

Selective internal radiation therapy (SIRT) (also known as radio-embolisation) through transarterial delivery of microspheres loaded with yttrium-90, (a beta radiation emitter with a physical half-life of approximately 2.5 days) can be used as palliative treatment for unresectable primary liver cancer. It may also be used as a neoadjuvant treatment before surgery in patients being considered for curative treatments such as resection or orthotopic liver transplantation. It aims to deliver radiation directly into the tumour, minimising the risk of radiation damage to healthy surrounding tissues.

What the procedure involves

Before undertaking the treatment, a nuclear medicine liver-to-lung shunt study is carried out to assess the risk of radioactive microspheres causing lung

damage. Radiographic imaging and selective coil embolisation of arteries to the stomach and duodenum are also commonly carried out.

Using local anaesthesia, radioactive glass or resin microspheres that are designed to lodge in the small arteries are injected into branches of the hepatic artery, usually by a percutaneous femoral approach.

SIRT is sometimes delivered in 2 separate treatments (a few weeks apart) if both lobes of the liver need treatment. The procedure may be repeated depending on the response achieved. Different products are available for this procedure.

Because of the radioactive nature of the treatment, patients and carers are provided with radiation protection advice.

The Administration of Radioactive Substances Advisory Committee has issued 'Notes for guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources'[1].

Patient selection

A consensus panel report from the Radioembolization Brachytherapy Oncology Consortium (REBOC)[2] makes reference to patient selection criteria for SIRT.

Clinical assessment

Child-Turcotte-Pugh assessment of liver disease

A total score of 5–6 is considered grade A (well-compensated disease), 7–9 is grade B (significant functional compromise) and 10–15 is grade C (decompensated disease).

Okuda staging system for hepatocellular carcinoma (HCC)

Includes parameters related to the liver's functional status and tumour stage:

- albumin (3 g/dl [0 points] or more, or 3 g/dl [1 point] or less)
- ascites (no [0 points]; yes [1 point])
- bilirubin(3 mg/dl [0 points] or more, or 3 mg/dl [1 point] or less)
- tumour stage (more than [1 point] or less than [0 point] 50% of liver area involved).

Okuda stage I: 0 points; Okuda stage II: 1 or 2 points; Okuda stage III: 3 or 4 points.

Barcelona Clinic Liver Cancer (BCLC) staging and treatment schedule for HCC

- Stage 0 (less than 2 cm and carcinoma in situ) suitable for curative treatments.
- Stage A with early HCC are candidates for radical therapies (resection, liver transplantation or percutaneous treatments).
- Stage B with intermediate HCC may benefit from chemo-embolisation.
- Stage C with advanced HCC may receive new agents in the setting of randomised controlled trials.
- Stage D with end-stage disease will receive symptomatic treatment.

Model for End-Stage Liver Disease (MELD) score

The MELD score calculates 3-month mortality for people with liver disease. Calculations are based on the evaluation of 3 different blood tests: international normalised ratio (INR), bilirubin and creatinine. The score ranges from 6 to 40. The higher the score, the worse off the patient is.

Outcome measures

The World Health Organization (WHO) criteria for tumour response assessment are:

- Complete response (CR): disappearance of target tumour.
- Partial response (PR): more than 50% reduction in tumour size.
- No response (NR) or stable disease (SD): less than 50% reduction in tumour size and less than 25% increase in tumour size.
- Progressive disease (PD): more than 25% increase in tumour size.

Objective response (OR) is the aggregation of complete response and partial response results.

Response Evaluation Criteria in Solid Tumors (RECIST)

- Complete response (CR): disappearance of all target lesions.
- Partial response (PR): at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
- Stable disease (SD): insufficient shrinkage to qualify for PR or insufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
- Progressive disease (PD): at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Grade 1: mild adverse event; grade 2: moderate adverse event; grade 3: severe adverse event; grade 4: life-threatening or disabling adverse event; grade 5: death related to adverse event.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to selective internal radiation therapy for primary liver cancer. Searches were conducted of the following databases, covering the period from their commencement to November 2012: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with primary liver cancer
Intervention/test	Selective internal radiation therapy
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview – hepatocellular carcinoma

This overview is based on 1382 patients from 5 non-randomised comparative studies[3-6;15], 10 case series[7-10;17-20;22-23] and 6 case reports[11-14;16;21] in patients with primary hepatocellular carcinoma.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2a) have been listed in appendix A.

Table 2a Summary of key efficacy and safety findings on SIRT for primary liver cancer - hepatocellular carcinoma

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Salem R (2011)[3] Non randomised comparative study Recruitment period: not reported; data closed on 31/12/2008 Study population: patients with unresectable HCC; 8.6% had previously been treated by RFA or resection. n = 245 (123 SIRT vs 122 TACE) Age: median 66 years(SIRT); median 61 years (TACE) Sex: 77% male Patient selection criteria: Patients with unresectable HCC and bilirubin <3.0mg/dL included. Patients who were previously treated with either Y90 or chemoembolization, exhibited portal vein thrombosis, extrahepatic metastases or lacked imaging follow-up were excluded from analysis. Technique: SIRT with glass-based Y90 microspheres (TheraSphere, MDS Nordion) undertaken following MAA scanning. Prophylactic coil embolisation was done in 33% (40/123) of the patients. Median number of treatments: 1.	Number of patients analysed: 123 vs 122 **Overall survival (uncensored)** Overall mean survival was 20.5 months (95% CI 15.7 to 29.1) in patients treated by SIRT vs 17.4 months (95% CI 13.9 to 18.7) in patients treated by TACE (p=0.23). Study reported survival was not different between groups after excluding patients that had been censored to curative therapies (data not reported). **Death** 44% (54/123) of patients treated by SIRT and 48% (59/122) of patients treated by TACE died by follow-up. **Response rate(WHO criteria)** Overall response rate: 49% (60/123) of the patients treated by and 36% (44/122) in patients treated by TACE (p=0.05). **Time to progression** Median time to progression was longer following SIRT compared against TACE (13.3 months vs 8.4 months; p=0.05). **Days in hospital** Mean cumulative days hospitalised was 0 days for patients treated by SIRT vs 3.4 days for patients treated by TACE.	Adverse events were reported at any time following treatment ; results for complications that occurred <30 days were not presented separately.	**Follow-up issues:** • Patients were followed until death or censored at last known clinic follow-up. Number of patients censored were 31 treated by SIRT and 44 treated TACE because 73 underwent transplantation and 2 underwent resection. **Study design issues:** • Data collected over a 9 year period. • Survival, time-to-response, and time to progression analyses were performed from date of first treatment and censored to curative therapy. **Study population issues:** • Patients treated by SIRT were significantly older. Majority of patients (>90%) in both groups were treatment naïve and had comparable rates of portal hypertension, ascites, cirrhosis, tumour distribution, bilirubin and cancer stage.

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Follow-up: median 23 months for patients treated by SIRT and median 33 months for patients treated by TACE. Conflict of interest/source of funding: Four authors are advisors to MDS Nordion. None of the other authors listed any conflict of interest.			

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Lewandowski RJ (2009)[4] **Non-randomised comparative study** USA Recruitment period: 2000–08 Study population: patients with unresectable HCC stage T3 (without PVT or extra-hepatic metastases). n=**86 (43 SIRT vs 43 TACE)** Age: mean 67 years Sex: 86% male Patient selection criteria: stage T3 patients treated by SIRT or TACE as bridge to transplantation. Technique: following MAA scanning, SIRT with Y90 (TheraSphere MDS Nordion). Mean 1.8 treatments and median dose 110.2 Gy administered to treatment site. All patients underwent mesenteric angiography and MAA scanning to minimise the risk of non-target embolisation. Follow-up: **SIRT: median 34 months; TACE: median 52 months** Conflict of interest/source of funding: One author is an advisor to MDS Nordion.	Number of patients analysed: **78** **Downstaging (imaging analysis)** SIRT (n=43) / TACE (n=35) From T3 to T2[a,b] (median time to downstaging: 'within 6 months'): 58% (25) / 31% (11) Transplanted: 21% (9) / 26% (11) Downstage to resection: 1 / 1 Downstage to RFA (<3cm): 42% (18) / 23% (8) [a] The trend favouring SIRT for downstaging was maintained for all lesion sizes. [b] p=0.02 **Tumour response (WHO criteria)** SIRT (n=43) % (n) / TACE (n=35) % (n) **CR**: 0 / 0 **PR**[c]: 61 (26) / 37 (13) **SD**: 37 (16) / 49 (17) **PD**: 2(1) / 14 (5) [c] p=0.07; . Median time to partial response (months): 4.2 SIRT vs 10.9 TACE (p=0.03) **Time to progression** Overall 1-year progression rate: 15% SIRT vs 32% TACE (p=0.005) (defined as progression by WHO, EASL, UNOS or UNOS/new lesion). Time to overall progression: median 33.3 months for SIRT (CI 17.8 to 33.8) vs 12.8 (CI 7.9 to19.6) for TACE (p=0.005). **Survival** Event-free survival (months): 17.7 SIRT vs 7.1 TACE (p=0.002).	Death: There were no deaths reported in the SIRT group compared with 3 deaths reported in the TACE groups. Post-embolisation syndrome: -fatigue and transient nonspecific flu like symptoms: lasting 7–10 days observed in 60% of patients in the SIRT group; and -nausea, fatigue, low-grade fever : was observed in 60% of patients in the TACE group. **Abnormal liver function** Bilirubin toxicity was determined using NCI criteria. Grade 1/2 (mild/moderate adverse event) bilirubin toxicity was reported in 60% (26) of patients treated by SIRT and 60% (26) of patients treated by TACE (denominators not reported). Grade 3/4 (severe/life-threatening adverse event) bilirubin toxicity was reported in 7% (3) in the SIRT group and 26% (11) in the TACE group (denominators not reported).	**Follow-up issues:** ● 8 patients in the TACE group did not have follow-up imaging (3 patients were lost to follow, 3 died from adverse events, and 2 had an early post-TACE transplant). ● Imaging follow-up was at 1 month and subsequently at 90-day intervals. **Study design issues:** ● Treatment by SIRT or TACE was by consensus of a multidisciplinary team. The radiologist performing the baseline staging was blinded to whether patients received transplantation. ● The primary aim of the study was to compare rates of downstaging in T3 to T2 status by imaging criteria. ● Assessment of downstaging was for the entire treated lesion rather than only the enhancing portions of viable tissue. ● The study reported that follow-up for imaging was stratified by 3-month intervals to reduce 'imaging follow-up time' bias. **Study population issues:** ● Selected subset of stage T3 patients from 276 patients. Higher percentage of patients with large tumours (>8 cm) in TACE group (34%) compared with SIRT group (16%), but not significant.

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
	Overall median survival (months; uncensored): 41.6 SIRT vs 19.2 TACE (p=0.008). Median survival (months; censored): 35.7 SIRT vs 18.7 TACE (p=0.18).		

	SIRT	TACE
1 year	81%	75%
2 year	69%	42%
3 year	59%	19%

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
D'Avola D (2009)[5] Non randomised comparative studies (historical control) Spain Recruitment period: 1996-2008 Study population: patients with unresectable HCC; 94% Child-Pugh class A; 51% BCLC stage B. n = 88 (35 SIRT vs 43 control [supportive care or active therapy]) Age: 63 years Sex: 80% male Patient selection criteria: patients >18 years, preserved liver function, a platelet count >40 were included. Patients who had been treated by liver transplantation, surgical resection or percutaneous ablation; TAE or TACE for single, non bulky tumours, or with lung shunting were excluded. Technique: SIRT undertaken with Y90 (SIR-Spheres). Extrahepatic collateral vessels embolised. Median activity was 2.0 GBq. Follow-up: unclear Conflict of interest/source of funding: One of the authors received lecture fees from Sirtex Medical Europe GmBH. The work was funded in part by Accion Transversal contra el	Number of patients analysed: 35 vs 43 **Survival (actuarial)** Median (95% CI) survival from diagnosis was significantly longer in patients treated by SIRT 16.0 months (7.77 to 24.4) compared against the control group , 8.0 months (95% CI 5.5 to 10.4 months) ; p<0.001 (adjusted for cirrhosis, multinodular disease, bilobar involvement or vascular invasion). The difference in survival between patients in the control group (receiving active treatment or best supportive care) was not significant. Difference in survival was also observed when patients who received sorafenib were censored. Multivariate analysis showed treatment with Y90 was independently associated with a better survival (OR 3.5 (95% CI 1.9 to 6.5); p<0.05) **Deaths:** 64% (56/88) patients had died at time analysis (no further details). **Further treatment** 20% (7/35) patients received second-line treatment after SIRT • 8.5% (3/35) patients with SD had a second course of SIRT. • 17% (6/35; 3 with SD; 3 with PD) were treated by sorafenib for a mean period 3.4 months (2 to 12 months after SIRT).	No complications reported.	**Follow-up issues:** • **3 patients lost to follow-up (reasons unclear).** **Study design issues:** • Retrospective evaluation • Survival was calculated using actuarial method**.** **Study population issues:** • There was no statistically significant difference in demographics, clinical, laboratory or radiological variables. Time from diagnosis to treatment was not significantly different between the 2 groups • Patients included in control group were those who were either diagnosed before March 2004 or had technical contraindications to SIRT. These patients received either supportive care only (32%) or standard therapy (typically systemic or iv therapies)

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Cancer from Instituto de Salud Carlos III.			

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Steel J (2004)[6] **Non-randomised comparative study** USA Recruitment period: not reported Study population: patients with 79% stage III–IV HCC (unclear what scale) n=**28 (14 Y90 vs 14 HAI with cisplatin)** Age: 59 years Sex: 71% male Patient selection criteria: patients over 18 years of age with biopsy-proven diagnosis of HCC included. Patients with poor physical and mental health were excluded. Technique: treatment with HAI of glass microspheres (TheraSphere, Nordion) described as 'embolisation of 90-yttrium glass microspheres into the hepatic artery' (administered 1–2 times over a 6-month period). HAI cisplatin administered 3–4 times over a 6-month period. Follow-up: **6 months** Conflict of interest/source of funding: supported by a grant from the American Cancer Society	Number of patients analysed: **28 (15 vs 13**) [as reported] **Overall HRQoL** **Y90** / **Cisplatin** **Baseline**: 77.2 (17.4) (n=15) / 88.3 (6.8) (n=13) **3 months**[a]: 74.5 (18.6) (n=15) / 76.0 (6.2) (n=13) **6 months**: 47.3 (23.8) (n=9) / 52.0 (17.1) (n=5) Data reported as mean (SD). [a]p<0.001 **HRQoL subscales**- at 3 month follow-up physical well-being[a]: Y90 (n=15) 20.0(5.5); Cisplatin (n=13) 19.0(3.3) social and family well-being[b]: 22.3(2.4); 21.7(3.5) functional well-being[a]: 17.0(5.3); 14.6(3.7) [a]difference was statistically significant (p<0.05); [b]p<0.01 At 6-month follow-up the overall HRQoL was not significantly different, but significantly higher functional well-being scores were reported in the Y90 group (p<0.04). **Survival** Survival was 'similar' for patients treated by Y90 compared with patients treated with Cisplatin at 6-month follow-up (actual numbers not reported).	Study did not report on safety outcomes.	**Follow-up issues:** • 5 patients in the Y90 and 9 patients in the cisplatin group were lost to follow-up at 6 months (reasons not reported). **Study design issues:** • Single-centre study. Methods used to recruit patients not described. • HRQoL assessed with FACT-Hep (combination of FACT-General and hepatobiliary module FACT-G, a 27-item questionnaire including physical, social, family, emotional and functional well-being). The hepatobiliary module is an 18-item questionnaire on the symptoms of the disease and side effects of the treatment. FACT items are rated on 5-point scales (0=not at all to 4=very much) with higher scores indicating better quality of life or fewer symptoms. • Study reported that patients receiving microspheres were likely to be at 2 months post-treatment, and those receiving cisplatin were likely to be 2–4 weeks post-treatment when HRQoL assessments were administered. **Study population issues:** • Study reported 'significantly higher' functional and overall HRQoL scores at baseline in the cisplatin group (p value not

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Study details	Key efficacy findings	Key safety findings	Comments
			reported). **Other issues:** • Inconsistency in the reported number of patients in both groups at baseline and number of patients included in analysis.

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Sangro B (2011)[7] Case series European centres Recruitment period: 2003-09 Study population: patients with unresectable HCC. n = 325 Age: mean 65 years Sex: 82% males Patient selection criteria: Patients were excluded from treatment if pre-treatment workup showed that hepato-pulmonary shunt was >20% and if embolisation of microspheres into the GI tract could not be prevented. Technique: radioembolisation was performed using 90Y-resin microspheres. Median activity was 1.6 GBq and 93% received a single administration of the microspheres. Follow-up: median 10 months Conflict of interest/source of funding: not reported.	Number of patients analysed: 325 Overall survival The median overall survival was 12.8 months (95% CI 10.9 to 15.7). Survival by BCLC staging: Staging (n) / Months (95% CI); BCLC disease stage A (n=52) / 24.4 (18.6 to 38.1) (p<0.001) BCLC disease stage B (n=87) / 16.9(12.8 to 22.8) BCLC disease stage C (n=183) / 10.0 (7.7 to 10.9) BCLC disease stage C (n=3) / 5.2 (2.2 to NR) Survival also varied significantly by: ECOG performance status, hepatic function, tumour burden, and presence of extrahepatic disease. Death (at follow-up): 61.8% (201/325) Further treatment/ bridge to transplantation: • liver transplantation (n=5) • resection (n=3) • percutaneous ablation (n=3)	Procedure-related clinical adverse events[a]: Complications[b] / %(n) Fatigue (occurring in first few weeks after procedure and lasting 1-2 weeks) / 54.5 (177) Nausea and/or vomiting / 32.0(104) Abdominal pain / 27.1(88) Fever / 12.3(40) GI ulceration (cause of death in 1 patient) / 3.7(12) [a]evaluated from day 1 to 7; radiation-related events (long-term fatigue, GI ulceration and pneumonitis) evaluated from day 8 to 3 months. [b]all events were usually mild to severe (grades 1 to 3); treated with medication if necessary and subsided in less than 48 hours. In 1	**Study design issues:** • Retrospective analysis of consecutive patients. 109 patients were followed up prospectively. • All adverse events were graded using CTCAE and analysis of clinical and laboratory adverse events was performed up to 90 days. **Study population issues:** • 56.3% of patients were classified as BCLC stage C (advanced); good ECOG (stage 0-1) status 87.7% of patients **Other issues:** • Procedure-related laboratory adverse events (total bilirubin, albumin, ALT, INR, creatinine and platelets) were evaluated at 3 months after the procedure and are therefore not reported in the safety column.

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
		patient with GI ulceration, severity was rated as grade 5 (patient died at 3 months).	

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details

Salem R (2010)[8]

Case series

USA

Recruitment period: 2004–08

Study population: patients with HCC; 87% treatment-naive; 52% uni-lobar disease; 33% UNOS T4b; 52% BCLC stage C.

n=291 (526 treatments)

Age: median 65 years

Sex: 77% male

Patient selection criteria: patients with confirmed diagnosis of HCC (biopsy or imaging). Patients with PVT and/or limited extra-hepatic metastases were also included.

Technique: following MAA scanning, treatment with glass microspheres (TheraSphere). The target dose was 100–120 Gy. Pretreatment angiography and scanning were performed to assess gastrointestinal flow and lung shunting. 37% of patients needed coil embolisation of extra-hepatic vessels before treatment.

Follow-up: median 31 months

Conflict of interest/source of funding: not reported

Key efficacy findings

Number of patients analysed: 291

Median (months) survival (95% CI)

BCLC stage; n	Patients without extra-hepatic metastases (n=245)	Patients with extra-hepatic metastases (n=46)
A	26.9 (17 to 30.2)	-
B	17.2(13.4 to 29.6)	-
C	7.3 (6.5 to 10.1)	5.4 (2.7 to 7.5)
D	2.5 (1 to 3.7)	2.3 (CI 'not calculable')

Downstaging – curative intent

12% (34/291) underwent treatment with curative intent.

32 had transplants and 2 had resections.

Achievement of partial response (WHO criteria)

BCLC stage	Patients without extra-hepatic metastases % (n)	Patients with extra-hepatic metastases % (n)
A	46 (21)	-
B	51 (42)	-
C	40 (40)	28 (11)
D	0	0

Time to partial response: 6.6 months (WHO criteria)

Median time to progression (months) (95% CI)

BCLC stage	Patients without extra-hepatic metastases (n=232)	Patients with extra-hepatic metastases (n=41)
A	25.1 (8 to 27)	-
B	13.3(4.4 to 18.1)	-
C	6. (4.6 to 8.8)	3.1 (1.2 to 5.1)

Key safety findings

Death

Death (30 days) was reported in 3% (9/291) of patients.

63% (183/291) patients died (62% [114] with disease progression and 38% [69] with stable disease) at the end of the study.

Other complications (assessed using NCI criteria)

Clinical toxicities (grade 1/2: mild/moderate adverse event)	% (n)
Fatigue	57 (167)
Abdominal pain	23 (67)
Nausea/vomiting	20 (57)
Anorexia	15 (45)
Diarrhoea	2 (7)
Fever/chills	3 (10)
Weight loss	1 (4)
Abnormal liver function grade 3/4 (severe/life-threatening adverse event)	
bilirubin toxicities	19 (54)
aspartate aminotransferase	19 (55)

Comments

There may be some overlap of patients with the Lewandowski (2009)[1] study

Follow-up issues:

- 94% (n=273) had imaging follow-up.

Study design issues:

- Prospective single-centre study.
- Lack of control group.
- Outcomes stratified by: Child-Pugh, UNOS, and BCLC staging systems and reported separately for patients with and without extra-hepatic metastases.
- Partial response reported for both WHO and EASL criteria.
- Imaging endpoints and toxicities (recorded at any time during follow-up) censored to curative therapies (transplantation or resection).

Study population issues:

- Authors noted patient sample is 'confounded' by inclusion of patients with PVT, advanced disease and metastases.

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments

D	2.1 (upper CI 2.3)	0.6 (CI 'not calculable')

Time to progression (n=273): 7.9 months (95% CI 6 to 10.3)

albumin	18 (53)
alanine aminotranferase	5 (14)
alkaline phosphatase	4 (11)

No gastric ulcers were observed.

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details

Geschwind JFH (2004)[9]

Case series

USA and Canada (4 centres)

Recruitment period: 1992–96, 2000–02

Study population: patients with unresectable HCC.44% had bi-lobar disease and 68% were Okuda stage I.

n=**80**

Age: 50% > 65 years

Sex: 73% male

Patient selection criteria: patients with concurrent malignancy and HCC of infiltrative type. Prior intra-arterial liver-directed, or external beam radiation, Patients with uncorrectable flow to GI tract on angiography or MAA scanning were excluded.

Technique: treatment with glass microspheres (TheraSphere). Median dose ranged from 111–236 Gy. Patients with bi-lobar disease received whole-liver treatment (in 1 centre). Lobe with dominant tumour burden was treated in the remaining patients.

Follow-up: **3 months for adverse events**

Conflict of interest/source of funding: supported in part by MDS Nordion.

Key efficacy findings

Number of patients analysed: **80**

Survival

Outcome	n	Median follow-up (days)
Death	48	326
Alive (without alternative intervention)	15	727
Transplantation	4	727

1-year survival rates were 63% for Okuda stage I patients and 51% for Okuda stage II patients (p=0.02).

Key safety findings

Complications	Number of events
Hepatic	
Bilirubin toxicity[a]	13
Ascites	6
Encephalopathy (33 days after procedure)	1 (treated by lactulose)
Liver failure (91 days after last treatment)[b]	1 (patient died)
GI	
Gastric/duodenal ulcer	3
Nausea	2
Cholecystitis[a]	2 (needed emergency cholecystectomy 21 and 243 days after treatment)
Circulatory	
Oedema[a] (168 days after treatment)	1 (treated by diuretics)
Hypotension	1
Hypertension	1
Pulmonary	
Pleural effusion	1
Aspiration pneumonia[c] (0 days from treatment)	1 (patient hospitalised, condition resolved, no further details)
Other (1 each: allergic reaction, hyponatremia, fatigue, malaise, fall)	5

[a] possibly related to treatment. [b] probably related to treatment. [c] definitely related to treatment.

Comments

Follow-up issues:

- After initial treatment with Y90, 9 patients received TACE/TAE with Y90 because of excessive lung shunting (n=5) or because it was more appropriate (n=4). 4 patients received chemotherapy.

Study design issues:

- Adverse event grading based on the Southwest Oncology Group grading criteria of at least grade 3 (severe) to grade 5 (fatal). Data collected from first treatment until disease progression, without any further treatment planned.
- Survival data were from first treatment until death (censored if patient received an alternative treatment or patient alive by November 2003).

Study population issues:

- Patients selected from a database of 180 patients.

Other issues:

- Study includes data from Dancey (2000) (included in appendix A).

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Kulik LM (2006)[10] Case series USA Recruitment period: 2001–05 Study population: patients with stage T3 (UNOS) unresectable HCC. n=35 Age: 51% <69 years Sex: 86% male Patient selection criteria: patients at stage T3 were selected from 150 patients with unresectable HCC who were treated by Y90 microspheres. Technique: following coil embolisation and MAA scanning, treated by glass/resin microspheres (TheraSphere, MDS Nordion). The mean number of treatments per patient was 1.6 and the mean dose administered was 511 Gy. Follow-up: imaging follow-up at 1 month, followed by every 90 days subsequently. Clinical follow-up 2 weeks after treatment and bi-monthly subsequently. Conflict of interest/source of funding: one author is a consultant and another is an employee of MDS Nordion. Sponsored by MDS Nordion.	Number of patients analysed: 34 **Survival** Median survival: 800 days 1 year: 84% 2 years: 54% 3 years: 27% **Disease progression** 3 patients progressed (to T4a and T4b) after treatment and 12 patients maintained T3 status (although the lesion progressed in 1 patient). 17/34 patients had a 50% partial response rate (>50% imaging response by WHO criteria). Median time to partial response was 75 days. **Downstaging – T3 to T2** 56% (19/34) patients were successfully downstaged. Downstaging/bridging – to transplantation 8 patients had transplants (timing ranged from 12 days to 210 months after treatment). **Downstaging – to RFA** Downstaging to RFA (3 cm lesion or less) was successful in 32% (11/34) patients ('none of the patients opted for completion RFA'). **Resection** Following initial treatment with SIRT, 1 patient underwent right hepatectomy 40 days after treatment (instead of completion treatment with SIRT).	**Complications** (n) Bilirubin toxicity (grade 3): 1 Fatigue and transient flu-like symptoms (lasting 7–10 days): NR Infected right groin (following placement of an arterial closure device requiring surgical repair): 1 No cases of GI ulceration or radiation pneumonitis observed. None of the patients experienced significant post-embolisation syndrome, fever, epigastric pain, nausea, vomiting or evidence of radiation-induced liver disease reported.	**Follow-up issues:** • **1 patient excluded from the response and downstaging analysis (transplanted 12 days after treatment).** **Study design issues:** • Retrospective evaluation. • Two-centre study. • Patients were treated with the specific intent to downstage to liver transplantation, surgical resection or RFA. **Study population issues:** • Highly selected subset from 150 patients with smaller tumours detected at an earlier stage.

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Leung TWT (1995)[11] Leong QM (2009)[12] Minocha (2011)[13] Ng (2008)[14] Kooby (2010)[15] Aloia (2009)[16] Popperl (2005)[17] **Reports of 'radiation-induced' safety events (from non-randomised comparative study, case series and case reports)** Hong Kong, USA, Singapore, Germany Conflict of interest/source of funding: Leong (2009) and Kooby (2010) studies reported that none of the authors had identified a conflict of interest.	**Radiation pneumonitis** **Leung (1995):** case report of 5 patients (4 inoperable HCC, 1 colorectal liver cancer) who developed radiation pneumonitis in a series of 80 patients. None of the patients had extra-hepatic disease. Intervention: Y90 microspheres (dose ranging from 4 to 5 GBq) following scan to determine lung shunt. Lung shunting ranged from 15.9 to 45.6%. Outcome: patients developed symptoms of dry cough and progressive exertional dyspnoea without a fever (median 3 months). The 4 patients with HCC (who had achieved partial response [n=3] or static disease [n=1]) developed radiation pneumonitis (confirmed histopathologically) 1 to 6 months after treated with SIRT (all patients were treated with prednisone 20 mg/day continuously, with symptom improvement reported in 1 patient). Severe fibrosis was observed on CT in 1 patient (between 7 and 11 months after SIRT). Three patients died of progressive respiratory failure and 1 from progressive cancer. **Radiation dermatitis** **Leong (2009):** case report of a 52-year-old man with inoperable HCC who developed new tumours. Intervention: SIRT with a 1.3 GBq dose of resin microspheres (SIR-Spheres, Sirtex Medical) delivered via a microcatheter advance into the right hepatic artery. MAA scanning showed 8% hepatopulmonary shunting. Outcome: patient reported minor epigastric discomfort and a purpuric rash appeared (on the following day) between the xiphoid process and the umbilicus. Radiation dermatitis (caused by shunting of microspheres to the anterior abdominal wall via a patent falciform artery) was confirmed by a scan. Skin lesions regressed (patient recovered by 5 weeks). **Radiation-induced biliary stricture** **Minocha (2011):** case report of a 73-year-old man with HCC with a 3 cm HCC. Intervention: 5 GBq vial of glass microspheres. Outcome: there were no immediate complications following the procedure. At 1-month follow-up patient reported mild fatigue and anorexia. Patient became progressively jaundiced and fatigued with grade 3 and grade 4 bilirubin toxicity (NCI criteria). An ischaemic stricture in the bile duct was treated by balloon dilatation and biliary stent, and the patient's symptoms returned to baseline. **Ng (2008):** case report of a 68-year-old man with inoperable recurrent HCC. Intervention: 1 treatment of 1.5 GBq of Y90 microspheres. Outcome: patient presented with jaundice (treated by percutaneous trans-hepatic biliary drainage) and epigastric discomfort (4 months after treatment). Severe cholestasis, cholangitis and fibrosis (confirmed with liver biopsy) were present, consistent with radiation-induced bile duct damage. Patient died of sepsis from recurrent attacks of cholangitis (unsuccessfully treated by antibiotics and percutaneous trans-hepatic biliary drainage) at 8 months.		

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
	Radiation gastritis **Kooby (2010):** Non-randomised comparative study (historical control) of 71 patients (27 SIRT vs 44 chemoembolisation) who underwent SIRT of chemoembolization as their only form of therapy. Patients with pulmonary shunt fraction >20% were excluded. 83% were male and the mean age was 60 years. The number of patients with any complication was significantly lower for patients receiving SIRT compared to TACE (44% vs 70%; p=0.05) Ulceration caused by radiation was reported in 11% (3/27) of patients treated by SIRT and gastritis and/or temporary ulceration was reported in 20% (9/44) of patients treated by chemo-embolisation . Two of these patients in the SIRT group were treated by subtotal gastrectomy; there were no further details on the other patient. Gastritis with no evidence of spheres was found in a patient treated by SIRT. **Aloia (2009):** Case report of a 64-year-old woman with early-stage HCC (UNOS T2). Intervention: following albumin study confirming absence of hepatopulmonary shunts, treated by Y90 microsphere embolisation (no further details). Outcome: patient experienced nausea, vomiting and weight loss (4 weeks after the procedure). Upper endoscopy with biopsy revealed antral gastritis and embolic microspheres in the gastric antrum. Patient subsequently underwent OLT and explant showed an extensive but incomplete tumour necrosis and radiation-induced chronic cholecystitis. Patient experienced an acute complete gastric outlet obstruction (requiring an open gastrojejunostomy bypass) 8 months after the transplant. **Radiation pancreatitis** **Popperl (2005):** Case series of 23 patients (2 with non-resectable HCC) who had undergone systemic chemotherapy. 57% were male, and the mean age was 56 years. Exclusion criteria included patients with extrahepatic manifestations, liver or lung shunting >20%. Intervention: SIRT with resin microspheres (SIR-Spheres), at a mean activity of 2270 MBq, following MAA scanning. To avoid extra-hepatic deposition the gastroduodenal artery, right gastric artery or pancreaticoduodenal branches were coiled before treatment. Outcome: transient increase in pancreatic enzymes was reported in 22% (5/23) of patients and 1 patient subsequently developed mild pancreatitis (unclear if this was in a patient with HCC).		

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Garin (2010)[18] Kim (2010)[19] McCann (2010)[20] **Case series** Reporting on safety event-radiation exposure to staff Conflict of interest/source of funding: Kim (2010) study was supported by a Phase IV study sponsored by Hoin Medibiz Co. McCann (2012) study reported none of the authors have identified a conflict of interest.	**Garin (2010):** A retrospective analysis of 15 patients (13 with HCC). The mean age was 65 years and 80% were male. Radiation exposure to the operators at the thorax and the fingers was measured. Treatment was contraindicated if extrahepatic uptake of MAA occurred other than into the lungs (<30Gy) or the gallbladder. Intervention: following coiling of collateral gastrointestinal vessels and MAA scan, treatment using glass microspheres, (TheraSphere) at an average dose of 3.18 GBq. 3 HCC patients also received sorafenib. Outcome: Radiation exposure monitoring was available for 11 injections at a mean dose of 3.8 GBq. The average radiation exposure to the nuclear medicine physician carrying out the injections was 64 uSv to the fingers and 8 uSv to the thorax. The radiation exposure to the thorax of the interventional radiologist was 15.9 uSV for the first angiography and 7.9 uSV for the second angiography. **Kim (2010):** A case series of 18 patients (mean age 67 years, 89% male) with unresectable HCC. Study measured the radiation exposure emitting from the patients after treatment. Patients with liver to lung shunt >20% were excluded. Intervention: following MAA scanning, resin microspheres (SIR-Sphere, SIRTex) at mean activity 1.2 GBq. Outcome: the measured ambient radiation exposure rate was 2.31–185 uSv, which was higher than the 'theoretical' range (0.8 to 10). The study noted that this was less than the upper limit (1 mSv) at which a patient can be released without a written instruction from confinement. **McCann (2012):** A case series of 86 patients (25 treatments administered in patients with HCC) aiming to estimate the possible radiation dose to other people in different clinical scenarios. The majority of patients had a lung shunt fraction <10%. Intervention: treatment by resin (n=6; SIR-Spheres, Sirtex) and glass (n=19; TheraSphere, Nordion) microspheres. Mean administered activity was 0.71 GBq (resin) and 2.75GBq (glass). Outcome: in 16% (3/19) of HCC patients treated by glass microspheres, the recommendation threshold (1mSv) was exceeded for contact with 'significant caregiver' (2.2 uSv/h).		

Abbreviations used: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; EASL, European Association for the Study of the Liver; GBq, gigabecquerel (SI unit of radioactivity); GI, gastrointestinal; Gy, Gray (SI unit of absorbed dose); HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; HRQol, health-related quality of life; INR, international normalised ratio; MAA, ^{99}Tc-macroaggregated albumin; MBq, megabecquerel (SI unit of radioactivity); NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; OLT, orthotopic liver transplantation; PD, progressive disease; PR, partial response; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; SD, stable disease; TACE, trans-arterial chemo-embolisation; TAE, trans-arterial embolisation; UNOS, United Network for Organ Sharing; uSv, microsievert (radiation dose for biological tissue); WHO, World Health Organization; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Yang C-W (2010)[21] Carr BI (2004)[22] Mantravadi RVP(1982)[23] **Case series and report of haematological complications** Taiwan, USA Conflict of interest/source of funding: not reported	**Yang (2010)** Case report of a 67-year-old man with advanced-stage HCC. Intervention: following coil embolisation of collateral arteries supplying the gastroduodenal region and MAA scanning (lung shunting ratio 2%), 1 GBq of resin microspheres (SIR-Spheres) was delivered into the left hepatic artery and 2 GBq of microspheres were infused into the right hepatic artery. Outcome: patient complained of prolonged bleeding and experienced dyspnoea upon exertion (at 1 month after procedure). Patient displayed bone marrow suppression resulting in transient thrombocytopenia. The platelet count decreased from 174x10^3/microlitres (before treatment) to 4x10^3/microlitres at 30 days, and increased to 120x10^3/microlitres at 27 weeks after the procedure. **Carr (2004)** Case series: 65 patients with biopsy-proven unresectable HCC; median age 69 years; 72% male. Intervention: median dose of 134 Gy of glass microspheres (TheraSphere) delivered into the hepatic artery. 46 patients had 1 cycle of treatment. Median time between repeat treatments was 90 days. Outcome: more than a 75% lymphocyte decrease in 33% (n=19) of patients, a 50–75% decrease in 49.1% (n=28) of patients, a 25–50% decrease in 10.5% (n=6) of patients, and less than a 25% decrease in 7.1% (n=4) of patients (denominator not reported). Lymphopenia lasted longer than 12 months and no clinical consequences of prolonged lymphopenia were reported (the condition reversed in 2 transplanted patients). Minimal decreases in platelet and absolute granulocyte counts were observed. **Mantravadi (1982)** Case series: 15 patients (1 primary HCC; chemotherapy naive) Intervention: resin Y90 microspheres Outcome: pancytopenia was reported in 1 patient (unclear if this is the patient with primary HCC).		

List of studies included in the overview – cholangiocarcinoma

This overview is based on 192 patients from 6 case series[24-28;30], and 1 case report[29] in patients with cholangiocarcinoma. Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2b) have been listed in appendix A.

Table 2b Summary of key efficacy and safety findings on SIRT for primary liver cancer - cholangiocarcinoma

Abbreviations used: CCA, cholangiocarcinoma; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperation Oncology Group; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GBq, gigabecquerel (SI unit of radioactivity) Gy, Gray (SI unit of absorbed dose); MBq, megabecquerel; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SIRT, selective internal radiation therapy; Y90, yttrium-90.

Study details

Ibrahim SM (2008)[24]

Case series (prospective)

USA

Recruitment period: not reported

Study population: patients with unresectable ICC; 67% with liver-only disease and 33% with extra-hepatic metastases. 71% of patients were chemotherapy-naive, 67% had bi-lobar disease and 62% had no PVT.

n=**24 (48 treatments administered)**

Age: median 68 years

Sex: 67% male

Patient selection criteria: patients with histologically proven diagnosis of ICC, adequate haematology and liver function were included. Patients with non-correctable flow to GI tract or lung shunt exceeding 30 Gy (in single administration) or 50 Gy (multiple administration) were excluded.

Technique: following coil embolisation and MAA scanning, SIRT with glass resin microspheres (TheraSphere, MDS Nordion) administered in a lobar or segmental fashion. The median radiation dose was 105.1 Gy and patients received 1 treatment (n=9), 2 treatments (n=9) or ≥3 treatments (n=2). Patients with bi-lobar disease were treated 30–60 days after the first treatment.

Follow-up: **median 18 months**

Conflict of interest/source of funding: one author is an advisor and three authors received research support from MDS Nordion.

Key efficacy findings

Number of patients analysed: **24**

Survival

Median overall survival for the 24 patients was 14.9 months.

Survival: ECOG status

ECOG status	n	Months
0	10	31.8
1	12	6.1
2	2	1

P<0.0001(not specified which comparison this refers to)

The median survival times for patients with previous exposure to systemic chemotherapy (n=7) and chemotherapy-naive patients (n=17) were 4.4 and 31.8 months respectively (p=0.03).

There was no significant difference in survival for patients with or without extra-hepatic disease, or solitary lesion vs multifocal disease.

Tumour response

Tumour response (WHO criteria)	n=22 % (n)
Partial response	27 (6)
Stable disease	68 (15)
Disease progression	5 (1)

Downstaging

1 patient was downstaged to resection after treatment (no further details).

1 patient was bridged to orthotopic liver transplantation (no further details).

Key safety findings

Death

Death (30 days) was reported in 2 patients (ECOG status 2). 1 patient was hospitalised for pulmonary embolus and the other patient had a tumour burden >50%.

54% died (timing unclear).

Other complications	% (n)
Albumin toxicity (grade 3)	17 (4)
Bilirubin toxicity (grade 3)	4 (1)
Fatigue	75 (18)
Abdominal pain (transient)	38 (9)
Vomiting	13 (3)
Anorexia	8 (2)
Nausea	4 (1)
Gastroduodenal ulcer (because of inadvertent delivery of microsphere into a collateral vessel)	4 (1) (refractory to medical management and patient needed antrectomy and gastrojejunostomy)
Ascites[a]	14 (3)
Pleural effusion[a] (no further details)	9 (2)

[a]Data available in 22 patients.

Comments

Follow-up issues:

- Patients were evaluated at 1 month, 3 months and every subsequent 3 months.

Study design issues:

- Single centre study.
- Method of patient recruitment not reported.

Abbreviations used: CCA, cholangiocarcinoma; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperation Oncology Group; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GBq, gigabecquerel (SI unit of radioactivity) Gy, Gray (SI unit of absorbed dose); MBq, megabecquerel; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SIRT, selective internal radiation therapy; Y90, yttrium-90.

Study details

Saxena A (2009)[25]

Case series (prospective)

Australia

Recruitment period: 2004–09

Study population: patients with unresectable ICC. Extra-hepatic metastases were present in 48% of patients, and 80% had bi-lobar disease. 24% had received no prior treatment.

n=**25**

Age: mean 57 years

Sex: 52% male

Patient selection criteria: patients aged 18–85 with unresectable ICC and ECOG status of 0–2 with adequate haematology, renal and hepatic function included.

Technique: following prophylactic embolisation and MAA scanning, SIRT with resin microspheres (SIR-spheres) was injected through a temporary hepatic artery catheter percutaneously via the femoral or brachial artery. Treatment for bi-lobar liver disease was done in the same procedure. Mean dose was 1.76 GBq. 28% of patients underwent treatment with systemic chemotherapy after SIRT. Temporary balloon occlusion was done whenever possible if arteriovenous lung shunting >20%.

Follow-up: **median 8 months.**

Conflict of interest/source of funding: Not reported

Key efficacy findings

Number of patients analysed: **25**

Survival

Median survival after first treatment: 9.3 months

Time	%
6 months	56%
1 year	40%
2 years	27%
3 years	13%

Median survival was significantly longer in patients with ECOG performance status 0 (18.3 months; n=15) compared with patients with ECOG performance status 1 or 2 (2.4 months; n=10) (p<0.001).

There was no significant difference for survival in patients with prior systemic chemotherapy vs chemotherapy naïve, with or without extra-hepatic metastasis, bilobar vs lobar tumour distribution, by percentage of tumour burden, sex or age.

Tumour response (n=23)

Tumour response- RECIST criteria	% (n)
Partial response	24 (6)
Stable disease	48 (11)
Progressive disease	20 (5)

Downstaging

1 patient who had a partial response to treatment was downstaged to resection after treatment.

Key safety findings

Death (30 days): 2 patients (ECOG status 2) died. 1 patient died from hypercalcaemia (11 days after treatment) and another patient died from progressive hepatic and extra-hepatic disease (28 days after treatment).

Death (last follow-up): **72% (18/25)**

	% (n)
Biochemical toxicities (grade 3)	
Albumin	8 (2)
Bilirubin	8 (2)
Alkaline phosphatase	4 (1)
Clinical toxicities:	
Fatigue	64 (16)
Abdominal pain (self-limiting)	40 (10)
Nausea	16 (4)
Anorexia	16 (4)
Vomiting	8 (2)
Shortness of breath	8 (2)
Duodenal ulcer (because of malperfusion of microspheres) no further details	4 (1) (self-limiting)
Ascites*	16 (4)
Pleural effusion (no further details)*	8 (2)
Pulmonary embolus*	4 (1)

*data available for 23 patients

No other serologic toxicities were observed.

Comments

Follow-up issues:

- 92% (23/25) patients followed up beyond 1 month after initial treatment (tumour response).
- Follow-up at 1 month and then at 3-month intervals until death.

Study design issues:

- Single-centre study.

Abbreviations used: CCA, cholangiocarcinoma; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperation Oncology Group; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GBq, gigabecquerel (SI unit of radioactivity) Gy, Gray (SI unit of absorbed dose); MBq, megabecquerel; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SIRT, selective internal radiation therapy; Y90, yttrium-90.

Study details

Rafi S (2012)[26]

Case series

USA

Recruitment period: 2002-10

Study population: patients with unresectable standard-chemorefractory ICC. From diagnosis of ICC to first treatment was 9.9 months.4% had been previously treated by TACE.

n = 19

Age: mean 63 years

Sex: 37% male

Patient selection criteria: patients with histologically proven diagnosis of ICC unsuitable for resection or transplantation, progressive disease while receiving standard systemic chemotherapy, ECOG status of 0,1, or 2, adequate haematology, renal and hepatic function, with pulmonary shunt fraction <20% were included.

Technique: SIRT undertaken using Y90 resin-based (SIRT-Spheres, Sirtex Medical) microspheres. Mean number of treatments 1.6

Follow-up: median 15 months

Conflict of interest/source of funding: The authors declared that they have no conflict of interest.

Key efficacy findings

Number of patients analysed: 19

Overall survival (median (95% CI)):

From diagnosis: 25.1 months (12.5 to 37.7)

From first treatment: 11.5 months (3.2 to 19.8)

Univariate analysis of factors affecting overall survival showed prior treatment with TACE was a significant predictor (median 22.1 months (95% CI 5.1 to 39.1; n=4).

Tumour response (RECIST criteria; assessed at 3 months)

	%(n)
CR	0(0)
PR	11(2)
SD	68(13)
PD	21(4)

Median time to tumour progression: 4.8 months.

Key safety findings

Treatment-related toxicity within 30 days of the first Y90 treatment

	%(n)
Any complications	89 (17)
Major complications (grade 3-5)	2(11)
Grade 1[a]	53(10)
Grade 2	26(5)
Grade 3	11(2)
Specific:	
Gastrointestinal	32(6)
Haematologic[b]	5(1)
Hepatic dysfunction	32(6)
Other	21(4)

[a] abdominal pain (n=6); fatigue (n=4) all patients observed for 2-6 hours and discharged on day of treatment.

[b] thrombocytopenia (grade 3) developed in 1 patient

There were no deaths <30 days or serious GI complications (such as gastritis or ulceration) related to microspheres.

Comments

Follow-up issues:

- **No patients were lost to follow-up.**

Study design issues:

- Survival analysis estimated by the Kaplan-Meier method.
- Adverse events assessed according to CTCAE criteria**.**

Study population issues:

- ECOG status was 0 in 5% (1) of patients, 1 in 74%(14) of patients, 2 in 21%(4) of patients.

Abbreviations used: CCA, cholangiocarcinoma; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperation Oncology Group; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GBq, gigabecquerel (SI unit of radioactivity) Gy, Gray (SI unit of absorbed dose); MBq, megabecquerel; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SIRT, selective internal radiation therapy; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Hoffmann RT (2012)[27] **Case series** Germany Recruitment period: 2007–10 Study population: patients with unresectable CCA or chemotherapy-refractory liver metastases from CCA. 79% of patients previously had chemotherapy. 515% had ECOG status 0. n=**33** Age: mean 65 years Sex: 55% male Patient selection criteria: included patients with histologically confirmed non resectable CCA or liver metastases from cholangiocellular carcinoma which have not responded to other types of treatment, with adequate biochemical and haematological functions, <20% arteriovenous shunting to the lung and no severe comorbidities. Technique: SIRT with resin microspheres (SIR-Spheres, Sirtex). The overall liver dose was 1538 mBq. Follow-up: **median 10 months** Conflict of interest/source of funding: None	Number of patients analysed: **33** **Tumour response (3 months)** **Tumour response (RECIST criteria)** / **% (n)** Complete response: 0 Partial response: 36.4 (12) Stable disease: 51.5 (17) Progressive disease: 15.2 (5) **Survival** Median overall survival since treatment was 22 months (95% CI 7.9 to 29.4) and 43.7 months since first disease-specific diagnosis. Patients with partial response (median 35.3 months) showed significant prolonged survival compared with those with stable disease (17.7 months) and progressive disease (5.7 months) (p<0.001). Median survival was significantly longer in patients with an ECOG status score of 0 (29.4 months) compared with those with an ECOG status score of 1 (10 months) or 2 (5.1 months) (p<0.001). No significant difference on median survival according to prior chemotherapy or prior surgery. A significant improvement in overall survival was observed for patients with a CA-19-9 response compared with those without a response of the serum tumour marker. **Time to progression** Median time to progression since treatment was 9.8 months (n=18). Patients with a partial response (median 31.9 months) showed significantly longer time to progression compared with those with stable disease (9.8 months) and progressive disease (2.5	**Death** 55% (18/33) of patients died (reported at the end of the study). **Complications** / **% (n)** Abdominal pain: 84.8 (28) Nausea: 60.6 (20) Vomiting: 27.3 (9) Bilirubin: 69.7 (23) No radiation-induced liver disease was observed. No 'clinical relevant acute or delayed toxicities' were noted.	**Study design issues:** • Number of patients with primary CCA not reported. • Outcomes not reported separately for patients with CCA and liver metastases. **Study population issues:** • Retrospective study. Patient selection criteria was not defined by strict inclusion criteria. **Other issues:** No patient had to abandon treatment. No reduction in the calculated radioactivity because of extensive shunting of the microspheres to the lung was observed.

Abbreviations used: CCA, cholangiocarcinoma; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperation Oncology Group; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GBq, gigabecquerel (SI unit of radioactivity) Gy, Gray (SI unit of absorbed dose); MBq, megabecquerel; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SIRT, selective internal radiation therapy; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
	months) ($p<0.001$). Patients with ECOG status score of 0 had a longer time to progression (17.5 months) compared with ECOG status score1 (6.9 months), or 2 (2.4 months). Time to progression was not significant according to previous chemotherapy , pervious surgery or CA19-9 response.		

Abbreviations used: CCA, cholangiocarcinoma; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperation Oncology Group; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GBq, gigabecquerel (SI unit of radioactivity) Gy, Gray (SI unit of absorbed dose); MBq, megabecquerel; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SIRT, selective internal radiation therapy; Y90, yttrium-90.

Study details

Jiao LR (2007)[28]

Case series

UK

Recruitment period: 2004

Study population: patients with unresectable primary or secondary liver cancer. 100% of cancers were refractory to chemotherapy. None of the patients had shunts >15%

n=**21 (3 with primary tumours: 2 with CCA and 1 with HCC)**

Age: mean 58 years

Sex: 48% male

Patient selection criteria: patients considered for enrolment following discussions at multidisciplinary team meeting.

Technique: Following coil embolisation and MAA scanning patient treated by SIRT with glass microspheres (SIR-Spheres, SIRTEX). The mean dose was 1.9 GBq, and 1 patient received 2 doses.

Follow-up: **followed up at 3 monthly basis**

Conflict of interest/source of funding: not reported

Key efficacy findings

Number of patients analysed: 15

Tumour response (confirmed with CT imaging)

Tumour response	% (n)
Partial response	13 (2)
Progressive disease	27 (4)
Stable disease	60 (9)

Key safety findings

Complications	n
Cholecystitis followed by fibrosis	1
Portal hypertension (8 weeks after treatment, confirmed with biopsy and CT scan)	1
Peptic ulceration (confirmed on endoscopy)[a]	1
Radiation hepatitis (resolved spontaneously)	2
Obstructive jaundice (2.5 months after treatment requiring stenting; occurred because of tumour invasion of the liver hilum)	1 (not considered a direct consequence of treatment)
Minor degree of nausea and abdominal pain	In 'most' patients. 1 patient needed hospital admission for analgesia
Fever ('lasting up to several weeks')	In 'majority' of patients (considered to be related to the embolic effect of the microspheres).

[a]Patient had prior embolisation of the gastroduodenal artery for upper GI bleeding

Comments

- **Follow up issues:** 23 patients underwent assessment but 2 were not considered further on account of excessive shunts.

Study design issues:

- Outcomes not reported separately for primary and secondary tumours.

Other issues:

- **Death**

Death was reported in 33% (7/21) of patients (timing unclear). Cause of death from disease progression – 1 pancreatic, 1 unknown origin and 5 colorectal primaries.

Abbreviations used: CCA, cholangiocarcinoma; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperation Oncology Group; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GBq, gigabecquerel (SI unit of radioactivity) Gy, Gray (SI unit of absorbed dose); MBq, megabecquerel; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SIRT, selective internal radiation therapy; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
		There was no significant alteration in either clinical haematology or liver function tests following treatment.	

Abbreviations used: CCA, cholangiocarcinoma; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperation Oncology Group; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GBq, gigabecquerel (SI unit of radioactivity) Gy, Gray (SI unit of absorbed dose); MBq, megabecquerel; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SIRT, selective internal radiation therapy; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Wijlemans JW (2011)[29] **Case report** Netherlands Recruitment period: not reported Study population: Case report 1: patient with a gallbladder carcinoma with infiltration into the liver parenchyma; case report 2: patient with a large ICC (stage T3) with ECOG score 1 complaining of fatigue and weight loss. n=**2** Age: case report 1: 66 year old; case report 2: 60 year old Sex: Male Patient selection criteria: case reports of patients who needed treatment of tumours originating from the biliary tree. Technique: Following embolisation of non-target vessels and MAA, scan, treatment with SIRT with Y90 microspheres Follow-up: case report 1: 9 months; case report 2: **2 years** Conflict of interest/source of funding: not reported	Number of patients analysed: **2** **Case report 1:** Intervention: 915 MBq of Y90 injected (SIR-Spheres) Outcome: No complication occurred and the patient reported no side effects (timing unclear). Progressive disease at 9 months follow-up. **Case report 2:** Intervention: Treatment was in two phases, 2 weeks apart (doses of 386 MBq and 1789 MBq). Outcome: Stable disease was reported at 1-month follow-up (RECIST/EASL criteria) and at 7-month follow-up (MRI). Fatigue was reported for 5 days. Mild jaundice was also reported (duration not given). Patient died of local progressive disease (2 years after initial treatment). [not considered to be a safety event].		**Follow up issues:** • Patient described in case report 1 was lost to follow-up (reasons not reported). **Other issues:** • Unclear if patient in case report 2 was treated by glass or resin microspheres. • In case report 2, Lung shunt was reported but dose reduction was not considered to be needed as maximum dose (600 MBq) would not be reached.

Abbreviations used: CCA, cholangiocarcinoma; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperation Oncology Group; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GBq, gigabecquerel (SI unit of radioactivity) Gy, Gray (SI unit of absorbed dose); MBq, megabecquerel; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SIRT, selective internal radiation therapy; Y90, yttrium-90.

Study details	Key efficacy findings	Key safety findings	Comments
Sulpice L (2012)[30] **Case series** France Recruitment period: 1997-2011 Study population: patients with partial hepatectomies for ICC performed with curative intent n=87 (complete tumour removal achieved in 75% of patients) Age: mean 66 years (at time of resection) Sex: 72% male Patient selection criteria: patients with hilar bile duct, periductal infiltrating type, intraductal growth type and gallbladder cholangiocarcinoma were excluded. Patients with ICC who underwent orthotopic liver transplantation were also excluded. Technique: of the 25 patients who had intrahepatic recurrence only, 14 patients underwent Y90 radiotherapy, systemic chemotherapy, repeat hepatectomy, or a combination of these three treatments. 11 patients had no treatment. For SIRT, MAA scanning was done at first stage. and treatment with Y90(TheraSphere, MDS Nordion) at second stage. Follow-up: mean 30 months. Conflict of interest/source of funding: authors declared no conflict of interest.	Number of patients analysed: 87 **Overall survival** Median survival was 33 months, with 1, 3 and 5 year actuarial survival rates of 79%, 47% and 31% respectively. **Disease-free survival** Median disease-free survival was 13 months, with 1, 3 and 5 year actuarial survival rates of 54%, 28% and 19% respectively. **Recurrence** Recurrence occurred in 54% (43/85) of patients who were still alive after the postoperative period. Median time to recurrence was 8 months (range 1 to 54). Median survival after recurrence was 13 months (range 0 to 115). Univariable analysis showed that Y90 (p=0.05) and repeat hepatectomy (p=0.003) were significantly associated with increased survival rate after recurrence. Effect of post recurrence chemotherapy was not statistically significant (p=0.35).		**Follow up issues:** • End of follow-up was set between August to November 2011 or at time of death. **Study design issues:** • Retrospective analysis

Efficacy – hepatocellular carcinoma

Overall survival

A non-randomised comparative study of 86 patients, with 43 treated by SIRT and 43 treated by TACE, reported overall median survival (uncensored) of 42 months in the SIRT group and 19 months in the TACE group (p=0.008)[4].

A case series of 325 patients reported overall median survival was 12.8 months; this varied significantly by disease stage (BCLC stage A: 24.4 months; BCLC stage B: 16.9 months, BCLC stage C: 10 months)[7].

Tumour response

The non-randomised comparative study of 86 patients, with 43 treated by SIRT and 43 treated by TACE, reported a partial response (WHO criteria) in 61% (26/43) of the patients treated by SIRT and 37% (13/35) of the patients treated by TACE (p=0.07). Median time to partial response was 4 months in the SIRT group and 11 months in the TACE group (p=0.03). Progressive disease was reported in 2% of patients in the SIRT group and 14% of patients in the TACE group (level of significance not reported)[4].

A non-randomised comparative study of 245 patients, with 123 treated by SIRT and 122 treated by TACE, reported an overall response rate (assessed using WHO criteria) in 49% (60/123) of the patients treated by SIRT (median follow-up 23 months) and 36% (44/122) in patients treated by TACE (median follow-up 33 months) (p=0.05) [3].

Time to progression

The non-randomised comparative study of 86 patients, with 43 treated by SIRT and 43 treated by TACE, reported a median time to overall progression of 33 months in the SIRT group compared with 13 months in the TACE group (level of significance not reported)[4].The non-randomised comparative study of 245 patients reported a significantly longer median time to progression of 13.3 months in patients treated by SIRT compared against 8.4 months in patients treated by TACE (p=0.05)[3].

A case series of 291 patients reported time to progression (n=273) was 8 months (95% CI 6 to 10)[8].

Downstaging (disease control)

The non-randomised comparative study of 86 patients, with 43 treated by SIRT and 43 treated by TACE, reported downstaging from stage T3 to stage T2 in 58% (25/43) of patients in the SIRT group and 31% (11/35) of patients in the TACE group; ‘median time to downstaging was within 6 months’ for both groups (p=0.02)[4].

Downstaging (curative intent)

The case series of 291 patients treated by SIRT reported that 12% (34/291) of patients underwent treatment with curative intent (32 had a transplant and 2 had resection) (median follow-up 31 months)[8].

Bridging to transplantation

A case series of 35 patients treated by SIRT reported that 8 patients were bridged to liver transplantation (timing ranged from 12 days to 210 months after treatment)[5].

Quality of life

A non-randomised comparative study of 28 patients, with 14 treated by SIRT and 14 treated by cisplatin, reported health-related quality of life measured on the FACT-Hep scale (responses were scored on a scale of 0–4; a higher score indicated better quality of life or fewer symptoms). The overall health-related quality of life score was 47 for the SIRT group (n=9) and 52 for the cisplatin group (n=5) at 6-month follow-up. This difference was reported as not significant (p value not reported)[6].

Safety – hepatocellular carcinoma

Death

Death (within 30 days) was reported in 3% (9/291) of patients in the case series of 291 patients[8] .

Gastrointestinal complications

Ulceration caused by radiation was reported in 11% (3/27) of patients treated by SIRT (after prophylactic coil embolisation of the gastroduodenal arteries) and gastritis and/or temporary ulceration was reported in 20% (9/44) of patients treated by chemo-embolisation in the non-randomised comparative study of 71 patients. Two of the patients in the SIRT group were treated by subtotal gastrectomy; there were no further details on the other patient[15].

Radiation-induced biliary stricture

Radiation-induced biliary stricture was described in a case report. The patient became progressively jaundiced and fatigued, with mild or moderate bilirubin toxicity (timing not reported)[13].

Cholecystitis

Cholecystitis reported as 'possibly related to treatment' occurred in 2 patients in a case series of 80 patients treated by SIRT (both treated by emergency cholecystectomy 21 and 243 days after treatment)[9].

Post-embolisation syndrome

Post-embolisation syndrome was reported in 60% of patients in both the SIRT and TACE groups (absolute numbers not reported) in the non-randomised comparative study of 86 patients. The symptoms (fatigue and transient non-specific flu-like symptoms) lasted 7 to 10 days in the SIRT group (no further details)[4].

Radiation pneumonitis

Radiation pneumonitis was reported in 4 patients with hepatocellular carcinoma between 1 and 6 months after treatment by SIRT (a scan to determine lung shunting had been done before treatment with SIRT) in a case series of 80 patients. All patients were treated by steroids. Three patients died of progressive respiratory failure and 1 from progressive cancer[11].

Haematological complications

Bone marrow suppression resulting in transient thrombocytopenia was reported 1 month after SIRT in a case report [21].

Lymphocyte decrease of more than 75% was reported in 33% (19/65) of patients treated by SIRT, in a case series of 65 patients[22].

Abnormal liver function: bilirubin toxicity

Bilirubin toxicity (grade 3/4) was reported in 7% (3/43) of patients treated by SIRT (median follow-up 34 months) and 26% (11/35) treated by TACE in the non-randomised comparative study of 86 patients (median follow-up 52 months)[4].

Radiation exposure to staff

Radiation exposure to the caregiver (from the patient) was assessed and found to exceed the recommended threshold (1 mSv) in 16% (3/19) in a case series of 19 patients[20].

Efficacy –cholangiocarcinoma

Survival

A case series of 24 patients reported a median survival of 4 months in patients with previous exposure to systemic chemotherapy (n=7), compared with 32 months in patients who were chemotherapy-naive (n=17) (p=0.03)[24].

A case series of 19 patients reported a median survival of 11.5 months from first treatment[26].

Tumour response

The case series of 24 patients reported stable disease (using WHO criteria) in 68% (15/22) of patients, partial response in 27% (6/22) of patients, and disease progression in 5% (1/22) of patients at a median follow-up of 18 months[24].

The case series of 19 patients reported stable disease (using RECIST criteria) in 68% (13/19) of patients, partial response in 11% (2/19) of patients, and disease progression in 21% (4/19) of patients 3 months after the procedure[26].

Downstaging (curative intent)

Downstaging to resection was reported in 1 patient in the case series of 24 patients (median 18-month follow-up)[24], and in 1 patient who had a partial response to treatment in a case series of 25 patients (median 8-month follow-up)[25].

Bridging to liver transplantation was reported in 1 patient in a case series of 24 patients (median 18-months follow-up)[21].

Safety –cholangiocarcinoma

Death

Death within 30 days was reported in 2 patients (1 patient was hospitalised for pulmonary embolus and the other patient had a tumour burden greater than 50%) in the case series of 24 patients[24].

Gastroduodenal ulcer

Gastroduodenal ulcer (because of inadvertent delivery of microspheres into a collateral vessel; no further details on when the ulcer was diagnosed) was reported in 4% (1/24) of patients treated by SIRT (and prophylactic gastrointestinal arterial embolisation) in the case series of 24 patients[24].

Post-embolisation syndrome

Fatigue (64%), nausea (16%) and vomiting (8%) were reported in the case series of 25 patients (median 8-month follow-up)[25].

Thrombocytopenia

Severe thrombocytopenia (within 30 days of first treatment) was reported in 1 patient in the case series of 19 patients[26].

Pleural effusion

Pleural effusion (no further details given) was reported in 9% (2/22) of patients in the case series of 24 patients at a median follow-up of 18 months.

Validity and generalisability of the studies

- There were no randomised controlled trials identified. Several of the studies concluded that a trial comparing outcomes from TACE with those from SIRT is needed.
- Studies included mainly report SIRT as a 'stand-alone' treatment.
- Quality of life was reported in only 1 study in patients with hepatocellular carcinoma.
- In studies with mixed populations (primary and secondary cancers), some studies reported outcomes for all patients rather than specifically for those with hepatocellular carcinoma or cholangiocarcinoma.
- Studies included a mixed group of patients with regard to chemotherapy history. Patients who were chemotherapy-naive and patients with chemotherapy-refractory disease were included.
- Studies included a very heterogeneous group of patients with a wide range of tumour sizes.

Existing assessments of this procedure

There were 3 published assessments from other organisations identified at the time of the literature search. A report from the Canadian Agency for Drugs and Technologies in Health (CADTH)[31] concluded that: 'Y-90 microsphere radioembolisation appears to be a safe and efficient therapy for patients with unresectable primary or secondary liver tumours. It is not certain whether it is more effective than chemoembolisation therapy when considering the median overall survival of patients. Y-90 microsphere radioembolisation may be combined with systemic chemotherapy to produce promising results. More commonly, it is used as a last line of therapy in patients with liver tumours that were refractory to other treatments and its place as a first or second-line treatment for primary or secondary liver tumours has yet to be determined.'

A health technology assessment (Sweden)[32] concluded that the 'quality of evidence for radioembolisation with ^{90}Yttrium microspheres on the effects on survival as well as on tumour response is very low' and the 'reporting of adverse effects and toxicity was inconsistent between studies, varying in type of toxicity, grade of toxicity, time of occurrence after treatment and the possible relation to treatment'.

A clinical practice guideline developed by the European Society for Medical Oncology – European Society of Digestive Oncology[33] stated that: the role of radioembolisation with glass or resin Y-90 spheres may be competitive with sorafenib or TACE in subsets of patients, such as those with prior TACE failure, excellent liver function, macrovascular invasion and the absence of extra-hepatic disease. Only one study (Sangro 2011) reporting on radioembolisation was included. The Sangro (2011) study has been included in table 2a.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Selective internal radiation therapy for non-resectable colorectal metastases in the liver. NICE interventional procedures guidance 401 (2011). Available from www.nice.org.uk/guidance/IPG401

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr Hassan Malik, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Dr Graham Munneke, British Society of Interventional Radiology. Dr Andrew Scarsbook, Dr Ricky Sharma, Faculty of Clinical Oncology.

- Two Specialist Advisers reported that they perform the procedure regularly and 2 reported that they have never performed this procedure.
- One Specialist Adviser described the procedure as established and no longer new, 1 noted it was a minor variation on an existing procedure, 1 noted it was definitely novel and of uncertain safety and efficacy and 1 noted that this procedure is the first in a new class of procedure.
- Three Specialist Advisers stated that fewer than 10% of specialists are engaged in this area of work.
- Comparator procedures include chemo-embolisation, chemotherapy and radiofrequency ablation.

- Theoretical adverse events are altered liver function, death, gastrointestinal ulceration, lethargy, liver failure, portal hypertension, pancytopenia caused by bone marrow suppression, radiation cholecystitis, radiation hepatitis, radiation pancreatitis, radiation pneumonitis, radiation-induced liver disease, and transient mild post-embolisation syndrome.
- Adverse events reported in the literature were abdominal pain, fever, fatigue, inadvertent delivery of treatment to other organs (leading to pancreatitis, cholecystitis or gastritis), portal hypertension, pancytopenia due to bone marrow suppression, gastrointestinal ulceration, and pancreatitis.
- Anecdotal adverse events are cholecystitis, pancreatitis, fibrosis and skin ulceration.
- Key efficacy outcomes are overall survival, quality of life, improvement in time to progression, downsizing or downstaging to potentially curative treatments, bridging to liver transplantation and objective response.
- Three Specialist Advisers stated that if safe and efficacious the procedure is likely to be carried out in a minority of hospitals and 1 stated that this cannot be predicted. In terms of the number of patients eligible for treatment and use of resources, 3 Specialist Advisers stated that the impact would be minor and one stated that it would be moderate.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- The evidence for hepatocellular carcinoma and cholangiocarcinoma are reported separately in this overview.
- The evidence relates to SIRT using yttrium-90 only. Other agents identified in the literature search (Lipiodol, rhenium, holmium) are not considered here because these may not be used in regular clinical practice in the UK or may only be used in research.
- It is proposed that the evidence included in this overview should be separated to produce 2 guidance documents 'Selective internal radiation therapy with for primary hepatocellular carcinoma' and 'Selective internal radiation therapy with for primary cholangiocarcinoma'.
- One Specialist Adviser has suggested the title should be more specific: Selective internal radiation therapy for inoperable hepatocellular carcinoma.
- Studies that included mixed populations (primary and secondary liver cancer) have been included in this overview to highlight any safety events identified by the Specialist Advisers, even though the outcomes may not have been reported separately for the different groups.
- Ongoing trials:

- NCT01482442: Sorafenib Versus Radioembolization in Advanced Hepatocellular Carcinoma (Sarah); RCT; Location: France; Estimated enrolment: 400; Estimated primary completion date: March 2015.
- NCT01135056. Study to Compare Selective Internal Radiation Therapy (SIRT) Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (HCC); RCT; Estimated enrolment: 360; Location: multinational. Estimated study completion date: July 2015.
- NCT01556490. Efficacy Evaluation of TheraSphere in Patients With Inoperable Liver Cancer (STOP-HCC). RCT; Location: USA and France; Estimated enrolment: 400; Study completion date: October 2016.
- NCT00589030. A treatment of unresectable hepatocellular carcinoma with TheraSphere (Yttrium-90 Glass Microspheres). Case series; Location: USA; Estimated enrolment: 100; Estimated completion date: March 2019.
- NCT01126645. SORAMIC trial. Evaluation of Sorafenib in combination with local micro-therapy guided by Gd-EOB-DTPA enhanced MRI in patients with inoperable hepatocellular carcinoma. RCT; Location: Multi-national; Estimated enrolment: 665 ; Estimated completion date: September 2014

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Appendix A: Additional papers on selective internal radiation therapy for primary liver cancer

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Andrews JC, Walker SC, Ackermann RJ et al. (1994) Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up. Journal of Nuclear Medicine 35:1637–44.	n=24 (1 HCC) Follow up=53 months	Patient with hepatoma had no response to therapy. No patient developed pulmonary symptoms or signs.	Larger studies included in table 2a.
Atassi B, Bangash AK, Lewandowski RJ et al. (2008) Biliary sequelae following radioembolization with Yttrium-90 microspheres. Journal of Vascular and Interventional Radiology 19:691–97.	n=327 (33 had follow-up imaging of which 7 were HCC patients) Follow up=mean 270 days	Symptomatic or asymptomatic toxicities were seen in 15.2% of the HCC patients.	Larger studies included in table 2a.
Blanchard RJ, Morrow IM, and Sutherland JB. (1989) Treatment of liver tumors with yttrium-90 microspheres alone. Canadian Association of Radiologists Journal 40:206–10.	n=16 (1 hepatoma) Follow up=unclear	No complications were observed in the patient with hepatoma. Survival period was 40 weeks.	Larger studies included in table 2a.
Barakat O, Skolkin MD, Toombs BD et al. (2008) Major liver resection for hepatocellular carcinoma in the morbidly obese: a proposed strategy to improve outcome. World Journal of Surgical Oncology 6:100	n=1 Follow up=17 months	In the normal liver parenchyma, there was evidence of postembolisation effects, mainly focal areas of foreign body giant cell reaction, but minimal fibrosis and no steatosis. There was no evidence of recurrence 17 months after tumour resection.	Larger studies included in table 2a.
Cao X, He N, Sun J et al. (1999) Hepatic radioembolization with Yttrium-90 glass microspheres for treatment of primary liver cancer. Chinese Medical Journal 112:430–32.	n=17 (16 primary liver cancer) Follow up= unclear	All patients demonstrated fever and symptoms of gastrointestinal tract. Mean survival was 19.5 months.	Larger studies included in table 2.
Carr BI Konderagunta V, Buch SC et al. (2010) Therapeutic equivalence in survival for hepatic arterial	n=99 SIRT vs 691 chemo-embolisation vs 142 without treatment	Overall survival was significantly longer in patients treated by SIRT:11.5 months vs	Patients in the SIRT group had milder disease and SIRT

chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma Cancer; 116:1305–14	Follow up=50 months	8.5 months for the SIRT and TACE group respectively ($p<0.05$). Partial response was 38% in the SIRT group compared with 55% in the TACE group.	cohort is not large (only the TACE group is large). Larger studies included in table 2a.
Chaudhury PK, Hassanain M, Bouteaud JM. et al. (2010) Complete response of hepatocellular carcinoma with sorafenib and Y radioembolization. Current Oncology 17 (5) 67–9	n=1 (SIRT+ sorafenib) Follow up= 23 months	A pathologic complete response was achieved and patient was made amenable to surgery with sorafenib in combination with (90)Y radioembolisation. Patient died because of general deterioration as a result of extensive extrahepatic metastases.	Larger studies included in table 2a.
Chui A, Rao A, Island E et al. (2004) Multimodality tumor control and living donor transplantation for unresectable hepatocellular carcinoma. Transplantation Proceedings 36:2287– 8.	n=27 HCC (2 treated by SIRT) Follow up= mean 20 months	2 postoperative deaths were reported.	Larger studies included in table 2a.
Dancey JE, Shepherd FA, Paul K et al. (2000) Treatment of nonresectable hepatocellular carcinoma with intrahepatic 90Y-microspheres. Journal of Nuclear Medicine 41:1673–1681.	n=22 Follow up= unclear	All 22 treated patients experienced at least 1 adverse event. Of the 31 (15%) serious adverse events, the most common were elevations in liver enzymes and bilirubin and upper GI ulceration. The response rate was 20%. The median duration of response was 127 weeks; the median survival was 54 weeks.	There may be some overlap of patients included in Geschwind (2004) in table 2a.
Ettorre GM, Sangro B, Cianni D et al. (2012) European multicentre evaluation of the impact of prior procedures on survival and safety following radioembolization in patients with unresectable hepatocellular carcinoma	n=325 (retrospective review)	No significant differences were observed in overall survival between the prior procedure and treatment-naïve groups (median [95% CI]: 13.1 [10.9–19.6] vs. 12.5 [10.3–15.9] months; $p = 0.289$). Analysis of clinical and	Outcomes reported in table 2a.

		laboratory adverse events found that theyvaried little between patients stratified by any or no prior procedure.	
Ettorre GM, Santoro R, Claudio P et al. (2010) Short-term follow-up of radioembolization with yttrium-90 microspheres before liver transplantation: new perspectives in advanced hepatocellular carcinoma. Transplantation;90:930–1	N=1 Follow up= 2217 months (to second treatment) and additional 8 months (after liver transplant)	Patient was down-staged to liver transplantation.	Outcome reported in table 2a.
Gaba RC, Lewandowski RJ, Kulik LM et al. (2009) Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. Annals of Surgical Oncology;16:1587–96.	n = 20 (hepatocellular carcinoma, n=17; peripheral cholangiocarcinoma, n=3) Follow up = unclear	Initial absolute right and left HLV was 955 cm^3 (range 644–1,842 cm3, rHLV = 57%) and 719 cm^3 (range 328–1,387 cm3, rHLV = 43%), respectively. Following 90Y, absolute right HLV decreased to 460 cm3 (range 185–948 cm3, 52% reduction, rHLV = 31%, DA = 26%, $p < 0.0001$), while absolute left HLV increased to 1,004 cm^3 (range 560–1,558 cm^3, 40% increase, rHLV = 69%, DH = 26%, $P < 0.0001$). No grade 3 or 4 bilirubin toxicities were encountered. Tumour response ranged from 55% to 70% by size criteria.	Clinical outcomes reported in tables 2a and 2b.
Goin JE, Salem R, Carr BI et al. (2005) Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: Factors associated with liver toxicities. Journal of Vascular and Interventional Radiology.16 (2I) 205–13.	n=88 Follow up= unclear	68 liver toxicities occurred in 42% (37/99) patients. Risk of liver toxicities increases with increasing pre-treatment total bilirubin level and liver radiation dose to a maximum of 150 Gy for a single administration.	Safety outcomes reported in table 2a.
Goin JE, Dancey JE, Roberts CA et al. (2004) Comparison of post-embolization syndrome in the treatment of patients with unresectable hepatocellular carcinoma: Trans-catheter arterial chemo-embolization	n=63 (34 Y90 glass microspheres vs 29 TACE)	The incidence of post embolisation syndrome was 3.8-times (95% confidence interval 1.6-16.3) higher after TACE(69% [20/29])	Larger studies included in table 2a.

versus yttrium-90 glass microspheres. World Journal of Nuclear Medicine 3:49–56		than after Y90(18% [6/34])treatment; (p=.003). Median survival was similar for Y90(N=20; 378 days, CI 209-719) and TACE (N=29; 343 days, CI 217-511) patients.	
Goin JE, Salem R, Carr BI et al. (2005) Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: a risk-stratification analysis. Journal of Vascular and Interventional Radiology;16:195–203	n=33	Survival analyses were performed to identify those variables most strongly associated with 3-month mortality. 49% (16/33) patients assigned to the high-risk group did not survive the first 3 months after treatment, compared with 7% (6/88) patients assigned to the low-risk group (p < 0.0001). Median survival for the low- and high-risk groups were 466 days and 108 days, respectively (hazard ratio, 6.0; p < .0001). Eleven of 12 patients who experienced a treatment-related major complication ending in death were included in the high-risk group.	Outcome reported in table 2a.
Haug AR, Heinemann V, Bruns CJ et al. 18F-FDG PET independently predicts survival in patients with cholangiocellular carcinoma treated with 90Y microspheres. European Journal of Nuclear Medicine and Molecular Imaging 2011;38:1037–45.	n = 26 Follow up = unclear	5 (22%) showed a partial response, 15 (65%) stable disease and 3 (13%) progressive disease. The change in all FDG values significantly predicted survival by Kaplan-Meier analysis after radioembolization; ΔVol(2SD) responders had a median survival of 97 weeks versus 30 weeks in nonresponders (P = 0.02), whereas ΔSUV(max) and ΔSUV(mean) responders had a median survival of	Clinical outcomes reported in table 2b.

		114 weeks (responder) versus 19 weeks (nonresponder) and 69 weeks in patients with stable disease ($P < 0.05$). Pretherapeutic MAA scintigraphy or MRI did not predict survival, nor did the presence of extrahepatic metastases, or prior therapies	
Herba MJ, Illescas FF, Thirlwell MP et al. (1988) Hepatic malignancies: improved treatment with intra-arterial Y-90. Radiology 169:311–314.	n=15 (1 hepatoma) Follow up=mean 7 months	Death occurred after oesophageal variceal haemorrhage in a patient with primary hepatoma. A transient fever was present in all patients for a few days after treatment.	Safety outcomes reported in table 2a.
Hickey R and Lewandowski RJ. (2011) Hepatic radioembolization complicated by radiation cholecystitis. Seminars in Interventional Radiology 28:230–233.	n= 1 Follow up= unclear	Cholecystisis was reported in a patient who underwent SIRT.	Safety outcome reported in table 2a.
Hilgard P, Hamami M, Fouly AE et al. (2010) Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology 52:1741–1749.	n=108 Follow up=at 1 week, 30,60, and 90 days and every 3 months.	According to EASL criteria, 9% of patients showed complete and 35% partial response while 53 % developed stable disease. Only 3% of patients primarily showed progression. Time to progression (TTP) was 11.0 months. Median overall survival was 16.4 months. No lung or visceral toxicity was observed, the main adverse events were a transient fatigue-syndrome and lymphopenia.	Larger studies included in table 2a.
Högberg J, Rizell M, Hultborn R et al. Radiation exposure during liver surgery after treatment with 90Y microspheres, evaluated with computer simulations and	n = 2 Follow up = unclear	The simulations showed a good agreement with the averaged absorbed dose rates based on TLD measurements performed on resected tissue,	No clinical outcomes reported.

dosimeter measurements. Journal of Radiological Protection 2012; 32: 439–46.		differing by 13% and 4% respectively. The absorbed dose rates at the measured maximum hotspots were twice as high as the average dose rates for both patients.	
Holt A, Wagman LD, Senthil M et al. (2010) Transarterial radioembolization with Yttrium-90 for regional management of hepatocellular cancer: the early results of a nontransplant center. American Surgeon 76:1079–1083.	n=20 Follow up= median 12 months	After the first therapy, CT assessment of the treated area showed stable disease (n=15), partial response (n=3), and progression (n=2). Of the 2 patients who progressed, 1 was retreated with a subsequent complete response. The other patient died of progressive disease. The most common side effects were mild fatigue, anorexia, and nausea.	Larger studies included in table 2a.
Houle S, Yip TK, Shepherd FA et al. (1989) Hepatocellular carcinoma: pilot trial of treatment with Y-90 microspheres. Radiology 172:857–860.	n=9 Follow up=unclear	None of the patients showed any evidence of significant toxicity. Radiation exposure to personnel was minimal.	Larger studies included in table 2a.
Ibrahim SM, Kulik L, Baker T et al. (2012) Treating and downstaging hepatocellular carcinoma in the caudate lobe with yttrium-90 radioembolization. Cardiovascular and Interventional Radiology 35(5):1094-1101	n = 8 Follow up =5 years	Caudate lobe radioembolisation was successfully performed in all eight patients. Half were United Network for Organ Sharing (UNOS) stage T3 (n = 4, 50%). Fatigue was reported in half of the patients (n = 4, 50%). One (13%) grade 3/4 bilirubin toxicity was reported. One patient (13%) showed complete tumour response by WHO criteria, and 3 patients (38%) showed complete response using EASL guidelines	Larger studies reported in table 2a.
Iñarrairaegui M, Thurston KG, Bilbao JI et al. (2010)	n=25	Globally, controlled disease was	Larger studies included in

Radioembolization with use of yttrium-90 resin microspheres in patients with hepatocellular carcinoma and portal vein thrombosis. Journal of Vascular and Interventional Radiology 21:1205–12.	Follow up=6 months	achieved in 66.7% of patients at 2 months and 50% of patients at 6 months. No significant changes were observed in liver-related toxicities according to Common Toxicity Criteria (version 3.0) at 1 and 2 months after treatment. Median survival time was 10 months (95% CI, 6.6-13.3 months)	table 2a.
Iñarrairaegui M, Pardo F, Bilbao JI et al. (2012) Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. European Journal of Surgical Oncology 38:594–601.	n=118 (21 UNOS T3 included in analysis) Follow up= every 2 to 3 months	29% (6/21) patients were downstaged and treated radically between 2 and 35 months post-radioembolisation. Three patients had resection, 2 received liver transplantation and 1 had ablation and then resection. The median overall survival (OS) was 27.0 months (95% CI 5.0-48.9), varying significantly between those treated radically (OS not reached after a median follow-up of 41.5 months since radical therapy) and those who received palliative treatment only (22.0 months; 95% CI 15.0-30.9).	Larger studies included in table 2a.
Iñarrairaegui M, Bilbao JI, Rodríguez M et al. (2010) Liver radioembolization using 90Y resin microspheres in elderly patients: tolerance and outcome. Hospital Practice (Minneapolis) 38:103–9	n=255 (primary or metastatic) Follow up=unclear	The median overall survival of patients with hepatocellular carcinoma was similar in elderly and younger groups (13 months, 95% confidence interval [CI], 10.4-15.5 and 12 months, 95% CI, 4.2-15.7; p = 0.4). 10.4% of elderly patients and 9.9% of younger patients developed radioembolisation-induced liver disease (p = 1.000). Only 1.5% of elderly patients developed	Outcomes reported in table 2a.

		gastrointestinal ulceration and no patient in the elderly group developed pneumonitis.	
Jakobs TF, Hoffmann RT, Poepperl G et al. (2007) Mid-term results in otherwise treatment refractory primary or secondary liver confined tumours treated with selective internal radiation therapy (SIRT) using (90)Yttrium resin-microspheres. European Radiology 17:1320–1330.	n=18 (5 HCC) Follow up=up to 9 months	All HCC-patients showed stable disease/partial response at 2–3 months with no progressive disease at 5–8 months. The median time-to-progressive disease was 8 months.	Larger studies included in table 2a.
Kennedy AS, McNeillie P, Dezarn WA et al. (1-8-2009) Treatment parameters and outcome in 680 treatments of internal radiation with resin 90Y-microspheres for unresectable hepatic tumors. International Journal of Radiation Oncology, Biology, Physics 74:1494–1500.	n=515 (79 HCC, 13 CCA) Follow up=90 days	3 HCC patients died. Few patients developed grade 3 liver toxicity and none developed grade 4 toxicity.	Larger studies in tables 2a and 2b.
Keppke AL, Salem R, Reddy D et al. (2007) Imaging of hepatocellular carcinoma after treatment with yttrium-90 microspheres. AJR American:768–75	n=42 Follow up=mean 125 days	The response rate was 23% according to RECIST criteria, 26% according to WHO criteria, 57% according to necrosis criteria, and 59% according to combined criteria. Hyperbilirubinaemia, groin haematoma, infected closure device in groin and ascites were reported.	Larger studies included in table 2a.

Khalaf H, Alsuhaibani H, Al-Sugair A et al. (2010) Use of yttrium-90 microsphere radioembolization of hepatocellular carcinoma as downstaging and bridge before liver transplantation: a case report. Transplantation Proceedings 42:994–998.	n=1 Follow up=1 year	Patient treated by SIRT to downstage tumour and as a bridge for orthotopic liver transplantation (OLT). No sign of tumour recurrence at follow-up.	Outcome reported in table 2a.
Khodjibekova M, Szyszko T, Singh A et al. (2007) Treatment of primary and secondary liver tumours with selective internal radiation therapy. Journal of Experimental and Clinical Cancer Research 26:561–570.	n=30 (unclear how many patients with HCC) Follow up= unclear	4 cases of complications were reported: cholecystitis and portal hypertension, peptic ulcer and 2 cases of radiation hepatitis. Treatment was well tolerated with improvement in survival and quality of life.	Safety events reported in table 2a.
Kim DY, Kwon DS, Salem R et al. (2006) Successful embolization of hepatocelluar carcinoma with yttrium-90 glass microspheres prior to liver transplantation. Journal of Gastrointestinal Surgery 10:413–416.	n=1 Follow up=2 years	3 months after treatment by SIRT patient underwent an OLT. Following OLT patient underwent systemic adjuvant chemotherapy.	Outcome reported in table 2a.
Kooby DA, Egnatashvili V, Srinivasan S et al. (2010) Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. Journal of Vascular and Interventional Radiology 21: 224–30	n= 71 (27 SIRT vs 44 chemoembolisation) Follow up=6 months	The 1-year survival rate was 16% (4/27) in patients treated by SIRT, compared with 20% (9/44) in patients treated by chemo-embolisation (p not reported). SIRT was associated with a significantly shorter mean hospital length of stay vs TACE (1.7 vs 6.0 days, respectively; p=0.05)	Larger studies reporting efficacy outcomes included in table 2a. Radiation-induced safety event reported in table 2a.
Kucuk ON, Soydal C, Lacin S et al. (2011) Selective intraarterial radionuclide therapy with Yttrium-90 (Y-90) microspheres for unresectable primary and metastatic liver tumors. World Journal of Surgical Oncology 9:86-	n=78 (25 HCC) Follow up=unclear	In the evaluation of treatment response; 43(55%) patients were responder (R) and 35 (45%) patients were non-responder (NR) in the sixth week. The mean overall survival time of R group was calculated as 25 months and NR group's 20 (p=0.04).	Larger studies included in table 2a.
Kulik LM, Mulcahy MF, Hunter RD et al. (2005) Use of yttrium-90 microspheres (TheraSphere)	n=1	1 month follow-up showed a positive tumour response	Outcomes reported in

in a patient with unresectable hepatocellular carcinoma leading to liver transplantation: a case report. Liver Transplantation 11:1127–1131.	Follow up=4 months	and patient was downstaged from T3 to T2. Patient underwent OLT 42 days after treatment with SIRT.	table 2a.
Kulik LM, Carr BI, Mulcahy MF et al. (2008) Safety and efficacy of ^{90}Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis Hepatology 47(1): 71–81	n=108 Follow up=6 months	The partial response rate using world Health Organization (WHO) criteria was 42.2%. Using European Association for the Study of the Liver (EASL), the response rate was 70%. Kaplan-Meier survival varied depending on location of PVT and presence of cirrhosis. The adverse event (AE) rates were highest in patients with main PVT and cirrhosis. There were no cases of radiation pneumonitis.	Studies with longer follow included in table 2a.
Lambert B, Sturm E, Mertens J et al. (2011) Intra-arterial treatment with ^{90}Ymicrospheres for hepatocellular carcinoma: 4 years experience at the Ghent University Hospital Eur J Nucl Med Mol Imaging 38:2117–24	n=43 Follow up=mean interval of 181 days	In 4 patients severe clinical adverse events were encountered, however these were clearly related to the therapy in only 1 patient. Twenty patients were assessable by RECIST: complete response in 15%, partial response in 35%, stable disease in 30% and progression in 20% were observed. A median survival of 12.3 months (95% confidence interval 9.4-15.2) was estimated.	Outcomes reported in table 2a.
Lance C, McLennan G, Obuchowski N et al. (2011) Comparative analysis of the safety and efficacy of transcatheter arterial chemoembolization and yttrium-90 radioembolization in patients with unresectable hepatocellular carcinoma. Journal of Vascular and Interventional Radiology	n=79 (38 SIRT vs 35 chemoembolisaton) Follow up=median 14 months	There was no significant difference in survival between the radioembolisation (median 8.0 months) and chemo-embolization (median 10.3 months) cohorts	Larger studies included in table 2a.

22:1697–1705.		(P=0.33). Postembolisation syndrome was significantly more severe in patients who underwent chemo-embolization, which led to increased total hospitalisation rates in these patients. The rates of other complications and rehospitalisation were similar between groups.	
Lau WY, Leung WT, Ho S et al. (1994) Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study Br J Cancer. 1994 November; 70(5): 994–9.	n=18 Follow up= unclear	Median survival of all patients was 31 weeks. No mortality or major complications were reported.	Larger studies included in table 2a.
Lau WY, Lai ECH, Leung TWT (1994) Current role of selective internal irradiation with yttrium-90 microspheres in the management of hepatocellular carcinoma: a systematic review Int J Radiation Oncology Biol. Phys 81(2): 460–7	N=7 studies (results presented for 7 studies reporting survival)	Yttrium 90 microspheres are safe and well-tolerated therapy for unresectable HCC . The median survival range 7 to 21.6 months.	Studies have been included either in table 2a or appendix A.
Lau WY, Ho S, Leung TW et al. (1998) Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intra-arterial infusion of ^{90}yttrium microspheres. International Journal of Radiation Oncology, Biology, Physics 40: 583–92	n=71 Follow up= 28 months	Median survival from diagnosis was 9.4 months. 70%(50/71) of patients died (reasons include intrahepatic residual or recurrent diseases, bone metastases, lung metastases, bleeding oesophageal varices and uncontrolled sepsis from acute cholecystitis which may have been induced by microspheres).	Larger studies in table 2a.
Lewandowski RJ, Riaz A, Ryu RK et al (2009) Optimizationof radioembolic effect with extended-shelf-life yttrium-90 microspheres: results from a pilot study Journal of Vascular Interventional Radiology 20:1557–63	n=50 (13 HCC) Follow up=unclear	Clinical toxicities included fatigue (28 patients, 56%), abdominal pain (19 patients, 38%), and nausea/vomiting (6 patients, 12%). Grade 3–4 bilirubin toxicity was seen in 1 patient. Two gastroduodenal ulcers were	Outcomes reported in table 2a.

		observed.	
Lim L, Gibbs P, Yip D et al. (2005) Prospective study of treatment with selective internal radiation therapy spheres in patients with unresectable primary or secondary hepatic malignancies. Internal Medicine Journal 35:222–227.	n=46 (5 HCC) Follow up=median 9.8 months	There were 2 partial responses in patients with HCC. The median duration of response for all patients was 8.6 months.	Larger studies included in table 2a.
Liu MD, Uaje MB, Al-Ghazi MS et al. (2004) Use of Yttrium-90 TheraSphere for the treatment of unresectable hepatocellular carcinoma. American Surgeon 70:947–53.	n=11 Follow up=11 months	One patient (9%) had a complete response, 8 patients (78%) had a partial response, and 2 patients (18%) showed no response. No patients developed liver toxicity or died because of treatment. Five patients (45%) died of progressive disease at a median of 7 months post-treatment. Six patients (54%) were alive at a median of 11 months.	Larger studies included in table 2a.
Luna LE, Kwo PY, Roberts LR et al. (2009) Liver transplantation after radioembolization in a patient with unresectable HCC. [Review] [19 refs]. Nature Reviews Gastroenterology and Hepatology 6:679–83.	n=1 Follow up=6 months	Patient underwent OLT 1 year after 2 treatments with SIRT at 1 year.	Outcome reported in table 2a.
Mazzaferro V, Sposito C, Bhoori S et al. (2012) Yttrium90 radioembolization for intermediate-advanced hepatocarcinoma: A phase II study. Hepatology ePub doi: 10.1002/hep.26014	n = 52 Follow up = median 36 months	Median TTP was 11 months with no significant difference between portal vein thrombosis (PVT) vs. no-PVT (7 vs. 13 mo). Median OS was 15 mo (95%CI: 12-18) with a non-significant trend in favour of non-PVT vs. PVT patients (18 vs. 13 mo). Five complete responses occurred (9.6%) and the 2yr-progression rate was 62%. Mortality at 30-90 days was 0%-3.8%.	Outcomes reported in table 2a.
Memon K, Kulik L,Lewandowski RJ et al.(2012) Radioembolization for hepatocellular carcinoma with portal vein thrombosis: Impact of	n = 291 FU = 1 month following treatment (and 2 to 3 month	Median survival and TTP were 13.8 and 5.6 months in Child-Pugh (CP)-A and 6.5 and 4.9 months in	Outcomes reported in table 2a.

liver function on systemic treatment options at disease progression. Journal of Hepatology ePub doi:10.1016/j.jhep.2012.09.003	intervals)	CP-B7 patients, respectively. Of the 29 CP-A patients who progressed, 45% maintained their CP status at progression (55% decompensated to CP-B). Of the 15 CP-B7 patients who progressed, 20% improved to CP-A, 20% maintained their CP score and 60% decompensated.	
Moreno-Luna LE, Yang JD, Sanchez W et al. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients withhepatocellular carcinoma. Cardiovascular and Interventional Radiology 2012 Oct 24; ePub doi: 10.1007/s00270-012-0481-2	n = 61 transarterial radioembolisation (TARE) vs 55 chemoembolisation (TACE) (retrospective case-control study)	Complete tumour response was more common after TARE (12 %) than after TACE (4 %) (p = 0.17). When complete response was combined with partial response and stable disease, there was no difference between TARE and TACE. Median survival did not differ between the two groups (15.0 months for TARE and 14.4 months for TACE; p = 0.47). Two-year survival rates were 30 % for TARE and 24 % for TACE. Compared with TACE, TARE was more likely to induce fatigue (p = 0.003) but less likely to cause fever (p = 0.02).	Comparison and outcomes reported in table 2a.
Neff R, Abdel-Misih R, Khatri J et al. (2008) The toxicity of liver directed yttrium-90 microspheres in primary and metastatic liver tumors. Cancer Investigation 26:173–77.	n=21 (1 HCC) Follow up=1 month	One mortality was secondary to fulminant hepatic failure after developing radiation hepatitis. Morbidities included radiation hepatitis (1) and peptic ulcer disease (6).	Outcomes reported in table 2a.
Nosher JL, Ohman-Strickland PA, Jabbour S et al. (2011) Changes in liver and spleen volumes and liver function after radioembolization with yttrium-90 resin microspheres. Journal	n=54 (4 HCC) Follow up=24 months	1 patient experienced fatal variceal haemorrhage 6 months after treatment that was	Outcome reported in table 2a.

of Vascular and Interventional Radiology.22 (12):1706-13.		possibly related to radioembolisation.	
Piana PM, Gonsalves CF, Sato T et al. (2011) Toxicities after radioembolization with yttrium-90 SIR-spheres: incidence and contributing risk factors at a single center. Journal of Vascular and Interventional Radiology 22:1373–1379.	n=81 (7 HCC) Follow up=29–571 days	2 patients died with symptoms and lab findings of radiation induced liver disease. Bilirubin normalised/stabilised at grade 1 in 60% (12/20) infusions at a median of 29 days (range 2–175 days). AST normalised/stabilised in 76% (44/58) of infusions at a median of 29 days (range 1–271 days). ALT normalised/stabilised in 86% (49/57) of infusions at a median of 20 days (range 5–271 days)	Outcomes reported in table 2a.
Reardon KA, McIntosh AF, Shilling AT et al. (2009) Treatment of primary liver tumors with Yttrium-90 microspheres (TheraSphere) in high risk patients: analysis of survival and toxicities. Technology in Cancer Research and Treatment 8:71–77.	n=21 (19 HCC ; 2 CCA) Follow up=2.5 months	The results of this study showed that median survival for all the patients was 120 days. Twenty of 21 patients were categorised as high-risk with a median survival of 114 days. It was also found that 1 high-risk patient has survived 858 days with no recurrence of disease. Acute grade 3-5 toxicities were recorded for 9 patients and consisted of elevations in AST and bilirubin, thrombocytopenia, abdominal pain, ascites, nausea, fatigue, and death.	Studies with longer follow-up period included in tables 2a and 2b.
Rhee TK, Naik NK, Deng J et al. (2008) Tumor response after yttrium-90 radioembolization for hepatocellularcarcinoma: comparison of diffusion-weighted functional MR imaging with anatomicMR imaging. Journal of Vascular and Interventional Radiology;19:1180–6	n = 20 Follow up = 3 months	HCC tumour response assessed with diffusion-weighted imaging(DWI) at 1 month preceded anatomic size changes at 3 months after (90)Y therapy. DWI may assist in early determination of the response or	Clinical outcomes not reported.

		failure of (90)Y therapy for HCC.	
Riaz A, Gates VL, Atassi B et al. (1-1-2011) Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. International Journal of Radiation Oncology, Biology, Physics 79:163–71.	n=84 Follow up=3 months (toxicities)	Grade 3/4 biochemical toxicities were observed in 8 patients (9%). Median time to progression was 13.6 months (95% confidence interval, 9.3–18.7 months); median survival was 26.9 months (95% confidence interval, 20.5–30.2 months).	Larger studies included in table 2a.
Riaz A, Kulik L, Lewandowski RJ et al. (2009) Radiologic–pathologic correlation of hepatocellular carcinomatreated with internal radiation using Yttrium-90 microspheres. Hepatology 49:1185–93	n = 35 Follow up = unclear	Post-radioembolisation imaging findings of response by EASL and WHO criteria are predictive of the degree of pathologic necrosis. Rim enhancement was an imaging characteristic that correlated well with histologic necrosis.	Clinical outcomes not reported.
Rivera L, Giap H, Miller W et al. (2006) Hepatic intra-arterial infusion of yttrium-90 microspheres in the treatment of recurrent hepatocellular carcinoma after liver transplantation: a case report. World Journal of Gastroenterology 12:5729–32	n = 1 Follow up =2 months	Efficacy was demonstrated by tumour necrosis on imaging and a decrease in alpha-fetoprotein level. There were no adverse consequences of initial treatment.	Larger studies included in table 2a.
Rosler H, Triller J, Baer HU et al. (1994) Superselective radioembolization of hepatocellular carcinoma: 5-year results of a prospective study. Nuclear-Medizin 33:206–14	n=20 Follow up=5 years	The overall survival was 56%, 38% and 14% at 1,2, and 3 years.	Larger studies included in table 2a.
Rowe BP, Weiner R, Foster J et al. (2007) 90Yttrium microspheres for non-resectable liver cancer: the University of Connecticut Health Center experience. Connecticut Medicine 71:523–28.	n=24 (7 HCC) Follow up=unclear	Median survival was 3.5 months. 6 patients had abdominal pain, 5 anorexia, 2 had nausea and 2 had fatigue1 patient had gastric ulcer and a femoral artery plaque rupture with subsequent thromboembolism in the lower extremity.	Larger studies included in table 2a.
Sabet A, Ahmadzadehfar H, Schafer N (2012) Survival after	n=1 FU= 19 months	Patient developed sever watery	Outcome reported in

accidental extrahepatic distribution of Y90 microspheres to the mesentry during a radiembolization procedure Cardiovascular and Interventional Radiology 35:954-7		diarrhoea without any abdominal pain (9 days after treatment)- this was interpreted to be a sign of radiation-induced injury of gastrointestinal tract. Symptoms lasted 7 days and there were no signs of late side effects.	table 2a.
Salem R, Lewandowski R, Roberts C et al. (2004) Use of Yttrium-90 glass microspheres (TheraSphere) for the treatment of unresectable hepatocellular carcinoma in patients with portal vein thrombosis. Journal of Vascular and Interventional Radiology 15:335–345	n=15 Follow up=12 week intervals (CT imaging)	No procedural complications. Increased post-treatment bilirubin levels were observed.	Larger studies included in table 2a.
Salem R, Lewandowski RJ, Atassi B et al. (2005) Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (therasphere): Safety, tumor response, and survival. Journal of Vascular and Interventional Radiology.16 (12) (pp 1627–1639), 2005.Date of Publication: December 2005. 1627–1639.	n=43 (retrospective review)	Median survival times of 24.4 months and 12.5 months by Okuda scores of I and II, respectively, were achieved (mean, 25.8 months vs 13.1).	Larger studies included in table 2a.
Salem R, Lewandowski RJ, Kulik L et al. (2011) Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 140:497–507.	n=245 (SIRT 123 vs 122 chemo-embolisation) Follow up=median follow-up 23 months and 33 months chemo-embolization.	Survival was not different between the groups after excluding patients that had been censored to curative therapies. Both groups experienced fatigue, nausea and anorexia.	Outcomes reported in table 2a.
Salem R Parikh P, Atassi B et al.(2008) Incidence of radiation pneumonitis after hepatic intra-arterial radiotherapy with yttrium-90 microspheres assuming uniform lung distribution. Am J Clin Oncol. 31(5):431–8	n=58 (43 HCC) Follow up= mean 7 months (HCC)	Imaging findings in 10 patients included pleural effusions, atelectasis and ground glass attenuation. None of the patients treated were diagnosed with radiation pneumonitis.	Larger studies included in table 2a.
Sangro B, Bilbao JI, Boan J et al. (2006) Radioembolization using 90Y-resin microspheres for patients with advanced hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics 66(3):792–800.	n=24 Follow up= median 13 months	, A reduction in size of target lesions (using RECIST criteria) was observed in 20/21 patients. When considering only target lesions, disease control rate	Larger studies included in table 2a.

		and response rate were 100% and 23.8%, respectively. However, 43% of patients progressed in the liver in the form of new lesions appearing a median time of 3 months after radioembolisation.	
Sato K, Lewandowski RJ, Bui JT et al. (2006) Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere): assessment of hepatic arterial embolization. Cardiovascular and Interventional Radiology 29:522–529.	n=30 (19 HCC; 1CCA) Follow up=3 months	Objective tumour response rates fro all patients were 24%, 31% and 72% for WHO, RECIST and EASL criteria, respectively.	Larger studies included in tables 2a and 2b.
Shepherd FA, Rotstein LE, Houle S et al. (1-11-1992) A phase I dose escalation trial of yttrium-90 microspheres in the treatment of primary hepatocellular carcinoma. Cancer 70:2250–2254.	n=10 Follow up=unclear	No patient had a complete or partial response, but 10 patients had stable disease. The median survival was 18 weeks (range, 2–150 weeks), and 3 patients lived longer than 1 year. Significant bone marrow or hepatic toxicity was not seen. One patient had a radiation-induced duodenal ulcer that needed surgical management.	Outcomes included in table 2a.
Strigari L, Sciuto R, Rea S et al. (2010) Efficacy and toxicity related to treatment of hepatocellular carcinoma with 90Y-SIR spheres: radiobiologic considerations. Journal of Nuclear Medicine 51:1377–1385.	n=63 Follow up= unclear	Complete response (1%), partial response, stable disease and progressive disease were seen in 1%, 53% 43% and 3% using RECIST criteria.	Larger studies included in table 2.
Szeto C, Wong T, Leung C et al (2001) Selective internal radiation therapy by yttrium-90 microspheres for hepatocellular carcinoma after renal transplantation. Clinical Transplantation;15:284–8	n = 1 FU =15 months	Serum alpha-fetal protein was normalized within 2 weeks. A follow-up abdominal CT scan revealed significant necrosis of the tumor and compensatory hypertrophy of non-diseased liver. The treatment was well	Larger studies included in table 2a.

		tolerated except for transient liver function deterioration. The patient had 15 months of symptom-free survival before death because of liver failure.	
Szyszko T, Al-Nahhas A, Tait P et al. (2007) Management and prevention of adverse effects related to treatment of liver tumours with 90Y microspheres. Nuclear Medicine Communications 28:21–24.	n=21 (1 HCC; 2 CCA) Follow up=26 months	33% died because of extra-hepatic disease progression. Adverse events including cholecystitis, peptic ulceration and radiation induced hepatitis were reported.	Larger studies included in tables 2a and 2b.
Tian JH, Xu BX, Zhang JM et al. (1996) Ultrasound-guided internal radiotherapy using yttrium-90-glass microspheres for liver malignancies. Journal of Nuclear Medicine 37:958–963.	n=33 (27 HCC) Follow up=up to 32 months after treatment.	6 patients died of either end-stage disease or wide dispersion of tumour. Repeat biopsy showed complete tumour destruction in 8 patients.	Larger studies included in table 2a.
Tsai AL, Burke CT, Kennedy AS et al (2010) Use of Yttrium-90 microspheres in patients with advanced hepatocellular carcinoma and portal vein thrombosis JVIR 21(9): 1377–84	n=22 Follow up=30 day (safety and toxicity); 4 weeks (clinical data)	One death occurred 10 days after therapy. The partial response rate was 8% and progressive disease was seen in 42% of patients. Stable disease was achieved in 50% of treatments. Median OS was 7 months from initial treatment.	Larger studies included in table 2a.
Whitney R, Tatum C, Hahl M et al. (2011) Safety of hepatic resection in metastatic disease to the liver after yttrium-90 therapy. The Journal of Surgical Research; 166: 236-40.	N=44 (case reports of 2 patients with CCA)	2 patients with CCA treated with SIRT proceeded to resection because of downstaging of disease or no evidence of extrahepatic progression. One patient was disease-free at 8 month follow-up and the other patient (who also underwent ablation) was also disease free at18 months follow-up.	Outcome reported in table 2b.
Young JY, Rhee TK, Atassi B et al. (2007) Radiation dose limits and liver toxicities resulting from multiple yttrium-90	n=41 Follow up= median 190 days	A total of 13 toxicities occurred in 7 patients (16%). Patients with Okuda	Larger studies included in table 2a.

radioembolization treatments for hepatocellular carcinoma. Journal of Vascular and Interventional Radiology 18:1375–1382.		stage I disease were given a greater cumulative dose than patients with Okuda stage II disease before worsening of liver function.	

Appendix B: Related NICE guidance for selective internal radiation therapy for primary liver cancer

Guidance	Recommendations
Interventional procedures	**Selective internal radiation therapy (SIRT) for non-resectable colorectal metastases in the liver NICE interventional procedures guidance 401 (2011)** 1.1 Current evidence on the safety of selective internal radiation therapy (SIRT) for non-resectable colorectal metastases in the liver is adequate. 1.2 The evidence on its efficacy in chemotherapy-naive patients is inadequate in quantity. Clinicians should offer eligible patients who have not been previously treated by chemotherapy entry into well-designed research studies such as the FOXFIRE trial (www.octo-oxford.org.uk/alltrials/trials/FOXFIRE). For patients who are not eligible or who prefer not to enter a research trial, the procedure should be used with special arrangements for clinical governance, consent and audit. 1.3 For patients who have previously been treated with chemotherapy, there is evidence that SIRT can prolong time to progression of hepatic metastases, but more evidence is required on survival and quality of life (see section 1.7). Therefore for patients who have been previously treated with chemotherapy this procedure should be used with special arrangements for clinical governance, consent and audit. 1.4 Clinicians undertaking the procedure for patients outside research studies should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's efficacy and provide them with clear written information. In addition, the use of NICE's information for patients

	('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG401publicinfo). • Audit and review clinical outcomes of all patients having SIRT for non resectable colorectal metastases (see section 3.1). 1.5 Patients should be selected for SIRT or entry into trials by a hepatobiliary cancer multidisciplinary team including an interventional radiologist, in liaison with a colorectal cancer multidisciplinary team. 1.6 SIRT should only be carried out by clinicians with specific training in its use and in techniques to minimise the risk of side effects of the procedure. 1.7 The Committee considered that SIRT is a potentially beneficial treatment for patients with non-resectable colorectal metastases in the liver, but that more research and data collection are required to demonstrate its efficacy. A recommendation about research trials for chemotherapy-naive patients is given in 1.2 above. For patients who have previously been treated with chemotherapy, comparative trials are needed to determine whether SIRT prolongs survival compared with alternative forms of management or no further treatment, and to determine its effect on quality of life. There is also a need to identify which subgroups of patients are likely to derive clinical benefit from SIRT. Research studies should clearly describe the characteristics of treated patients, and the extent and histological details of their tumours. Outcomes should include survival and quality of life. Downstaging of metastases allowing resection or ablation should be clearly documented. 1.8 NICE may review the procedure on publication of further evidence.

Appendix C: Literature search for selective internal radiation therapy for primary liver cancer

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	22/11/2012	Issue 11 of 12, Nov 2012
Database of Abstracts of Reviews of Effects – DARE (CRD website)	22/11/2012	Issue 4 of 4, Oct 2012
HTA database (CRD website)	22/11/2012	Issue 4 of 4, Oct 2012
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	22/11/2012	Issue 11 of 12, Nov 2012
MEDLINE (Ovid)	22/11/2012	1946 to November Week 3 2012
MEDLINE In-Process (Ovid)	22/11/2012	November 21, 2012
EMBASE (Ovid)	22/11/2012	1974 to 2012 Week 46
CINAHL (NLH Search 2.0 or EBSCOhost)	22/11/2012	1981 to present
JournalTOCS	22/11/2012	n/a

Trial sources searched:

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched:

- National Institute for Health and Care Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- General internet search

MEDLINE search strategy

1 SIRT.tw.

2 (selective* adj3 internal* adj3 radiotherap*).tw.

3 (selective* adj3 internal* adj3 radiation* adj3 therap*).tw.

4 (internal* adj3 radiation* adj3 therap*).tw.

5 Brachytherapy/

6 brachytherap*.tw.

7 (radioemboli?ation or radio-emboli?ation).tw.

8 (intravascular adj3 radiation).tw.

9 (local adj3 radioablation).tw.

10 (radionuclide adj3 therap*).tw.

11 (targeted adj3 hepatic adj3 therap*).tw.

12 (transarterial adj3 radiotherap*).tw.

13 or/1-12

14 Yttrium/

15 exp Yttrium Radioisotopes/

16 yttrium*.tw.

17 (90Y or Y-90).tw.

18 or/14-17

19 microsphere*.tw.

20 Microspheres/

21 or/19-20

22 SIR-Sphere*.tw.

23 TheraSphere*.tw.

24 (sirtex or nordion).tw.

25 18 and 21

26 or/22-25

27 ((Liver* or hepatic*) and (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or

tumor* or malignan*)).tw.

28 exp Liver Neoplasms/

29 Carcinoma, Hepatocellular/

30 (carcinoma* adj3 hepatocellul*).tw.

31 hepatocarcinoma*.tw.

32 hepatoma*.tw.

33 Cholangiocarcinoma/

34 Cholangiocarcinoma$.tw.

35 or/27-34

36 13 and 35

37 26 and 35

38 or/36-37