SIR-Spheres for treating inoperable hepatocellular carcinoma

Medtech innovation briefing
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Summary

SIR-Spheres are a form of selective internal radiation therapy consisting of resin microspheres containing radioactive yttrium-90. They are designed to be used to treat patients with inoperable hepatocellular carcinoma. SIR-Spheres can also be used to downstage tumours for resection or liver transplantation, or as a bridge to transplantation. SIR-Spheres deliver radiation directly to tumours through the hepatic artery, which limits damage to normal liver cells. The evidence from 11 studies summarised in this briefing is of mixed quality. Where overall survival was a primary outcome, studies generally showed mixed results. For example, 2 comparative studies (1 prospective, 1 retrospective) showed no significant difference in disease control with SIR-Spheres compared with drug-eluting bead transarterial chemoembolisation (DEB-TACE) using doxorubicin or with sorafenib. The evidence also generally showed no significant difference in adverse events between SIR-Spheres and transarterial chemoembolisation (TACE), and between SIR-Spheres and sorafenib. One study reported fewer any-grade adverse effects with SIR-Spheres compared with sorafenib but the incidence of severe adverse effects was similar. The list price of SIR-Spheres is £8,000, excluding VAT. The total price used to reimburse NHS centres is about £21,550, which covers the total cost of the SIR-Spheres treatment.

NICE has produced a medtech innovation briefing on another selective internal radiation therapy technology, TheraSphere.
<table>
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<tr>
<th><strong>Product summary and likely place in therapy</strong></th>
<th><strong>Effectiveness and safety</strong></th>
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<tr>
<td>• SIR-Spheres are a form of selective internal radiation therapy (SIRT) consisting of resin microspheres containing radioactive yttrium-90.</td>
<td>• The evidence in this briefing includes 11 studies (n=1089 patients). Three were non-randomised comparative, 3 were randomised comparative and 5 were non-comparative. The studies compared SIR-Spheres with conventional TACE, DEB-TACE, sorafenib either alone or in combination with SIR-Spheres, and with active or supportive care.</td>
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<tr>
<td>• SIR-Spheres can be used to treat inoperable hepatocellular carcinoma (HCC). It may be an alternative or adjunct to conventional transarterial chemoembolisation (TACE), drug-eluting bead TACE (DEB-TACE) or systemic drugs to control tumour size, extend life, reduce symptoms or to shrink tumours for resection or transplantation.</td>
<td>• One prospective, comparative study showed no significant difference between SIR-Spheres (n=12) and DEB-TACE (n=12) for progression-free survival (PFS), overall survival (OS), time to progression (TTP) and time to non-treatable progression (nTTP).</td>
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<td>• A prospective comparative study showed higher partial response (PR) rates with SIR-Spheres (n=13) than conventional TACE (n=15). However, progression-free survival (PFS) was longer in the TACE group than the SIR-Spheres group. The number of adverse events was similar in both treatment groups. This study was underpowered for statistical analysis.</td>
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<td></td>
<td>• A retrospective, comparative study showed no significant difference in median OS between SIR-Spheres (n=63) and sorafenib (n=74). However, TTP was significantly higher in the sorafenib cohort. There were fewer any-grade adverse effects with SIR-Spheres compared with sorafenib but the incidence of severe adverse effects was similar.</td>
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• Another prospective, comparative study compared SIR-Spheres and sorafenib (n=20) with sorafenib alone (n=20). No difference in tolerability or toxicity was observed between the 2 groups.

• A retrospective, comparative study showed that median survival of Barcelona clinic liver cancer (BCLC) stage C inoperable HCC patients was significantly higher with SIR-Spheres (n=25) than with no treatment (n=12).

• In 1 retrospective study a significantly higher median survival was observed for patients treated with SIR-Spheres (n=35) when compared with a historical control (n=43).

• In a retrospective, non-comparative study no significant difference in median OS or tolerability was observed in younger (<70 years, n=197) and older (≥70 years, n=128) patients when treated with SIR-Spheres.

• In another retrospective, non-comparative study, median OS, following treatment with SIR-Spheres (n=325), was shown to be affected by BCLC stage.

• A retrospective, non-comparative study showed high median survival and minor clinical toxicities following SIR-Spheres (n=45) treatment.

• SIR-Spheres (n=21) treatment was used in downstaging HCC for radical treatment in a prospective, non-comparative study.
### Technical and patient factors

- Pre-treatment imaging and planning is needed to ensure appropriate patient selection, minimise delivery of microspheres outside the liver, and limit the exposure of healthy liver tissue to radiation. This is usually an outpatient procedure.

- Patients usually stay overnight in hospital after SIR-Spheres treatment.

- SIR-Spheres treatment must be performed at specialist centres by established multidisciplinary teams that have adequate training and expertise.

- Centres providing SIR-Spheres must have the necessary approval to use radioactive materials, and should minimise radiation exposure to patients and staff.

### Cost and resource use

- The list price of SIR-Spheres is £8,000 (excluding VAT). This includes the single-use delivery system, reusable acrylic delivery box, v-vial and v-vial holder.

- There are additional costs associated with SIR-Spheres including pre-treatment imaging and procedural costs.

- The total price used to reimburse NHS centres for SIRT treatment of a different liver cancer indication is about £21,550, which covers the total cost of the SIR-Spheres treatment.

- The list price includes all training and supervision provided by the manufacturer.

- Most patients have 1 SIR-Spheres treatment.

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**Introduction**

Hepatocellular carcinoma (HCC), also called hepatoma, is a cancer of the liver parenchymal cells (hepatocytes) and is the most common type of primary liver cancer (European Association for the Study of the Liver 2012).

The UK incidence of HCC in 2007 was 3.4 per 100,000 for men and 0.9 per 100,000 for women (National Cancer Intelligence Network 2010). Risk factors for HCC include cirrhosis and increasing age, with 80% of cases diagnosed in people aged 60 years or older (Jelic and Sotiropoulos 2010).
During 2013, 1,648 deaths from HCC were registered in England and Wales (Office for National Statistics 2013). Survival rates are linked to the stage of cancer at diagnosis.

The choice of treatment for HCC depends on a number of factors, including the exact location and stage of the cancer and its effect on liver function. Several staging systems are used to grade HCC including the Barcelona Clinic Liver Cancer (BCLC) staging and treatment schedule, which incorporates the Child–Pugh assessment of liver disease.

Treatment for HCC aims to slow progression of the disease, improve quality of life and prolong survival. Surgical removal of the tumour, liver transplantation or radio-frequency ablation with the aim of providing a cure may be possible. However, only about 20% of patients with early disease may benefit from these surgical therapies (Abdel-Rahman and Elsayed 2013). Palliative treatment options include chemotherapy (oral, intravenous or by hepatic artery infusion), conventional transarterial chemoembolisation (TACE), drug-eluting bead TACE (DEB-TACE) and radiofrequency ablation.

SIR-Spheres are a type of selective internal radiation therapy (SIRT), also referred to as transarterial radioembolisation (TARE) or radioembolisation. SIRT is used to treat liver tumours, including hepatocellular carcinoma. It involves delivering microspheres containing the beta-emitting radionuclide yttrium-90 directly into the tumour by infusing them through the femoral artery into the hepatic artery. Liver tumours receive most of their blood supply from the hepatic artery, whereas normal liver tissue receives the majority of its blood from the portal vein. This means that microspheres are delivered preferentially to the tumour, minimising the risk of radiation damage to healthy surrounding tissues.

SIRT treatment can be applied to the whole liver or to separate lobes depending on the location of the tumour. Additionally, SIRT can be repeated or fractionated depending on the patient response and condition. SIRT delivery can also be more selective allowing specific segments of the liver to be targeted (segmental treatment).

**Technology overview**

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.
About the technology

CE marking

Sirtex Medical was awarded an active implantable medical device CE mark for SIR-Spheres in October 2002. The CE mark covers the yttrium-90 resin microspheres, delivery system and v-vial.

Description

SIR-Spheres are sterile, single-use, resin microspheres containing yttrium-90; the focus of this briefing is their use in inoperable HCC. SIR-Spheres are delivered through a catheter to the hepatic artery. They are supplied at 3 GBq yttrium-90 per vial in 5 ml water for injection in a shielded shipping vial. Each vial contains 40–80 million microspheres, ranging from 20–60 micrometres in diameter (median diameter 32.5 micrometres). The maximum range of beta emission in tissue is 11 mm with a mean of 2.5 mm.

A typical treatment with SIR-Spheres consists of infusing 1.4–2.0 GBq yttrium-90 (30–40 million resin microspheres), into the hepatic artery at the site of the tumour. The dose delivered to the patient's liver is calculated through the body surface area (BSA) method or through the partition model method. The BSA method is the recommended formula for most patients and the formula adjusts the amount of yttrium-90 given according to the size of the patient and the weight of the tumour compared to the liver (Kennedy et al. 2012). The procedure is usually performed under sedation and intravenous analgesia may be needed.

SIR-Spheres are supplied with the following accessories:

- 1 single use SIR-Spheres delivery system
- a reusable acrylic delivery box
- v-vial
- v-vial holder.

The dose of beta radiation needed by the patient is used to calculate the volume of SIR-Spheres needed. As the yttrium-90 is subject to radioactive decay (half-life 64.1 hours), the microspheres are supplied on demand. SIR-Spheres must be ordered by 3 pm (GMT) on the Wednesday of the week before treatment. They are delivered on the day of treatment (the calibration date) and may be used up to 24 hours after the calibration date with adjustment for radioactive decay. The volume
of SIR-Spheres needed to give the dose of yttrium-90 required is transferred to a shielded and sterile v-vial in preparation for infusion into the patient.

During the procedure the microspheres are infused into the hepatic artery at the site of the tumour using a flexible catheter passed through the femoral artery. The microspheres are infused into the delivery catheter from the v-vial using standard 10 ml or 20 ml syringes (Giammarile et al. 2011). SIR-Spheres are administered with the delivery system, using water for injection or 5% glucose to pulse push. Another syringe containing contrast medium can be connected to the delivery system, allowing intermittent contrast medium injection to maintain forward flow throughout. SIR-Spheres are introduced at a rate of no more than 5 ml per minute to reduce reflux in the hepatic artery and accidental delivery to other organs. The procedure takes about 1 hour and is carried out under X-ray guidance. The SIR-Spheres travel in the bloodstream into the microvasculature of the tumour, becoming lodged. Once lodged, the microspheres release beta radiation that kills tumour cells. Most patients are discharged within 24 hours of the procedure.

SIR-Spheres remain permanently implanted in the liver tissue and trace levels of radiation will remain for a long period of time after the initial treatment. Radioactive waste following SIR-Spheres administration should be safely disposed of in line with local procedures.

Features of SIR-Spheres that are different from other SIRT technologies include:

- The alternating injection of water and contrast medium, which allows direct monitoring of the procedure.
- The ability to individualise the dose.
- The shelf life of 24 hours, limiting flexibility in patient scheduling.
- The potential for introducing errors when calculating the volume of SIR-Spheres needed to give the correct dose of yttrium-90 and when transferring them to the v-vial. The need to transfer the SIR-Spheres may result in a radiation risk to the person preparing the dose (Giammarile et al. 2011).
- SIR-Spheres microspheres are made of resin whereas TheraSphere microspheres are made of glass.

**Setting and intended use**

SIR-Spheres are intended for use in treating advanced inoperable liver cancer by implantation into hepatic tumours through the hepatic artery. The scope of this briefing is limited to HCC.
Patients’ tumours should be accurately staged according to international standards based on clinical history, physical examination, laboratory values and performance status (Giammarile et al. 2011).

Administration of SIRT requires both specialist facilities and a significant amount of pre-treatment work-up and is therefore carried out in specialist centres. Patients undergo general health checks, liver function tests, specialist imaging techniques and hepatic arteriography. Selective coil embolisation of arteries to the stomach and duodenum is carried out to limit the delivery of microspheres outside the liver. The procedure is carried out under local anaesthesia in an angiography suite by an interventional radiologist. A trans-femoral catheter is placed under X-ray guidance to enable selective catheterisation of the hepatic artery. After embolisation, technetium-99m labelled macro-aggregated albumin (MAA) is injected through the catheter with the tip positioned at the level where SIR-Spheres will be delivered and a nuclear medicine scan is done. This maps the distribution of the isotope in the liver, to determine the extent of arteriovenous shunting to the lungs, and to ensure that gastric and duodenal flow are absent. Patients may need an additional pre-SIRT embolisation procedure if there is evidence of extra-hepatic uptake.

Although treatment planning aims to selectively deliver microspheres to the tumour, any SIRT procedure will invariably result in some degree of irradiation of normal liver tissue.

Centres providing SIRT must have adequate training and expertise. A vital part of offering SIRT treatment is establishing a multidisciplinary team which includes interventional radiology; medical, radiation and surgical oncology; transplant surgery; nuclear medicine; hepatology; medical physics and radiation safety.

Clinicians wishing to administer radioactive medicinal products to people must have a certificate issued by Administration of Radioactive Substances Advisory Committee (ARSAC) in accordance with the Medicines (Administration of Radioactive Substances) Regulations (MARS) Regulations 1978.

**Current NHS options**

Current treatment options for patients with HCC depend on tumour stage. Barcelona clinic liver cancer (BCLC) staging classification is a widely used staging system for treatment allocation. Treatments include liver resection, transplantation, local ablation, chemoembolisation and transcatheter therapies, and systemic therapies (European Association for the Study of the Liver 2012).
NICE guidance on **SIRT for primary hepatocellular carcinoma** states that current evidence on the efficacy and safety of SIRT for primary hepatocellular carcinoma is adequate for use with normal arrangements for clinical governance, consent and audit. However, uncertainties remain about its comparative effectiveness, and clinicians are encouraged to enter eligible patients into trials comparing the procedure against other forms of treatment. NICE also recommends microwave ablation and radiofrequency ablation to treat HCC provided that normal arrangements for clinical governance, consent and audit are in place.

NICE guidance on **sorafenib for the treatment of advanced HCC** states that sorafenib is not recommended for patients for whom surgical or loco-regional therapies have failed or are not suitable. Sorafenib is currently available through the UK Cancer Drugs Fund for certain patients with advanced HCC.

NICE guidance states that resection of the liver can be carried out using laparoscopic methods or through assistance from a radiofrequency generating device as a treatment option for liver cancer. In addition, ex-vivo hepatic resection and reimplantation can be carried out under special arrangements for clinical governance, consent and audit or research.

The European Society for Medical Oncology (ESMO) and European Society of Digestive Oncology (ESDO) guidance on HCC states that SIRT may be an option for a subset of patients with intermediate to advanced HCC for whom TACE or sorafenib are recommended (Verslype et al. 2012).

NICE is aware of the following CE-marked device that appears to fulfil a similar function to SIR-Spheres:

- **TheraSphere (Biocompatibles UK)** – indicated for operable and inoperable HCC. NICE has produced a medtech innovation briefing on TheraSphere.

### Costs and use of the technology

The cost of a single treatment of SIR-Spheres is £8,000 (excluding VAT). There are no additional costs for service and maintenance. Most patients will have a single treatment. Depending on the patient's condition, life expectancy and tumour response, treatment can be repeated or fractionated.

The cost includes a single-use SIR-Spheres delivery system, reusable acrylic delivery box, v-vial and v-vial holder, shipping and delivery. Sirtex Medical provides a training, evaluation and certification programme at no extra cost for all new users. In addition, it provides on-site support and
supervision by a consultant interventional radiologist, with experience of treating more than 50 patients with SIR-Spheres, for the pre-treatment work-up and treatment of the first 3 patients at each new site.

Patients having SIR-Spheres treatment for HCC will have a work-up procedure, usually as an outpatient, to ensure that SIRT is suitable for them. The following tariffs are used to reimburse NHS centres providing SIRT treatment through the NHS England Commissioning through Evaluation Programme, which is studying SIRT for other forms of liver cancer rather than for primary hepatocellular carcinoma, the focus of this briefing. The costs should therefore be regarded as illustrative.

**Work-up tariff:**

- **RC31Z IR Procedures – Hepatobiliary – Major** is £5,386 (*NHS 2015–16 best practice tariff*)

**Treatment tariff:**

- **GB02B – Endoscopic/Radiology category 3 with Intermediate CC**: £1,877 or **GB02C – Endoscopic/Radiology category 3 without CC**: £1,707 (*NHS England 2015–16 enhanced tariff option*)


The price used to reimburse NHS centres is about £21,550, which covers the total cost of the SIR-Spheres treatment.

**Likely place in therapy**

SIR-Spheres could be used in patients with inoperable HCC as an alternative or adjunct to 1 of several options currently offered (including liver resection, transplantation, local ablation, chemoembolisation and transcatheter therapies, and systemic therapies), depending on multiple factors including the patient’s general health and tumour stage.

**Specialist commentator comments**

One specialist commentator noted that HCC remains a clinical challenge with a poor prognosis for the majority of patients, particularly for those in certain subgroups. They added that survival of patients with HCC is influenced by factors including the extent of disease spread and the impact of
cirrhosis on liver function reserve. Survival is also influenced by the suitability for patients of a range of therapies such as surgery and ablation, loco-regional therapies (including TACE and SIRT) and systemic chemotherapy or biological agents. The specialist commentator stated that SIRT is one of the loco-regional therapy options listed in the guidelines by the US National Comprehensive Cancer Network (NCCN), the American Hepato-Pancreato-Biliary Association (AHPBA), Society of Surgical Oncology (SSO), Society for Surgery of the Alimentary Tract (SSAT) and the European Society of Medical Oncology (ESMO).

One specialist commentator noted that SIR-Spheres can be used in some patients who have good performance status (a generic term covering general wellbeing and ability to carry out day-to-day activities) and liver function, as a method of downstaging to resection or transplantation and as a bridge to transplantation. This represents a curative option for some patients. Another specialist commentator noted that SIRT’s role in downstaging may be limited and that more evidence is needed.

One specialist commentator noted that SIR-Spheres are usually delivered in 1 sitting for bilobar disease. Very few patients are eligible for repeat or subsequent treatment.

One specialist commentator noted that in most centres where TACE and SIRT are carried out, SIRT is better tolerated than TACE with fewer incidences of post-embolisation syndrome and shorter inpatient hospital stays. It was noted that TACE and SIRT are not necessarily comparable as they can be used in different patient groups.

One specialist commentator noted that SIR-Spheres are currently indicated for patients with intermediate HCC (BCLC stage B) and for patients in whom TACE has been ineffective or is unsuitable. Another commentator noted that SIRT can potentially be used in the following subgroups of patients with HCC with well-compensated liver function (that is, Child–Pugh class A or B ≤7 points) who are:

- candidates for downstaging to resection or transplantation or as a bridge to transplantation
- candidates for TACE; patients with unresectable BCLC stage A or B with unilobar disease or few (1–5) nodules
- patients for whom TACE is not suitable; those with BCLC stage B with bilobar disease and/or multiple (>5) nodules
- patients whose disease has previously not responded to TACE or sorafenib
candidates for sorafenib; patients with BCLC stage C, particularly those with portal vein thrombosis (PVT).

Two specialist commentators stated that curative therapy is suitable for 15–20% of people with HCC. Options include transplantation, resection, radiofrequency ablation and, in limited cases, ethanol injection. They added that for unresectable HCC, radiofrequency ablation, TACE, transarterial embolisation, hepatic artery infusion or a combination of these methods may be used. In advanced disease sorafenib may be offered. If other treatments have failed or the patient has reached end-stage disease, palliation is offered. One commentator noted that SIRT for HCC is currently limited to patients participating in clinical trials or self-funded patients, because of a lack of funding.

One specialist commentator noted that the current options for NHS patients with unresectable HCC are TACE and sorafenib (currently available through the Cancer Drugs Fund).

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

HCC is more common in older people and affects more men than women. Cancer is considered to be a disability under the Equality Act from the point of diagnosis. SIRT is contraindicated in women who are pregnant or breastfeeding. The use of SIR-Spheres has not been studied in children.

Patient and carer perspective

A spokesperson acting on behalf of Liver4Life, a UK liver health charity that supports people affected by liver conditions, disease and cancer, gave the following patient perspectives on SIRT in general:

- They feel that SIRT shows benefits to people who are affected by HCC.
• If any technology shows a cost-effective improvement in patient health it should be available as a treatment option on the NHS.

• Liver4Life received feedback from patients who may need treatment for HCC in the future, and they stated that they would be willing to accept treatment if it had 'relatively' tolerable side effects provided the outcome was effective.

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the MHRA website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this technology.

A search of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE) between February 2005 and September 2015 identified 11 medical device reports relating to SIR-Spheres. Four reports were relevant to this briefing, based on the clinical indication being HCC (1 report) or unspecified liver cancer (2 reports) and there was 1 unspecified technical report. Based on the description provided, the relationship of all events to the SIR-Spheres treatment were categorised as probable (2) and unlikely (2). In 1 of the 2 probable events, the patient was unharmed but had a lower dose of SIR-Spheres as a result of occlusion of the micro-catheter used during the procedure. In the other instance, SIR-Spheres were found in the delivery box stopcock; however, the effect on the patient was not stated. One death was reported 81 days post-treatment and 1 patient was diagnosed with acute myelocytic leukaemia about 1 year after the procedure; however, neither of these events were thought to be related to the procedure.

The MAUDE database houses reports on medical devices which have been submitted to the FDA because of suspected device-associated deaths, serious injuries and malfunctions. Reports are submitted by mandatory reporters such as manufacturers, importers and facilities where the devices are used and voluntary reporters such as healthcare professionals, patients and consumers.

It should be noted that the MAUDE database is a passive surveillance system and potentially includes incomplete, inaccurate, untimely, unverified or biased data. The incidence of an event cannot be determined from this reporting system alone because of potential under-reporting of events and lack of information about frequency of device use (FDA, 2015).
Clinical evidence

A total of 11 studies have been included in this MIB. The NICE interventional procedures guidance overview on selective internal radiation therapy for primary liver cancer summarises the evidence published up to 2012 on SIRT/TARE in patients with HCC. Two key studies from the guidance overview have been included in this briefing. A further 22 studies published since 2012 were identified as relevant to this briefing and 9 of them have been included. Detailed summaries of the included studies can be found in the Appendix and key outcomes are summarised in Table 1.

Table 1 Summary of results from selected studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Results</th>
<th>Summary of findings</th>
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<tr>
<td>SIR-Spheres for treating inoperable hepatocellular carcinoma (MIB63)</td>
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<tr>
<td>Chow et al. (2014)</td>
<td>SIRT (SIR-Spheres; n=29) followed by initiation of sorafenib (400 mg twice daily) 14 days post-radioembolisation given until tumour progression or drug-related adverse events were observed. Tumour classification: Inoperable, intermediate (BCLC B; n=11) and advanced Mean age (years): 64.6</td>
<td>Twenty eight (97%) patients experienced CTCAE ≥grade 1 toxicity; 15 (52%) grade ≥3 Tumour response BCLC B: Complete response (CR) 9%, partial response (PR) 36%, stable disease (SD) 55%, progressive disease (PD) 0% BCLC C: CR 6%, PR 6%, SD 53%, PD 29% Disease control rate (DCR; CR+PR+SD), % patients (95% CI): BCLC B: 100% (72–100) BCLC C: 65% (38–86) Median time to progression (TTP), months (95% CI): BCLC B: 15.2 (4.6–nr);</td>
<td>Patients with BCLC B showed a higher DCR, TTP, PFS and OS than patients with BCLC C. Nearly all patients experienced ≥grade 1 toxicity. The authors highlighted that this is a single-arm study with low patient numbers.</td>
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<td>BCLC C: 9.0 (3.5–nr)</td>
<td>Median progression-free survival (PFS), months (95% CI)</td>
<td>BCLC B: 15.2 (4.6–nr); BCLC C: 6.5 (3.5–9.1)</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Comparator</td>
<td>Outcome Measures</td>
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<td>D'Avola et al. (2009)</td>
<td>Retrospective, non-randomised, consecutive, case series with a historical control</td>
<td>Single-centre; Spain.</td>
<td>SIRT (SIR-Spheres) compared with patients having active (conventional chemotherapy, experimental drugs and external beam therapy) treatment (67%) and patients having supportive care (32%). (n=35 SIR-Spheres; n=43 control group) Unresectable HCC Mean age (years): 63 SIR-Spheres; 61 control group</td>
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<td>treated with sorafenib for a mean period 3.4 months (2 to 12 months after SIR-Spheres).</td>
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</table>
Golfieri et al. (2013)  
Retrospective, consecutive, case series.  
Multicentre; Europe.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Median OS, months (95% CI)</th>
<th>All-cause mortality post-procedure, n (%)</th>
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<tbody>
<tr>
<td>&lt;70 years</td>
<td>12.8 (10.8–17.9)</td>
<td>Day 30: &lt;70 years 2 (1%); ≥70 years 0 (0%) (p=0.521)</td>
</tr>
<tr>
<td>70 years</td>
<td>14.5 (10.6–16.8)</td>
<td>Day 60: &lt;70 years 8 (4.1%); ≥70 years 5 (3.9%; p=1.00)</td>
</tr>
<tr>
<td>70 years  or over</td>
<td></td>
<td>Day 90: &lt;70 years 13 (6.6%); ≥70 years 9 (7.0%; p=1.00)</td>
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</table>

No significant difference in median OS was observed between younger and older patients. Additionally, there was no significant difference in the tolerability of the treatment between the 2 groups. The results show that SIR-Spheres are as effective and tolerable in older patients as in younger patients.

No significant difference in fatigue, nausea or vomiting, abdominal pain, fever or GI ulceration was observed between the under 70 years and 70 years or over groups.
Gramenzi et al. (2015)  
Retrospective, consecutive, comparative case series.  
Single-centre; Italy.

TARE (SIR-Spheres) versus sorafenib (400 mg, twice daily)  
(n=63 SIR-Spheres; n=74 sorafenib)  
Intermediate (BCLC B) and advanced (BCLC C) HCC  
Mean age (years): 66 SIR-Spheres; 71 sorafenib.

Median OS, months (95% CI): SIR-Spheres 11.2 (6.7–15.7); sorafenib 13.1 (1.2–25.9; p=0.392)  
1-year, 2-year, 3-year survival rates:  
SIR-Spheres 44.7%, 19.0% and 9.5%; sorafenib 53.1%, 23% and 15.3%  
TTP, months (range):  
SIR-Spheres 3 (1–21); sorafenib 5 (1–36.5; p=0.012)  
The most common SIR-Spheres-related side effect was fatigue (9%)  
The most common sorafenib-related AEs were diarrhoea (41%), hand or foot skin reaction (29%), fatigue (35%),  

SIR-Spheres and sorafenib showed no significant difference in median OS. However, TTP was significantly higher in the sorafenib cohort. The authors highlighted that there were low patient numbers in both groups and that the study was retrospective in design.
<p>|                  | nausea or vomiting (18%), weight loss (15%), hypertension (15%) and rash or erythema (14%). |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Region</th>
<th>Median Age (years)</th>
<th>Treatment After Downstaging</th>
<th>Radical Treatment Results</th>
</tr>
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<tbody>
<tr>
<td>Inarralegui et al. (2012)</td>
<td>Prospective consecutive study with retrospective analysis, non-comparative.</td>
<td>Spain</td>
<td>72</td>
<td>6/21 patients were downstaged and radically treated after treatment with SIR-Spheres: Liver transplantation (n=2) Resection (n=3) RFA followed by resection (n=1).</td>
<td>Patients treated radically were significantly younger (62 versus 73 years, p = 0.006) and had higher tumour volume (583 ml versus 137 ml, p=0.001) than patients who did not have radical treatment. Across the whole series, the median OS was 27.0 months (95% CI 5.0 to 48.9), varying significantly between those treated radically (OS not reached) and those who were not. SIR-Spheres were used for downstaging of HCC for radical treatment. This gave rise to the possibility of long-term survival in a substantial although selected subgroup of patients with otherwise limited possibilities.</td>
</tr>
</tbody>
</table>

RE (SIR-Spheres) (n=21) UNOS T3 HCC | 6/21 patients were downstaged and radically treated after treatment with SIR-Spheres: Liver transplantation (n=2) Resection (n=3) RFA followed by resection (n=1). | 5/21 patients were downstaged and radically treated after treatment with SIR-Spheres: Liver transplantation (n=2) Resection (n=3) RFA followed by resection (n=1). | 6/21 patients were downstaged and radically treated after treatment with SIR-Spheres: Liver transplantation (n=2) Resection (n=3) RFA followed by resection (n=1). | 6/21 patients were downstaged and radically treated after treatment with SIR-Spheres: Liver transplantation (n=2) Resection (n=3) RFA followed by resection (n=1). | 6/21 patients were downstaged and radically treated after treatment with SIR-Spheres: Liver transplantation (n=2) Resection (n=3) RFA followed by resection (n=1). |

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<p>| after a median follow-up of 41.5 months since radical therapy) and those who had palliative treatment only (22.0 months; 95% CI 15.0 to 30.9). |  |  |
| SIR-Spheres for treating inoperable hepatocellular carcinoma (MIB63) |
|---|---|---|
| Kolligs et al. (2015) | SIRT (SIR-Spheres) compared with conventional TACE (epirubicin, lipiodol and occlusive particles) (n=13 SIR-Spheres; n=15 TACE) | Health-related quality of life (HRQoL) (for only 18 patients due to missing data), baseline median scores: SIR-Spheres (n=8) 82.0; TACE (n=10) 96.0 (p=0.04). After 12 weeks scores were not significantly different. PR rates (using response evaluation criteria in solid tumours [RECIST] 1.0): SIR-Spheres 30.8%; TACE 13.3% DCR (CR+PR+SD): SIR-Spheres 76.9%; TACE 73.3% Median PFS, months (95% CI): SIR-Spheres 3.6 (2.3–6.2); TACE 3.7 (1.6–11.0) Survival (% alive) at 6 and |
| Prospective, pilot randomised controlled comparative trial. Multicentre; Spain and Germany. | Unresectable HCC Mean age (years): 65 SIR-Spheres; 66.7 TACE | Median HRQoL scores were lower for SIR-Spheres than TACE in the first 12 weeks of treatment; however, there was no significant difference after 12 weeks. Although difference between PR rates, PFS and overall survival were observed between the 2 treatments, the study was underpowered and so statistical analysis on these parameters could not be carried out. The authors showed that SIR-Spheres and TACE were well tolerated. However, patients having TACE needed more procedures than those having SIR-Spheres. |</p>
<table>
<thead>
<tr>
<th>12 months:</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIR-Spheres 69.2, 46.2; TACE 86.7, 66.7</td>
</tr>
</tbody>
</table>

Treatment-related adverse events (AE)s:
- SIR-Spheres 23.1%; TACE 33.3%

Treatment-related serious adverse event (SAE; n):
- SIR-Spheres 2; TACE 2
  - (p=0.445)

Clinically abnormal laboratory results (n):
- SIR-Spheres 4; TACE 3
  - (p=0.670)
| Study: Kwok et al. (2014) | RE (SIR-Spheres) versus no RE  
(n=25 RE, n=12 no RE)  
Inoperable HCC  
BCLC stage A (n=4 RE, n=1 no RE)  
BCLC stage B (n=13 RE, n=6 no RE)  
BCLC stage C (n=13 RE, n=9 no RE).  
Mean age (years): 65.1  
SIR-Spheres; 65.9 non-RE | Median survival, months (95% CI):  
BCLC stage A  
>31.9 RE, >17.7 no RE;  
BCLC stage B  
14.5 (6.8–22.1) RE, 4.3 (0–14.3) no RE (p=0.1);  
BCLC stage C  
5.2 (3.9–6.4) RE, 3.8 (2.3–5.3) no RE (p=0.047) | The median survival for patients with BCLC stage C was significantly higher in those who had RE than in those who did not. In addition, median survival was significantly higher in patients with portal vein invasion and fewer than 3 nodules for those who have RE compared with those who did not. Therefore, patients with inoperable HCC at BCLC stage C, portal vein thrombus and with fewer than 3 nodules benefited from RE.
Pitton et al. (2015)  
Prospective, randomised, comparative study.  
Single-centre; Germany.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS (days) mean and standard error</th>
<th>OS (days) mean and standard error</th>
<th>TTP (days) mean and standard error</th>
<th>nTTP (days) mean and standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIR-Spheres</td>
<td>SIR-Spheres 180, 120/414, 266±55; DEB-TACE 216, 88/355, 237±49 (p=0.6193)</td>
<td>SIR-Spheres 592, 192/-, 437±72; DEB-TACE 788, (178/950), 583±119 (p=0.9271)</td>
<td>SIR-Spheres 371, 132/561, 353±69; DEB-TACE 336, 91/609, 315±69 (p=0.5764)</td>
<td>SIR-Spheres 488, 148/925, 490±114; DEB-TACE</td>
</tr>
<tr>
<td>DEB-TACE</td>
<td></td>
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<td></td>
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</tbody>
</table>

No significant difference was observed between the 2 treatments for PFS, OS, TTP and nTTP. Although SIR-Spheres showed fewer cases of tumour progression than DEB-TACE, it had a higher number of liver failure cases. This paper highlights the effectiveness of both treatments for HCC. The authors highlighted that this was a pilot study that could be used for sample size calculations in larger studies in future.
<p>| TACE 647, 182/-, 416±83 (p=0.9322) | Causes of death (n): SIR-Spheres tumour progression (1), liver failure (4), cardiovascular event (1), non-conclusive (1); DEB-TACE tumour progression (4), liver failure (1), cardiovascular event (1), non-conclusive (1) |
| Ricke et al. (2015) | RE (SIR-Spheres) followed by sorafenib at 200 mg twice daily for 1 week then 400 mg twice daily compared with sorafenib only at the same dosage as the RE arm (n=20 RE + sorafenib; n=20 sorafenib only) Unresectable intermediate (BCLC stage B, n=14) or advanced (BCLC stage C, n=26) HCC Median age (years): 71.5 SIR-Spheres + sorafenib; 68.5 sorafenib | Incidence of total grade and grade ≥3 AEs: SIR-Spheres + sorafenib 196 and 43; sorafenib only 222 and 47 (p&gt;0.05). No significant differences, between the 2 treatment groups, in total or grade 3/4 toxicities for total bilirubin, albumin, liver enzymes, ascites, Child–Pugh, fatigue, hand or foot skin reaction, blood pressure or diarrhoea. All grade infection: SIR-Spheres + sorafenib 10%; sorafenib only 50% (p=0.014) | This study focused on safety and tolerability outcomes and did not report outcomes such as OS or PFS. SIR-Spheres plus sorafenib does not show increased toxicity or tolerability issues compared with sorafenib alone. The presented parity of safety outcomes needs to be coupled with survival data to gain a full picture of SIR-Spheres plus sorafenib treatment compared with sorafenib treatment alone. |</p>
<table>
<thead>
<tr>
<th>Sangro et al. (2011)</th>
<th>SIRT (SIR-Spheres) (n=325)</th>
<th>Median OS, months (95% CI): 12.8 (10.9–15.7)</th>
<th>Median OS is affected by BCLC stage with a significantly higher median OS observed in patients with BCLC stage A than other BCLC stages. However, survival was observed across all BCLC stages highlighting that SIR-Spheres may be used for different HCC populations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-comparative, retrospective, multicentre case-series. Multicentre; Europe.</td>
<td>HCC</td>
<td>Median OS by BCLC stage, months (95% CI): BCLC stage A 24.4 (18.6–38.1) (p&lt;0.001 comparison between other BCLC stage median OS); BCLC stage B 16.9 (12.8–22.8); BCLC stage C 10 (7.7–10.9); BCLC stage D 5.2 (2.2–nr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BCLC stage A (n=52), BCLC stage B (n=87), BCLC stage C (n=183), BCLC stage D (n=3). Mean age (years): 64.5</td>
<td>Death at median follow-up of 10 months: 201/325 (61.8%). Further treatment/bridge to transplantation: liver transplantation (n=5), resection (n=3), percutaneous ablation (n=5)</td>
<td></td>
</tr>
<tr>
<td>Procedure-related clinical AEs: fatigue (n=177), nausea and/or vomiting (n=104), abdominal pain (n=88), fever (n=40) and GI ulceration (n=12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Group Description</td>
<td>Results</td>
<td>Notes</td>
</tr>
<tr>
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<tr>
<td>Saxena et al. (2014)</td>
<td>SIRT (SIR-Spheres) (n=45) Unresectable HCC</td>
<td>Median survival, months: 27.7 with 26% survival observed after 36 months. Multivariate analysis showed that poor radiological response to treatment was associated with a poorer prognosis: hazard ratio (HR), 24.17 (95% CI, 5.37–108.86; p&lt;0.001)</td>
<td>SIRT with SIR-Spheres showed a high median survival with just over a quarter of patients still alive after 36 months. Clinical toxicities, when they happened, were minor and resolved with no extra treatment.</td>
</tr>
</tbody>
</table>

Mean age (years): 63.6

Clinical toxicity: 13 (29%) patients developed minor (Grade II/III) clinical toxicity after treatment that resolved without active intervention. No patients died as a result of treatment. 5 patients were lost to follow-up leaving 40 patients.
Recent and ongoing studies

Five ongoing or in-development trials on SIR-Spheres for HCC were identified in the preparation of this briefing. Trials are presented with the ID number, patients or indications included, and current status.

NCT02305459: Registry on SIR-Spheres for liver carcinoma. Status: recruiting


NCT01482442: SIR-Spheres compared to sorafenib in hepatocellular carcinoma. Status: ongoing; however, recruitment is complete.

NCT01135056: SIR-Spheres compared to sorafenib in hepatocellular carcinoma. Status: recruiting.

NCT01126645: SIR-Spheres and sorafenib compared to sorafenib alone in hepatocellular carcinoma. Status: recruiting.
Costs and resource consequences

A conference abstract (Chaplin et al. 2015) reported a cost-effectiveness analysis of SIRT (TheraSphere) compared with sorafenib treatment for HCC in the UK. Although this study did not use SIR-Spheres it may give an indication of the cost consequences for SIRT overall. The study used published evidence (Llovet et al. 2008; Salem et al. 2011) which showed that SIRT improved time to progression compared to sorafenib (6.2 months versus 4.9 months) and median overall survival (13.8 months versus 9.7 months). The abstract reported that the total lifetime cost of SIRT was lower than sorafenib (£21,441 compared with £34,050). SIRT was associated with a quality adjusted life year (QALY) gain of 0.27 compared with sorafenib at a lower total cost. SIRT was therefore considered to have dominated sorafenib.

An Italian Health Technology Assessment (HTA) of SIRT (including SIR-Spheres) for colorectal metastases (Chiarolla et al. 2013) reported the total median cost of the SIRT procedure including the costs of diagnostic work-up, treatment and follow-up as £10,879 (15,229 euro) ranging from £9,703 (13,582 euro) to £12,409 (17,370 euro). Specific costs for individual SIRT technologies were not reported.

A cost-effectiveness model comparing SIR-Spheres with best supportive care in patients with metastatic colorectal cancer reported a cost of £14,248 for the SIR-Spheres procedure and work-up (Pennington et al. 2015). The model was designed from the perspective of the NHS with a lifetime horizon. The total discounted cost for SIR-Spheres was £35,487 compared to £12,730 for best supportive care. The improved survival following treatment with SIR-Spheres resulted in a cost per life year gained of £20,323 and cost per QALY of £28,216 in the model’s base case. The impact of different disease indications (metastatic colorectal cancer compared with HCC) is uncertain.

Strengths and limitations of the evidence

This briefing includes 11 selected studies. Six of the studies were comparative (D’Avola et al. 2009; Gramenzi et al. 2015; Kolligs et al. 2015; Kwok et al. 2014; Pitton et al. 2015; Ricke et al. 2015); and 4 were described as prospective studies (Chow et al. 2014; Kolligs et al. 2015; Pitton et al. 2015; Ricke et al. 2015). Three were retrospective non-comparative studies (Golfieri et al. 2013; Sangro et al. 2011; Saxena et al. 2014) and 1 non-comparative study was carried out prospectively with retrospective analysis (Inarrairaegui et al. 2012).

All studies presented standardised outcomes such as overall survival and progression-free survival. All reported safety outcomes and were of good quality. Three of the 6 comparative studies were
randomised (Kolligs et al. 2015; Pitton et al. 2015; Ricke et al. 2015). Gramenzi et al. (2015) compared SIR-Spheres with sorafenib. This study had a relatively large patient sample. The remaining randomised studies had small patient samples, with 1 study in particular lacking power to carry out meaningful statistical analysis (Kolligs et al. 2015). None of the randomised studies were blinded, which may give rise to bias in subjective outcomes such as health-related quality of life.

Generally, the retrospective studies (D’Avola et al. 2009; Golfieri et al. 2013; Gramenzi et al. 2015; Kwok et al. 2014; Sangro et al. 2011; Saxena et al. 2014) included large patient samples, except Kwok et al. (2014), which compared 25 patients having SIRT with 12 patients not having SIRT. In addition, the treatment in the Kwok et al. (2014) study was funded by the patients themselves, potentially biasing the findings. Although the study by Sangro et al. (2011) had a large patient sample, it was a multicentre study where patient selection and treatment protocol varied between enrolled centres. The retrospective study by D’Avola et al. (2009) was comparative but the groups were not homogeneous in relation to disease severity. Some patients from both groups in the study by Gramenzi et al. (2015) were treated with second-line treatments which may have confounded the analysis.

The study by Inarrairaegui et al. (2012) highlighted the use of SIRT in downstaging HCC for radical treatment (ablation, resection and liver transplantation) and as a bridge to liver transplantation. However, this study was not comparative and patient numbers were low.

The choice of treatment for HCC is dependent on several factors including disease stage and response to previous therapies. Two of the 11 studies included in this briefing compared SIR-Spheres with TACE or DEB-TACE. SIR-Spheres were compared with sorafenib in 2 studies, and with no treatment or best-supportive care in 2 other studies. Other comparator treatments such as TACE, sorafenib and best supportive care currently used in the NHS are represented in the evidence in this briefing.

Relevance to NICE guidance programmes

NICE has issued the following guidance:

**Selective internal radiation therapy for primary hepatocellular carcinoma** (2013) NICE interventional procedure guidance 460

**Selective internal radiation therapy for primary intrahepatic cholangiocarcinoma** (2013) NICE interventional procedure guidance 459
Selective internal radiation therapy for non-resectable colorectal metastases in the liver (2011) NICE interventional procedure guidance 401

Microwave ablation of hepatocellular carcinoma (2007) NICE interventional procedure guidance 214

Radiofrequency ablation of hepatocellular carcinoma (2003) NICE interventional procedure guidance 2

Sorafenib for the treatment of advanced hepatocellular carcinoma (2010) NICE technology appraisal guidance 189

References


Chiarolla E, Paone S, Lo Scalzo A et al. (2013) HTA report: Selective internal radiation therapy (SIRT) in colorectal liver metastases. Rome

Chow PKH, Poon DYH, Khin MW et al. (2014) Multicenter phase II study of sequential radioembolization-sorafenib therapy for inoperable hepatocellular carcinoma. PLoS ONE [Electronic Resource], 9, (3) e90909


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Search strategy and evidence selection

Search strategy

A literature search covering the period to 2012 was carried out to produce an interventional procedures overview (IPO) for the NICE guidance on selective internal radiation therapy for primary liver cancer. Two studies from the IPO were included in this briefing (D'Avola et al. 2009 and Sangro et al. 2011). An updated search was carried out to identify current evidence on SIR-Spheres for HCC.

The strategy was developed in MEDLINE (Ovid) using a combination of subject indexing terms and free text search terms for the indication and procedure. The search included both TheraSphere and SIR-Spheres technologies. The strategy was adapted for the following databases: Medline in Process, Embase, Cochrane Library (CENTRAL, CDSR, DARE, HTA, NHS EED), EconLit, Pubmed ('epub ahead of press'), Scopus and Web of Science (WoS – Science Citation Index and Conference Proceedings Citation Index-Science).

The searches returned 1,010 references, which was reduced to 512 after automated removal of conference abstracts, non-English language papers, case reports, and non-systematic reviews. Information supplied by the manufacturer was checked for relevant studies.

ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) were searched to identify ongoing or in-development trials.

Evidence selection

Retrieved results were sifted by 2 researchers using the selection criteria below.

- Population: patients with hepatocellular carcinoma (operable or inoperable)
- Intervention: yttrium-90 selective internal radiation therapy
- Comparators: any (including TACE, best supportive care, chemotherapy, surgery, none)
- Outcomes:
  - overall survival
  - progression-free survival
- quality of life
- tumour response
- toxicity
- complications/adverse events/side effects
- downstaging or bridging to transplantation.

Following the first sift, 446 records were removed for the reasons listed below, to leave 66 potentially eligible studies:

Non-systematic reviews and background information: 46

Duplicate record: 1

Case reports: 12

Editorial, retraction, no abstract, protocol: 65

Non-HCC population (or HCC results not presented separately): 114

Non-English language: 1

Outcomes not relevant to the scope, for example papers focusing on imaging methodologies, pre-SIRT treatment approaches, technical findings, dosimetry: 195

Non-yttrium-90 technology: 4

Non-human study: 5

Twenty two studies using SIR-Spheres from the 2012 onwards search met the inclusion criteria. Of these, 11 were selected for full data extraction and have been summarised in table 1 with full study details presented in the appendix (Tables 2 to 20). Studies were prioritised according to design and sample size (from highest to lowest) as follows: prospective comparative, retrospective comparative, non-comparative with larger sample size. Studies were also prioritised if key outcomes were focused on efficacy and safety of SIRT. One study (Inarrairaegui et al. 2012) was included to highlight the use of SIR-Spheres in downstaging of liver tumours for resection, liver transplantation and as a bridge to transplantation.
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Table 5: Summary of results of the D'Avola et al. (2009) study

Table 6: Overview of the Golfieri et al. (2013) study

Table 7: Summary of results of the Golfieri et al. (2013) study

Table 8: Overview of the Gramenzi et al. (2015) study

Table 9: Summary of results of the Gramenzi et al. (2015) study

Table 10: Overview of the Inarrairaegui et al. (2012) study

Table 11: Overview of the Kolligs et al. (2015) study

Table 12: Summary of results of the Kolligs et al. (2015) study

Table 13: Overview of the Kwok et al. (2014) study

Table 14: Overview of the Pitton et al. (2015) study

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Table 17: Overview of the Sangro et al. (2011) study
Table 20: Summary of results of the Saxena et al. (2014) study

Table 2 Overview of the Chow et al. (2014) study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/ hypotheses</td>
<td>To evaluate the safety and efficacy of sequential radioembolisation-sorafenib in patients with HCC not amenable to curative therapies.</td>
</tr>
<tr>
<td>Study design</td>
<td>Prospective, non-comparative case series.</td>
</tr>
<tr>
<td>Setting</td>
<td>Multicentre; 7 Asia-Pacific centres (Malaysia, Myanmar, Singapore and South Korea). Patients were enrolled between June 2008 and May 2009.</td>
</tr>
<tr>
<td>Intervention and comparator</td>
<td>Intervention: Radioembolisation with yttrium-90-resin microspheres (SIR-Spheres, Sirtex Medical Limited, North Sydney, Australia) followed by initiation of sorafenib (400 mg twice daily) 14 days post-radioembolisation, given continuously until tumour progression or the emergence of drug-related adverse events.</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>Inclusion criteria: Patients with inoperable HCC including those with extrahepatic disease (except CNS metastases) and/or major vascular involvement were eligible for inclusion. Adults with confirmed diagnosis of HCC with measurable disease (defined as ≥1 lesion of ≥10 mm), adequate renal function, haemopoietic function, and ECOG performance status 0 or 1. In addition, eligible patients were required to have: 1) sufficient liver function for safe delivery of radioembolisation, 2) hepatic arterial anatomy that would enable safe delivery of microspheres to the liver only; 3) without excess hepato-pulmonary shunting (&gt;20%); or 4) without main trunk PVT. Premenopausal, sexually active individuals were required to use 2 forms of contraception during the study. Exclusion criteria: Pregnant or breastfeeding women or patients previously treated with external beam radiotherapy to the liver or currently having any other investigational agent.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Safety/tolerability and best overall response rate (ORR; using RECIST version 1.0) Secondary outcomes included disease control rate (DCR), time to progression (TTP), progression-free survival (PFS), overall survival (OS) and health-related quality of life (HRQoL).</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>Best ORR was calculated with 95% exact CI. Baseline patient characteristics, ORR, DCR, PFS and OS were stratified by BCLC stage to allow meaningful comparisons with other treatment modalities. PFS and OS were summarised using the Kaplan–Meier technique; median values and 95% CI were reported.</td>
</tr>
<tr>
<td>Patients included</td>
<td>n=29 Mean age 64.6 years (SD±10.6). 72% male</td>
</tr>
<tr>
<td>Results</td>
<td>28 patients experienced toxicity ≥grade 1 in severity; 15 (52%) grade ≥3. Best ORR was 25%, including 2 (7%) CR and 5 (18%) PR, and 15 (54%) SD. Disease control was 100% and 65% in BCLC stage B and C, respectively. 2 patients (7%) had sufficient response to enable radical therapy. Median survivals for BCLC stage B and C were 20.3 and 8.6 months, respectively.</td>
</tr>
</tbody>
</table>
Conclusions

The results of the study provide provisional evidence of the potential efficacy and manageable toxicity of sorafenib and radioembolisation in a population with predominantly advanced disease.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BCLC, Barcelona Clinic for Liver Cancer; CI, confidence interval; CNS, central nervous system; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; INR, International Normalized Ratio; n, number of patients; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria In Solid Tumors; SD, standard deviation; SIRT, selective internal radiation therapy; SD, stable disease; SD, standard deviation; TTP, time to progression.

Table 3 Summary of results from the Chow et al. (2014) study

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>≤90 days post-radioembolisation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>n=29</td>
<td>n=29</td>
</tr>
<tr>
<td><strong>Primary outcomes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory adverse events (n (%) patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin:</td>
<td>2 (7), 0</td>
<td>14 (48), 2 (7)</td>
</tr>
<tr>
<td>Albumin:</td>
<td>22 (76), 0</td>
<td>20 (69), 5 (17)</td>
</tr>
<tr>
<td>ALT:</td>
<td>17 (59), 0</td>
<td>20 (69), 1 (3)</td>
</tr>
<tr>
<td>AST:</td>
<td>21 (72), 1 (3)</td>
<td>20 (69), 8 (28)</td>
</tr>
<tr>
<td>ALP:</td>
<td>9 (31), 1 (3)</td>
<td>13 (45), 4 (14)</td>
</tr>
<tr>
<td><strong>Treatment related toxicities</strong></td>
<td>Twenty eight of 29 (97%) patients experienced toxicity ≥ grade 1 in severity following the treatment; 15 (52%) were grade 3 or higher. Toxicities in 5 (17%) patients occurred post-radioembolisation and before sorafenib administration; all were grade 1–2 except 1 grade 3 ascites.</td>
<td></td>
</tr>
<tr>
<td><strong>Best ORR (n (%) patients):</strong></td>
<td>BCLC stage B (n=11)</td>
<td>BCLC stage C (n=17)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (9%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (36%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Stable response</td>
<td>6 (55%)</td>
<td>9 (53%)</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>---------</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>Not done</td>
<td>0</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Selected secondary outcomes:</td>
<td>BCLC stage B (n=11)</td>
<td>BCLC stage C (n=17)</td>
</tr>
<tr>
<td>DCR (CR+PR+SD), % patients (95% CI)</td>
<td>100% (72–100)</td>
<td>65% (38–86)</td>
</tr>
<tr>
<td>TTP Months, median (95% CI)</td>
<td>15.2 (4.6–nr)</td>
<td>9.0 (3.5–nr)</td>
</tr>
<tr>
<td>PFS Months, median (95% CI)</td>
<td>15.2 (4.6–nr)</td>
<td>6.5 (3.5–9.1)</td>
</tr>
<tr>
<td>OS Months, median (95% CI)</td>
<td>20.3 (10.9–nr)</td>
<td>8.6 (5.6–14.2)</td>
</tr>
</tbody>
</table>

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CR, complete response; DCR, disease control rate; n, number of patients; ORR, overall response rate; PR, partial response; SD, stable disease; nr, not reached.

Table 4 Overview of the D'Avola et al. (2009) study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/hypotheses</td>
<td>To determine the impact of yttrium-90-radioembolisation (SIR-Spheres) on survival when used as a first-line treatment for unresectable HCC.</td>
</tr>
</tbody>
</table>
Study design | Retrospective, non-randomised, consecutive, case series with a historical control.
---|---
Intervention and comparator | Intervention: yttrium-90-labelled resin microspheres (SIR-Spheres, Sirtex). Control: Patients having active treatment (67%) and patients having supportive care only (32%).
Inclusion/exclusion criteria | Inclusion criteria:
18 years and above, preserved liver function, a platelet count >40/pl, no contraindication to angiography and provided consent.
The control group were potential candidates for SIR-Spheres but had received conventional care due to unavailability or technical contraindications.
Exclusion criteria:
Patients treated with liver transplantation, surgical resection or percutaneous ablation; TAE or TACE for single, non-bulky tumours, or with lung shunting, had cirrhosis, had a serum bilirubin >2 mg/dl, had a platelet count <40/pl, or had clinical ascites.
Patients treated with SIR-Spheres in whom MMA activity co-localised poorly with liver nodules were also excluded.
Primary outcomes | Overall median survival
(Secondary outcomes included deaths and further treatment).
Statistical methods | Survival was plotted using the Kaplan–Meier method and compared using log rank test. A p value of <0.05 was considered significant.
Patients included | n=88 (35 SIR-Spheres and 43 control group)
Mean age: 63 years (SIR-Spheres) and 61 years (control group).
80% male (SIR-Spheres), 86% males (control group).
Results

Median survival from diagnosis was significantly higher in the SIR-Spheres group compared with controls (16 versus 8 months; p<0.05), even after adjusting for cirrhosis, multi-nodular disease, bilobar involvement or vascular invasion. In a multivariate analysis, treatment with radioembolisation was the only prognostic factor independently associated with improved survival. In an intention-to-treat analysis, patients evaluated for radioembolisation (finally treated or not) survived longer than controls (13 versus 10 months; p<0.05).

Conclusions

SIR-Spheres are likely to improve survival among patients with unresectable HCC compared with conventional treatment. Further prospective studies are needed to evaluate the potential of this new treatment modality in unresectable HCC.

Abbreviations: 99mTc-MAA, technitium-99m-labelled macroaggregated albumin; HCC, hepatocellular carcinoma; mg/dl, milligrams per decilitre; n, number of patients; pl, picolitre; TACE, transarterial chemoembolisation; TAE, transarterial embolisation.

Table 5 Summary of results from the D’Avola et al. (2009) study

<table>
<thead>
<tr>
<th></th>
<th>SIRT (SIR-Spheres)</th>
<th>Control</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>n=35</td>
<td>n=43</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome:</strong></td>
<td>16.0 months (95% CI 7.7 to 24.4).</td>
<td>8.0 months (95% CI 5.5 to 10.4).</td>
<td>p&lt;0.001 (adjusted for cirrhosis, multi-nodular disease, bilobar involvement or vascular invasion).</td>
</tr>
<tr>
<td><strong>Median survival (actuarial)</strong></td>
<td>The difference in survival between patients in the control group (having active treatment or best supportive care) was not significant.</td>
<td>Difference in survival was also observed when patients who had sorafenib were censored.</td>
<td>Multivariate analysis showed treatment with yttrium-90 was independently associated with a better survival. OR 3.5 (95% CI 1.9 to 6.5); p&lt;0.05.</td>
</tr>
</tbody>
</table>
Selected secondary outcomes:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>64% (56/88) patients had died at time analysis</td>
</tr>
<tr>
<td>Further</td>
<td>20% (7/35) patients had second-line treatment after SIRT</td>
</tr>
<tr>
<td>treatment</td>
<td>• 8.5% (3/35) patients with SD had a second course of SIRT.</td>
</tr>
<tr>
<td></td>
<td>• 17% (6/35; 3 with SD; 3 with PD) were treated with sorafenib for a mean period 3.4 months (2 to 12 months after SIRT).</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; n, number of patients; OR, objective response; PD, progressive disease; SD, stable disease; SIRT, selective internal radiation therapy.

Table 6 Overview of the Golfieri et al. (2013) study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/ hypotheses</td>
<td>To evaluate the outcomes among older (≥70 years) and younger patients (&lt;70 years) with unresectable hepatocellular carcinoma (HCC) who received radioembolisation at 8 European centres.</td>
</tr>
<tr>
<td>Study design</td>
<td>Retrospective, consecutive case series.</td>
</tr>
<tr>
<td>Setting</td>
<td>Multicentre; Europe. Patients had radioembolisation between 25/09/2003 and 17/12/2009.</td>
</tr>
<tr>
<td>Intervention and comparator</td>
<td>Intervention: Radioembolisation with ⁹⁰Y resin microspheres (SIR-Spheres).</td>
</tr>
</tbody>
</table>
## Inclusion/exclusion criteria

**Inclusion criteria:**
ECOG performance status of 0–2; untreated life expectancy of >12 weeks; not amenable to curative therapy; uncompromised pulmonary function; adequate haematological parameters.

All patients in these analyses had a confirmed diagnosis of HCC with liver-only or liver-dominant tumours, which had either progressed following surgical resection or loco-regional treatment and/or who were considered poor candidates for TACE because of presence of portal vein invasion or thrombosis or extensive tumour burden.

**Exclusion criteria:**
Evidence of any uncorrectable flow to the GI tract observed on angiography MAA; estimated radiation dose greater than 30 Gy (16.5 mCi) delivered to the lungs in a single administration or 50 Gy on multiple administrations; abnormal organ or bone marrow function; limited hepatic reserve; or ascites or other clinical signs of liver failure on physical examination.

## Outcomes

**Primary outcomes:** Overall median survival

**Secondary outcomes:** Included procedure-related clinical adverse events and laboratory toxicities.

## Statistical methods

The Kaplan–Meier product-limit method was used to compute non-parametric estimates of survival. The p-values for continuous baseline variables were assessed by 1-way ANOVA; the p-values for dichotomous variables by the Fisher’s exact test, and p-values for nominal categorical variables by the Chi-square general association test. The Cochran-Mantel–Haenszel was used to compare the CTCAE distribution between cohorts.

## Patients included

- **Total n=325**
  - ≥70 years (n=128):
    - 79.7% male. Mean age was 74.3 (SD ±3.97) years.
  - <70 years (n=197):
    - 82.7% male. Mean age was 58.1 (SD ±8.86) years.

## Results

Kaplan-Meier analysis revealed no significant difference in overall median survival following radioembolisation between older and younger patients (median 14.5 [95% CI 10.6–16.8] months versus 12.8 [95% CI 10.8–17.9] months, respectively; p=0.942).
Conclusions

Radioembolisation appears to be as well tolerated and effective for older people as it is for younger patients with unresectable HCC. Age alone should not be a discriminating factor for managing HCC.

Abbreviations: MAA, $^{99}$Tc-macroaggregated albumin; ANOVA, analysis of variance; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; g/dl, grams per decilitre; GI, gastrointestinal; Gy, gray; HCC, hepatocellular carcinoma; mCi, millicurie; mg/dl, milligrams per decilitre; n, number of patients; SD, standard deviation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation.

Table 7 Summary of results from the Golfieri et al. (2013) study

<table>
<thead>
<tr>
<th></th>
<th>Younger (&lt;70 years)</th>
<th>Older (≥70 years)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>n=197</td>
<td>n=128</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome:</strong></td>
<td></td>
<td></td>
<td>p=0.942</td>
</tr>
<tr>
<td>Overall median survival</td>
<td>12.8 months (95% CI 10.8–17.9)</td>
<td>14.5 months (95% CI 10.6–16.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Selected secondary outcomes:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Post-procedure day 30: n=2 (1.0%)</td>
<td>Post-procedure day 30: n=0 (0%)</td>
<td>Day 30, p=0.521</td>
</tr>
<tr>
<td></td>
<td>Post-procedure day 60: n=8 (4.1%)</td>
<td>Post-procedure day 60: n=5 (3.9%)</td>
<td>Day 60, p=1.00</td>
</tr>
<tr>
<td></td>
<td>Post-procedure day 90: n=13 (6.6%)</td>
<td>Post-procedure day 90: n=9 (7.0%)</td>
<td>Day 90, p=1.00</td>
</tr>
</tbody>
</table>

201 deaths were recorded over a median follow-up of 10 months, 3 (0.9%) were considered to be definitely related to the procedure and 11 (3.4%) were considered to be probably related to the procedure.
Main procedure-related clinical adverse events in the first 3 months post-treatment (All grades)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Older Population</th>
<th>Younger Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>n=109 (55.3%)</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>n=63 (32%)</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>n=57 (28.9%)</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Fever</td>
<td>n=21 (10.7%)</td>
<td>Fever</td>
</tr>
<tr>
<td>GI ulceration</td>
<td>n=9 (4.6%)</td>
<td>GI ulceration</td>
</tr>
</tbody>
</table>

Laboratory toxicities between baselines and month 3.

Severe increases in total bilirubin (to grade ≥3) at 3 months compared with baseline were observed in 4.3% and 6.9% of older and younger populations, respectively (p=0.432). A greater number of older patients experienced hypoalbuminemia (p=0.018) and elevated ALT (p=0.015) at 3 months, although these changes were restricted to grade 1–2.

Abbreviations: ALT, alanine transaminase; CI, confidence interval; n, number of patients.

Table 8 Overview of the Gramenzi et al. (2015) study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/hypotheses</td>
<td>The study compares the outcomes achieved with sorafenib and TARE in HCC patients potentially amenable to either therapy.</td>
</tr>
<tr>
<td>Study design</td>
<td>Retrospective, consecutive, comparative case series.</td>
</tr>
<tr>
<td>Setting</td>
<td>Single-centre; Italy. TARE patients were enrolled from September 2005 to October 2012. Sorafenib patients were enrolled between May 2008 and September 2012.</td>
</tr>
</tbody>
</table>
### Intervention and comparator

<table>
<thead>
<tr>
<th>Intervention and comparator</th>
<th>Intervention: TARE with $^{90}$Y resin microspheres (SIR-Spheres). Comparator: Sorafenib administered at 400 mg twice daily.</th>
</tr>
</thead>
</table>

### Inclusion/exclusion criteria

**SIR-Spheres inclusion criteria:**
- Age ≥ 18 years, life expectancy ≥ 3 months,
- ECOG-PS ≤ 1, serum bilirubin ≤ 2 mg/dl, BCLC stage B or C; granulocyte count ≥ 1.5 x 10⁹/l and platelet count ≥ 50 x 10⁹/l.

**SIR-Spheres exclusion criteria:**
- Tumour extension > 50% of liver volume, unmeasurable tumour burden, extrahepatic metastases, diuretic uncontrolled ascites, Child–Pugh score > 8, serum creatinine > 2 mg/dl, pulmonary insufficiency, acute uncontrolled infections, previous radiation therapy or systemic chemotherapy, previous transplant or other immunodeficiency conditions, contraindication for angiography or selective visceral catheterisation, evidence of hepatopulmonary shunt > 20% at $^{99}$mTc-MAA scintigraphy, evidence of any detectable $^{99}$mTc-MAA delivery to the stomach or duodenum after embolisation of the gastroduodenal artery (if needed) and pregnancy or contraindication for oral contraception in premenopausal females.

### Outcomes

**Primary outcome:** Overall survival  
**Secondary outcomes:** Included tumour response, TTP and treatment toxicity.

### Statistical methods

Continuous data were expressed as mean±standard deviation or median and range, as appropriate. The Mann–Whitney U-test, chi-squared test or Fisher’s exact test was used to compare variables. OS was calculated from treatment start to death, with values censored at 31 December 2012 or at the last patient evaluation (drop-outs). A further survival analysis was performed censoring patients who had sorafenib after SIR-Spheres at the time of sorafenib starting. Survival estimates were obtained by Kaplan–Meier analysis and compared with the log-rank test. A 2-tailed p < 0.05 was considered statistically significant.

### Patients included

n=137 (n=63 SIR-Spheres versus n=74 sorafenib)  
Mean age 66 years (SIR-Spheres), 71 years (sorafenib).  
79.4% male (SIR-Spheres), 86.5% male (sorafenib)
Results

Median overall survivals of the 2 groups were comparable, being 14.4 months (95% CI: 4.3–24.5) in sorafenib and 13.2 months (95% CI: 6.1–20.2) in SIR-Spheres patients, with 1-, 2- and 3-year survival rates of 52.1%, 29.3% and 14.7% versus 51.8%, 27.8% and 21.6% respectively. Two SIR-Spheres patients underwent liver transplantation after successful downstaging. To minimise the impact of confounding factors on survival analysis, a propensity model matched 32 patients of each group for median age, tumour gross pathology and the independent prognostic factors. Even after matching, the median survival did not differ between sorafenib (13.1 months; 95% CI: 1.2–25.9) and SIR-Spheres patients (11.2 months; 95% CI: 6.7–15.7), with comparable 1-, 2- and 3-year survival rates.

Conclusions

In cirrhotic patients with intermediate-advanced or not-otherwise-treatable HCC, sorafenib and SIR-Spheres provide similar survival. Downstaging allowing liver transplantation only occurred after SIR-Spheres.

Abbreviations: 99mTc-MAA, technetium-99 m macroaggregated albumin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; mg/dl, milligrams per decilitre; n, number of patients; OS; overall survival; PS, performance status; TARE, transarterial radioembolisation; TTP, time to tumour progression.

Table 9 Summary of results from the Gramenzi et al. (2015) study

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>TARE (SIR-Spheres)</th>
<th>Sorafenib</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=63</td>
<td>11.2 months; 95% CI: 6.7–15.7</td>
<td>13.1 months; 95% CI: 1.2–25.9</td>
<td>p=0.392</td>
</tr>
<tr>
<td>1-year, 2-year and 3-year survival rates were 44.7%, 19.0% and 9.5%.</td>
<td>1-year, 2-year and 3-year survival rates were 53.1%, 23% and 15.3%.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome: Overall median survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected secondary outcomes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median TTP</td>
<td>3 months (range 1–21)</td>
<td>5 months (1–36.5)</td>
<td>p=0.012</td>
</tr>
</tbody>
</table>
AEs occurred in 37 (59%) of patients. The most common side effect was fatigue (9%) lasting few weeks after SIR-Spheres; severe (grade 3/4) fatigue was observed in 2%. Other side effects included grade 1/2 fever (6%), severe (grade 3/4) fever (2%), nausea/vomiting (2%) and abdominal pain (8%) easily controlled with medication in 48 hours. Child–Pugh score deterioration occurred within 1 month in 6 patients, within 6 months in 6 patients, and thereafter in 9 patients.

Severe AEs (grade 3/4) were radiation pneumonia (8%), RILD (8%) and cholecystitis (5%).

Table 10

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/hypotheses</td>
<td>Occasionally, patients with hepatocellular carcinoma (HCC) who have radioembolisation with palliative intent are downstaged for radical treatments. The aim of this study was to describe and analyse the overall survival (OS) in these patients compared with patients of the same baseline stage (UNOS T3), who were not eligible for radical treatment after radioembolisation.</td>
</tr>
<tr>
<td>Study design</td>
<td>Prospective non-comparative consecutive study with retrospective subgroup analysis.</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Intervention and comparator</td>
<td>Intervention: Radioembolisation using resin microspheres labelled with the radionuclide yttrium-90 (SIR-Spheres). Patients were analysed in 2 groups, those who were downstaged (had radical treatment) and those who were not downstaged (did not have radical treatment).</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>Inclusion: Patients with UNOS T3 stage HCC, nodule &gt;5 cm, or 2 or 3 nodules, at least 1 &gt;3 cm, without vascular invasion who after radioembolisation were downstaged for radical treatments. Patients were considered for radioembolisation if they had progressed on previous TACE, were not good candidates for TACE, or could achieve intense tumour response with segmental radioembolisation.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Downstaging and radical treatment. (Secondary outcomes included overall survival and time-to-progression).</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>Mann–Whitney U test was used for continuous variables to compare differences in patient, tumour and treatment characteristics between the 2 groups. Fisher exact test tested the associations of independent categorical variables. Overall survival (OS) and time to progression was plotted using Kaplan–Meier and between groups differences were compared using log-rank test. Survival was calculated from time of radioembolisation (patients were not censored to radical therapies).</td>
</tr>
</tbody>
</table>
| Patients included | n=21  
Median age 72 years  
n=17 male |
Results

In total, 6 of 21 (29%) patients were downstaged and treated radically between 2 and 35 months post-radioembolisation. Three patients were resected, 2 had liver transplantation and 1 had RFA followed by surgical resection 1 year later. Patients treated radically were significantly younger (62 versus 73 years, p=0.006) and had higher tumour volume (583 ml versus 137 ml, p=0.001) than patients who did not achieve radical treatment. Across the whole series, the median 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 had palliative treatment only (22.0 months; 95% CI 15.0–30.9).

Conclusions

Salvage surgery (partial hepatectomy or liver transplantation) following tumour downstaging with radioembolisation provides the possibility of long-term survival in a selected subgroup of patients with otherwise limited possibilities.

Abbreviations: BCLC, Barcelona clinic liver cancer; CI, confidence interval; HCC, hepatocellular carcinoma; n, number of patients; OS, overall survival; RFA, radiofrequency ablation; UNOS, United Network for Organ Sharing.

Table 11 Overview of the Kolligs et al. (2015) study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/hypotheses</td>
<td>To compare selective internal radiation therapy (SIRT) with conventional transarterial chemoembolisation (TACE) with lipiodol, the standard-of-care for intermediate-stage unresectable, hepatocellular carcinoma (HCC), as first-line treatment.</td>
</tr>
<tr>
<td>Study design</td>
<td>Prospective, randomised controlled comparative trial.</td>
</tr>
<tr>
<td>Setting</td>
<td>Multicentre; Spain and Germany.</td>
</tr>
<tr>
<td>Intervention and comparator</td>
<td>Intervention: SIRT with (^{90})Y-resin microspheres (SIR-Spheres). Comparator: TACE was administered using epirubicin 50 mg/m(^2), lipiodol and embolising agent (Embosphere 150–300 micrometres or 300–500 micrometres; Merit Medical, Maastricht, The Netherlands).</td>
</tr>
</tbody>
</table>
### Inclusion/exclusion criteria

**Inclusion:**
- Adults with unresectable HCC, confirmed by either histology/cytology or the EASL diagnostic criteria, with preserved liver function and an ECOG performance status ≤2, and absence of any form of vascular invasion or extrahepatic spread. Only patients with ≤5 liver lesions (≤20 cm total maximum diameter), including at least one quantifiable lesion, or a single lesion ≤10 cm were recruited.

**Exclusion:**
- Patients with significant extrahepatic uptake on $^{99m}$Tc-MAA scan precluding safe administration of SIRT or >15% arteriovenous shunting from liver to lungs.

### Outcomes

Primary outcomes: HRQoL
Secondary outcomes: Included efficacy, PFS, survival, safety and tolerability.

### Statistical methods

Continuous variables were assessed by 1-way ANOVA, dichotomous variables by Fisher’s exact test and Chi-square general association test for nominal categorical variables. HRQoL data were analysed by the Kruskal–Wallis test.

### Patients included

- $n=28$ (n=13 SIR-Spheres versus n=15 TACE)
- Mean age: SIR-Spheres 65.8±6.73 years, TACE 66.7±9.04 years.
- 84.6% male (SIR-Spheres), 86.7% male (TACE)

### Results

Twenty eight patients with BCLC stage A (32.1%), B (46.4%) or C (21.4%) had either a mean of 3.4 (median 2) TACE interventions (n=15) or a single SIR-Spheres procedure (n=13). Both treatments were well tolerated. Despite SIR-Spheres patients having significantly worse physical functioning at baseline, at week 12, neither treatment had a significantly different impact on HRQoL. Both TACE and SIR-Spheres were effective for the local control of liver tumours. Best overall response-rate (RECIST v1.0) of target lesions were 13.3% and 30.8%, disease control rates were 73.3% and 76.9% for TACE and SIR-Spheres, respectively. Two patients in each group were downstaged for liver transplantation (n=3) or radiofrequency ablation (n=1).

### Conclusions

Single-session SIR-Spheres appeared to be as safe and had a similar impact on HRQoL as multiple sessions of TACE, suggesting that SIR-Spheres might be an alternative option for patients eligible for TACE.
Abbreviations: ANOVA, analysis of variance; BCLC, Barcelona-Clinic Liver Cancer; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperative Oncology Group; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary questionnaire; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; MAA, macroaggregated albumin; n, number of patients; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumours; SIRT, selective internal radiation therapy; SD, standard deviation; TACE, transarterial chemoembolisation.

Table 12 Summary of results from the Kolligs et al. (2015) study

<table>
<thead>
<tr>
<th>Analysis</th>
<th>SIRT (Sir-Spheres)</th>
<th>Conventional TACE (with lipiodol)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>n=13</td>
<td>n=15</td>
</tr>
</tbody>
</table>
| **Primary outcome:** HRQoL (for 18 patients in total due to missing baseline data) | n=8
  Baseline median score: 82.0 | n=10
  Baseline median score: 96.0 | p=0.04
  The SIR-Spheres group had lower scores throughout the first 12 weeks of treatment but differences between the treatment groups were not statistically significant by week 12. |
| **Selected secondary outcomes:** | PR rates=30.8% (using RECIST 1.0) Disease control rates (CR + PR + SD)=76.9%
  1 patient was downstaged for liver transplantation and 1 was downstaged for radiofrequency ablation. | PR rates=13.3% (using RECIST 1.0) Disease control rates (CR + PR + SD)=73.3%
  2 patients were downstaged for liver transplantation. |
Table 13 Overall Overview of the Kwok et al. (2014) study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/hypotheses</td>
<td>To compare the survival in a cohort of patients having radioembolisation (RE) or no radioembolisation.</td>
</tr>
<tr>
<td>Study design</td>
<td>Retrospective, comparative case series.</td>
</tr>
<tr>
<td>Setting</td>
<td>Single-centre; China.</td>
</tr>
<tr>
<td>Intervention and comparator</td>
<td>Intervention: RE with SIR-Spheres (Sirtex). In those having RE, coil embolisation was performed in 13.</td>
</tr>
<tr>
<td></td>
<td>Comparator: No RE</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse events; CI, confidence interval; CR, complete response; PFS, progression free survival; PR, partial response; SIRT, selective internal radiation therapy; RECIST, Response Evaluation Criteria In Solid Tumours; SAE, serious adverse event; SD, stable disease; TACE, transarterial chemoembolisation.
Inclusion/exclusion criteria

Inclusion:
Patients referred for RE due to inoperable HCC.

Exclusion from RE group to no RE group:
More than 20% lung shunting in 11 patients, poor tissue to normal liver uptake ratio in 1, unpreventable risk of $^{90}$Y particles reflux to extrahepatic arteries in 2, subclinical ruptured HCC just before the MAA assessment test in 1, and common hepatic artery dissection during catheterisation of RE in 1 patient.

Primary outcome

Overall survival
Secondary outcomes were complications

Statistical methods

The survival time was calculated from the date of MAA assessment in both groups. The survival function was studied with Kaplan–Meier analysis and log-rank test; $p<0.05$ was considered significant.

Patients included

n=46 (30 RE and 16 non RE), 38 males and 8 females.
Mean age 65.1 years (RE), 65.9 years (non RE) $p=0.82$.

Results

There was significantly longer survival in patients having RE if they were in BCLC stage C ($p=0.047$), had portal vein tumour invasion ($p=0.04$), or had less than 3 nodules ($p=0.004$). There is also a trend of longer survival in patients having RE if they were in Child–Pugh class A, had ECOG score of 1 or 2, in BCLC stage B, or there is no portal vein invasion.

REILD occurred in 4 patients. Grade 2 side effects following RE included epigastric pain (n=5); vomiting (n=2) and fever (n=3)

Conclusions

RE treatment may be an independent predictive factor for longer survival in patients with inoperable HCC. Those with BCLC stage C tumour, with portal vein thrombus, and with less than 3 nodules benefit more with RE.

Abbreviations: BCLC, Barcelona Clinic of Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; MAA, $^{99}$Tc-macroaggregated albumin; n, number of patients; RE, radioembolisation; REILD, radioembolisation-induced liver disease.

Table 14 Overview of the Pitton et al. (2015) study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Objectives/hypotheses</th>
<th>To prospectively compare SIRT and DEB-TACE for treating HCC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Prospective, randomised, comparative study.</td>
</tr>
<tr>
<td>Setting</td>
<td>Single-centre; Germany.  Patients were enrolled between April 2010 and July 2012.</td>
</tr>
<tr>
<td>Intervention and comparator</td>
<td>Intervention: SIRT using resin-based $^{90}$Y loaded microparticles (SIR-Spheres)  Comparator: TACE using drug-eluting beads (DC Beads 100–300 micrometres, Terumo) loaded with a maximum dose of 150 mg doxorubicin per session.</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>Inclusion:  Age ≥18 years, HCC, proven by histology or according to EASL criteria  Intermediate stage HCC (stage B according to BCLC), at least 1 measurable lesion in MRI, tumour load ≤50 % and preserved liver function (Child–Pugh A – B7).  Exclusion:  Patients feasible for curative treatment, previous TACE or SIRT, chemotherapy during the last 4 weeks, Child–Pugh stage C, BCLC stage C, ECOG Performance Status &gt;0, tumour involvement &gt;50% of the liver, extrahepatic tumour, Serum bilirubin &gt;2.0 mg/dl; serum albumin 2.8 g/dl, serum creatinine &gt;2 mg/dl; leukocytes &lt;3,000/ml; thrombocytes &lt;50,000/ml, clinically apparent ascites (ascites only in CT/MRI are not exclusion criteria), oesophageal bleeding during the last 3 months, hepatic encephalopathy, transjugular intrahepatic portosystemic shunt (TIPS), infiltration or occlusion of the portal vein, hepatopulmonary shunt ≥20% in the macroaggregated albumin (MAA) scan, contraindications against angiography and gravidity.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Progression-free survival (PFS).  (Secondary outcomes included overall survival (OS), time to progression (TTP) and time to non-treatable progression (nTTP), cause of death and clinical events).</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>Primary and secondary outcome measures (PFS, OS, TTP and nTTP) were compared using the log-rank test. Time-to-event data were analysed by the Kaplan–Meier method and descriptive statistics of all other parameters were provided. The null hypothesis was that there is no difference in PFS for intermediate stage HCC patients treated with DEB-TACE or SIR-Spheres.</td>
</tr>
</tbody>
</table>
Patients included
n=24 (n=12 SIR-Spheres versus n=12 DEB-TACE)
Mean age 71.8 years (SIR-Spheres), 70.5 years (DEB-TACE).
Male n=8/12 (SIR-Spheres), male n=10/12 male (DEB-TACE).

Results
Median PFS was 180 days for SIR-Spheres versus 216 days for DEB-TACE patients (p = 0.6193) with a median TTP of 371 days versus 336 days, respectively (p=0.5764). Median OS was 592 days for SIR-Spheres versus 788 days for DEB-TACE patients (p=0.9271). Seven patients died in each group. Causes of death were liver failure (n=4 SIR-Spheres group; n=1DEB-TACE), tumour progression (n=1 SIR-Spheres group; n=4 DEB-TACE group), cardiovascular events, and inconclusive (both n=1 in each group).

Conclusions
No significant differences were found in median PFS, OS, and TTP. The lower rate of tumour progression in the SIR-Spheres group was nullified by a greater incidence of liver failure. This pilot study is the first prospective randomised trial comparing SIR-Spheres and TACE for treating HCC, and results can be used for sample size calculations of future studies.

Abbreviations: BCLC, Barcelona clinic liver cancer; DEB-TACE, drug-eluting bead-transarterial chemoembolisation; CT, computerised tomography; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; MAA, macroaggregated albumin; mg/dl, milligrams per decilitre; MRI, magnetic resonance imaging; nTTP, time to non-treatable progression; PFS, progression-free survival; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation; TIPS, transjugular intrahepatic portosystemic shunt; TTP, time to progression.

Table 15 Summary of results from the Pitton et al. (2015) study

<table>
<thead>
<tr>
<th></th>
<th>SIRT (SIR-Spheres)</th>
<th>DEB-TACE</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>n=12</td>
<td>n=12</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS (days)</td>
<td>180, 120/414, 266±55</td>
<td>216, 88/355, 237±49</td>
<td>p=0.6193</td>
</tr>
<tr>
<td><strong>Selected secondary outcomes:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study component</td>
<td>Description</td>
<td></td>
<td></td>
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<tr>
<td>-----------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Objectives/ hypotheses</td>
<td>Safety analyses for the first 40 patients randomised to radioembolisation with yttrium-90 ($^{90}$Y) resin microspheres followed by sorafenib or sorafenib only in the SORAMIC study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>Prospective, randomised, comparative study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td>Multicentre; Europe.</td>
<td></td>
<td></td>
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</tbody>
</table>

**Table 16 Overview of the Ricke et al. (2015) study**

<table>
<thead>
<tr>
<th>OS (days)</th>
<th>Median, Q1/Q3, mean and standard error are shown</th>
<th>592, 192/437±72</th>
<th>788, (178/950), 583±119</th>
<th>p=0.9271</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP (days)</td>
<td>Median, Q1/Q3, mean and standard error are shown</td>
<td>371, 132/561, 353±69</td>
<td>336, 91/609, 315±69</td>
<td>p=0.5764</td>
</tr>
<tr>
<td>nTTP (days)</td>
<td>Median, Q1/Q3, mean and standard error are shown</td>
<td>488, 148/925, 490±114</td>
<td>647, 182/-, 416±83</td>
<td>p=0.9322</td>
</tr>
<tr>
<td>Causes of death (n)</td>
<td>Tumour progression=1, Liver failure=4, Cardiovascular event=1, Non-conclusive=1</td>
<td>Tumour progression=4, Liver failure=1, Cardiovascular event=1, Non-conclusive=1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DEB-TACE, drug-eluting bead-transarterial chemoembolisation; SIRT, selective internal radiotherapy; n, number of patients; nTTP, time to non-treatable progression; OS, overall survival; PFS, progression-free survival; TTP, time to progression; -, not reported.
Intervention and comparator

| Intervention (combination-treatment arm): Radioembolisation with $^{90}\text{Y}$-resin microspheres (SIR-Spheres) followed by sorafenib (Nexavar; Bayer Healthcare, Leverkusen, Germany) on day 3 after last radioembolisation procedure at 200 mg twice daily for 1 week before increasing the dose to 400 mg twice daily. | Comparator (control arm): Sorafenib (Nexavar; Bayer Healthcare, Leverkusen, Germany) at 200 mg twice daily for 1 week before increasing the dose to 400 mg twice daily. |

Inclusion/exclusion criteria

| Inclusion criteria: Adults with unresectable intermediate or advanced HCC (BCLC stage B or C), good liver function (Child–Pugh ≤B7), ECOG performance status <2, at least 16 weeks untreated life expectancy and who were considered poor candidates for TACE. Patients who had undergone previous hepatic treatments for HCC (except external beam radiation therapy) were eligible provided that: the remnant liver following resection or ablation had sufficient functional reserve for radioembolisation as indicated by the inclusion/exclusion criteria; transarterial therapies had been conducted at least 12 weeks before to screening, and there was sufficient hepatic vasculature to access either pre-existing lesion(s) and/or sufficient collateral flow to new lesions to permit the infusion of $^{90}\text{Y}$-resin microspheres. | Exclusion criteria: Extensive tumour involvement in the, or extrahepatic metastases (beyond those identified in the bone, lymph nodes and adrenal glands), as well as those with abnormal organ or bone marrow function, clinical signs of liver failure (uncontrolled ascites), women who were pregnant or breast feeding, or any other contraindication to the study treatments or procedures, or any pre-existing condition that could limit the conduct or interpretation of the study results. |

Primary outcomes

| Adverse events |

Statistical methods

| Differences in adverse events between the 2 groups were analysed using Fisher's exact test. All tests were performed 2-sided at a 0.05 level of significance. |
Patients included

n=40 (n=20 SIR-Spheres + sorafenib versus n=20 sorafenib only)

Median age 71.5 years (SIR-Spheres + sorafenib), 68.5 years (sorafenib only) p=0.378.

80% male (SIR-Spheres + sorafenib), 70% male (sorafenib only) p=0.716.

Results

The incidence of total (196 versus 222) and grade ≥3 (43 versus 47) adverse events was similar in combination-treatment arm and control arm respectively (p>0.05). No significant differences in the number of total or grade 3/4 toxicities were recorded for: total bilirubin, albumin, liver enzymes, ascites, Child–Pugh, fatigue, hand–foot skin reaction, blood pressure or diarrhoea. A significant difference in all grade infection was observed between the combination-treatment and control arms (10% and 50% respectively, p=0.014). Two patients (1 in each arm) died; neither was considered to be treatment-related.

Conclusions

In conclusion, this interim safety analysis indicates that ⁹⁰⁹⁰Y-radioembolisation followed by escalation of the sorafenib dose is not associated with increased toxicity compared with sorafenib alone in patients with advanced HCC. Patients having radioembolisation benefited from the same intensity and duration of sorafenib treatment as the control arm.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; g/dl, grams per decilitre; HCC, hepatocellular carcinoma; n, number of patients; SORAMIC, SORAfenib in combination with local MICro-therapy guided by gadolinium-EOB-DTPA-enhanced MRI; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; TAE, transarterial embolization.

Table 17 Overview of the Sangro et al. (2011) study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/ hypotheses</td>
<td>To evaluate the main prognostic factors driving survival after radioembolisation using ⁹⁰⁹⁰Y-labelled resin microspheres in patients with HCC.</td>
</tr>
<tr>
<td>Study design</td>
<td>Non-comparative, non- consecutive retrospective, multicentre case-series.</td>
</tr>
</tbody>
</table>
### Setting
Multicentre; Europe. Data collected at 8 European centres between 25/10/03 and 17/12/2009. Patients were followed from date of treatment until 01/07/2010 or until date of death. Median follow-up was 10 months.

### Intervention and comparator
**Intervention:** Patients were treated with $^{90}$Y-labelled resin microspheres (SIR-Spheres).

### Inclusion/exclusion criteria
**Inclusion criteria:**
The criteria for patient selection and some details of the treatment protocol varied between centres.

RE was considered for patients not suitable for radical therapies and not good candidates for transarterial or systemic therapies.

**Exclusion criteria:**
Patients were excluded from treatment if pre-treatment workup showed that hepato-pulmonary shunt was >20%, if the shunt would result in 30 Gy being delivered in a single or 50 Gy in multiple infusions and if embolisation of microspheres into the GI tract could not be prevented.

### Primary outcomes
Overall survival and survival by BCLC staging.

### Statistical methods
Patient survival was summarised using the Kaplan–Meier product-limit method. Univariate Cox proportional hazards models were applied to identify single-vector prognostic factors associated with survival and to compare prognostic variables. A multivariate model was constructed to test the significance of prognostic indicators of survival in addition to BCLC. Associations between covariates (yes/no) and CTCAE grade were tested by Fisher's exact test and Cochran–Mantel–Haenszel row mean score. Transitions in CTCAE grades were tested by the exact McNemar's test.

### Patients included
n=325. Mean age 64.5 years (range 22–87 years). 81.5% male and 18.5% female.

### Results
The median overall survival was 12.8 months which varied significantly by disease stage (BCLC A, 24.4 months; BCLC B, 16.9 months; BCLC C, 10.0)).
**Conclusions**

This analysis provides robust evidence of the survival achieved with radioembolisation, including those with advanced disease and few treatment options.

**Abbreviations:** BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; Gy, gray; $^{90}$Y, yttrium-90.

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**Table 18 Summary of results from the Sangro et al. (2011) study**

<table>
<thead>
<tr>
<th>SIRT (SIR-Spheres)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td>n=325</td>
</tr>
</tbody>
</table>

**Primary outcomes:**

- **Overall survival**: Median overall survival was 12.8 months (95% CI, 10.9–15.7)

**Survival by BCLC staging**

- **Stage A** (n=52) = 24.4 months (95% CI, 18.6–38.1, p<0.001 comparison between other BCLC stage median OS)
- **Stage B** (n=87) = 16.9 months (95% CI, 12.8–22.8)
- **Stage C** (n=183) = 10.0 months (95% CI, 7.7–10.9)
- **Stage D** (n=3) = 5.2 months (95% CI, 2.2–NR)

**Selected secondary outcomes:**

- **Death**: 201/325 (61.8%)

- **Further treatment/bridge to transplantation**
  - Liver transplantation (n=5)
  - Resection (n=3)
  - Percutaneous ablation (n=5)

- **Procedure-related clinical adverse events**
  - All events (grades 1 to 3):
    - Fatigue = n=177 (54.5%)
    - Nausea and/or vomiting, n=104 (32.0%)
    - Abdominal pain, n=88 (27.1%)
    - Fever, n=40 (12.3%)
    - GI ulceration n=11(3.4%)

  Additionally there was 1 case (0.3%) of Grade 5 GI ulceration which was reported as the cause of death

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Main procedure-related laboratory adverse events | Change of CTCAE grade between pre-radioembolisation and month 3 shown as the percentage of individuals with decreased, the same and increased grades respectively:
- Total bilirubin = 4.8%, 59.2%, 36.0% (p<0.001)
- Albumin = 12.2%, 68.8%, 19.0% (p=0.500)
- ALT = 15.4%, 69.5%, 15.1% (p=0.289)
- INR = 4.0%, 81.2%, 14.8% (p=0.063)
- Creatinine = 1.8%, 90.9%, 7.2% (p=0.250)
- Platelets = 9.3%, 72.4%, 18.3% (p=0.581)

Abbreviations: ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; INR, international normalized ratio; NR, not reported.

Procedure-related clinical adverse events were evaluated from day 1 to day 7.

Table 19 Overview of the Saxena et al. (2014) study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/hypotheses</td>
<td>To report our Australian experience on the safety and efficacy of $^{90}$Y radioembolisation for unresectable HCC. As a secondary objective, prognostic factors for overall survival after $^{90}$Y radioembolisation were identified.</td>
</tr>
<tr>
<td>Study design</td>
<td>Retrospective, consecutive, non-comparative case series.</td>
</tr>
<tr>
<td>Setting</td>
<td>Single-centre; Australia. Patients who underwent $^{90}$Y radioembolisation between May 2006 and September 2012.</td>
</tr>
<tr>
<td>Intervention and comparator</td>
<td>Intervention: SIRT (SIR-Spheres).</td>
</tr>
</tbody>
</table>
Inclusion/exclusion criteria

**Inclusion:**
Adults with radiologically proven HCC not amenable to curative surgical resection, ability to undergo angiography and selective visceral catheterisation, ECOG performance status of 0–2 and adequate haematology, renal function and hepatic function.

**Primary outcomes**
Overall survival and tumour response
Secondary outcomes included treatment safety and prognostic factors for overall survival.

**Statistical methods**
Clinicopathological and treatment-related variables were analysed for an association with a treatment response (CR/PR or SD) and overall survival. Categorical variables were compared using Chi-square analysis or Fisher’s exact test where appropriate. Survival analysis was performed by using Kaplan–Meier method and compared using the log-rank test. To assess the variation in each liver function test over the previous follow up, we used the one-way analysis of variance.

**Patients included**
n=45
Mean age 63.6 years (SD ±11.3)
Male n=37

**Results**
Follow-up in the complete cohort was 7.8 (range, 0.1–41.8) months. The median survival after 90Y radioembolisation was 27.7 months with a 36-month survival of 26%. By RECIST criteria of the 40 patients followed-up beyond 2 months, CR to treatment was observed in 1 patient (3%), PR in 18 (45%), SD in 11 (22%) and PD in 10 (25%). On multivariate analysis only radiological response to treatment was independently associated with improved survival: CR/PR to treatment versus SD versus PD; p<0.001. 13 patients (29%) developed clinical toxicity after treatment; all complications were minor (grade I/II) and resolved without active intervention.

**Conclusions**
90Y radioembolisation is a safe and effective treatment for advanced, unresectable HCC.

**Abbreviations:**
CR, complete response; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; n, number of patients; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours; SD, stable disease; SD, standard deviation; SIRT, selective internal radiation therapy.
Table 20 Summary of results from the Saxena et al. (2014) study

| **SIRT (SIR-Spheres)** |  
| --- | --- |
| **Efficacy** | **n=45** |
| **Primary outcome: Safety and efficacy** |  
| Clinical toxicity: |  
| No patient died as a result of treatment. A total of 13 (29%) patients developed clinical toxicity after treatment. Clinical toxicities included nausea/vomiting in 6 patients (13%); fatigue in 6 patients (13%), non-specific self-limiting abdominal pain in 4 patients (9%); anorexia in 3 patients (7%); and shortness of breath in 1 patient (3%). These complications were minor (Grade I/II) and resolved without active intervention. Post-procedural imaging findings demonstrated ascites and pleural effusion and in 2 patients (4%) each, respectively. |
| Treatment response (n=40, 5 patients lost to follow-up): |  
| 40 patients (89%) were followed up beyond 2 month after initial radioembolisation therapy and underwent follow-up CT imaging from which hepatic tumour response was assessed in accordance with RECIST criteria. Overall, a CR was observed in 1 patient (of 40, 3%), PR was observed in 18 patients (45%), SD in 11 patients (22%), and PD in 10 patients (25%). |
| **Selected secondary outcomes: Overall survival** |  
| The median follow-up period for all patients was 7.8 months (range, 0.1-41.8 months), with none lost to follow-up. The median survival after the first treatment was 27.7 months with 6-month and 12-month, 18-month, 24-month, 30-month, and 36-month survival of 74%, 62%, 50%, 50%, 43% and 26%, respectively. |
| Univariate analysis identified 6 factors associated with overall survival: Extent of replacement of hepatic parenchyma by tumour (<25% versus 26-50% versus ≥51%, p=0.016), ECOG status (0 versus 1; p=0.003), number of previous lines of chemotherapy (0 versus 1–2; p=0.033), Child–Pugh status (A versus B/C; p=0.006), radiological response to treatment (CR/PR versus SD versus PD, p<0.001) and preoperative bilirubin (<19 versus ≥19; p=0.012). |
| On multivariate analysis, a poor radiological response to treatment (HR, 24.17; 95% CI, 5.37–108.86; p<0.001) was associated with a poorer prognosis. |

Abbreviations: CI, confidence interval; CR, complete response; CT, computerised tomography; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours; SD, stable disease; SIRT, selective internal radiation therapy.
Update information

August 2016: Changes to the summarised evidence and the effectiveness and safety quadrant of the table.

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and are not formal NICE guidance.

Development of this briefing

This briefing was developed for NICE by Cedar. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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Cedar

Medical Technologies Evaluation Programme, NICE

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• Medical Technologies Evaluation Programme, NICE

Specialist commentators

The following specialist commentators provided comments on a draft of this briefing:

• Professor Ricky Sharma, Consultant Oncologist, Oxford University

• Dr Teik Choon See, Consultant Interventional Radiologist, Addenbrooke's Hospital, Cambridge

• Dr Jeremy Lawrance, Consultant Interventional Radiologist, The Christie NHS Foundation Trust, Manchester.

Declarations of interest

Professor Ricky Sharma has received consultancy fees from Sirtex Europe and Biocompatibles UK (BTG) in addition to receiving research funding from Sirtex Medical. Dr Jeremy Lawrance has been a proctor for Sirtex on approximately 5 occasions and was paid for this. Dr Teik Choon See did not declare any interests relevant to this briefing.

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