NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL (MTA)

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

The following documents are made available to consultees and commentators:

1. **Appraisal Consultation Document (ACD)** issued to consultees and commentators after ACM1 on 6 November 2019

2. **Response to consultee and commentator on the Appraisal Consultation Document (ACD)**

Documents considered at ACM2 on 22 January 2020

3. **Comments on the Appraisal Consultation Document from:**
   - a. **BTG International**
     - i. Response form
     - ii. Response on AG model
   - b. **Sirtex medical**
     - i. Response form
   - c. **Terumo Europe**
     - i. Response form

4. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - a. British Liver Trust
   - b. British Liver Transplant Group-British Society of Interventional Radiology-British Nuclear Medicine Society-HCC UK-commissioned NHS England SIRT centres
   - c. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

5. **Comments on the Appraisal Consultation Document from experts:**
   - a. Teik See – clinical expert, nominated by BTG International
   - b. Helen Reeves – clinical expert, nominated by BTG International
   - c. Patient expert, nominated by Liver4Life

   Comments on the Appraisal Consultation Document received through the NICE website
   None received.

6. **Assessment Group addendum following ACM2 for consultation** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

Documents considered at ACM3 on 4 August 2020

7. Company response on the Assessment Group addendum:
- a. **BTG International**
  - i. Response form
  - ii. Response on Executable model
- b. **Sirtex medical**
  - i. Response form
  - ii. Response on Executable model
- c. **Terumo Europe**
  - i. Response form

8. Consultee and commentator response on the Assessment Group addendum from:
- a. British Liver Trust
- b. British Society of Interventional Radiology

9. Clinical and Patient expert response on the Assessment Group addendum from:
- a. Teik See – clinical expert, nominated by BTG International
- b. Helen Reeves – clinical expert, nominated by BTG International
  - i. Response form
  - ii. Response on Executable model

10. Response to consultee and commentator comments on the redacted Assessment Group addendum from Centre for Reviews and Dissemination and Centre for Health Economics – York
- a. AG Addendum following ACM2 (post ACD consultation)

Documents considered at ACM4 on 2 December 2020

11. Documents provided by BTG International post ACM3:

a. Article: “Liver Transplant following Yttrium-90 radioembolization: 15 year experience in 207-patient cohort”, Gabr et al, 16 May 2020

b. Article: “Correlation of Y90-absorbed radiation dose to pathological necrosis in hepatocellular carcinoma: confirmatory multicenter analysis in 45 explants”, Gabr et al, 27 July 2020

c. Paper: “Discussion on the LEGACY study and additional supportive studies”, 7 October 2020

d. Editorial: “Radioembolisation with personalised dosimetry: improving outcomes for patients with advanced hepatocellular carcinoma”, 6 November 2020

e. Article: “Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial”, 6 November 2020

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Selective internal radiation therapies (SIRTs) for treating hepatocellular carcinoma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using QuiremSpheres, SIR-Spheres and TheraSphere in the NHS in England. The appraisal committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: November 2019

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using QuiremSpheres, SIR-Spheres and TheraSphere in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 8 January 2020

Second appraisal committee meeting: 22 January 2020

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 The selective internal radiation therapies (SIRTs) QuiremSpheres, SIR-Spheres and TheraSphere are not recommended, within their CE marking, for treating hepatocellular carcinoma in adults.

Why the committee made these recommendations

Treatment for hepatocellular carcinoma (HCC) depends on the stage of cancer and the liver function. It includes surgery, ablation, transarterial therapies, chemotherapy (such as lenvatinib and sorafenib) and best supportive care. Treatment does not cure the disease for most people.

QuiremSpheres, SIR-Spheres and TheraSphere are SIRTs. These are small radioactive beads that are injected into the liver's blood supply to treat liver cancer. In clinical trials, SIR-Spheres has not been shown to improve survival compared with available treatment options. There is very limited clinical evidence to compare the effectiveness of QuiremSpheres and TheraSphere with other treatments. Also, there are not enough data to compare the effectiveness of the 3 SIRTs with each other.

There is not enough evidence to consider SIRTs a cost-effective use of NHS resources for early and intermediate stage HCC. For people with advanced stage HCC, the economic analysis shows that SIRTs are less clinically effective and cost more than lenvatinib or sorafenib. Because of this, SIRTs are not recommended.

2 Information about QuiremSphere, SIR-Spheres and TheraSphere

QuiremSpheres (Terumo Europe)	
CE marking	QuiremSpheres received its CE mark on 1 April 2015. It is classified as an Active Implantable Medical Device (AIMD) by Council Directive 90/385/EEC. It is indicated for treating unresectable liver tumours.

Dosage in the CE mark	The company has stated that the typical number of particles that are given by QuiremSpheres is approximately 20 to 30 million.
Price	The company has stated that the cost of QuiremSpheres is £9,896 for a single treatment. The company has a commercial arrangement (simple discount patient access scheme), which would have applied if the technology had been recommended.

SIR-Spheres (SIRTEX)	
CE marking	SIR-Spheres received its CE mark as a class III active medical device in October 2002. It is indicated for treating advanced inoperable liver tumours.
Dosage in the CE mark	SIR-Spheres is given through a catheter to the hepatic artery. It is supplied at 3 GBq yttrium-90 per vial in 5 ml water for injection in a shielded shipping vial. Each vial contains 40 to 80 million microspheres, ranging from 20 to 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. The average number of particles implanted is 30×10^6 to 60×10^6.
Price	The company has stated that the cost of SIR-Spheres is £8,000 for a single treatment. Costs may vary in different settings because of negotiated procurement discounts.

TheraSphere (BTG)	
CE marking	TheraSphere received its CE mark as a class III active medical device in September 2014. It is indicated for treating hepatic neoplasia.
Dosage in the CE mark	TheraSphere is given through a catheter to the hepatic artery. It is supplied in 6 dose sizes: 3 GBq, 5 GBq, 7 GBq, 10 GBq, 15 GBq or 20 GBq in 0.6 ml pyrogen-free water supplied in a 1 ml vial, inside an acrylic shield. Custom dose sizes are also available in increments of 0.5 GBq between 3 GBq and 20 GBq. A single treatment with TheraSphere contains 1.2 to 8 million microspheres. The recommended dose to the liver is 80 Gy to 150 Gy.
Price	The company has stated that the cost of Thera-Spheres is £8,000 for a single treatment. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 5) considered evidence from a number of sources. See the committee papers for full details of the evidence.

Potential new treatment option

People with hepatocellular carcinoma would welcome a new treatment option

3.1 Hepatocellular carcinoma (HCC) is the most common form of liver cancer in England. Treatment depends on the location and stage of the cancer, and how well the liver is functioning. Treatment options include surgery or ablation in early disease, transarterial therapies in intermediate stage disease, and chemotherapy in advanced stage disease, as well as best supportive care. Treatment does not cure the disease for many people. Patient experts explained that HCC can have a substantial impact on quality of life. People with HCC and their carers live with uncertainty and hopelessness. Often people with HCC also live with stigma and isolation because of underlying causes of disease such as alcohol. Clinical experts highlighted that people with advanced HCC have a poor prognosis with median life expectancy of less than 12 months. The committee concluded that people with HCC would welcome a new treatment option.

People with HCC and portal vein thrombosis are a relevant subgroup

3.2 The clinical experts explained that portal vein involvement, such as portal vein thrombosis (PVT), is a common comorbidity that might negatively affect prognosis. PVT happens when a blood clot narrows the vein that takes blood to the liver from the intestines. The committee understood that people with PVT were included in the NICE scope for this appraisal. It concluded that evidence for people with HCC and PVT should be considered.

This appraisal assesses 3 selective internal radiation therapies (SIRTs) for treating hepatocellular carcinoma

3.3 QuiremSpheres, SIR-Spheres and TheraSphere are SIRTs. These are small radioactive beads that are injected into the liver's blood supply to treat liver cancer. The 3 SIRTs are medical devices with CE marks for their licenced indications. QuiremSpheres is indicated for treating unresectable liver tumours, SIR-Spheres for treating advanced inoperable liver tumours and TheraSphere for treating hepatic neoplasia. The committee was aware that the scope for the appraisal was narrower than the CE marks, because it only included unresectable hepatocellular carcinoma. The committee agreed that the 3 SIRTs should be compared with each other and with available treatments to assess their cost effectiveness for treating hepatocellular carcinoma.

SIRTs might have fewer and less severe side effects than other treatment options

3.4 Clinical and patient experts stated that there were fewer and less severe side effects with SIRTs than with other treatments. Also, side effects from SIRTs are temporary, whereas side effects from chemotherapies such as sorafenib and lenvatinib can continue for the whole treatment course. The clinical experts also stated that SIRTs might extend life expectancy in advanced stage disease. The committee agreed that SIRTs might have fewer and less severe side effects than current treatments.

SIRTs are already used in the NHS, but not for HCC

3.5 The clinical experts and NHS England explained that SIRTs are available in some specialist centres across England for other cancers (such as metastatic colorectal cancer). The clinical experts explained that SIRTs for HCC have been used in England through compassionate schemes, but are not currently available through routine commissioning. The committee understood that SIRTs are currently not commissioned for HCC in the NHS but that the infrastructure exists in some specialist centres.

Clinical management

Stage of cancer and liver function characterises the disease and therefore people with HCC are a heterogenous population

3.6 There are different causes of HCC, including cirrhosis, alcohol, fatty liver disease and hepatitis. Therefore, people with HCC are a heterogenous population and their disease is characterised by both cancer and liver function. Treatment choice is multifaceted because both the cancer and liver function affect treatment outcomes. Clinical experts advised that clinicians use the Barcelona Clinic Liver Cancer (BCLC) staging system and the Child-Pugh score to help treatment decisions.

- BCLC staging looks at the number and size of tumours in the liver. There are 5 stages: very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), intermediate stage (BCLC C) and terminal stage (BCLC D). The committee agreed that stages A, B and C align with the scope for this appraisal.
- The Child-Pugh score looks at the liver function. It has 5 components: serum albumin levels, bilirubin levels, time for blood to clot, presence of ascites (fluid in the peritoneal cavity) and presence of hepatic encephalopathy. There are 3 classes: class A (the liver is working normally), class B (mild to moderate liver damage), class C (severe liver damage). Clinical experts advised that the BCLC stage and the Child-Pugh score together inform treatment choice. People with BCLC A to C can have either good liver function (Child-Pugh A) or mild to moderate liver damage (Child-Pugh B).
- More recently an alternative measure, the albumin-bilirubin (ALBI) grade, was developed to look at liver function. The committee was aware that in previous NICE guidance for HCC, the Child-Pugh score was used as a criterion for treatment, but that ALBI was not. The committee noted that both might help to inform treatment decisions. The clinical experts advised that ALBI is less frequently used for this

purpose, and that Child-Pugh is expected to be the measure of choice for the foreseeable future.

Treatment of HCC differs between the 3 BCLC stages and is influenced by Child-Pugh score

3.7 Treatment options include ablation and transplant in early disease, and conventional transarterial therapies (CTT) such as transarterial chemoembolisation (TACE) or transarterial embolisation (TAE) in intermediate stage disease. In advanced stage disease, treatment options are chemotherapy or systemic therapy with sorafenib or lenvatinib or regorafenib. In some people the aim of treatment might be to reduce the tumour size ('downstaging') to allow subsequent transplantation that could cure the disease. The committee understood that people with HCC have different treatment options depending on the stage of their disease as assessed by BCLC and Child-Pugh.

There are 3 distinct subgroups relevant to this appraisal

3.8 The committee concluded that there are 3 subgroups relevant for this appraisal:

- People for whom liver transplant is appropriate, including people with BCLC A and Child-Pugh A or B.
- People for whom CTT is appropriate, including people with BCLC B and Child-Pugh A or B.
- People for whom CTT is inappropriate, including people with BCLC C and Child-Pugh A or B.

In people with early stage disease, ablation and transplant are the standard of care in current NHS practice in England

3.9 Treatment options for early stage disease (BCLC A) are ablation and transplant. However, 1 clinical expert explained that transplants might not be available for people with good liver function (Child-Pugh A). The

committee concluded that both ablation and transplant are the standard of care for people with early stage disease in clinical practice in England.

In people with intermediate stage disease, CTTs are the standard of care in current NHS practice in England

3.10 Treatment for intermediate stage disease (BCLC B) are CTTs including transarterial chemoembolisation (TACE), drug-eluting bead transarterial chemoembolisation (DEB-TACE) and transarterial embolisation (TAE). The committee accepted that all CTTs available in the NHS in England are appropriate comparators for people with intermediate stage disease.

In people with advanced stage disease, sorafenib is the standard of care in current NHS practice in England

3.11 Systemic therapies, sorafenib and lenvatinib are both recommended for advanced HCC (BCLC C) in people with Child-Pugh grade A liver impairment (NICE technology appraisal guidance on sorafenib for treating advanced hepatocellular carcinoma and lenvatinib for untreated advanced hepatocellular carcinoma). Regorafenib is only recommended after treatment with sorafenib (NICE technology appraisal guidance on regorafenib for previously treated advanced hepatocellular carcinoma). The committee understood that sorafenib is the standard of care in clinical practice in England because there are subsequent treatments available after progression with sorafenib. Lenvatinib is now rarely used. The committee concluded that sorafenib is the appropriate comparator for SIRTs in people with advanced stage disease and with Child-Pugh grade A.

Clinical evidence

The systematic review included non-randomised controlled trials (RCTs) when not enough RCT evidence was identified

3.12 The assessment group (AG) did a systematic review of the clinical evidence on SIRTs and comparators. The research protocol is registered

on PROSPERO, the international prospective register of systematic reviews in health and social care; registration number CRD42019128383. RCTs were eligible for inclusion in the review. The AG had identified all the RCTs that were also identified by the companies in their submissions. The committee was aware of non-RCT evidence and agreed with the AG's approach to only include non-RCT evidence in the review when there was not enough RCT evidence. The committee understood that some studies might include a mixed population. It agreed to exclude these studies from the network meta-analyses if they did not provide separate results for the 3 subgroups of interest (see section 3.8). The committee used the AG's report for its decision making. This was because it included evidence for all 3 SIRTs and so was more comprehensive than the companies' submissions.

There is not enough clinical evidence for QuiremSpheres in the 3 subgroups relevant to this appraisal

3.13 The clinical evidence for QuiremSpheres came from 1 retrospective case series including 9 people that showed a 56% response rate. The committee heard that a mixed population was included, and results were only presented for the whole study population. The committee concluded that the single, small retrospective study did not provide enough data to assess clinical effectiveness of QuiremSpheres in any of the 3 subgroups relevant to this appraisal (see section 3.8).

There is limited randomised clinical evidence with a high risk of bias for TheraSphere compared with TACE for people when transplant is appropriate

3.14 The committee heard that 2 small RCTs (PREMIERE and Kulik 2014) for TheraSphere were identified that included people for whom transplant is appropriate (see section 3.8). The committee was also aware of 10 non-RCT studies, including 7 prospective comparative studies that included people from the 3 subgroups relevant to this appraisal. The PREMIERE study was done in the US and included 45 people for whom transplant would be appropriate. It compared TheraSphere with TACE as an

alternative to prepare for transplant. The AG advised that PREMIERE had a high risk of bias because of concerns with randomisation and potential deviations from the intended interventions. Also, the baseline characteristics were different in the 2 arms so that people in the TACE arm had better prognosis than people in the TheraSphere arm. Overall survival of people who had a transplant was numerically, but not statistically significantly, longer in the TheraSphere arm. The median overall survival was 18.6 months (95% confidence interval [CI] 7.4 to 32.5) compared with 17.7 months (95% CI 7.4 to 32.5). The committee concluded that there was limited evidence, with a high risk of bias, to establish whether TheraSphere was better than TACE in people for whom transplant is appropriate.

There is limited evidence with high risk of bias for TheraSphere compared with TheraSphere with sorafenib in people when transplant is appropriate

3.15 The study by Kulik 2014 was done in the US and included 20 people for whom transplant would be appropriate. It compared TheraSphere with TheraSphere and sorafenib in combination. The AG had some concerns with the randomisation process, potential deviations from the intended interventions and measurement of outcomes. The baseline characteristics were different in the 2 arms so that people in the TheraSphere plus sorafenib arm had a better prognosis. There was no difference in overall survival between the 2 arms (3 deaths in the TheraSphere arm, 2 deaths in the combination arm). The committee was aware that TheraSphere with sorafenib in combination was not included in the licence of sorafenib or the CE mark of TheraSphere. The committee concluded that there was limited evidence with high risk of bias to establish whether TheraSphere is better than TheraSphere with sorafenib in people when transplant is appropriate.

Non-randomised evidence comparing TheraSphere with non-SIRT treatments is not robust and should not be used for decision making

3.16 Of the 7 prospective comparative non-RCTs, only 4 reported overall survival or progression-free survival. Of these, 2 compared TheraSphere with TACE or DEB-TACE across the 3 subgroups. The AG's assessment suggested that both studies had high risk of bias and differences in baseline characteristics. The committee concluded that results from these studies might be unreliable for decision making. Another study compared TheraSphere with TheraSphere and sorafenib in combination, in people for whom CTT is inappropriate. This study also had a high risk of bias and was only published as an abstract. The remaining prospective study was done in people for whom CTT is inappropriate. This compared TheraSphere in people with PVT with TheraSphere in people without PVT and best supportive care. The AG advised that this study had a high risk of bias, and that the people in the treatment arms had very different baseline characteristics. Because of this, the committee concluded that these studies should not be used for decision making. It also concluded that there was not enough evidence to establish whether TheraSphere is better than other treatments in people for whom CTT is appropriate and in people for whom CTT is inappropriate.

There were no data identified to establish the clinical effectiveness of SIR-Spheres compared with non-SIRT treatments in people for whom transplant is appropriate

3.17 The AG identified 1 RCT comparing SIR-Spheres with TACE (SIR-TACE) that included people for whom transplant was appropriate. SIR-TACE was done in Germany and Spain, and included 28 people with early, intermediate and late stage disease. Only overall results for the mixed population were available. The AG assessed that the study had a high risk of bias because of the randomisation process, missing outcome data and measurement of the outcome. Only overall results were published, and the company could not provide subgroup-specific data. The committee

concluded that there were insufficient data to establish whether SIR-Spheres are better than TACE in people when transplant is appropriate.

It is unclear whether SIR-Spheres is better than DEB-TACE or TACE in people for whom CTT is appropriate

3.18 The AG identified 2 RCTs that compared SIR-Spheres with TACE (SIR-TACE) or DEB-TACE (Pitton 2015) that included people for whom CTT is appropriate in their trial populations. SIR-TACE is described in section 3.17. Pitton 2015 was done in Germany and included 24 people with intermediate stage disease (BCLC B). Overall survival and progression-free survival were longer in the DEB-TACE arm compared with SIR-Spheres arm, but this was not statistically significant (788 days compared with 592 days and 216 days compared with 180 days, respectively). Based on the identified evidence, the committee concluded that it could not establish whether SIR-Spheres was better than TACE or DEB-TACE in people for whom CTT is appropriate.

SARAH and SIRveNIB may not be generalisable to the NHS in England, but they are preferable to non-randomised evidence in people when CTT is inappropriate

3.19 The AG identified 2 RCTs comparing SIR-Spheres with sorafenib (SARAH and SIRveNIB) in people for whom CTT is inappropriate:

- SARAH was done in France between 2011 and 2015 and included a heterogenous population of people with HCC. This included, for example, people with advanced HCC, people with HCC that were previously treated with 2 treatments of TACE and people with Child-Pugh A or B. There was no difference in overall survival or progression-free survival between the treatment arms. The median overall survival was 8.0 months (95% CI 6.7 to 9.9) for SIR-Spheres and 9.9 months (95% CI 8.7 to 11.4) for sorafenib, with hazard ratios (HRs) of 1.15 (95% CI 0.94 to 1.41) for the intention-to-treat (ITT) population and 0.99

(95% CI 0.79 to 1.24) for the per-protocol (PP) population. The median progression-free survival was 4.1 months (95% CI 3.8 to 4.6) for SIR-Spheres and 3.7 months (95% CI 3.3 to 5.4) for sorafenib with a HR of 1.03 (95% CI 0.85 to 1.25) for the ITT population. More adverse events were reported with sorafenib than SIR-Spheres. A post-hoc analysis of SARAH focused on people with ALBI grade 1 and low tumour burden (equal or less than 25% tumour burden). Again, there was no difference in overall or progression-free survival between the treatment arms. The median overall survival was 21.9 months (95% CI 15.2 to 32.5) for SIR-Spheres and 17.0 months (95% CI 11.6 to 20.8) for sorafenib, with a HR of 0.73 (95% CI 0.44 to 1.21). The median progression-free survival HR was 0.65 (95% CI 0.41 to 1.02). The clinical experts advised that the SARAH trial had more people with a high tumour burden, PVT and impaired liver function than people seen in clinical practice in England. The committee understood that because of this, people in the SARAH trial had poorer prognosis than people seen in clinical practice in England. It concluded that results from the SARAH trial may not be generalisable to people seen in the NHS in England.

- SIRveNIB was done in the Asia-Pacific region between 2010 and 2018. The clinical experts explained that results from SIRveNIB might not be generalisable to the NHS in England. This was because in the Asia-Pacific region HCC is often caused by hepatitis B and C, whereas in the UK fatty liver disease and alcohol are the most common causes. There was no difference in overall survival or progression-free survival between the treatment arms. The median overall survival was 8.8 months for SIR-Spheres and 10.0 months for sorafenib, with HRs of 1.12 (95% CI 0.9 to 1.4) for the ITT population and 0.86 (95% CI 0.7 to 1.1) for the PP population. The median progression-free survival was 5.8 months for SIR-Spheres and 5.1 months for sorafenib, with HRs of 0.89 (95% CI 0.7 to 1.1) for the ITT population and 0.73 (95% CI 0.6 to 0.9) for the PP population. More adverse events were reported with

sorafenib than SIR-Spheres. The committee concluded that results from the SIRveNIB may not be generalisable to people seen in the NHS.

- The committee considered including non-RCT evidence identified by the AG. The AG assessed the 3 non-RCT studies as having a high risk of bias. So the committee concluded that the RCT evidence from SARAH and SIRveNIB was preferable for decision making in people for whom CTT is inappropriate.

There is no evidence in people for whom transplant is appropriate and in people for whom CTT is appropriate to compare the 3 SIRTs' effectiveness

3.20 The clinical evidence for comparative effectiveness of the 3 SIRTs came from 5 retrospective studies that reported overall survival or progression-free survival. Of these, 4 compared SIR-Spheres with TheraSphere and 1 small study of 30 people compared all 3 SIRTs. The AG advised that most of these studies had a high risk of bias. None of the studies included people for whom transplant was appropriate. The study comparing all 3 SIRTs potentially included people for whom CTTs were appropriate but there were no results presented for this subgroup. The committee concluded that there was no evidence identified for people when transplant or CTT was appropriate.

There is not enough direct evidence for people when CTT is inappropriate to compare the 3 SIRTs' effectiveness, so mixed treatment comparison should be considered

3.21 The AG identified 5 retrospective studies that included people for whom CTT is inappropriate (see section 3.20). The study comparing all 3 SIRTs also included people for whom CTTs were appropriate, but no results for subgroups were presented. The committee was aware that the populations were different across these studies and acknowledged that this meant results were difficult to compare. The committee was also aware that the baseline characteristics were different in most studies, and that this might affect prognosis and outcomes between the arms. In 2

studies that compared TheraSphere with SIR-Spheres, there was no difference in overall survival. In van der Gucht et al. (2017, n=77), the median overall survival was 7.0 months for TheraSphere (95% CI 1.6 to 12.4) compared with 7.7 months for SIR-Spheres (95% CI 7.2 to 8.2). In Bhangoo et al. (2015, n=17) the median overall survival for TheraSphere was 8.4 months (95% CI 1.3 to 21.1) compared with 7.8 months for SIR-Spheres (95% CI 2.3 to 12.5). In 2 studies (Biederman et al. 2015 and Biederman et al. 2016) that compared TheraSphere with SIR-Spheres in people with PVT, overall survival was better in the TheraSphere arm than the SIR-Spheres arm. The committee concluded that there was not enough direct evidence to establish the relative effectiveness of the 3 SIRTs in people with HCC, and so decided to consider mixed treatment comparisons for decision making.

Mixed treatment comparisons

Data are not robust enough to provide a meaningful comparison between treatment options when transplant is appropriate

3.22 The AG assessed the feasibility of a mixed treatment comparison to estimate comparative effectiveness between available treatment options in people when transplant is appropriate. There are 2 RCTs that could be included in this analysis. Both were done in the US and compared TheraSphere with TACE (n=45) or with a combination of TheraSphere and sorafenib (n=20). The committee agreed that the evidence base was small, and not generalisable to people seen in the NHS (see section 3.9). Because of limited data, results from the mixed treatment comparison would be very uncertain. The committee concluded that a mixed treatment comparison in this population would not help decision making for the subgroup in whom transplant is appropriate.

The comparative effectiveness of treatment options for people for whom CTT is appropriate is very uncertain, and so is not suitable for decision making

3.23 After consultation on the assessment report, the AG did a mixed treatment comparison in people for whom CTT was appropriate. There were 6 RCTs that could be included in this analysis: 5 compared different CTTs with each other and 1 compared SIR-Spheres with DEB-TACE (n=24). The AG also included 1 retrospective study that compared SIR-Spheres with TheraSphere (n=77). From this study, only a subgroup of 35 people with early or intermediate HCC could be included in the analysis. The study had a high risk of bias because its 2 treatment groups were not similar at baseline (people with small tumour volumes were preferentially treated with TheraSphere). The committee agreed that there was little evidence to link SIR-Spheres and TheraSphere to the network of treatments. Results from the mixed treatment comparison for overall survival and progression-free survival were uncertain (see Table 1 and Table 2). The committee concluded that the results from the mixed treatment comparison in this population were uncertain, and that there was not enough evidence to compare SIR-Spheres with TheraSphere, and the SIRTs with TACE, DEB-TACE and TAE, in this population.

Table 1 Mixed treatment comparison for overall survival, (HRs of less than 1 indicate better overall survival)

	TACE comparator	SIR-Spheres comparator	TheraSphere comparator	DEB-TACE comparator	TAE comparator

TACE treatment mean HR (95% CI)	–	–	–	–	–
SIR-Spheres treatment mean HR (95% CI)	1.06 (0.21 to 3.31)	–	–	–	–
Thera-Sphere treatment mean HR (95% CI)	1.02 (0.13 to 3.77)	0.96 (0.34 to 2.18)	–	–	–
DEB-TACE treatment mean HR (95% CI)	0.88 (0.29 to 2.09)	0.95 (0.35 to 2.56)	1.41 (0.28 to 4.34)	–	–
TAE treatment mean HR (95% CI)	0.98 (0.61 to 1.57)	1.60 (0.27 to 5.25)	2.08 (0.24 to 8.01)	1.48 (0.42 to 3.77)	–

Table 2 Mixed treatment comparison for progression-free survival, (HRs of less than 1 indicate better progression-free survival)

	TACE comparator	SIR-Spheres comparator	TheraSphere comparator	DEB-TACE comparator	TAE comparator
TACE treatment mean HR (95% CI)	–	–	–	–	–
SIR-Spheres treatment mean HR (95% CI)	1.20 (0.22 to 3.82)	–	–	–	–
Thera-Sphere treatment mean HR (95% CI)	1.14 (0.15 to 4.20)	0.95 (0.36 to 2.05)	–	–	–
DEB-TACE treatment mean HR (95% CI)	0.86 (0.26 to 2.15)	0.92 (0.31 to 2.12)	0.94 (0.26 to 3.44)	–	–
TAE treatment mean HR (95% CI)	0.87 (0.61 to 1.20)	0.93 (0.21 to 4.05)	1.58 (0.20 to 5.97)	1.35 (0.38 to 3.50)	–

The comparative effectiveness of treatment options in people for whom CTT is inappropriate is uncertain, but is useful for decision making

3.24 The AG did a mixed treatment comparison to estimate comparative effectiveness between available treatment options in people when CTT is inappropriate. There were 3 RCTs included in this analysis. Of these, 1 RCT compared lenvatinib with sorafenib and 2 compared sorafenib with SIR-Spheres. To include TheraSphere in the network, 2 retrospective studies comparing TheraSphere with SIR-Spheres were included in sensitivity analyses. In the main analysis, in people for whom CTT is inappropriate and with Child-Pugh grade A, there was no evidence of a difference between SIR-Spheres, sorafenib and lenvatinib. The mean HR in the PP population for SIR-Spheres compared with sorafenib was 0.94

(95% credible interval [CrI] 0.77 to 1.14), for lenvatinib compared with sorafenib it was 1.06 (95% CrI 0.79 to 1.4), and for lenvatinib compared with SIR-Spheres the HR was 1.14 (95% CrI 0.79 to 1.58). In the ITT population for SIR-Spheres compared with sorafenib the HR was 1.13 (95% CI 0.96 to 1.32), for lenvatinib compared with sorafenib or SIR-Spheres the HRs were 1.06 (95% CI 0.79 to 1.4) or 0.92 (95% CI 0.67 to 1.29) respectively. A value of less than 1 indicates better overall survival. When the retrospective evidence was included, TheraSphere was shown to be more effective than SIR-Spheres, sorafenib and lenvatinib. The mean HR in the PP population for SIR-Spheres compared with sorafenib was 0.94 (95% CrI 0.77 to 1.13) For lenvatinib compared with sorafenib or SIR-Spheres it was 1.06 (95% CrI 0.79 to 1.4) or 1.13 (95% CrI 0.79 to 1.57) respectively. The mean HRs for TheraSpheres compared with sorafenib or SIR-Spheres or lenvatinib were 0.41 (95% CrI 0.20 to 0.77) or 0.44 (95% CrI 0.20 to 0.84) or 0.4 (95% CrI 0.18 to 0.78) respectively. In the ITT population the mean HR for SIR-Spheres compared with sorafenib was 1.13 (95% CrI 0.96 to 1.32), for lenvatinib compared with sorafenib or SIR-Spheres the HRs were 1.06 (95% CrI 0.79 to 1.4) or 0.95 (95% CrI 0.67 to 1.29) respectively. For TheraSpheres compared with sorafenib or SIR-Spheres or lenvatinib the HRs were 0.47 (95% CrI 0.21 to 0.88) or 0.41 (95% CrI 0.20 to 0.77) or 0.45 (95% CrI 0.20 to 0.89) respectively. In an alternative analysis with a wider population, SIR-Spheres was less effective than sorafenib. In the corresponding sensitivity analysis including the retrospective evidence, TheraSphere was again more effective than SIR-Spheres, sorafenib and lenvatinib. The AG assessment suggested that the retrospective studies had a high risk of bias and uncertain results (see section 3.16). The committee agreed that the retrospective studies should not be included in the analysis because of the risk of bias. It agreed that the comparative effectiveness results based on RCT evidence could be used in a cost-effectiveness analysis. The committee concluded that the estimates of comparative effectiveness were uncertain, but were suitable to inform decision making.

Cost-effectiveness evidence

The AG's model was used for decision making

3.25 There were 2 companies that included economic analyses in their submissions. For SIR-Spheres, the company submitted a cost-minimisation analysis for people when CTT was appropriate, and a cost-utility analysis for people when CTT was inappropriate. The cost-utility analysis was restricted to people with ALBI grade 1 and low tumour burden, a subpopulation from the SARAH trial (see section 3.19). For TheraSphere the company submitted 2 cost-utility analyses, 1 for people when CTT was appropriate and 1 for people when CTT was inappropriate. The committee acknowledged the submission of the companies' models. It noted that the AG model used a similar structure (see section 3.26) as the companies' cost-utility analyses, and that the AG used inputs from the company models, such as costs and treatment frequency. The committee concluded that there was not enough evidence to support an economic analysis in people for whom CTT was appropriate (see section 3.23). It also concluded that when CTT was inappropriate the AG model was the most comprehensive analysis, because it included all 3 SIRTs as specified in the NICE scope (see section 3.3).

The structure of the AG model for people when CTT is appropriate is acceptable for decision making

3.26 The AG did a cost-utility analysis for people with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, when CTT is inappropriate, with or without macroscopic vascular invasion but without extrahepatic disease. The model consisted of a decision tree and partitioned survival model with 3 health states. The decision tree represented the outcome of the work-up procedure that happens before SIRT. The partitioned survival model was like that used by the companies. The interventions were SIR-Spheres, TheraSphere and QuiremSpheres, which were assumed to have equal effectiveness in the base case. The comparators were sorafenib and lenvatinib. Because sorafenib and

lenvatinib are recommended only for people with Child-Pugh grade A, the base case was restricted to this population. The committee concluded that the model structure was acceptable for decision making.

Sorafenib is the only relevant comparator for cost effectiveness in people for whom CTT is inappropriate

3.27 In line with the NICE scope, the AG included sorafenib and lenvatinib as comparators in the model. The AG used the hazard ratio from the mixed treatment comparison to include lenvatinib in the model and assumed proportional hazards over time. Therefore, they chose the Weibull function to model overall survival and progression-free survival, even though it was not the best-fitting function. Following consultation on the AG report, sorafenib was considered to be the only relevant comparator (see section 3.11). The generalised gamma was used to fit overall survival and progression-free survival in the revised base case, because the proportional hazards assumption was no longer needed. The committee concluded that sorafenib is the only appropriate comparator, and that the best-fitting function should be used to estimate overall survival and progression-free survival.

There is not enough robust data for the ALBI grade 1 and low tumour burden subgroup for decision making

3.28 The AG presented scenario analyses that restricted the population to people with ALBI grade 1 and low tumour burden. The clinical experts explained that ALBI grade could be a more objective measure than Child-Pugh score for liver dysfunction and that people with ALBI grade 1 have good liver function. However, this measure is not routinely used in the NHS, and the Child-Pugh score is expected to be the standard assessment method for liver dysfunction for the foreseeable future (see section 3.6). The committee was aware that clinical outcomes for the ALBI grade 1, low tumour burden subgroup came from a post-hoc analysis of the SARAH trial (n=85) (see section 3.19). It agreed that this analysis was not robust because the subgroup was not prespecified and the numbers

were small. It concluded that it had not seen sufficiently robust data in this subgroup, but agreed that more evidence may be useful for decision making.

Usually, only 1 lobe is treated at a time in people with bilobar disease

3.29 HCC can be unilobar (tumour is in 1 lobe of the liver) or bilobar (tumours in both lobes of the liver). The clinical experts explained that people with bilobar disease have a higher risk of liver impairment, and therefore usually only 1 lobe is treated at a time. The same lobe might be treated twice to reduce the size of the tumour. The committee concluded that it is not appropriate for a model to assume that both lobes are treated simultaneously in bilobar disease.

Downstaging of HCC might benefit some people with advanced HCC, but the proportion of people and subsequent outcomes are uncertain

3.30 The clinical experts explained that downstaging might be a treatment aim for some people who have SIRT, to potentially allow for subsequent liver transplantation. However, these people are rarely included in clinical trials because trials mainly include people with advanced stage disease. This means there is limited evidence on downstaging and overall survival in advanced HCC. The committee concluded that downstaging may be an appropriate consideration for a small proportion of people with advanced HCC, so the base-case model should include downstaging. However, the proportion of people who have tumours that downstage, and subsequent outcomes, are uncertain.

Some aspects of health-related quality of life might not be captured in the utility values

3.31 Both the SARAH and SIRveNIB trials collected data on health-related quality of life. SARAH used the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC-QLQ-C30) questionnaire, which the company mapped onto the EQ-5D scale using the Longworth et al. algorithm. The AG used these

estimates in its model. The committee noted that utility values were similar between SIRTs and systemic therapies (sorafenib or lenvatinib) for the following disease states: progression-free survival, progressive disease and post-transplant. There were only small differences in utilities between progression-free survival and progressive disease. The clinical experts explained that people who have sorafenib for a long time may have a long-lasting negative effect on their quality of life. SIRTs are given in 1 procedure, meaning there is a shorter duration of impaired health-related quality of life. The committee considered that the potential difference in long-term quality of life might not be captured in clinical trial results because quality-of-life data are collected at fixed time points. It acknowledged that the cancer, liver function and other comorbidities affect health-related quality of life in people with HCC. The committee concluded that some aspects of health-related quality of life might not be captured in the utility values, but it was not presented with evidence comparing this benefit with the relevant non-SIRT comparator, sorafenib.

Cost-effectiveness results

In the AG's model sorafenib dominated SIRTs in all plausible scenarios using confidential patient access schemes for QuiremSpheres and sorafenib

3.32 The probabilistic base case of the AG model, including confidential patient access schemes for QuiremSpheres and sorafenib, showed that all SIRTs were less effective and more expensive than sorafenib (exact incremental cost-effectiveness ratios [ICERs] are confidential and cannot be reported here). Because of uncertainties in the evidence, the AG presented 17 scenario analyses, for example using alternative functions to model overall survival and progression-free survival (see section 3.27). The committee noted that ICERs did not change much if alternative functions were used. The committee also accepted that alternative costs and utility values did not have a big effect on ICERs. It acknowledged that in scenarios that restricted the population to people with ALBI grade 1 and low tumour burden (see section 3.28), TheraSphere was more cost

effective than sorafenib. However, the committee agreed that such scenarios are not plausible because this population is not relevant to NHS practice in England (see section 3.28). TheraSphere was also more effective in the scenario that included retrospective studies with high risk of bias. The committee agreed that this scenario should not be considered because of the high risk of bias and uncertainty of the data (see section 3.24). The committee agreed that while the modelling may not capture all health-related quality-of-life outcomes for people with HCC and SIRT, this was unlikely to change the cost-effectiveness estimates for SIRTs enough to change its conclusions. The committee concluded that sorafenib dominated SIRTs in all plausible scenarios. Therefore, it did not consider SIRTs to be a cost-effective use of NHS resources for treating unresectable HCC.

End of life

The end-of-life criteria are not met

3.33 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal.

- When transplant or CTT is appropriate, people have a life expectancy of more than 24 months. This means that the life-expectancy criterion (that is, the treatment is indicated for patients with a short life expectancy, normally less than 24 months) was not met for these subgroups.
- When CTT is inappropriate, in advanced stage disease, people have a poor prognosis with a life expectancy of less than 24 months. Therefore, the short life-expectancy criterion was met for this subgroup.
- In all plausible scenarios, there was no increase in the modelled undiscounted life expectancy with SIRTs compared with sorafenib. The committee concluded that the life-extending criterion (that is, there is sufficient evidence that the treatment could extend life, normally by a

mean value of at least an additional 3 months, compared with current NHS treatment) was not met.

Because both parts of the criteria were not met, the committee concluded that the end-of-life criteria were not met.

Innovation

No evidence was identified showing additional benefits of SIRT, above those captured in the cost-effectiveness analysis

3.34 The companies considered SIRTs to be innovative because they offer a more personalised treatment option. The patient experts stated that SIRTs would be a substantial change in treating HCC because they could offer a chance for subsequent curative treatment for people who would not otherwise have this option. The committee concluded it was not shown evidence of any additional benefits that were not captured in the measurement of quality-adjusted life years in the model.

Equality

3.35 No equality or social judgement issues were identified.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
November 2019

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Verena Wolfram
Technical lead

Jamie Elvidge
Technical adviser

Louise Jafferally
Project manager

ISBN: [to be added at publication]

Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Clinical expert 1	TS	The recommendation is based on limited evidence and primarily on two main RCTs (SARAH and SIRveNIB) which as we discussed cannot be generalised to the patient population in the UK. We have seen reports of the effectiveness of SIRT in HCCs and until we have a robust RCT in the UK it is not appropriate to exclude SIRT from the HCC treatment algorithm.	Comment noted. The committee considered all the available evidence, including evidence from clinical trials and its generalisability to NHS practice, patient and clinical experts, the company's submissions and the AG's report. It also carefully considered the comments received in response to the ACD and subsequent evidence. The committee considered the available non-RCT evidence but concluded that RCT evidence was more suitable for decision making (see sections 3.11 and 3.15 of the FAD).
2	Clinical expert 1	TS	Clinically certain groups of patients will be disadvantaged particularly those who are in the intermediate and some in the advanced stage of the disease. The evidence may be weak but it should not be ignored.	Comment note. The committee considered all the available evidence, including evidence from clinical trials, patient and clinical experts, the company's submissions and the AG's report. It also carefully considered the comments received in response to the ACD and subsequent evidence. The committee considered several subgroups during its discussions (see sections 3.23, 3.24, 3.25 and 3.34 of the FAD).
3	Clinical expert 1	TS	Cost effectiveness may be improved by addressing the actual cost of the spheres.	Comment noted. All companies have submitted commercial arrangements (simple discount patient access scheme). These discounts were included in the cost-effectiveness analysis that helped decision making. Exact incremental cost-effectiveness ratios [ICERs] are confidential and cannot be reported in the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
4	Clinical expert 1	TS	Commissioning through Evaluation for SIRT in HCC could well be the model as was the case for SIRT in colorectal liver metastases.	Comment noted. The committee was aware that SIRTs for metastatic colorectal cancer are covered by NHS England based on the outcome of a commissioning through evaluation program. It considered whether it was appropriate to recommend SIRTs with ongoing evidence generation in HCC (sections 3.40 and 3.41 FAD). The committee concluded that SIRTs were not suitable for use in the Cancer Drugs Fund, and that the ongoing research was not sufficient to support a research recommendation.
5	Clinical expert 2	HR	Has all of the relevant evidence been taken into account' **The answer is no – not because of any criticism of NICE and the AG, but because there is currently insufficient evidence from a representative UK population.** I think it is very important here to highlight again that 'the relevant evidence' is very poorly representative of the UK population patients – especially those managed in the North of England where the commonest cause of HCC is none alcoholic fatty liver disease (NAFLD). NAFLD-HCC patients are considerable older, with comorbidities – both of which exclude them from many 'standard' therapies. These patients have not been included in earlier trials of TACE, and are very poorly represented in later trials of medical therapies. Importantly – post hoc analyses of the SHARP and Asia pacific trials indicate very clearly that the benefit from sorafenib in 'non-HCV' patients is very small in deed. Furthermore, NAFLD-HCC do not tolerate the drug well. We desperately need treatments for our own patient cohort. Our experience with SIRT in Newcastle (approximately 70-80 patients treated) clearly indicates that there are those who do extremely well treated with SIRT – even patients who are cured. For these, where there are no good alternatives, it will be quite tragic to lose the option to use SIRT. As we have some experience, I have suggested below those patients in whom we might consider it, with evidence collection, in a 'real life UK cohort'. We could also provide evidence from our treated UK patients	Comment noted. The committee considered all the available evidence, including evidence from clinical trials and its generalisability to NHS practice, patient and clinical experts, the company's submissions and the AG's report. It also carefully considered the comments received in response to the ACD and subsequent evidence. The committee considered several subgroups during its discussions including people with large tumours, people who cannot have sorafenib, people with ALBI grade 1 and low tumour burden and people with PVT. It concluded that there was insufficient evidence to recommend SIRTs for these subgroups (see sections 3.23, 3,24,2.25 and 3.34). The committee also considered whether it was appropriate to recommend SIRTs with ongoing evidence generation in HCC (sections3.40 and 3.41 FAD). It concluded that the ongoing research was not sufficient to support a research recommendation.
6	Clinical expert 2	HR	Are the summaries of clinical and cost effectiveness reasonable interpretations These are reasonable. But please can I point out again a very important factor that I am sure	Comment noted. See response to comment 5.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			you are all very much aware of already. The RCT analyses have all been done on an intention to treat basis. There are good reasons for this. BUT – as ~15% of patients are excluded from actually having SIRT AFTER randomisation to SIRT, because they have a technical issue such as shunting that excludes them, the analyses could be reconsidered. i.e. focus on patients after assessing eligibility for a treatment. Considering only those patients passing the pre-SIRT phase, focused only on those actually treated, would possibly yield different outcomes. It is also worth just noting again, that the superiority of SIRT in terms of tolerability and quality of life, should not be underestimated for these individuals. **MY OWN SUGGESTIONS** 1. SIRT could be considered as an alternative to TACE: - In patients with single lesions >7cm. TACE is tolerated poorly in these patients. It can shorten life rather than prolong it. On the other hand SIRT is tolerated well. This strategy is perhaps pertinent particularly for older non-cirrhotic patients (commonly seen in NAFLD cohort), who have ALBI 1 liver function and no other therapies proven benefit. - Some patients in this category may ultimately be downstaged to resection and cure 2. SIRT could be considered as an alternative to medical therapy, in those with preserved liver function, but with factors predicting a poor response to medical therapy. Namely: - Those with an etiology that is not HCV - Those with a partial portal vein thrombosis - Those with an elevated NLR. I do apologise for lack of references - consequent to my poor planning and lack of access right now to databases (travelling). If it would be helpful, I could provide these to the AG in advance of the meeting on 22nd.	
7	Patient expert	LIVER4LIFE	In discussion with my clinical colleagues, with regard to proposed patient profiles and subgroups, it was felt that some patient subgroups would benefit from treatment by SIRT;	Comment noted. No action needed.
8	Patient expert	LIVER4LIFE	*In patients with portal vein thrombosis (PVT) as an alternative to transarterial chemoembolization (TACE)* 1. Based primarily on clinical experience. 2. *Consultation group's viewpoint:* a. Based on clinical experience this is a valuable population to be treated with SIRT as effective treatment options are limited, but there is a lack of published evidence. b. To fill the gaps in the data, a single-arm Commissioning through Evaluation (CtE) programme may be useful with this subgroup population. c. A difficulty would be to find a control group. Sorafenib treatment may act as a control but often patients receiving SIRT may also receive sorafenib. d. Furthermore, patients with malignant/tumour thrombus may have poorer outcomes than those with bland thrombus, and so some level of patient stratification may be needed in any study/programme.	Comment noted. See response to comment 5.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			e. Glass microspheres potentially have a better safety profile than resin microspheres in this setting as they have a lower embolic effect (due to the size of the spheres). f. A CtE would be better than trying to extract data from a published study such as SORAMIC,[3] as patient numbers are likely to be low in such subgroup analyses. g. It may be necessary to collect data (e.g., from a prospective registry) of outcomes in this group of patients who are treated based on local protocols (as some will not have access to SIRT). This would give some justification, and a control population, for any subsequent CtE. h. In conclusion, a CtE involving this patient subgroup (with stratification for malignant thrombus and bland thrombus) is recommended to provide further evidence for effectiveness of SIRT. A prospective registry to collect data on this subgroup being treated according to local protocols may be useful before a CtE. *In patients with ≥1 large tumour (>7 cm) ± PVT as an alternative to TACE* • Based upon data from the DOSISPHERE trial, from which interim data have been presented.[4] • *Consultation group's viewpoint:* o Based on clinical experience this is a valuable population to be treated with SIRT, but as for option 2, there is a lack of comparative clinical trial data. o As for option 2, a CtE programme may be useful with this subgroup population. It would be important to include the option of subsequent treatments if, for example, tumours became amenable to surgical resection. o A single CtE could include both patient subgroups (from option 2 and option 3). o The consultation group postulated that an alternative subgroup of patients would be those with tumours ≥5cm (±PVT as an alternative to TACE), as the 7 cm cut-off may be too restrictive and may exclude patients who could potentially benefit from SIRT. o In conclusion, the group recommend a CtE in this subgroup, but amended to include patients with at least one tumour ≥5cm in diameter, and this CtE could include this patient subgroup and the patient subgroup discussed in option 2. *4. As an alternative to sorafenib in patients unable to tolerate sorafenib* • Based primarily on clinical experience and the unmet need for more effective treatments in this setting. • *Consultation group's viewpoint:* o Based on clinical experience this is a valuable population (both patients who are ineligible for sorafenib and patients who discontinue sorafenib due to adverse events). o A perception may exist that although the SARAH trial[1] was not powered to demonstrate equivalence, the patients had similar outcomes with SIRT as with sorafenib. o Similar precedents exist in the UK such as funding for the use of SIRT in patients	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			with metastatic colorectal cancer that cannot tolerate chemotherapy, or the use of radium-223 in cancer patients that cannot tolerate taxanes. o In conclusion, this would be a suitable subgroup to assess via a CtE programme, and as for the subgroups discussed in option 2 and 3, data may need to be gathered (retrospective or prospective) to gain information on a suitable comparator population before initiating a CtE. **References:** 1. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. (2017) Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 18:1624-1636. 2. Palmer DH, Hawkins NS, Vilgrain V, Pereira H, Chatellier G, Ross PJ. (2019) Tumor burden and liver function in HCC patient selection for selective internal radiation therapy: SARAH post-hoc study. *Future Oncol*. DOI: 10.2217/fon-2019-0658 3. Ricke J, Klumpen HJ, Amthauer H, Bargellini I, Bartenstein P, de Toni EN, et al. (2019) Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. *J Hepatol* 71:1164-1174. 4. Garin E, Tselikas L, Guiu B, et al. A multicentric randomised study demonstrating the impact of MAA based dosimetry on tumour response with Y90 loaded glass microsphere SIRT for HCC: interim analysis of IIS Dosisphere. Global Embolization Cancer Symposium; 2019 May 9-12; New York.	
9	Patient expert	LIVER4LIFE	*General and concluding comments* • The subgroups mentioned in options 2, 3 and 4 would benefit from a CtE programme. • The consultation group could not prioritise these three subgroups: subgroup populations in options 3 and 4 may have the greatest clinical need, but the evidence for SIRT in the subgroup in option 2 is stronger. • The group did not think they were in a position to give accurate estimates of the patient numbers in each of these subgroups in the UK. • From the patient perspective, any treatment that avoids the side effects of other treatments of HCC is an important advantage. • Furthermore, the quality of life data from the SARAH trial were favourable for SIRT,[1] and other studies and clinical experience show the potential for SIRT to down-size tumours for subsequent curative treatment. Both these aspects of SIRT should be considered alongside the efficacy data for SIRT.	Comment noted. See response to comment 5. The committee considered the available evidence for downstaging and the extent to which it should be captured in the cost-effectiveness analysis (see section 3.36 of the FAD). After consultation and additional analysis by the AG, the committee re-evaluated quality of life data (section 3.37 of the FAD) and considered analyses applying disutility values for adverse events of grade 3 and above, and for adverse events of any grade (section 3.38 of the FAD). It concluded that some aspects of health-related quality of life might not be captured in the utility values and agreed to include a QALY gain for SIRTs because of adverse event disutility.
10		NCRI-ACP-RCP-RCR	**Proposed patient profiles and subgroups** *1. Patients with ALBI score 1 and tumour burden of ≤25%*	Comment noted. See response to comment 5.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			This is the only evidence-based subgroup of patients who are most likely to benefit from SIRT. It is based on a post-hoc analysis of those with a tumour burden ≤25%, and who have an ALBI score of 1 (Palmer D et al 2019: dx.doi.org/10.1093/annonc/mdx369) (Palmer DH, Hawkins NS, Vilgrain V, Pereira H, Chatellier G, Ross PJ. (2019) Tumor burden and liver function in HCC patient selection for selective internal radiation therapy: SARAH post-hoc study. *Future Oncol*. DOI: 10.2217/fon-2019-0658). Patients with a tumour burden ≤25% of the liver volume, an ALBI grade 1 and dose of radiation ≥100 Gy to the tumours were the best responders to SIRT in the SARAH trial (Hermann A-L et al. J Hepatol. 2018 Apr 13;68:S13). Liver function has traditionally been measured with the Child-Pugh classification; however, it is considered that it does not adequately capture the hepatic functional reserve. Although the ALBI score is not currently a routinely undertaken and accepted measure it is based on a calculation using 2 routinely measured outcomes: bilirubin and albumin levels. The ALBI score was not developed at the time of the SARAH trial, however, bilirubin and albumin levels are routinely measured in clinical practice. A potential criticism is that ALBI is not currently used in most centres (Child-Pugh classification is more widely used) and so identification of these patients would not be routine. However, since ALBI has been developed by leading UK clinicians (oncology, surgery, hepatology) who know what is applicable in the clinic, clinicians who manage these patients agree that ALBI could be applied in the clinic if there was a clinical reason to do so. Both the tumour burden and the ALBI grade can be estimated using routine CT scans and routine lab tests (albumin and bilirubin). *2. In patients with portal vein thrombosis (PVT) as an alternative to transarterial chemoembolization (TACE)* This indication is based primarily on clinical experience and clinical need. Experts view that this is a valuable population to be treated with SIRT as effective treatment options are limited, but there is a lack of published evidence. This subgroup has previously been discussed by the NHSE HPB CRG and the committee agreed that this patient subgroup are currently inadequately treated with current available therapies, particularly sorafenib and TACE. To fill the gaps in the data, a single-arm Commissioning through Evaluation (CtE) programme should be advocated with this subgroup population. Patients with malignant/tumour thrombus have poorer outcomes than those with bland thrombus, and so some level of patient stratification may be needed in any CtE programme. An additional difficulty would be to find a control group. Sorafenib treatment is the current standard for this subgroup of patients, but there are no systematic data on the prognosis for this subgroup on sorafenib. These data on patients treated in routine clinical practice could be collected via the same UK Registry as the SIRT data. *3. As an alternative to sorafenib in patients unable to tolerate sorafenib* This indication is also based primarily on clinical experience and clinical need. A significant sub-population of patients are ineligible for sorafenib or lenvatinib, or discontinue either of these drugs due to adverse events. They are currently not offered any alternative therapies, although it is possible that immunotherapy may be offered in the future depending on trial results and NICE review. A similar precedent exists in the UK such as funding for the use of SIRT in	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			patients with metastatic colorectal cancer who cannot tolerate chemotherapy, or the use of radium-223 in metastatic prostate cancer patients that cannot tolerate taxanes. This subgroup would be a suitable patient group to assess via a CtE programme, and as for the subgroup discussed above, and a single CtE could include multiple subgroups in order to gather the necessary clinical data. Likely patient numbers for both subgroups were accurately estimated in the original NICE consultation document.	
11	Patient and professional group	British Liver Transplant Group, the British Society of Interventional Radiology, the British Nuclear Medicine Society, HCC-UK, and the commissioned NHS England SIRT centres. Lead	As a group of NHS practitioners with clinical expertise in selective internal radiation therapy (SIRT), we are disappointed that the committee is unable to give a positive recommendation for SIRT in a subgroup of patients with hepatocellular carcinoma (HCC). NICE should be commended for the comprehensive review in this extremely heterogenous disease group. The complexity of the review highlights the challenges in interpreting the data with most studies reporting across mixed populations. The randomised controlled trials reviewed by the committee focus on patients with advanced stage HCC. These trials were designed before patient selection, technical aspects of SIRT and dosimetry had been optimised. Recruitment for studies involving medical devices in interventional oncology is challenging and the majority of the available evidence is based on non-randomised studies and registry data, which reflect real world practice. SIRT is reimbursed for the treatment of HCC in many European countries and in North America. SIRT has evolved in recent years with advances in patient selection and personalised dosimetry. The NHS has been at the forefront of this innovation and, as an expert group, we recognise the importance of the application of this therapy in clearly defined groups who would benefit from SIRT, which includes patients who have the potential for cure from downstaging to surgical resection. **The subgroups that we would like to propose as an expert group are defined below. Funding in these patient groups, potentially through the Cancer Drug Fund (CDF), will continue to promote innovation in the NHS and improve patient outcomes for patients with HCC.**	Comment noted. The committee considered whether it was appropriate to recommend SIRTs with ongoing evidence generation in HCC (see sections 3.40 and 3.41 of the FAD). The committee made optimised recommendations for the use of SIR-Spheres and TheraSphere. It concluded that SIRTs were not suitable for use in the Cancer Drugs Fund, and that the ongoing research was not sufficient to support a research recommendation.
12	Patient and professional group	British Liver Transplant Group, the British Society of Interventional Radiology, the British Nuclear Medicine Society, HCC-UK, and the commissioned NHS England SIRT centres.	**1: As an alternative to TACE in patients with a solitary large tumour (≥7 cm)** There is a clear unmet need in patients who are not good TACE candidates (lesion size ≥7cm) within the intermediate stage of BCLC. This proposed subgroup is based upon data from the DOSISPHERE trial, from which interim data have been presented.[1] We feel that this is a valuable population to be treated even though there is a lack of comparative clinical trial data. Support through the Cancer Drug Fund would be invaluable with this subgroup population, allowing access while further evidence is collected. It would be important to include the option of subsequent treatments if, for example, tumours became amenable to surgical resection. Based on clinical experience our members have had excellent outcomes in this patient cohort and have successfully downstaged patients who are not appropriate for TACE within BCLC B to curative resection.[2]	See response to comment 5.

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		Lead	An international working group[3] define the group of patients eligible for this 'radiation lobectomy' approach as, Child-Pugh A patients who would otherwise be resected but: a) have an inadequate future liver remnant (FLR); and/or b) embedded test-of-time is desired for tumour biology; and/or c) need the treated tumour to be retracted away from hepatic vein and/or IVC d) demonstrating tumour response prior to surgery is preferable. Patients should be considered potentially operable candidates without comorbidities that would preclude surgery. 1. Garin E, Tselikas L, Guiu B, et al. A multicentric randomised study demonstrating the impact of MAA based dosimetry on tumour response with Y90 loaded glass microsphere SIRT for HCC: interim analysis of IIS Dosisphere. Global Embolization Cancer Symposium; 2019 May 9-12; New York. 2. Mafeld S, Littler P, Hayhurst H, Manas D, Jackson R, Moir J, et al. (2019) Liver resection after selective internal radiation therapy with yttrium-90: safety and outcomes. *J Gastrointest Cancer* DOI: 10.1007/s12029-019-00221-0. 3. Salem R, Padia SA, Lam M, Bell J, Chiesa C, Fowers K, et al. (2019) Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. *Eur J Nuc Med Mol Imaging* 46:1695-1704.	
13	Patient and professional group	British Liver Transplant Group, the British Society of Interventional Radiology, the British Nuclear Medicine Society, HCC-UK, and the commissioned NHS England SIRT centres. Lead	**2: As an alternative to TACE or sorafenib in patients with segmental or subsegmental portal vein thrombosis (PVT)** PVT confers a poor prognosis. Significant survival gains have been demonstrated with good tumour targeting and personalised dosimetry.[1] Based on clinical experience this is a valuable population to be treated with SIRT as effective treatment options are limited, but there is a lack of published evidence. A Commissioning through Evaluation (CtE) programme involving this patient subgroup (with stratification for malignant thrombus and bland thrombus) may be valuable to provide further evidence for effectiveness of SIRT in this population. 1. Garin E, Rolland Y, Edeline J, Icard N, Lenoir L, Laffont S, et al. (2015) Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. *J Nucl Med* 56:339-346.	See response to comment 5.
14	Patient and professional group	British Liver Transplant Group, the British Society of Interventional Radiology, the British Nuclear Medicine Society, HCC-UK, and the	**3: As an alternative to systemic therapy in patients when systemic therapy is not feasible** ESMO HCC guidelines published in 2018 recommend SIRT for patients with liver-confined disease and preserved liver function, in which neither TACE nor systemic therapy is possible.[1] It is well recognised that SIRT is better tolerated than TACE or systemic therapy with favourable quality of life data in SARAH.[2] SIRT presents a favourable treatment option in this small patient cohort. Based on clinical experience this is a valuable population who have no other treatment options (both patients who are ineligible for sorafenib and patients who discontinue sorafenib due to adverse events).	See response to comment 5.

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		commissioned NHS England SIRT centres. Lead	1. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. (2019) Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 30:871-873. 2. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. (2017) Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 18:1624-1636.	
15	Patient and professional group	British Liver Transplant Group, the British Society of Interventional Radiology, the British Nuclear Medicine Society, HCC-UK, and the commissioned NHS England SIRT centres. Lead	**4: Patients with ALBI score 1 and tumour burden of ≤25%** A post-hoc analysis of the ITT population of the published SARAH trial,[1] by Palmer et al in Future Oncology,[2] suggested that this group of patients benefitted most from SIRT (compared with sorafenib in the SARAH trial). The authors acknowledged that this analysis is hypothesis generating only. A major problem with this subgroup is that ALBI is not used in most centres (Child-Pugh classification is more widely used), and so identification of these patients would not be routine. Furthermore, there is not a well-established correlate (e.g. among the Child-Pugh classification groups) for this population. In addition, patients with a tumour burden of ≤25% are not the patients most centres are selecting for SIRT. However, the ALBI score has been developed by leading UK clinicians (hepatology, oncology, surgery) and could easily be applied in the clinic setting to identify this subgroup of patients who were identified as best responders in this post-hoc analysis. 1. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. (2017) Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 18:1624-1636. 2. Palmer DH, Hawkins NS, Vilgrain V, Pereira H, Chatellier G, Ross PJ. (2020) Tumor burden and liver function in HCC patient selection for selective internal radiation therapy: SARAH post-hoc study. *Future Oncol* 16:4315-4325.	See response to comment 5.
16	Patient and professional group	British Liver Transplant Group, the British Society of Interventional Radiology, the British Nuclear Medicine Society, HCC-UK, and the commissioned NHS England	The groups defined above represent a small cohort of patients with HCC and we believe that the therapy will be cost-effective in these groups. A positive recommendation supporting the funding of SIRT in selected patients with the collection of real world data will enable us to deliver better survival outcomes and improved quality of life for patients with HCC whilst promoting innovation and delivering world-class care in the NHS. Similar precedents exist in the England such as funding for the use of SIRT in patients with metastatic colorectal cancer that cannot tolerate chemotherapy, or the use of radium-223 in cancer patients that cannot tolerate taxanes.	See response to comment 5.

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		SIRT centres. Lead		
17		British Liver Trust	The British Liver Trust is extremely disappointed by this decision. Although this consultation document clearly considers the evidence submitted by the companies and the current research, we are concerned that not enough weight has been given to the experience of patients and the submissions from the patient organisations. We also felt that the patient voice was not sufficiently listened to during the meeting and that this is reflected in the document. Since receiving this consultation document, we have spoken and fed back informally the initial recommendation to three of the many patients we consulted originally (in order to respond to this process) and they are obviously disappointed. There is a perception that the economic evidence is the only evidence that is considered and the patient submission is simply a “tick box exercise”. There is good evidence from patients and clinicians that SIRT undoubtably provides extra years of life for patients. In the words of one clinician, “It would be a tragedy not to try harder to learn how to use this treatment and for it to be available as an option”.	Comment noted. The committee considered all the available evidence, including evidence from clinical trials, patient and clinical experts, the company’s submissions and the AG’s report. It also carefully considered the comments received in response to the ACD and subsequent evidence. The committee was aware that patients with HCC would welcome an effective treatment option (section 3.1 of the FAD). It did consider several subgroups that might benefit from SIRT more than others (see response to comment 5). It also agreed that SIRT had a better safety profile than sorafenib (section 3.26 of the FAD) and concluded to apply a QALY gain because of adverse event disutility (see response to comment 9). The committee also considered commercial arrangements (simple discount patient access scheme) submitted by all 3 companies in its decision making. The committee made optimised recommendations for the use of SIR-Spheres and TheraSphere.
18		British Liver Trust	We recognise that the committee has agreed that SIRT might have fewer and less severe side effects than other treatments. However, we are concerned that this quality of life factor has not been given enough weight in the recommended decision. We apologise if we did not provide enough information on this in our original submission. Some people who take the alternative treatments (Sorafenib and Lenvatinib) report extreme side effects. Callers to the British Liver Trust Helpline and comments from our online forum (over 18,000 members) have been very vocal on this. For example: *"I have had a very rough time lately due to taking Sorafanib. The stuff has been poisoning me, I lost a lot of weight, become dehydrated and become incontinent."* *“My brother Patrick died on 4 January 2019. His stomach was so distended it was like he was 9 months pregnant. I truly believe the sorafenib hastened his death because the bad reaction he had from it was so severe it took days to get it out of his system even though nurses gave him*	See response to comment 17.

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			intravenous liquid to flush it out." *"I had 12mths of sorafenib after TACE. Although it held things steady for 12mths, I felt terrible. I had diarrhoea and was unable to leave the house for the entire time….."* *"My AFP increases when I reduce the dose of sorafenib because of side effects e.g. skin blisters, painful round swelling of palm and sole,sore tongue, mouth etc. But sometimes after healing of skin and other problems I start start full dose of sorafenib then again side effects reappears and AFP comes down." (sic)* Patients who have had SIRT report feeling well two to three weeks after treatment. One patient ran an ultra-marathon (150 miles) 6 weeks after treatment. Another patient reported feeling well enough to go abroad on holiday with his wife to visit their grandchildren and their quality of life improved.	
19		British Liver Trust	Undertaking a robust RCT in this patient group for interventional oncology is challenging, The majority of evidence that we are aware of comes from real world evidence, reports from patients and non-randomised studies. Clinically certain groups of patients will be disadvantaged, particularly those who are in the intermediate and some in the advanced stage of the disease if SIRT is not made available. The evidence may be weak but it should not be ignored. Although the biomarkers have not yet been identified to guide treatment selection, there are undoubtably patients who would benefit, get extra years of life and even cure.	Comment noted. The committee considered all the available evidence, including evidence from clinical trials, patient and clinical experts, the company's submissions and the AG's report. It did consider several subgroups that might benefit from SIRT more than others (see response to comment 5). It also carefully considered the comments received in response to the ACD and subsequent evidence.
20		British Liver Trust	Is there any way that NICE can provide guidance on how we could take this forward for the benefit of patients? Is there any option for this treatment to be included as an interim measure in the Cancer Drugs Fund? Could Commissioning through Evaluation for SIRT in HCC be in an interim solution? Could further studies be commissioned? A positive recommendation for at least a sub group of patients could enable the collection of real-world data to improve the evidence base whilst at the same time saving lives	See response to comment 11.
21		TERUMO Europe	We are extremely concerned by these provisional recommendations as it would mean depriving HCC patients, who have limited treatment options and generally poor prognosis of a treatment alternative that is reimbursed in most European countries and readily accessible in the US. The Committee's discussions in November – reflected in the ACD - highlighted the anticipated benefit in HRQoL between a systemic agent (such as sorafenib) vs a one-off treatment (such as SIRT). The ACD also notes that this benefit may not be appropriately reflected and captured by the QoL results of the relevant RCTs. But unfortunately, this uncertainty around (QoL) results has not been considered in the provisional recommendations. (see point 3) We believe that the original decision to look at the 3 SIRT technologies as 3 separate	See response to comment 9 The committee noted that there was only relatively low-quality evidence for TheraSphere, and very limited evidence with high uncertainty for QuiremSpheres. It considered whether it was appropriate to assume the 3 SIRTs were equally effective (see section 3.32 of the FAD) and consequences this had for the cost-effectiveness estimates.

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			treatments has led to significant issues in the interpretation of the evidence. Firstly because it created an unrealistic number of ICERs and therefore unnecessary complexity in result reporting which may have been detrimental to SIRT. Secondly because it led to the Committee's decision to solely rely on the Assessment Group's report, which does not constitute a representative summary of all the submissions received. (see point 4) We would urge the Committee to simplify the set of results needed for decision-making. We would also urge the Committee to consider a "coverage with evidence development" decision (similar to the Cancer Drugs Fund) so that appropriate data can be collected whilst the treatment is being offered in the NHS (see point 3).	Also, the committee considered commercial arrangements (simple discount patient access scheme) submitted by all three companies within its cost-effectiveness analysis. See response to comment 11.
22		TERUMO Europe	Could we ask that NICE clearly states the following when describing QuiremSpheres®: Quirem Medical (manufacturer)/TERUMO Europe (distributor)	Comment noted. Section 2 'Information about QuiremSpheres, SIR-Spheres and TheraSphere' has been updated.
23		TERUMO Europe	The "dosage in CE Mark" information is not in line with the one from SIR-Spheres® and TheraSphere®. We suggest to add the following for QuiremSpheres® QuiremSpheres® is given through a catheter to the hepatic artery. The product is supplied as a customized, patient-specific dose. The maximum range of the emitted beta particles in tissue is 8.7 mm with a mean of 2.5 mm. In addition, Holmium-166 emits primary gamma photons (81 KeV). The half-life is 26.8 hours, which means more than 90% of the radiation is delivered within the first 4 days following the administration procedure. At planned moment of treatment, the activity per microsphere is 200-400 Bq. The number of particles implanted depends on the targeted liver volume and ranges on average between 10 and 30 million	Comment noted. Section 2 'Information about QuiremSpheres, SIR-Spheres and TheraSphere' has been updated.
24		TERUMO Europe	**We do not believe that the provisional recommendations to be sound and a suitable basis for guidance to the NHS.** **We would urge the Committee to consider recommending SIRT as an available treatment option under a "coverage with evidence development" scheme (such as the Cancer Drug Fund or other schemes detailed below)** We are concerned that it will deprive patients with HCC as well as their families and carers of what the ACD describes as a "potential new treatment option". The ACD describes the likely difference in terms of HRQoL of a systemic therapy such as sorafenib and a "one-off" treatment such as SIRT. (see 3.31 pg 23-24). In particular, t*he Committee concluded that some aspects of health-related quality of life might not be captured in the utility values, but it was not presented with evidence comparing this benefit with the relevant non-SIRT comparator, sorafenib.* Data collection could focus on appropriate measures for HRQoL, taking into account patient preferences and patient-reported outcomes rather than the more generic EQ-5D, and be measured for a longer time that the trials follow-up so that the "transient" vs "systemic" impact can be reflected. Several "coverage with evidence development" schemes have been put in place over the years	See responses to comments 9 and 11.

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>within Technology Appraisals, more recently and famously the Cancer Drug Fund. In previous years the use of laparoscopic surgery for colorectal cancer was initially rejected by NICE and recommended only in the context of a clinical trial which was ongoing. When the treatment was reconsidered at a later date it received positive guidance on the basis of evidence provided by the clinical trial.
For the treatment of multiple sclerosis, the UK's NHS agreed a conditional pricing arrangement regarding the use of interferon beta or glatiramer acetate. The treatments were funded on the condition that their effect on disease progression in a cohort of patients was monitored for 10 years. Potential price adjustments were to be made every 2 years to ensure an agreed cost per QALY gained of the therapy was no more than £36,000.

3.31 pg 23-24
The committee noted that utility values were similar between SIRTs and systemic therapies (sorafenib or lenvatinib) for the following disease states: progression-free survival, progressive disease and post-transplant. There were only small differences in utilities between progression-free survival and progressive disease. The clinical experts explained that people who have sorafenib for a long time may have a long-lasting negative effect on their quality of life. SIRTs are given in 1 procedure, meaning there is a shorter duration of impaired health-related quality of life. The committee considered that the potential difference in long-term quality of life might not be captured in clinical trial results because quality-of-life data are collected at fixed time points. It acknowledged that the cancer, liver function and other comorbidities affect health-related quality of life in people with HCC. The committee concluded that some aspects of health-related quality of life might not be captured in the utility values, but it was not presented with evidence comparing this benefit with the relevant non-SIRT comparator, sorafenib.</td><td></td></tr>
<tr><td>25</td><td></td><td>TERUMO Europe</td><td>We do not believe that the provisional recommendations to be sound and a suitable basis for guidance to the NHS. The UK would be at odds with guidelines and clinical practice in Europe and globally.

Summary of specific reimbursement recommendations and ESMO guidelines informing on patient subgroups recommended in Europe
<table>
<tr><th>Country</th><th>Patient populations</th></tr>
<tr><td>France (TheraSphere)</td><td>HAS 2018

Indication for reimbursement:
Palliative treatment of HCC, BCLC B/C, with portal thrombosis, for patients with ECOG O-1, preserved hepatic function (Child-Pugh A or B) non eligible of after failing sorafenib</td></tr>
<tr><td>France (SIR-Spheres)</td><td>HAS 2019

Indication for reimbursement
Palliative treatment of HCC, BCLC B/C, without occlusion of portal vein, for patients with ECOG O-1, preserved hepatic function (Child-Pugh A or B) non eligible of after failing sorafenib</td></tr>
</table></td><td>Comment noted.</td></tr>
</table>

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Netherlands (HCC, Yttrium-90)</td><td>SIRT in HCC is reimbursed for the following patients:
Zorg Instituut, 2011

Inoperable HCC with favorable tumor staging (such as tumor volume <70% of the total liver volume, no PVT and acceptable liver function and general condition).</td></tr>
<tr><td>European guidelinesSMO HCC 2018</td><td>The recent ESMO HCC guidelines published in 2018 (include link) present the treatment options according to BCLC stage. SIRT features as an alternative treatment available in BCLC 0-A and BCLC B: for patients with liver-confined disease and preserved liver function in whom neither TACE nor systemic therapy is possible, SIRT may be considered. The subgroup considered overlaps with this toolbox recommendation and will keep UK practice in line with the European oncological recommendations.</td></tr>
</table>
</td><td></td></tr>
<tr><td>26</td><td></td><td>TERUMO Europe</td><td>We do not believe that all of the relevant evidence has been taken into account by the Committee to make its recommendations. In particular, we would like to argue against its decision on page 10 “the Committee used the AG’s report for its decision making”. The rationale being “This was because it included evidence for all 3 SIRTs and so was more comprehensive than the companies’ submissions.”

We are surprised by this statement and would like the Committee to reconsider the full breadth of evidence:
- since the creation of NICE and its Technology Appraisal process, there have been 46 TA recommendations for medical devices out of 925 total recommendations (NICE website as of Dec 2019)
- All technology appraisals for medical devices have assumed a class effect ie that the different technologies available on the market are not appraised individually
- This has always been the position of the IP Committee at NICE as they have always evaluated SIRT in their different guidance (and not SIR-Spheres or TheraSphere or QuiremSpheres)
- This is also the conclusion from the Committee as there is not enough evidence to compare the technologies
- It’s had a significant impact on the appraisal so far as it has rendered the description of results almost impossible to grasp considering the unrealistic number of ICERs presented
- And the statement above is simply unfair as individual company submissions could <u>not</u> have been expected to include comprehensive evidence on all technologies

Therefore we would recommend that the Committee considers all sources of evidence with equal attention to make its decision – the excellent York evaluation report as well as</td><td>Comment noted. The committee considered all the available evidence, including evidence from clinical trials, patient and clinical experts, the company’s submissions and the AG’s report. It also carefully considered the comments received in response to the ACD and subsequent evidence. The committee considered the available non-RCT evidence but concluded that RCT evidence was more suitable for decision making (see sections 3.11 and 3.15 of the FAD).
The committee noted that there was only relatively low-quality evidence for TheraSphere, and very limited evidence with high uncertainty for QuiremSpheres. It considered whether it was appropriate to assume the 3 SIRTs were equally effective (see section 3.32 of the FAD) and consequences this had for the cost-effectiveness estimates.</td></tr>
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			all manufacturers submissions, submissions from Patient organisations and medical societies, and input during Committee hearings. The decision to limit treatment options available to HCC patients should be based on the wide variety of input and not only on the AG report, especially if the rationale for solely using the AG report is questionable.	
27		Sirtex Medical United Kingdom Ltd.	Given that - based on the results for the overall SARAH trial population - the estimated population average costs and outcomes are likely similar for SIR-Spheres and sorafenib, that sorafenib is associated with significant adverse effects including diarrhoea, fatigue and hand and foot skin reaction compared to SIR-Spheres, and there is evidence that treatment with SIR-Spheres is associated with a higher likelihood of subsequent treatment with curative intent it would seem reasonable that individual **patients should have the option to receive SIR-Spheres treatment based on their preferences regarding adverse effects and potential outcomes**. This opinion was also raised by the patient expert at the open session of the committee meeting on November 6th 2019. In addition, there is evidence that it is possible to select a group of patients who may experience better and cost-effective outcomes with SIR-Spheres based on their liver function and tumour morphology. • **SIR-Spheres result in similar or better health outcomes than sorafenib** In the unselected (intention-to-treat) trial population (using Committee's recommended base case with downstaging) the health outcomes are similar with a population average of -0.105 incremental QALY based on the non-significant differences in overall survival. In the proposed subgroup for SIR-Spheres results in an additional 0.601 QALYs. • **SIR-Spheres and sorafenib have similar or lower costs, or for the proposed subgroup have cost-effective outcomes even with a discount for sorafenib** In the unselected (intention-to-treat) population (after correction for factual errors) SIR-Spheres results in a cost saving of £6,142 per patient. Assuming a substantial 50% discount for sorafenib, SIR-Spheres still results in a cost saving of £858. This indicates provision of SIRT as an alternative treatment option for patients would be cost saving. In the proposed subgroup SIR-Spheres results in a saving of £1,784 per patient, or assuming a 50% discount for sorafenib, the 0.601 QALY gain comes at an incremental cost of £4,534 resulting in an incremental cost-effectiveness ratio of £7,546 per QALY. For the factual inaccuracies mentioned here, we would like to bring the Committee's attention to the next comment.	Comment noted. After consultation and additional analysis by the AG, the committee re-evaluated quality of life data (section 3.37 of the FAD) and considered analyses applying disutility values for adverse events of grade 3 and above, and for adverse events of any grade (section 3.38 of the FAD). It concluded that some aspects of health-related quality of life might not be captured in the utility values and agreed to include a QALY gain for SIRTs because of adverse event disutility. Confidential discounts for SIRTs, sorafenib and regorafenib were included in the cost-effectiveness analysis. Exact incremental cost-effectiveness ratios [ICERs] are confidential and cannot be reported in the FAD.
28		Sirtex Medical United Kingdom Ltd.	**We are concerned that factual errors remain in the Assessment Group Report.** These include the following: • **The cost of SIR-Spheres is overestimated.** The Assessment Group assumed the use of an additional procedure for the administration of SIR-Spheres compared to TheraSphere based on differences in the wording of the two company submissions. This interpretation is incorrect. As previously noted by Sirtex, SIR-Spheres and TheraSphere are administered using the same imaging and equipment and therefore have exactly the same administration costs.	Comment noted. The AG has responded to factual errors and updated its report and additional analysis accordingly.

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			Given that the Assessment Group and Committee have chosen to assume equal efficacy for SIR-Spheres and TheraSphere (based on data specific to SIR-Spheres); the costs, health benefits and cost-effectiveness of SIR-Spheres and TheraSphere should be the same. • **The cost of sorafenib is underestimated.** As the cost of sorafenib is an influential input in the model, the duration of treatment needs to be precise. In the Assessment Group model, instead of using the treatment duration observed in the SARAH trial (on which the efficacy data is based in this model), an estimate based on the median duration observed in SARAH and an assumed distribution were used. This underestimates the duration of sorafenib treatment by 23.46 days and the cost of sorafenib by £2,429 (at the list price). This incorrect assumption was previously noted by Sirtex; however, it was not addressed by the Assessment Group. The correct duration based on patient-level data from the SARAH trial was provided by Sirtex in the company submission.	
29		Sirtex Medical United Kingdom Ltd.	**We are concerned, that despite the evidence, and the Committee's recommendations, downstaging, a crucial benefit of SIRT treatment for patients with hepatocellular carcinoma (HCC), has not been taken into account in the economic model. This omission has a significant impact on the cost-effectiveness results.** • **Evidence is available to support the role of SIR-Spheres in downstaging** For patients with advanced HCC, SIR-Spheres allows for patients to be downstaged to receive potentially curative therapies (i.e. liver transplant, surgical resection and percutaneous tumour ablation), as opposed to the current treatments recommended by NICE. This is supported by both a randomised European trial (SARAH trial) and non-randomised studies (e.g. the CIRSE Registry for SIR-Spheres Therapy in Europe, and the French series of patients with advanced HCC reported by Regnault H et al. P07-06 in EASL HCC Summit 2019: https://www.easl.eu/hcc2019/wp-content/uploads/2019/01/HCC-Summit-2019-Abstract-book.pdf). • **The Committee recommended the base case should include downstaging** The benefit of downstaging has been acknowledged by the Committee concluding that "*the base-case model should include downstaging*" (point 3.30 in the appraisal consultation document), despite this, downstaging was not included in the economic model reported in the appraisal consultation document. Although this document adds that the proportion of patients receiving subsequent curative therapies is uncertain, this proportion depends on the selection criteria of patients for SIR-Spheres. In the unselected population of the SARAH trial (ITT population), 5.1% of patients (12 out of 237 patients) were downstaged, although all had initially unresectable HCC and are very unlikely to become eligible for curative therapies after sorafenib according to the clinical experts. Indeed, in the same population, only 1.4% of patients (3 out of 222) were downstaged after sorafenib. In the ALBI grade 1 and low tumour burden subgroup (comment number 4 below), 13.5% of patients (5 out of 37) were downstaged after SIR-Spheres vs 2.1% after sorafenib (1	Comment noted. The committee considered the available evidence for downstaging and the extent to which it should be captured in the cost-effectiveness analysis (see section 3.36 of the FAD).

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			out of 48). This survival benefit of downstaging is not captured in the SARAH trial outcomes, as 13 out of 15 downstaged patient were alive and censored at the end of the follow-up period. This benefit is however relevant for patients, according to patient expert opinion elicited in the open session of the Committee meeting. The uncertainty on the proportion of patients receiving subsequent curative therapies should therefore not be considered a valid argument to exclude downstaging from the model but should instead be explored in sensitivity analyses. • **Downstaging has an important impact on cost-effectiveness estimates** In the unselected population of the SARAH trial (ITT population), the inclusion of downstaging results in SIR-Spheres being slightly less effective and less costly, and sorafenib not being cost-effective against SIR-Spheres (incremental cost-effectiveness ratio of £58,763 per quality adjusted life-year). With a large discount assumed for sorafenib (e.g. 50%), the costs and effectiveness of SIR-Spheres and sorafenib are then similar. In the ALBI grade 1 and low tumour burden subgroup, the inclusion of downstaging results in SIR-Spheres being more effective and less costly than sorafenib (at list price), i.e. SIR-Spheres dominating sorafenib. In this case, assuming even an 80% discount for sorafenib results in an incremental cost-effectiveness ratio of £13,855 per quality adjusted life-year for SIR-Spheres vs. sorafenib. The above estimates also include the factual corrections detailed in comment number 2 above. **Cost-effectiveness results in the appraisal consultation document should include downstaging as the Committee recommended base case. This document cannot be considered a reasonable summary of the economic evidence at this point.**	
30		Sirtex Medical United Kingdom Ltd.	**We are concerned that the population of patients with a low tumour burden (≤25% of the liver volume) and an Albumin-Bilirubin (ALBI) grade 1 liver function was dismissed as the base case population of the economic model for people for whom conventional transarterial therapies are inappropriate, given the evidence and the clinical expert opinion elicited in the open session of the Committee meeting on 6th November 2019.** Sirtex agrees that subgroups should be prespecified, clinically plausible, implementable, generalisable and evidence-based, and therefore respectfully request the Committee reconsider the following aspects supporting the ALBI grade 1 and low tumour burden subgroup as base case population of the model: • **Prespecified analysis was not possible** The SARAH trial is the only source of efficacy data used for SIRT in the economic model. Subgroup analyses using a ≤25% tumour burden threshold were prespecified in the SARAH trial and reported in the main publication of this trial (Vilgrain V et al. Lancet Oncol. 2017 Dec;18(12):1624–36). However, there are circumstances when clinically plausible, well-supported subgroups cannot be prespecified. In this instance, although the ALBI grade is estimated based	Comment noted. The committee considered several subgroups including the ALBI grade 1 subgroup. The committee concluded that there was not enough evidence for decision making for this subgroup (see section 3.34 of the FAD).

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			on blood tests for albumin and bilirubin, for which data was prospectively collected during the SARAH trial, the formula used to determine the ALBI grade was only published (Johnson PJ et al. J Clin Oncol. 2015 Feb 20;33(6):550–8) immediately after the enrolment period of the trial (from 05/12/2011 to 19/02/2015). The ALBI grade 1 and low tumour burden subgroup could therefore not have been prespecified in the SARAH trial and this argument is invalid to dismiss the subgroup as the model base case. • **Clinical plausibility is well established** This subgroup was proposed by clinicians with experience of SIRT, in accordance with clinical guidelines, to ensure that the patients who benefit the most would receive SIRT. Tumour burden is routinely assessed and the ≤25% criterion is already used by NHS England to determine the eligibility for SIRT of patients with colorectal liver metastases. The components of the ALBI grade are also routinely collected, and the score itself was developed in England and validated against UK cohorts of patients (Johnson PJ et al. J Clin Oncol. 2015 Feb 20;33(6):550–8). It was reported to outperform the Child-Pugh score as a predictor of overall survival following SIRT (Ali R et al. Cardiovasc Intervent Radiol. 2019 May;42(5):700–11; Antkowiak M et al. Cancers. 2019 Jun;11(6):879). Use of the ALBI grade is also recommended in European clinical guidelines to stratify patients in terms of prognosis within the Child-Pugh A class itself (Galle PR et al. J Hepatol. 2018 Jul;69(1):182–236; Vogel A et al. Ann Oncol. 2018 Oct 1;29(Supplement_4):iv238–55). This therefore contradicts the summary presented in the appraisal consultation document (point 3.6) that "*The clinical experts advised […] that Child-Pugh is expected to be the measure of choice for the foreseeable future*": both ALBI and Child-Pugh can co-exist in UK clinical practice, with the ALBI grade being used to further select patients for SIRT among all Child-Pugh A patients. • **Simple implementation in UK clinical practice** As described by the appraisal consultation document, in the open session of the Committee meeting, "*clinical experts explained that ALBI grade could be a more objective measure than Child-Pugh score for liver dysfunction*". It is however not reflected in this document, that in the open session, the clinical expert also added that the calculation of the ALBI grade is straightforward and can be performed using a published Nomogram as described in Johnson PJ et al. J Clin Oncol. 2015 Feb 20;33(6):550–8 or with a web-based app. The clinical expert furthermore reported that the ALBI grade was used in the UK and was recommended for the stratification of patients for locoregional treatments. Because the criterion of a tumour burden ≤25% is already used to determine patient eligibility for SIRT in the treatment of colorectal liver metastases, this raises no implementation issue. • **The subgroup is generalisable to patients seen in the NHS in England** The appraisal consultation document states in point 3.19 that "*The clinical experts*	

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			advised that the SARAH trial had more people with a high tumour burden, [portal vein thrombosis] and impaired liver function than people seen in clinical practice in England. The committee understood that because of this, people in the SARAH trial had poorer prognosis than people seen in clinical practice in England. It concluded that results from the SARAH trial may not be generalisable to people seen in the NHS in England". We agree with this statement and have proposed the ALBI grade 1 and low tumour burden subgroup to ensure that patients considered in the economic model reflect those most likely to receive SIRT in the NHS. • **Evidence supporting the subgroup is in the public domain** Analyses of the SARAH trial in the ALBI grade 1 and low tumour burden subgroup were presented at the European Society of Medical Oncology 2019 congress (Palmer DH et al. Ann Oncol. 2019 Oct 1;30(Supplement_5):mdz247.061) and recently published in full (Palmer DH et al. Future Oncol. 2020 Jan;16(1):4315–25). **Having addressed the arguments put forward in the appraisal consultation document to dismiss the ALBI grade 1 and low tumour burden subgroup, we suggest that the subgroup could be reasonably considered as the base case population in the economic model.**	
31		Sirtex Medical United Kingdom Ltd.	**We are concerned, that the comments regarding the reliability of the network meta-analysis are contradictory.** We agree with the recommendation in the appraisal consultation document point 3.24 that "*The comparative effectiveness of treatment options in people for whom [conventional transarterial therapies are] inappropriate is uncertain*". However, the appraisal consultation document continues: "*but [the comparative effectiveness] is useful for decision making*", subsequently describes the result of the network meta-analysis and presents it in a scenario analysis of the cost-effectiveness model. This could lead to the misleading interpretation that the network meta-analysis is appropriate and should be used for decision-making.	Comment noted. The committee's preferred cost-effectiveness analysis is based on data from the SARAH trial and does not include results from the network meta-analysis (see section 3.32 of the FAD).
32		Sirtex Medical United Kingdom Ltd.	Sirtex is committed to further collaborate with NICE and would be happy to provide any support required to reduce the time pressure that was experienced at the first Committee meeting. The time pressure constrained the input Sirtex was able to provide towards a fair assessment of all the available evidence and limited the company's ability to address all factual inaccuracies.	Comment noted.
33		BTG (A Boston Scientific Company)	BTG are extremely disappointed that the Committee felt unable to recommend selective internal radiation therapy as a treatment for hepatocellular carcinoma in adults. We understand the Committee's frustration around the lack of randomised controlled trials and comparative evidence for selective internal radiation therapy. However, we would like to point out that selective internal radiation therapy products are medical devices and not pharmaceutical products. Device manufacturers are not required to carry out randomised controlled trials to achieve approval by the licensing authorities. Randomised controlled trials for selective internal radiation therapy require a large sample size due to natural variation in outcomes due to patient factors and operator skill, which is challenging in terms of patient and investigator recruitment and cost.	Comment noted. The committee considered all the available evidence, including evidence from clinical trials, patient and clinical experts, the company's submissions and the AG's report. It also carefully considered the comments received in response to the ACD and subsequent evidence. The committee considered the available non-RCT evidence but concluded that RCT evidence was more suitable for decision making (see sections 3.11 and 3.15 of

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			Therefore, although there are a few randomised controlled trials for selective internal radiation therapy, the majority of the evidence is of a lower quality grade than one would expect to see with a pharmaceutical product. Many of the studies are small investigator led studies in mixed populations, which make them difficult to interpret or use for evidence synthesis. This issue was pointed out in early discussions between BTG and the National Institute for Health and Care Excellence. It should be noted that National Institute for Health and Care Excellence widen acceptable evidence and accept non-randomised data when considering medical devices within the Medical Technologies Guidance (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-medical-technologies-guidance). This is also the case when assessing new and existing highly specialised medicines and treatments within the National Health Service in England using the highly specialised technologies framework. The BTG submission included non-randomised evidence which shows that TheraSphere is life-extending. Furthermore, all network meta-analyses, whether carried out by the Assessment Group or by BTG, showed that TheraSphere is life-extending when non-randomised evidence is included. As mentioned in 3.12 of the Appraisal Consultation Document the Assessment Group only included some of the non-randomised evidence. We believe that the Committee were not provided with the totality of the evidence on which to base their decision. Interventional oncology is a fast-moving field. This means that data from more recent studies show improved outcomes with selective internal radiation therapy, due to improved technique, improved patient selection and personalised dosing. Personalised dosimetry, where the dose of radiation is tailored to the patient providing an optimised dose to the tumour, is a relatively new technique and has shown to result in improved survival outcomes compared to standard dosimetry. Data from both TheraSphere and SIR-Spheres have demonstrated survival benefit with personalised dosimetry[1-5]. A recent expert recommendation consensus paper (Salem 2019) reflects on the benefits of personalised dosimetry and stated that '*As new prospective trials are designed, incorporation of a refined and personalized dosimetry model will be essential for improved outcomes*'. We urge the Committee to take a pragmatic approach to the evidence-base for selective internal radiation therapy and allow three discrete subgroups of people with hepatocellular carcinoma access to life-extending treatment. These specific sub-populations include: • People with large (≥5 cm) tumours (with or without portal vein thrombosis), this subgroup are unable to receive conventional transarterial therapies. • People with portal vein thrombosis, this subgroup are unable to receive conventional transarterial therapies.	the FAD). The committee considered several subgroups during its discussions including people with large tumours, people who cannot have sorafenib, people with ALBI grade 1 and low tumour burden and people with PVT (see sections 3.23, 3.24, 3.25 and 3.34 of the FAD). It concluded that there was insufficient evidence to recommend SIRTs for these subgroups.

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			• People with advanced disease (stage C) who are unable to receive or tolerate the standard of care (systemic therapies, e.g. sorafenib). The use of selective internal radiation therapy gives these sub-populations a life-extending treatment and in the case of patients with intermediate disease the potential for cure via downstaging to transplant or resection. These discrete sub-populations represent only 7% of the total hepatocellular carcinoma population (199/2,935) in England in 2019: 96 people with large tumours and/or portal vein thrombosis and 103 people unable to tolerate sorafenib. Use of selective internal radiation therapy in these populations is within European treatment guidelines updated in 2019[6]. BTG believe that TheraSphere will be cost-effective when used in the right patient group, at the right dose and at the right price. [redacted]. We would also like to point out that the price of a vial of TheraSphere remains the same, regardless of the dose. In the following sections, all copy in bold is taken directly from the Appraisal Consultation Document. Comments are made on the Appraisal Consultation Document as they appear within the document and there is some repetition. 1. Garin E, Rolland Y, Edeline J, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. J Nucl Med 2015; 56(3): 339-46. 2. Garin E, Rolland Y, Pracht M, et al. High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with (90) Y-loaded glass microsphere radioembolization. Liver Int 2017; 37(1): 101-10. 3. Garin E, Tselikas L, Guiu B. Major impact of personalized dosimetry on the targeted tumor response using 90Y loaded glass microspheres SIRT in HCC : preliminary results of a prospective multicentric randomized study. European Conference on Interventional Oncology; 2019; Amsterdam 4. Hawkins N, Ross P, Palmer D, Chatellier G, Pereira H, Vilgrain V. Overall survival of patients with hepatocellular carcinoma receiving sorafenib versus selective internal radiation therapy with predicted dosimetry in the SARAH trial (poster). European Society for Medical Oncology 2019; Barcelona 5. Salem R, Padia SA, Lam M, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging 2019; 46(8): 1695-704. 6. Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO Clinical Practice	

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			Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019; 30(5): 871-3. 7. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol 2017; 18(12): 1624-36.	
34		BTG (A Boston Scientific Company)	1.1 Page 3 **There is very limited clinical evidence to compare the effectiveness of QuiremSpheres and TheraSphere with other treatments. Also, there are not enough data to compare the effectiveness of the 3 SIRTs with each other.** We agree that there is a paucity of data for QuiremSpheres, however, the evidence-base for TheraSphere is wide and includes data from both randomised and non-randomised studies (see TheraSphere submission, Table 4.2). In our response to the Assessment Group report we noted that techniques exist for combining randomised and non-randomised evidence in network meta-analysis (page 12/13). We are pleased that the Assessment Group carried out a mixed treatment comparison for the population in which conventional transarterial therapies are appropriate (intermediate disease, stage B) (Appraisal Consultation Document, 3.23). We suggest that the results may have been more robust if non-randomised data was included in the analysis.	Comment noted. The committee considered all the available evidence, including evidence from clinical trials, patient and clinical experts, the company's submissions and the AG's report. It also carefully considered the comments received in response to the ACD and subsequent evidence.
35		BTG (A Boston Scientific Company)	1.1 Page 3 **There is not enough evidence to consider SIRTs a cost-effective use of NHS resources for early and intermediate stage hepatocellular carcinoma** BTG believe that there is adequate data to support economic modelling in early/intermediate stage disease (where conventional transarterial therapies are appropriate) and that the BTG model is appropriate in the absence of a model from the Assessment Group (see 2.3.6 of our response to the Assessment Group report, page 17 and 18). Our model was validated by clinical experts in the field who reassured us that the model was both clinically appropriate and robust. The incremental cost effectiveness ratio was around £25,000 at list price in this population. [redacted] Alternatively, if we make the assumption that all three selective internal radiation therapy treatments are equivalent (as per the Assessment Group network meta-analysis) then a simple cost-minimisation approach could aid the Committee in making a decision. BTG believe that selective internal radiation therapy is an appropriate choice for people with early/intermediate disease who are unable to receive conventional transarterial therapies because they have large tumours ≥5 cm and/or portal vein thrombosis. The only alternative treatment in these patients is sorafenib. In order to be eligible for selective internal radiation therapy, people should have conserved liver function, good performance status, adequate hepatic reserve post-selective internal radiation therapy and none or limited extra hepatic disease. As mentioned earlier, interventional oncology is a fast-moving field and recent/ongoing studies using personalised dosimetry with TheraSphere have shown superior outcomes to standard dosimetry in these patient populations. A recent phase II, multicentre, randomised study (Dosisphere) was presented at the European Conference on Interventional Oncology 2019. Patients (stage A, B or C) had at least one tumour	Comment noted. The committee considered the available clinical and cost-effectiveness evidence in the early and intermediate stage populations; people for whom transplant is appropriate and people for whom CTT is appropriate (see sections 3.12 to 3.17 of the FAD). It concluded that there was insufficient robust clinical evidence for the SIRTs in these populations to conduct a robust economic evaluation. It considered the only population with enough evidence to support a suitable economic evaluation was the advanced population; people for whom CTT is inappropriate (see section 3.18 to 3.20 of the FAD).

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			≥7 cm and were randomised to TheraSphere either following standard dosimetry (120 ± 20 Gy) (n=28) or personalised dosimetry (>205 Gy) (n=28). Of the 56 patients 40 (71%) had portal vein thrombosis. Response rates were 78.6% and 42.9% in the personalised dosimetry and standard dosimetry arms respectively, by blinded central review, indicating superior efficacy with personalised dosimetry[3]. (page 11 of BTG response to the Assessment Group report). [redacted] A study by Garin et al[1] in hepatocellular carcinoma patients with portal vein thrombosis (n=41) revealed a significant improvement in overall survival with personalised dosimetry (>205 Gy) versus standard dosimetry (<205 Gy): 18.2 months versus 4.3 months, p<0.005. Further work by Garin et al[2] in a mixed intermediate/advanced disease population showed significantly improved overall survival in patients receiving personalised dosimetry versus standard dosimetry: median overall survival of 15.7 months versus 4.35 months, p=0.0004 in the portal vein thrombosis population (page 19 of BTG response to the Assessment Group report).	
36		BTG (A Boston Scientific Company)	1.1 Page 3 **The economic analysis shows that SIRTs are less clinically effective and cost more than lenvatinib or sorafenib** Lenvatinib should not be included here, as noted later in the Appraisal Consultation Document (3.27) sorafenib is the only relevant comparator for cost effectiveness in people for whom conventional transarterial therapies are inappropriate. We believe that clinical efficacy is at least comparable between TheraSphere, SIR-Sphere and sorafenib • The comparative effectiveness data (3.24) shows that there is no statistically significant difference in clinical efficacy between SIR-Sphere and sorafenib. The inclusion of TheraSphere via retrospective evidence indicates that TheraSphere is more effective than SIR-Sphere and sorafenib (3.2.4). It should be noted that the hazard ratios are not statistically significant (as indicated by the credible intervals), indicating that sorafenib, SIR-Sphere and TheraSphere are not significantly different in terms of survival. • We recently identified a potential modelling error with the Assessment group model (see Appendix) which means that quality adjusted life years for TheraSphere were underestimated in the Assessment Group model. • Given the concerns around the studies used to link TheraSphere with SIR-Spheres in the mixed treatment comparison, we believe that non-comparative evidence would be helpful in decision making (and as noted above, would be accepted if the selective internal radiation therapy was undergoing review via the Medical Technologies Guidance process). Non-comparative evidence (Table 4.7 in TheraSphere submission) indicates an extension to life of 12.3 to 22.1 months (nine cohort studies). • The clinical experts at the Committee meeting stated that **SIRTs might extend life expectancy in advanced stage disease** (Appraisal Consultation Document, 3.4) Assuming that TheraSphere and SIR-Spheres are similar in efficacy, which is not unreasonable	Comment noted. The committee concluded that sorafenib is the relevant comparator (see section 3.33 of the FAD). After consultation and additional analysis by the AG, the committee re-evaluated quality of life data (section 3.37 of the FAD) and considered analyses applying disutility values for adverse events of grade 3 and above, and for adverse events of any grade (section 3.38 of the FAD). It concluded that some aspects of health-related quality of life might not be captured in the utility values and agreed to include a QALY gain for SIRTs because of adverse event disutility. The AG has responded to factual errors and updated its report and additional analysis accordingly. The committee considered the available non-RCT evidence but concluded that RCT evidence was more suitable for decision making (see sections 3.11 and 3.15 of the FAD). Confidential discounts for SIRTs, sorafenib and regorafenib were included

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			given that they both deliver Y^{90} to the tumour site, the overlapping credible intervals and the non-comparative evidence noted above, then we can assume that TheraSphere and SIR-Spheres and sorafenib have comparable efficacy. The corrected Assessment Group model substantiates this claim. This would again be supportive of making any decisions based on a cost-minimisation basis. However, selective internal radiation therapy may be associated with an improved quality of life compared with sorafenib (as noted in the Appraisal Consultation Document, 3.3.1) **because people who have sorafenib for a long time may have a long-lasting negative effect on their quality of life. SIRTs are given in 1 procedure, meaning there is a shorter duration of impaired health-related quality of life**. The Appraisal Consultation Document also notes that **SIRTs might have fewer and less severe side effects than other treatment options** (Appraisal Consultation Document, 3.4) This is confirmed by data from the pivotal SARAH study for SIR-Spheres[7], in which 64% (139/216) of patients discontinued sorafenib for drug-related toxicity; of whom 108 (78%) permanently discontinued treatment. Therefore in SARAH, 50% (108/216) of people taking sorafenib permanently discontinued treatment due to intolerable side-effects, advice from BTG clinical advisors confirms discontinuation rates of around 50% in UK clinical practice. Quality of life was also significantly poorer in the sorafenib arm than with selective internal radiation therapy. We also heard at the Committee meeting that adverse events can be extremely unpleasant for people undergoing treatment with sorafenib and make continuation with treatment very challenging. The clinical experts agreed that adverse events with selective internal radiation therapy were short-lived and much easier to manage than those experienced by people taking sorafenib. Selective internal radiation therapy provides an alternative treatment option for people with advanced disease who are not eligible for sorafenib or unable to tolerate sorafenib. [redacted] It is important to note that we are asking the Committee to consider selective internal radiation therapy for a specific sub-population, who have no other alternative life-extending options if they are unable to take sorafenib.	in the cost-effectiveness analysis. Exact incremental cost-effectiveness ratios [ICERs] are confidential and cannot be reported in the FAD.
37		BTG (A Boston Scientific Company)	3.1 Page 5 **People with hepatocellular carcinoma would welcome a new treatment option** BTG are pleased that the Committee accept that people with hepatocellular carcinoma would welcome a new treatment option. We believe that selective internal radiation therapy offers an alternative life-extending treatment option to a selected group of people with hepatocellular carcinoma unable to take the standard of care.	Comment noted.
38		BTG (A Boston Scientific Company)	3.2 Page 5 **People with hepatocellular carcinoma and portal vein thrombosis are a relevant subgroup** BTG are pleased that the Committee accept that people with hepatocellular carcinoma and portal vein thrombosis should be included in the appraisal. This patient group is particularly challenging because portal vein thrombosis confers a poor prognosis with limited treatment options. Current 2019 guidelines recommend palliative treatment with sorafenib or best supportive care[6].	Comment noted. The committee considered several subgroups including people with portal vein thrombosis (see section 3.23). It concluded there was not enough robust evidence to establish the clinical effectiveness of SIRTs compared with non-SIRT treatments for people with PVT.

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			Excellent results have been shown with TheraSphere in people with hepatocellular carcinoma and portal vein thrombosis. As noted in our response to the Assessment Group report (page 7, page 30) A study by Garin et al[1] in hepatocellular carcinoma patients with portal vein thrombosis (n=41) revealed a significant improvement in overall survival with personalised dosimetry (>205 Gy) versus standard dosimetry (<205 Gy): 18.2 months versus 4.3 months, p<0.005. Further work by Garin et al[2] in a mixed intermediate/advanced disease population showed significantly improved overall survival in patients receiving personalised dosimetry versus standard dosimetry: median overall survival of 15.7 months versus 4.35 months, p=0.0004 in the portal vein thrombosis population. Earlier work with standard dosing has shown overall survival gains of 3.2 to 16.6 months depending on the location of the portal vein thrombosis (see Table 4.7 and Table 4.8 in the BTG original TheraSphere submission). Given the limited options and poor prognosis for this patient group and positive evidence using personalised dosimetry to deliver TheraSphere, BTG believe that TheraSphere is an alternative treatment in these people.	
39		BTG (A Boston Scientific Company)	3.8 Page 8 **There are 3 distinct subgroups relevant to this appraisal** This is correct, however, BTG would like to point out that there are specific patient groups who are unable to receive the standard of care. • People with a tumour at least one lesion 5 cm or above, because the size of their tumour means that conventional transarterial therapies cannot be used. • People with portal vein thrombosis (who may also have large lesions as above), because the portal vein thrombosis means that conventional transarterial therapies cannot be used. • People with advanced stage disease (stage C) in whom the toxicity of sorafenib is intolerable and are unable to continue with treatment. In order to be eligible for selective internal radiation therapy, people in these subgroups should have conserved liver function, good performance status, adequate hepatic reserve post-selective internal radiation therapy and none or limited extra hepatic disease.	Comment noted. The committee considered all the available evidence, including evidence from clinical trials, patient and clinical experts, the company's submissions and the AG's report. It also carefully considered the comments received in response to the ACD and subsequent evidence. The committee considered several subgroups during its discussions including people with large tumours, people who cannot have sorafenib and people with PVT (see sections 3.23, 3.24, 3.25 and 3.34). It concluded that there was insufficient evidence to recommend SIRTs for these subgroups.
40		BTG (A Boston Scientific Company)	3.10 Page 9 **In people with intermediate stage disease, CTTs are the standard of care in current NHS practice in England** BTG accept this statement and note that it is in line with current guidelines. However, people with intermediate stage hepatocellular carcinoma with large tumours (with or without portal vein thrombosis) are unsuitable for conventional transarterial therapies and selective internal radiation therapy offers an alternative treatment option in these patients. Without the option of selective internal radiation therapy, the only available treatments are palliative treatment with sorafenib or best supportive care.	Comment noted.
41		BTG (A Boston Scientific Company)	3.12 Page 9-10 **The systematic review included non-randomised controlled trials (RCTs) when not enough RCT evidence was identified**	Comment noted. The committee considered all the available evidence, including evidence from clinical trials,

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			BTG are pleased that the Committee understand that some non-randomised evidence was included in the AG report, however, we would like to point out that there is a considerable body of non-comparative evidence to support TheraSphere as outlined in our original submission to NICE, which was not considered by the Assessment Group. The Assessment Group made an explicit decision to exclude non-randomised studies, therefore, the Committee was not given all the information that they needed to make a decision.	patient and clinical experts, the company's submissions and the AG's report. It also carefully considered the comments received in response to the ACD and subsequent evidence. The committee considered the available non-RCT evidence but concluded that RCT evidence was more suitable for decision making (see sections 3.11 and 3.15 of the FAD).
42		BTG (A Boston Scientific Company)	3.16 Page 12 **Non-randomised evidence comparing TheraSphere with non-SIRT treatments is not robust and should not be used for decision making** We understand the Committee's point of view regarding quality of evidence, however, would like to re-iterate that selective internal radiation therapy is a medical device and not a pharmaceutical and therefore, randomised controlled trials are not required for device approval. The existing evidence, both comparative and non-comparative, suggests that TheraSphere is a life-extending treatment.	Comment noted. The committee considered all the available evidence, including evidence from clinical trials, patient and clinical experts, the company's submissions and the AG's report. It also carefully considered the comments received in response to the ACD and subsequent evidence. The committee considered the available non-RCT evidence but concluded that RCT evidence was more suitable for decision making (see sections 3.11 and 3.15 of the FAD).
43		BTG (A Boston Scientific Company)	3.20 Page 15 **Of these, 4 compared SIR-Spheres with TheraSphere and 1 small study of 30 people compared all 3 SIRTs.** BTG believe that this is an error, the five studies in question all compared TheraSphere and SIR-Spheres. See slide 32 of the pre-meeting briefing	Comment noted. The figures in section 3.21 of the FAD have been amended.
44		BTG (A Boston Scientific Company)	3.21 Page 15 **There is not enough direct evidence for people when CTT is inappropriate to compare the 3 SIRTs' effectiveness, so mixed treatment comparison should be considered** 3.24 Page 19 **The comparative effectiveness of treatment options in people for whom CTT is inappropriate is uncertain, but is useful for decision making** **The committee agreed that the retrospective studies should not be included in the analysis because of the risk of bias. It agreed that the comparative effectiveness results based on RCT evidence could be used in a cost-effectiveness analysis.** BTG concur that there is little direct evidence, however, we are concerned that other methods of comparison were not considered and that non-comparative evidence was excluded from the evidence synthesis (Response to Assessment Group report, page 12/13). As noted, selective internal radiation therapy products are medical devices and not pharmaceutical products and therefore their evidence base consists of numerous small non-randomised studies and real world evidence rather than more conventional randomised controlled trials that one would expect with pharmaceutical products.	Comment noted. The committee considered all the available evidence, including evidence from clinical trials, patient and clinical experts, the company's submissions and the AG's report. It also carefully considered the comments received in response to the ACD and subsequent evidence. The committee considered the available non-RCT evidence but concluded that RCT evidence was more suitable for decision making (see sections 3.11 and 3.15 of the FAD).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
45		BTG (A Boston Scientific Company)	3.25 Page 21 **The AG's model was used for decision making** BTG submitted two models – one for early/intermediate disease (in people in whom conventional transarterial therapies are appropriate) and one for later stage disease (in people in whom conventional transarterial therapies are inappropriate). The Assessment Group only produced a model for later stage disease. BTG are disappointed that in the absence of a model in early/intermediate disease the Assessment Group did not use the BTG model to aid Committee in making a decision (see 2.3.6 of our response to the Assessment Group report, page 17 and 18). Incremental cost effectiveness ratios were around £25,000 at list price in this population using the BTG model with all interventions at list price.	Comment noted. The committee considered the available clinical and cost-effectiveness evidence in the early and intermediate stage populations; people for whom transplant is appropriate and people for whom CTT is appropriate (see sections 3.12 to 3.17 of the FAD). It concluded that there was insufficient robust clinical evidence for the SIRTs in these populations to conduct a robust economic evaluation. It considered the only population with enough evidence to support a suitable economic evaluation was the advanced population; people for whom CTT is inappropriate (see section 3.18 to 3.20 of the FAD).
46		BTG (A Boston Scientific Company)	3.26 Page 21 **The structure of the AG model for people when CTT is appropriate is acceptable for decision making** This is a typographical error, it should read CTT is inappropriate	Comment noted. Section 3.31 of the FAD has been amended.
47		BTG (A Boston Scientific Company)	3.31 Page 23-24 **Some aspects of health-related quality of life might not be captured in the utility values** As noted in the Appraisal Consultation Document, **people who have sorafenib for a long time may have a long-lasting negative effect on their quality of life. SIRTs are given in 1 procedure, meaning there is a shorter duration of impaired health-related quality of life**. This is not captured within the economic modelling indicating that selective internal radiation therapy may have greater QALY gains than those suggested by existing modelling. The impact of adverse events from sorafenib impacts on quality of life and may lead to treatment discontinuation. BTG believe that TheraSphere offers a treatment option in this patient group, in whom there are no alternative life-extending treatments.	Comment noted. See response to comment 5. After consultation and additional analysis by the AG, the committee re-evaluated quality of life data (section 3.37 of the FAD) and considered analyses applying disutility values for adverse events of grade 3 and above, and for adverse events of any grade (section 3.38 of the FAD). It concluded that some aspects of health-related quality of life might not be captured in the utility values and agreed to include a QALY gain for SIRTs because of adverse event disutility.
48		BTG (A Boston Scientific Company)	3.32 Page 24 **In the AG's model sorafenib dominated SIRTs in all plausible scenarios using confidential patient access schemes for QuiremSpheres and sorafenib** [redacted]	Comment noted. Confidential discounts for SIRTs, sorafenib and regorafenib were included in the cost-effectiveness analysis. Exact incremental cost-effectiveness ratios [ICERs] are confidential and cannot be reported in the FAD.

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments: 5pm on **Wednesday 8 January 2020. Email: TACommC@nice.org.uk / NICE DOCS**

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	BTG (A Boston Scientific Company)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No past or current, direct or indirect links to, or funding from, the tobacco industry
Name of commentator person completing form:	Robert White

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments: 5pm on **Wednesday 8 January 2020. Email: TACommC@nice.org.uk** / NICE DOCS

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	BTG are extremely disappointed that the Committee felt unable to recommend selective internal radiation therapy as a treatment for hepatocellular carcinoma in adults. We understand the Committee's frustration around the lack of randomised controlled trials and comparative evidence for selective internal radiation therapy. However, we would like to point out that selective internal radiation therapy products are medical devices and not pharmaceutical products. Device manufacturers are not required to carry out randomised controlled trials to achieve approval by the licensing authorities. Randomised controlled trials for selective internal radiation therapy require a large sample size due to natural variation in outcomes due to patient factors and operator skill, which is challenging in terms of patient and investigator recruitment and cost. Therefore, although there are a few randomised controlled trials for selective internal radiation therapy, the majority of the evidence is of a lower quality grade than one would expect to see with a pharmaceutical product. Many of the studies are small investigator led studies in mixed populations, which make them difficult to interpret or use for evidence synthesis. This issue was pointed out in early discussions between BTG and the National Institute for Health and Care Excellence. It should be noted that National Institute for Health and Care Excellence widen acceptable evidence and accept non-randomised data when considering medical devices within the Medical Technologies Guidance (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-medical-technologies-guidance). This is also the case when assessing new and existing highly specialised medicines and treatments within the National Health Service in England using the highly specialised technologies framework. The BTG submission included non-randomised evidence which shows that TheraSphere is life-extending. Furthermore, all network meta-analyses, whether carried out by the Assessment Group or by BTG, showed that TheraSphere is life-extending when non-randomised evidence is included. As mentioned in 3.12 of the Appraisal Consultation Document the Assessment Group only included some of the non-randomised evidence. We believe that the Committee were not provided with the totality of the evidence on which to base their decision. Interventional oncology is a fast-moving field. This means that data from more recent studies show improved outcomes with selective internal radiation therapy, due to improved technique, improved patient selection and personalised dosing. Personalised dosimetry, where the dose of radiation is tailored to the patient providing an optimised dose to the tumour, is a relatively new technique and has shown to result in improved survival outcomes compared to standard dosimetry. Data from both TheraSphere and SIR-Spheres have demonstrated survival benefit with personalised dosimetry[1-5]. A recent expert recommendation consensus paper (Salem 2019) reflects on the benefits of personalised dosimetry and stated that '*As new prospective trials are designed,*

	incorporation of a refined and personalized dosimetry model will be essential for improved outcomes'. We urge the Committee to take a pragmatic approach to the evidence-base for selective internal radiation therapy and allow three discrete subgroups of people with hepatocellular carcinoma access to life-extending treatment. These specific sub-populations include: • People with large (≥5 cm) tumours (with or without portal vein thrombosis), this subgroup are unable to receive conventional transarterial therapies. • People with portal vein thrombosis, this subgroup are unable to receive conventional transarterial therapies. • People with advanced disease (stage C) who are unable to receive or tolerate the standard of care (systemic therapies, e.g. sorafenib). The use of selective internal radiation therapy gives these sub-populations a life-extending treatment and in the case of patients with intermediate disease the potential for cure via downstaging to transplant or resection. These discrete sub-populations represent only 7% of the total hepatocellular carcinoma population (199/2,935) in England in 2019: 96 people with large tumours and/or portal vein thrombosis and 103 people unable to tolerate sorafenib. Use of selective internal radiation therapy in these populations is within European treatment guidelines updated in 2019[6]. BTG believe that TheraSphere will be cost-effective when used in the right patient group, at the right dose and at the right price. [redacted] We would also like to point out that the price of a vial of TheraSphere remains the same, regardless of the dose. In the following sections, all copy in bold is taken directly from the Appraisal Consultation Document. Comments are made on the Appraisal Consultation Document as they appear within the document and there is some repetition.
2	1.1 Page 3 **There is very limited clinical evidence to compare the effectiveness of QuiremSpheres and TheraSphere with other treatments. Also, there are not enough data to compare the effectiveness of the 3 SIRTs with each other.** We agree that there is a paucity of data for QuiremSpheres, however, the evidence-base for TheraSphere is wide and includes data from both randomised and non-randomised studies (see TheraSphere submission, Table 4.2). In our response to the Assessment Group report we noted that techniques exist for combining randomised and non-randomised evidence in network meta-analysis (page 12/13).

	We are pleased that the Assessment Group carried out a mixed treatment comparison for the population in which conventional transarterial therapies are appropriate (intermediate disease, stage B) (Appraisal Consultation Document, 3.23). We suggest that the results may have been more robust if non-randomised data was included in the analysis.
3	1.1 Page 3 **There is not enough evidence to consider SIRTs a cost-effective use of NHS resources for early and intermediate stage hepatocellular carcinoma** BTG believe that there is adequate data to support economic modelling in early/intermediate stage disease (where conventional transarterial therapies are appropriate) and that the BTG model is appropriate in the absence of a model from the Assessment Group (see 2.3.6 of our response to the Assessment Group report, page 17 and 18). Our model was validated by clinical experts in the field who reassured us that the model was both clinically appropriate and robust. The incremental cost effectiveness ratio was around £25,000 at list price in this population. [redacted] Alternatively, if we make the assumption that all three selective internal radiation therapy treatments are equivalent (as per the Assessment Group network meta-analysis) then a simple cost-minimisation approach could aid the Committee in making a decision. BTG believe that selective internal radiation therapy is an appropriate choice for people with early/intermediate disease who are unable to receive conventional transarterial therapies because they have large tumours ≥5 cm and/or portal vein thrombosis. The only alternative treatment in these patients is sorafenib. In order to be eligible for selective internal radiation therapy, people should have conserved liver function, good performance status, adequate hepatic reserve post-selective internal radiation therapy and none or limited extra hepatic disease. As mentioned earlier, interventional oncology is a fast-moving field and recent/ongoing studies using personalised dosimetry with TheraSphere have shown superior outcomes to standard dosimetry in these patient populations. A recent phase II, multicentre, randomised study (Dosisphere) was presented at the European Conference on Interventional Oncology 2019. Patients (stage A, B or C) had at least one tumour ≥7 cm and were randomised to TheraSphere either following standard dosimetry (120 ± 20 Gy) (n=28) or personalised dosimetry (>205 Gy) (n=28). Of the 56 patients 40 (71%) had portal vein thrombosis. Response rates were 78.6% and 42.9% in the personalised dosimetry and standard dosimetry arms respectively, by blinded central review, indicating superior efficacy with personalised dosimetry[3]. (page 11 of BTG response to the Assessment Group report). [redacted] A study by Garin et al[1] in hepatocellular carcinoma patients with portal vein thrombosis

	(n=41) revealed a significant improvement in overall survival with personalised dosimetry (>205 Gy) versus standard dosimetry (<205 Gy): 18.2 months versus 4.3 months, p<0.005. Further work by Garin et al[2] in a mixed intermediate/advanced disease population showed significantly improved overall survival in patients receiving personalised dosimetry versus standard dosimetry: median overall survival of 15.7 months versus 4.35 months, p=0.0004 in the portal vein thrombosis population (page 19 of BTG response to the Assessment Group report).
4	1.1 Page 3 **The economic analysis shows that SIRTs are less clinically effective and cost more than lenvatinib or sorafenib** Lenvatinib should not be included here, as noted later in the Appraisal Consultation Document (3.27) sorafenib is the only relevant comparator for cost effectiveness in people for whom conventional transarterial therapies are inappropriate. We believe that clinical efficacy is at least comparable between TheraSphere, SIR-Sphere and sorafenib • The comparative effectiveness data (3.24) shows that there is no statistically significant difference in clinical efficacy between SIR-Sphere and sorafenib. The inclusion of TheraSphere via retrospective evidence indicates that TheraSphere is more effective than SIR-Sphere and sorafenib (3.2.4). It should be noted that the hazard ratios are not statistically significant (as indicated by the credible intervals), indicating that sorafenib, SIR-Sphere and TheraSphere are not significantly different in terms of survival. • We recently identified a potential modelling error with the Assessment group model (see Appendix) which means that quality adjusted life years for TheraSphere were underestimated in the Assessment Group model. • Given the concerns around the studies used to link TheraSphere with SIR-Spheres in the mixed treatment comparison, we believe that non-comparative evidence would be helpful in decision making (and as noted above, would be accepted if the selective internal radiation therapy was undergoing review via the Medical Technologies Guidance process). Non-comparative evidence (Table 4.7 in TheraSphere submission) indicates an extension to life of 12.3 to 22.1 months (nine cohort studies). • The clinical experts at the Committee meeting stated that **SIRTs might extend life expectancy in advanced stage disease** (Appraisal Consultation Document, 3.4) Assuming that TheraSphere and SIR-Spheres are similar in efficacy, which is not unreasonable given that they both deliver Y^{90} to the tumour site, the overlapping credible intervals and the non-comparative evidence noted above, then we can assume that TheraSphere and SIR-Spheres and sorafenib have comparable efficacy. The corrected Assessment Group model substantiates this claim. This would again be supportive of making any decisions based on a cost-minimisation basis. However, selective internal radiation therapy may be associated with an improved quality of life compared with sorafenib (as noted in the Appraisal Consultation Document, 3.3.1)

	because people who have sorafenib for a long time may have a long-lasting negative effect on their quality of life. SIRTs are given in 1 procedure, meaning there is a shorter duration of impaired health-related quality of life. The Appraisal Consultation Document also notes that **SIRTs might have fewer and less severe side effects than other treatment options** (Appraisal Consultation Document, 3.4) This is confirmed by data from the pivotal SARAH study for SIR-Spheres[7], in which 64% (139/216) of patients discontinued sorafenib for drug-related toxicity; of whom 108 (78%) permanently discontinued treatment. Therefore in SARAH, 50% (108/216) of people taking sorafenib permanently discontinued treatment due to intolerable side-effects, advice from BTG clinical advisors confirms discontinuation rates of around 50% in UK clinical practice. Quality of life was also significantly poorer in the sorafenib arm than with selective internal radiation therapy. We also heard at the Committee meeting that adverse events can be extremely unpleasant for people undergoing treatment with sorafenib and make continuation with treatment very challenging. The clinical experts agreed that adverse events with selective internal radiation therapy were short-lived and much easier to manage than those experienced by people taking sorafenib. Selective internal radiation therapy provides an alternative treatment option for people with advanced disease who are not eligible for sorafenib or unable to tolerate sorafenib. [redacted] It is important to note that we are asking the Committee to consider selective internal radiation therapy for a specific sub-population, who have no other alternative life-extending options if they are unable to take sorafenib.
5	3.1 Page 5 **People with hepatocellular carcinoma would welcome a new treatment option** BTG are pleased that the Committee accept that people with hepatocellular carcinoma would welcome a new treatment option. We believe that selective internal radiation therapy offers an alternative life-extending treatment option to a selected group of people with hepatocellular carcinoma unable to take the standard of care.
6	3.2 Page 5 **People with hepatocellular carcinoma and portal vein thrombosis are a relevant subgroup** BTG are pleased that the Committee accept that people with hepatocellular carcinoma and portal vein thrombosis should be included in the appraisal. This patient group is particularly challenging because portal vein thrombosis confers a poor prognosis with limited treatment options. Current 2019 guidelines recommend palliative treatment with sorafenib or best supportive care[6]. Excellent results have been shown with TheraSphere in people with hepatocellular carcinoma and portal vein thrombosis. As noted in our response to the Assessment Group report (page 7, page 30)

	A study by Garin et al[1] in hepatocellular carcinoma patients with portal vein thrombosis (n=41) revealed a significant improvement in overall survival with personalised dosimetry (>205 Gy) versus standard dosimetry (<205 Gy): 18.2 months versus 4.3 months, p<0.005. Further work by Garin et al[2] in a mixed intermediate/advanced disease population showed significantly improved overall survival in patients receiving personalised dosimetry versus standard dosimetry: median overall survival of 15.7 months versus 4.35 months, p=0.0004 in the portal vein thrombosis population. Earlier work with standard dosing has shown overall survival gains of 3.2 to 16.6 months depending on the location of the portal vein thrombosis (see Table 4.7 and Table 4.8 in the BTG original TheraSphere submission). Given the limited options and poor prognosis for this patient group and positive evidence using personalised dosimetry to deliver TheraSphere, BTG believe that TheraSphere is an alternative treatment in these people.
7	3.8 Page 8 **There are 3 distinct subgroups relevant to this appraisal** This is correct, however, BTG would like to point out that there are specific patient groups who are unable to receive the standard of care. • People with a tumour at least one lesion 5 cm or above, because the size of their tumour means that conventional transarterial therapies cannot be used. • People with portal vein thrombosis (who may also have large lesions as above), because the portal vein thrombosis means that conventional transarterial therapies cannot be used. • People with advanced stage disease (stage C) in whom the toxicity of sorafenib is intolerable and are unable to continue with treatment. In order to be eligible for selective internal radiation therapy, people in these subgroups should have conserved liver function, good performance status, adequate hepatic reserve post-selective internal radiation therapy and none or limited extra hepatic disease.
8	3.10 Page 9 **In people with intermediate stage disease, CTTs are the standard of care in current NHS practice in England** BTG accept this statement and note that it is in line with current guidelines. However, people with intermediate stage hepatocellular carcinoma with large tumours (with or without portal vein thrombosis) are unsuitable for conventional transarterial therapies and selective internal radiation therapy offers an alternative treatment option in these patients. Without the option of selective internal radiation therapy, the only available treatments are palliative treatment with sorafenib or best supportive care.
9	3.12 Page 9-10 **The systematic review included non-randomised controlled trials (RCTs) when not enough RCT evidence was identified**

	BTG are pleased that the Committee understand that some non-randomised evidence was included in the AG report, however, we would like to point out that there is a considerable body of non-comparative evidence to support TheraSphere as outlined in our original submission to NICE, which was not considered by the Assessment Group. The Assessment Group made an explicit decision to exclude non-randomised studies, therefore, the Committee was not given all the information that they needed to make a decision.
10	3.16 Page 12 **Non-randomised evidence comparing TheraSphere with non-SIRT treatments is not robust and should not be used for decision making** We understand the Committee's point of view regarding quality of evidence, however, would like to re-iterate that selective internal radiation therapy is a medical device and not a pharmaceutical and therefore, randomised controlled trials are not required for device approval. The existing evidence, both comparative and non-comparative, suggests that TheraSphere is a life-extending treatment.
11	3.20 Page 15 **Of these, 4 compared SIR-Spheres with TheraSphere and 1 small study of 30 people compared all 3 SIRTs.** BTG believe that this is an error, the five studies in question all compared TheraSphere and SIR-Spheres. See slide 32 of the pre-meeting briefing
12	3.21 Page 15 **There is not enough direct evidence for people when CTT is inappropriate to compare the 3 SIRTs' effectiveness, so mixed treatment comparison should be considered** 3.24 Page 19 **The comparative effectiveness of treatment options in people for whom CTT is inappropriate is uncertain, but is useful for decision making** **The committee agreed that the retrospective studies should not be included in the analysis because of the risk of bias. It agreed that the comparative effectiveness results based on RCT evidence could be used in a cost-effectiveness analysis.** BTG concur that there is little direct evidence, however, we are concerned that other methods of comparison were not considered and that non-comparative evidence was excluded from the evidence synthesis (Response to Assessment Group report, page 12/13). As noted, selective internal radiation therapy products are medical devices and not pharmaceutical products and therefore their evidence base consists of numerous small non-randomised studies and real world evidence rather than more conventional randomised controlled trials that one would expect with pharmaceutical products.
13	3.25 Page 21 **The AG's model was used for decision making**

	BTG submitted two models – one for early/intermediate disease (in people in whom conventional transarterial therapies are appropriate) and one for later stage disease (in people in whom conventional transarterial therapies are inappropriate). The Assessment Group only produced a model for later stage disease. BTG are disappointed that in the absence of a model in early/intermediate disease the Assessment Group did not use the BTG model to aid Committee in making a decision (see 2.3.6 of our response to the Assessment Group report, page 17 and 18). Incremental cost effectiveness ratios were around £25,000 at list price in this population using the BTG model with all interventions at list price.
14	3.26 Page 21 **The structure of the AG model for people when CTT is appropriate is acceptable for decision making** This is a typographical error, it should read CTT is inappropriate
15	3.31 Page 23-24 **Some aspects of health-related quality of life might not be captured in the utility values** As noted in the Appraisal Consultation Document, **people who have sorafenib for a long time may have a long-lasting negative effect on their quality of life. SIRTs are given in 1 procedure, meaning there is a shorter duration of impaired health-related quality of life**. This is not captured within the economic modelling indicating that selective internal radiation therapy may have greater QALY gains than those suggested by existing modelling. The impact of adverse events from sorafenib impacts on quality of life and may lead to treatment discontinuation. BTG believe that TheraSphere offers a treatment option in this patient group, in whom there are no alternative life-extending treatments.
16	3.32 Page 24 **In the AG's model sorafenib dominated SIRTs in all plausible scenarios using confidential patient access schemes for QuiremSpheres and sorafenib** [redacted]

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted

under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

References

1. Garin E, Rolland Y, Edeline J, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. *J Nucl Med* 2015; **56**(3): 339-46.
2. Garin E, Rolland Y, Pracht M, et al. High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with (90) Y-loaded glass microsphere radioembolization. *Liver Int* 2017; **37**(1): 101-10.
3. Garin E, Tselikas L, Guiu B. Major impact of personalized dosimetry on the targeted tumor response using 90Y loaded glass microspheres SIRT in HCC : preliminary results of a prospective multicentric randomized study. European Conference on Interventional Oncology; 2019; Amsterdam
4. Hawkins N, Ross P, Palmer D, Chatellier G, Pereira H, Vilgrain V. Overall survival of patients with hepatocellular carcinoma receiving sorafenib versus selective internal radiation therapy with predicted dosimetry in the SARAH trial (poster). European Society for Medical Oncology 2019; Barcelona
5. Salem R, Padia SA, Lam M, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. *Eur J Nucl Med Mol Imaging* 2019; **46**(8): 1695-704.
6. Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; **30**(5): 871-3.
7. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2017; **18**(12): 1624-36.

APPENDIX (BTG response)

Statement of potential problem

An issue has been identified with the AG model. This issue is that while the traces (model engines) for all interventions and comparators assume a cohort size of 1, when the results are generated, the lifetime costs and benefits for all SIRTS are reduced by the proportion of patients who are deemed ineligible for SIRT (see results tab F30:F45 for an example of this process). The process we are concerned about is demonstrated in the table below.

Table 1: Comparison of lifetime outputs from model traces and results sheets

	Sorafenib	**TheraSphere**
Values from relevant trace/ engine*		
Lifetime LYG	1.243	1.210
Lifetime QALYs	0.841	0.834
Lifetime costs (list price)	£26,360	£26,060
Values used in ICER calculations**		
Lifetime LYG	1.243	0.985
Lifetime QALYs	0.841	0.679
Lifetime costs	£26,360	£22,468

* Cells B35, B37, B39 on Engine Tx2 and Tx4; Values from Results tab cells H39, H42, H43, J39, J42,J43

Close inspection of the breakdown of costs in the TheraSphere arm (results F30:G45) indicate that some costs associated with no treatment have been included for patients deemed ineligible but they have all been assumed to accrue no benefit. In effect, these patients have been implicitly assumed to die immediately on entry into the model (see model Engine Tx5).

Removal of a proportion of the cohort in one arm but not another of the model when estimating benefit will bias the analysis against the treatment which was subject to the removal. In effect, you are comparing 100% of patients receiving one treatment with less than 100% of patients receiving another in all benefit calculations. We hypothesise that this is the main reason behind the model outputs of TheraSphere offering patients 0.162 fewer QALYs over their lifetime compared to sorafenib.

Changes made to AG model to evaluate the problem

We were working with the version of the model labelled ‘ID1276 HCC – SIRT AG model 16092019 LJ (redacted). The version of the model where we have made changes is labelled ‘ID1276 HCC – SIRT AG model 16092019 LJ (redacted)_BTGReview031219’

Changes made to the model are as follows (all highlighted yellow):

Tab: Results

- Addition of three switches (P7:P9)
- Addition of cells for sorafenib and TheraSphere PAS’s (P10:P11)
- Head to head ICER calculations (TheraSphere vs. Sorafenib (M13:P11)

- Copying original results to new cells (O18:Z24)
- Alteration of formulae in cells F30:G38 to allow differentiation between dropouts in costs and benefits

Tab: SIRT Costs

- Addition of cell linking to PAS entry on results sheet (K27)
- Alteration of formula for TheraSphere unit cost to account for PAS (C27)

Tab: Comparator costs

- Addition of cell linking to PAS entry on results sheet (C21)
- Alteration of formula for TheraSphere unit cost to account for PAS (E16)

Tab: Parameters

- Altered formulae for sorafenib PFS and PD utility to be same as TheraSphere (N35, N41)

Tab: Controls

- Altered formulae for the proportions of patients eligible for SIRT (N13:N16)
- Created a new decision tree parameter to cover costs of TheraSphere only (K23:N23)

Tab: Engine Tx2

- Amended formulae in columns Q,R,T to take in to account the same efficacy switch
- Added check columns (P,Y,AH,AN, AT, AZ)

Tab: Engine 4:

- Amended formulae in columns Q,R,T to take in to account the same efficacy switch

Impact of change on cost effectiveness results

The original results from the model are presented below (all costs list price).

Table 2: Original AG results

Intervention	Total			
	Costs	LYs	QALYs	
TheraSphere	£29,266	0.985	0.679	
SIR Spheres	£29,484	0.985	0.679	
Lenvatinib	£30,005	1.183	0.805	
Sorafenib	£32,082	1.243	0.841	
QuiremSpheres	£35,880	0.985	0.679	

Re-introducing the patients who were assumed ineligible into the calculation gives the results below (Table 3 - setting switch on results tab P8 to 1). In this scenario, the

incremental QALYs for TheraSphere compared to sorafenib is now -0.006 rather than -0.161 and the incremental costs (list price analysis) for the head to head analysis remains unchanged at -£2,817 (as shown in cells N14:O14).

Table 3: Results re-introducing the patients who were assumed ineligible

Intervention	Total			
	Costs	LYs	QALYs	
TheraSphere	£29,266	1.210	0.834	
Lenvatinib	£30,005	1.183	0.805	
Sorafenib	£32,082	1.243	0.841	
SIR Spheres	£33,869	1.210	0.834	
QuiremSpheres	£40,740	1.210	0.834	

If we further interpret the AG NMA results as indicative of no clinical difference between all treatments in terms of PFS and OS and set the model to use the same PFS and OS (turning on switch in cell P7 on results tab), the model gives the outputs shown in Table 4 below. In this scenario, the lifetime benefits for TheraSphere are higher than for sorafenib (+0.013 QALYs) and the incremental costs are -£2,516 (as shown in cells N14:O14).

Table 4: Results assuming no clinical difference between all treatments in terms of PFS and OS

Intervention	Total			
	Costs	LYs	QALYs	
TheraSphere	£29,266	1.210	0.834	
Lenvatinib	£30,005	1.183	0.805	
Sorafenib	£31,782	1.210	0.821	
SIR Spheres	£33,869	1.210	0.834	
QuiremSpheres	£40,740	1.210	0.834	

Implications of potential error on decision making

The brief analyses above indicate that while the incremental costs associated with TheraSphere compared to sorafenib are largely constant (assuming list prices), there could be a large impact of the potential error on incremental QALYs, and hence decision making. It is possible that rather than sorafenib offering more benefit than TheraSphere, the opposite is true.

The point raised in this briefing document is that as a company, we do not know what model to use as the basis of our internal decision making process around the design and magnitude of any commercial arrangement. We would therefore appreciate the assessment group reviewing their model, and in particular their approach to calculating lifetime costs and benefits for TheraSphere, with specific emphasis on how they have incorporated individuals who are not eligible for SIRT. We would be willing to join a teleconference with the assessment group to discuss this matter if desired.

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments: 5pm on **Wednesday 8 January 2020. Email: TACommC@nice.org.uk / NICE DOCS**

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Sirtex Medical United Kingdom Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No links to disclose.**
Name of commentator person completing form:	**Suki Shergill** **EVP Global Pricing, Reimbursement & Market Access**

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Given that - based on the results for the overall SARAH trial population - the estimated population average costs and outcomes are likely similar for SIR-Spheres and sorafenib, that sorafenib is associated with significant adverse effects including diarrhoea, fatigue and hand and foot skin reaction compared to SIR-Spheres, and there is evidence that treatment with SIR-Spheres is associated with a higher likelihood of subsequent treatment with curative intent it would seem reasonable that individual **patients should have the option to receive SIR-Spheres treatment based on their preferences regarding adverse effects and potential outcomes**. This opinion was also raised by the patient expert at the open session of the committee meeting on November 6th 2019. In addition, there is evidence that it is possible to select a group of patients who may experience better and cost-effective outcomes with SIR-Spheres based on their liver function and tumour morphology. • **SIR-Spheres result in similar or better health outcomes than sorafenib** In the unselected (intention-to-treat) trial population (using Committee's recommended base case with downstaging) the health outcomes are similar with a population average of -0.105 incremental QALY based on the non-significant differences in overall survival. In the proposed subgroup for SIR-Spheres results in an additional 0.601 QALYs. • **SIR-Spheres and sorafenib have similar or lower costs, or for the proposed subgroup have cost-effective outcomes even with a discount for sorafenib** In the unselected (intention-to-treat) population (after correction for factual errors) SIR-Spheres results in a cost saving of £6,142 per patient. Assuming a substantial 50% discount for sorafenib, SIR-Spheres still results in a cost saving of £858. This indicates provision of SIRT as an alternative treatment option for patients would be cost saving. In the proposed subgroup SIR-Spheres results in a saving of £1,784 per patient, or assuming a 50% discount for sorafenib, the 0.601 QALY gain comes at an incremental cost of £4,534 resulting in an incremental cost-effectiveness ratio of £7,546 per QALY. For the factual inaccuracies mentioned here, we would like to bring the Committee's attention to the next comment.
2	**We are concerned that factual errors remain in the Assessment Group Report.** These include the following: • **The cost of SIR-Spheres is overestimated.** The Assessment Group assumed the use of an additional procedure for the administration of SIR-Spheres compared to TheraSphere based on differences in the wording of the two company submissions. This interpretation is incorrect. As previously noted by Sirtex, SIR-Spheres and TheraSphere are administered using the same imaging and equipment and therefore have exactly the same administration costs. Given that the Assessment Group and Committee have chosen to assume equal efficacy for SIR-Spheres and TheraSphere (based on data specific to SIR-Spheres); the costs, health benefits and cost-effectiveness of SIR-Spheres and TheraSphere should be the same. • **The cost of sorafenib is underestimated.** As the cost of sorafenib is an influential input in the model, the duration of treatment needs to be precise. In the Assessment Group model, instead of using the treatment duration observed in the SARAH trial (on which the efficacy data is based in this model), an estimate based on the median duration observed in SARAH and an assumed distribution were used.

	This underestimates the duration of sorafenib treatment by 23.46 days and the cost of sorafenib by £2,429 (at the list price). This incorrect assumption was previously noted by Sirtex; however, it was not addressed by the Assessment Group. The correct duration based on patient-level data from the SARAH trial was provided by Sirtex in the company submission.
3	**We are concerned, that despite the evidence, and the Committee's recommendations, downstaging, a crucial benefit of SIRT treatment for patients with hepatocellular carcinoma (HCC), has not been taken into account in the economic model. This omission has a significant impact on the cost-effectiveness results.** • **Evidence is available to support the role of SIR-Spheres in downstaging** For patients with advanced HCC, SIR-Spheres allows for patients to be downstaged to receive potentially curative therapies (i.e. liver transplant, surgical resection and percutaneous tumour ablation), as opposed to the current treatments recommended by NICE. This is supported by both a randomised European trial (SARAH trial) and non-randomised studies (e.g. the CIRSE Registry for SIR-Spheres Therapy in Europe, and the French series of patients with advanced HCC reported by Regnault H et al. P07-06 in EASL HCC Summit 2019: https://www.easl.eu/hcc2019/wp-content/uploads/2019/01/HCC-Summit-2019-Abstract-book.pdf). • **The Committee recommended the base case should include downstaging** The benefit of downstaging has been acknowledged by the Committee concluding that "*the base-case model should include downstaging*" (point 3.30 in the appraisal consultation document), despite this, downstaging was not included in the economic model reported in the appraisal consultation document. Although this document adds that the proportion of patients receiving subsequent curative therapies is uncertain, this proportion depends on the selection criteria of patients for SIR-Spheres. In the unselected population of the SARAH trial (ITT population), 5.1% of patients (12 out of 237 patients) were downstaged, although all had initially unresectable HCC and are very unlikely to become eligible for curative therapies after sorafenib according to the clinical experts. Indeed, in the same population, only 1.4% of patients (3 out of 222) were downstaged after sorafenib. In the ALBI grade 1 and low tumour burden subgroup (comment number 4 below), 13.5% of patients (5 out of 37) were downstaged after SIR-Spheres vs 2.1% after sorafenib (1 out of 48). This survival benefit of downstaging is not captured in the SARAH trial outcomes, as 13 out of 15 downstaged patient were alive and censored at the end of the follow-up period. This benefit is however relevant for patients, according to patient expert opinion elicited in the open session of the Committee meeting. The uncertainty on the proportion of patients receiving subsequent curative therapies should therefore not be considered a valid argument to exclude downstaging from the model but should instead be explored in sensitivity analyses. • **Downstaging has an important impact on cost-effectiveness estimates** In the unselected population of the SARAH trial (ITT population), the inclusion of downstaging results in SIR-Spheres being slightly less effective and less costly, and sorafenib not being cost-effective against SIR-Spheres (incremental cost-effectiveness ratio of £58,763 per quality adjusted life-year). With a large discount assumed for sorafenib (e.g. 50%), the costs and effectiveness of SIR-Spheres and sorafenib are then similar. In the ALBI grade 1 and low tumour burden subgroup, the inclusion of downstaging results in SIR-Spheres being more effective and less costly than sorafenib (at list price), i.e. SIR-Spheres dominating sorafenib. In this case, assuming even an 80% discount for sorafenib results in an incremental cost-effectiveness ratio of £13,855 per quality adjusted life-year for SIR-Spheres vs. sorafenib. The above estimates also include the factual corrections detailed in comment number 2

	above. **Cost-effectiveness results in the appraisal consultation document should include downstaging as the Committee recommended base case. This document cannot be considered a reasonable summary of the economic evidence at this point.**
4	**We are concerned that the population of patients with a low tumour burden (≤25% of the liver volume) and an Albumin-Bilirubin (ALBI) grade 1 liver function was dismissed as the base case population of the economic model for people for whom conventional transarterial therapies are inappropriate, given the evidence and the clinical expert opinion elicited in the open session of the Committee meeting on 6th November 2019.** Sirtex agrees that subgroups should be prespecified, clinically plausible, implementable, generalisable and evidence-based, and therefore respectfully request the Committee reconsider the following aspects supporting the ALBI grade 1 and low tumour burden subgroup as base case population of the model: • **Prespecified analysis was not possible** The SARAH trial is the only source of efficacy data used for SIRT in the economic model. Subgroup analyses using a ≤25% tumour burden threshold were prespecified in the SARAH trial and reported in the main publication of this trial (Vilgrain V et al. Lancet Oncol. 2017 Dec;18(12):1624–36). However, there are circumstances when clinically plausible, well-supported subgroups cannot be prespecified. In this instance, although the ALBI grade is estimated based on blood tests for albumin and bilirubin, for which data was prospectively collected during the SARAH trial, the formula used to determine the ALBI grade was only published (Johnson PJ et al. J Clin Oncol. 2015 Feb 20;33(6):550–8) immediately after the enrolment period of the trial (from 05/12/2011 to 19/02/2015). The ALBI grade 1 and low tumour burden subgroup could therefore not have been prespecified in the SARAH trial and this argument is invalid to dismiss the subgroup as the model base case. • **Clinical plausibility is well established** This subgroup was proposed by clinicians with experience of SIRT, in accordance with clinical guidelines, to ensure that the patients who benefit the most would receive SIRT. Tumour burden is routinely assessed and the ≤25% criterion is already used by NHS England to determine the eligibility for SIRT of patients with colorectal liver metastases. The components of the ALBI grade are also routinely collected, and the score itself was developed in England and validated against UK cohorts of patients (Johnson PJ et al. J Clin Oncol. 2015 Feb 20;33(6):550–8). It was reported to outperform the Child-Pugh score as a predictor of overall survival following SIRT (Ali R et al. Cardiovasc Intervent Radiol. 2019 May;42(5):700–11; Antkowiak M et al. Cancers. 2019 Jun;11(6):879). Use of the ALBI grade is also recommended in European clinical guidelines to stratify patients in terms of prognosis within the Child-Pugh A class itself (Galle PR et al. J Hepatol. 2018 Jul;69(1):182–236; Vogel A et al. Ann Oncol. 2018 Oct 1;29(Supplement_4):iv238–55). This therefore contradicts the summary presented in the appraisal consultation document (point 3.6) that "*The clinical experts advised […] that Child-Pugh is expected to be the measure of choice for the foreseeable future*": both ALBI and Child-Pugh can co-exist in UK clinical practice, with the ALBI grade being used to further select patients for SIRT among all Child-Pugh A patients. • **Simple implementation in UK clinical practice** As described by the appraisal consultation document, in the open session of the Committee meeting, "*clinical experts explained that ALBI grade could be a more objective measure than Child-Pugh score for liver dysfunction*". It is however not reflected in this document, that in the open session, the clinical expert also added that the calculation of the ALBI grade is

	straightforward and can be performed using a published Nomogram as described in Johnson PJ et al. J Clin Oncol. 2015 Feb 20;33(6):550–8 or with a web-based app. The clinical expert furthermore reported that the ALBI grade was used in the UK and was recommended for the stratification of patients for locoregional treatments. Because the criterion of a tumour burden ≤25% is already used to determine patient eligibility for SIRT in the treatment of colorectal liver metastases, this raises no implementation issue. • **The subgroup is generalisable to patients seen in the NHS in England** The appraisal consultation document states in point 3.19 that "*The clinical experts advised that the SARAH trial had more people with a high tumour burden, [portal vein thrombosis] and impaired liver function than people seen in clinical practice in England. The committee understood that because of this, people in the SARAH trial had poorer prognosis than people seen in clinical practice in England. It concluded that results from the SARAH trial may not be generalisable to people seen in the NHS in England*". We agree with this statement and have proposed the ALBI grade 1 and low tumour burden subgroup to ensure that patients considered in the economic model reflect those most likely to receive SIRT in the NHS. • **Evidence supporting the subgroup is in the public domain** Analyses of the SARAH trial in the ALBI grade 1 and low tumour burden subgroup were presented at the European Society of Medical Oncology 2019 congress (Palmer DH et al. Ann Oncol. 2019 Oct 1;30(Supplement_5):mdz247.061) and recently published in full (Palmer DH et al. Future Oncol. 2020 Jan;16(1):4315–25). **Having addressed the arguments put forward in the appraisal consultation document to dismiss the ALBI grade 1 and low tumour burden subgroup, we suggest that the subgroup could be reasonably considered as the base case population in the economic model.**
5	**We are concerned, that the comments regarding the reliability of the network meta-analysis are contradictory.** We agree with the recommendation in the appraisal consultation document point 3.24 that "*The comparative effectiveness of treatment options in people for whom [conventional transarterial therapies are] inappropriate is uncertain*". However, the appraisal consultation document continues: "*but [the comparative effectiveness] is useful for decision making*", subsequently describes the result of the network meta-analysis and presents it in a scenario analysis of the cost-effectiveness model. This could lead to the misleading interpretation that the network meta-analysis is appropriate and should be used for decision-making.
6	Sirtex is committed to further collaborate with NICE and would be happy to provide any support required to reduce the time pressure that was experienced at the first Committee meeting. The time pressure constrained the input Sirtex was able to provide towards a fair assessment of all the available evidence and limited the company's ability to address all factual inaccuracies.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted,

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please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	TERUMO Europe (distributor) / Quirem Medical (manufacturer)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[none]

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

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Name of commentator person completing form:	Nathalie Verin, Director of Market Access, EMEA, TERUMO Europe
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
GENERAL	We are extremely concerned by these provisional recommendations as it would mean depriving HCC patients, who have limited treatment options and generally poor prognosis of a treatment alternative that is reimbursed in most European countries and readily accessible in the US. The Committee's discussions in November – reflected in the ACD - highlighted the anticipated benefit in HRQoL between a systemic agent (such as sorafenib) vs a one-off treatment (such as SIRT). The ACD also notes that this benefit may not be appropriately reflected and captured by the QoL results of the relevant RCTs. But unfortunately, this uncertainty around (QoL) results has not been considered in the provisional recommendations. (see point 3) We believe that the original decision to look at the 3 SIRT technologies as 3 separate treatments has led to significant issues in the interpretation of the evidence. Firstly because it created an unrealistic number of ICERs and therefore unnecessary complexity in result reporting which may have been detrimental to SIRT. Secondly because it led to the Committee's decision to solely rely on the Assessment Group's report, which does not constitute a representative summary of all the submissions received. (see point 4) We would urge the Committee to simplify the set of results needed for decision-making. We would also urge the Committee to consider a "coverage with evidence development" decision (similar to the Cancer Drugs Fund) so that appropriate data can be collected whilst the treatment is being offered in the NHS (see point 3).
1	Could we ask that NICE clearly states the following when describing QuiremSpheres®: Quirem Medical (manufacturer)/TERUMO Europe (distributor)
2	The "dosage in CE Mark" information is not in line with the one from SIR-Spheres® and TheraSphere®. We suggest to add the following for QuiremSpheres® QuiremSpheres® is given through a catheter to the hepatic artery. The product is

	supplied as a customized, patient-specific dose. The maximum range of the emitted beta particles in tissue is 8.7 mm with a mean of 2.5 mm. In addition, Holmium-166 emits primary gamma photons (81 KeV). The half-life is 26.8 hours, which means more than 90% of the radiation is delivered within the first 4 days following the administration procedure. At planned moment of treatment, the activity per microsphere is 200-400 Bq. The number of particles implanted depends on the targeted liver volume and ranges on average between 10 and 30 million
3	We do not believe that the provisional recommendations to be sound and a suitable basis for guidance to the NHS. We would urge the Committee to consider recommending SIRT as an available treatment option under a "coverage with evidence development" scheme (such as the Cancer Drug Fund or other schemes detailed below) We are concerned that it will deprive patients with HCC as well as their families and carers of what the ACD describes as a "potential new treatment option". The ACD describes the likely difference in terms of HRQoL of a systemic therapy such as sorafenib and a "one-off" treatment such as SIRT. (see 3.31 pg 23-24). In particular, t*he Committee concluded that some aspects of health-related quality of life might not be captured in the utility values, but it was not presented with evidence comparing this benefit with the relevant non-SIRT comparator, sorafenib.* Data collection could focus on appropriate measures for HRQoL, taking into account patient preferences and patient-reported outcomes rather than the more generic EQ-5D, and be measured for a longer time that the trials follow-up so that the "transient" vs "systemic" impact can be reflected. Several "coverage with evidence development" schemes have been put in place over the years within Technology Appraisals, more recently and famously the Cancer Drug Fund. In previous years the use of laparoscopic surgery for colorectal cancer was initially rejected by NICE and recommended only in the context of a clinical trial which was ongoing. When the treatment was reconsidered at a later date it received positive guidance on the basis of evidence provided by the clinical trial. For the treatment of multiple sclerosis, the UK's NHS agreed a conditional pricing arrangement regarding the use of interferon beta or glatiramer acetate. The treatments were funded on the condition that their effect on disease progression in a cohort of patients was monitored for 10 years. Potential price adjustments were to be made every 2 years to ensure an agreed cost per QALY gained of the therapy was no more than

	£36,000. *3.31 pg 23-24* *The committee noted that utility values were similar between SIRTs and systemic therapies (sorafenib or lenvatinib) for the following disease states: progression-free survival, progressive disease and post-transplant. There were only small differences in utilities between progression-free survival and progressive disease. The clinical experts explained that people who have sorafenib for a long time may have a long-lasting negative effect on their quality of life. SIRTs are given in 1 procedure, meaning there is a shorter duration of impaired health-related quality of life. The committee considered that the potential difference in long-term quality of life might not be captured in clinical trial results because quality-of-life data are collected at fixed time points. It acknowledged that the cancer, liver function and other comorbidities affect health-related quality of life in people with HCC. The committee concluded that some aspects of health-related quality of life might not be captured in the utility values, but it was not presented with evidence comparing this benefit with the relevant non-SIRT comparator, sorafenib.*
3	We do not believe that the provisional recommendations to be sound and a suitable basis for guidance to the NHS. The UK would be at odds with guidelines and clinical practice in Europe and globally. Summary of specific reimbursement recommendations and ESMO guidelines informing on patient subgroups recommended in Europe

Country	Patient populations
France (TheraSphere)	HAS 2018 Indication for reimbursement: Palliative treatment of HCC, BCLC B/C, with portal thrombosis, for patients with ECOG O-1, preserved hepatic function (Child-Pugh A or B) non eligible of after failing sorafenib
France (SIR-Spheres)	HAS 2019 Indication for reimbursement Palliative treatment of HCC, BCLC B/C, without occlusion of portal vein, for patients with ECOG O-1, preserved hepatic function (Child-Pugh A or B) non eligible of after failing sorafenib
Netherlands (HCC, Yttrium-90)	SIRT in HCC is reimbursed for the following patients: Zorg Instituut, 2011 Inoperable HCC with favorable tumor staging (such as tumor volume

		<70% of the total liver volume, no PVT and acceptable liver function and general condition).
	European guidelinesSMO HCC 2018	The recent ESMO HCC guidelines published in 2018 (include link) present the treatment options according to BCLC stage. SIRT features as an alternative treatment available in BCLC 0-A and BCLC B: for patients with liver-confined disease and preserved liver function in whom neither TACE nor systemic therapy is possible, SIRT may be considered. The subgroup considered overlaps with this toolbox recommendation and will keep UK practice in line with the European oncological recommendations.

4

We do not believe that all of the relevant evidence has been taken into account by the Committee to make its recommendations. In particular, we would like to argue against its decision on page 10 *"the Committee used the AG's report for its decision making"*. The rationale being *"This was because it included evidence for all 3 SIRTs and so was more comprehensive than the companies' submissions."*

We are surprised by this statement and would like the Committee to reconsider the full breadth of evidence:

- since the creation of NICE and its Technology Appraisal process, there have been 46 TA recommendations for medical devices out of 925 total recommendations *(NICE website as of Dec 2019)*
- All technology appraisals for medical devices have assumed a class effect ie that the different technologies available on the market are not appraised individually
- This has always been the position of the IP Committee at NICE as they have always evaluated SIRT in their different guidance (and not SIR-Spheres or TheraSphere or QuiremSpheres)
- This is also the conclusion from the Committee as there is not enough evidence to compare the technologies
- It's had a significant impact on the appraisal so far as it has rendered the description of results almost impossible to grasp considering the unrealistic number of ICERs presented
- And the statement above is simply unfair as individual company submissions could not have been expected to include comprehensive evidence on all technologies

Therefore we would recommend that the Committee considers all sources of evidence with equal attention to make its decision – the excellent York evaluation report as well as all manufacturers submissions, submissions from Patient organisations and medical societies, and input during Committee hearings. The decision to limit treatment options available to HCC patients should be

	based on the wide variety of input and not only on the AG report, especially if the rationale for solely using the AG report is questionable.
5	
6	

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**British Liver Trust**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

NICE National Institute for Health and Care Excellence

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The British Liver Trust is extremely disappointed by this decision. Although this consultation document clearly considers the evidence submitted by the companies and the current research, we are concerned that not enough weight has been given to the experience of patients and the submissions from the patient organisations. We also felt that the patient voice was not sufficiently listened to during the meeting and that this is reflected in the document. Since receiving this consultation document, we have spoken and fed back informally the initial recommendation to three of the many patients we consulted originally (in order to respond to this process) and they are obviously disappointed. There is a perception that the economic evidence is the only evidence that is considered and the patient submission is simply a "tick box exercise". There is good evidence from patients and clinicians that SIRT undoubtably provides extra years of life for patients. In the words of one clinician, "It would be a tragedy not to try harder to learn how to use this treatment and for it to be available as an option".
2	We recognise that the committee has agreed that SIRT might have fewer and less severe side effects than other treatments. However, we are concerned that this quality of life factor has not been given enough weight in the recommended decision. We apologise if we did not provide enough information on this in our original submission. Some people who take the alternative treatments (Sorafenib and Lenvatinib) report extreme side effects. Callers to the British Liver Trust Helpline and comments from our online forum (over 18,000 members) have been very vocal on this. For example: *"I have had a very rough time lately due to taking Sorafanib. The stuff has been poisoning me, I lost a lot of weight, become dehydrated and become incontinent."* *"My brother Patrick died on 4 January 2019. His stomach was so distended it was like he was 9 months pregnant. I truly believe the sorafenib hastened his death because the bad reaction he had from it was so severe it took days to get it out of his system even though nurses gave him intravenous liquid to flush it out."* *"I had 12mths of sorafenib after TACE. Although it held things steady for 12mths, I felt terrible. I had diarrhoea and was unable to leave the house for the entire time….."* *"My AFP increases when I reduce the dose of sorafenib because of side effects e.g. skin blisters, painful round swelling of palm and sole,sore tongue, mouth etc. But sometimes after healing of skin and other problems I start start full dose of sorafenib then again side effects reappears and AFP comes down." (sic)* Patients who have had SIRT report feeling well two to three weeks after treatment. One patient ran an ultra-marathon (150 miles) 6 weeks after treatment. Another patient reported feeling well enough to go abroad on holiday with his wife to visit their grandchildren and their quality of life improved.
3	Undertaking a robust RCT in this patient group for interventional oncology is challenging, The majority of evidence that we are aware of comes from real world evidence, reports from patients and

	non-randomised studies. Clinically certain groups of patients will be disadvantaged, particularly those who are in the intermediate and some in the advanced stage of the disease if SIRT is not made available. The evidence may be weak but it should not be ignored. Although the biomarkers have not yet been identified to guide treatment selection, there are undoubtably patients who would benefit, get extra years of life and even cure.
4	Is there any way that NICE can provide guidance on how we could take this forward for the benefit of patients? Is there any option for this treatment to be included as an interim measure in the Cancer Drugs Fund? Could Commissioning through Evaluation for SIRT in HCC be in an interim solution? Could further studies be commissioned? A positive recommendation for at least a sub group of patients could enable the collection of real-world data to improve the evidence base whilst at the same time saving lives
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6	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**This is a joint response supported by the British Liver Transplant Group, the British Society of Interventional Radiology, the British Nuclear Medicine Society, HCC-UK, and the commissioned NHS England SIRT centres.** Lead respondent: [redacted], Consultant Hepatobiliary and Transplant Surgeon, [redacted], [redacted], [redacted] British Society of Interventional Radiology (BSIR): [redacted], Consultant Interventional Radiologist, [redacted], [redacted] British Nuclear Medicine Society (BNMS): [redacted], Consultant Nuclear Medicine Physician, [redacted], [redacted] HCC-UK: [redacted]X, Consultant Hepatobiliary Oncologist, [redacted], [redacted] NHS England SIRT centres:

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	1. [redacted], Consultant Interventional Radiologist, [redacted], Consultant Radionuclide Radiologist, The Christie, Manchester 2. [redacted], Consultant Interventional Radiologist, [redacted], Consultant in Nuclear Medicine, The Royal Free, London 3. [redacted], Consultant Interventional Radiologist, University Hospital Southampton 4. [redacted], Consultant Interventional Radiologist, Nottingham General Hospital 5. [redacted], Consultant Interventional Radiologist, Addenbrooke's Hospital, Cambridge 6. [redacted], Consultant Interventional Radiologist, King's Hospital, London 7. [redacted], Consultant Interventional Radiologist, The Churchill Hospital, Oxford 8. [redacted], Consultant Interventional Radiologist, Queen Elizabeth Hospital, Birmingham 9. [redacted], Consultant in Nuclear Medicine, The Freeman Hospital, Newcastle
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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1	As a group of NHS practitioners with clinical expertise in selective internal radiation therapy

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	(SIRT), we are disappointed that the committee is unable to give a positive recommendation for SIRT in a subgroup of patients with hepatocellular carcinoma (HCC). NICE should be commended for the comprehensive review in this extremely heterogenous disease group. The complexity of the review highlights the challenges in interpreting the data with most studies reporting across mixed populations. The randomised controlled trials reviewed by the committee focus on patients with advanced stage HCC. These trials were designed before patient selection, technical aspects of SIRT and dosimetry had been optimised. Recruitment for studies involving medical devices in interventional oncology is challenging and the majority of the available evidence is based on non-randomised studies and registry data, which reflect real world practice. SIRT is reimbursed for the treatment of HCC in many European countries and in North America. SIRT has evolved in recent years with advances in patient selection and personalised dosimetry. The NHS has been at the forefront of this innovation and, as an expert group, we recognise the importance of the application of this therapy in clearly defined groups who would benefit from SIRT, which includes patients who have the potential for cure from downstaging to surgical resection. **The subgroups that we would like to propose as an expert group are defined below. Funding in these patient groups, potentially through the Cancer Drug Fund (CDF), will continue to promote innovation in the NHS and improve patient outcomes for patients with HCC.**
2	**1: As an alternative to TACE in patients with a solitary large tumour (≥7 cm)** There is a clear unmet need in patients who are not good TACE candidates (lesion size ≥7cm) within the intermediate stage of BCLC. This proposed subgroup is based upon data from the DOSISPHERE trial, from which interim data have been presented.[1]

	We feel that this is a valuable population to be treated even though there is a lack of comparative clinical trial data. Support through the Cancer Drug Fund would be invaluable with this subgroup population, allowing access while further evidence is collected. It would be important to include the option of subsequent treatments if, for example, tumours became amenable to surgical resection. Based on clinical experience our members have had excellent outcomes in this patient cohort and have successfully downstaged patients who are not appropriate for TACE within BCLC B to curative resection.[2] An international working group[3] define the group of patients eligible for this 'radiation lobectomy' approach as, Child-Pugh A patients who would otherwise be resected but: a) have an inadequate future liver remnant (FLR); and/or b) embedded test-of-time is desired for tumour biology; and/or c) need the treated tumour to be retracted away from hepatic vein and/or IVC d) demonstrating tumour response prior to surgery is preferable. Patients should be considered potentially operable candidates without comorbidities that would preclude surgery. 1. Garin E, Tselikas L, Guiu B, et al. A multicentric randomised study demonstrating the impact of MAA based dosimetry on tumour response with Y90 loaded glass microsphere SIRT for HCC: interim analysis of IIS Dosisphere. Global Embolization Cancer Symposium; 2019 May 9-12; New York. 2. Mafeld S, Littler P, Hayhurst H, Manas D, Jackson R, Moir J, et al. (2019) Liver resection after selective internal radiation therapy with yttrium-90: safety and outcomes. *J Gastrointest Cancer* DOI: 10.1007/s12029-019-00221-0. 3. Salem R, Padia SA, Lam M, Bell J, Chiesa C, Fowers K, et al. (2019) Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. *Eur J Nuc Med Mol Imaging* 46:1695-1704.
3	**2: As an alternative to TACE or sorafenib in patients with segmental or subsegmental portal vein thrombosis (PVT)** PVT confers a poor prognosis. Significant survival gains have been demonstrated with good tumour targeting and personalised dosimetry.[1] Based on clinical experience this is a valuable population to be treated with SIRT as effective treatment options are limited, but

	there is a lack of published evidence. A Commissioning through Evaluation (CtE) programme involving this patient subgroup (with stratification for malignant thrombus and bland thrombus) may be valuable to provide further evidence for effectiveness of SIRT in this population. 1. Garin E, Rolland Y, Edeline J, Icard N, Lenoir L, Laffont S, et al. (2015) Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. *J Nucl Med* 56:339-346.
4	**3: As an alternative to systemic therapy in patients when systemic therapy is not feasible** ESMO HCC guidelines published in 2018 recommend SIRT for patients with liver-confined disease and preserved liver function, in which neither TACE nor systemic therapy is possible.[1] It is well recognised that SIRT is better tolerated than TACE or systemic therapy with favourable quality of life data in SARAH.[2] SIRT presents a favourable treatment option in this small patient cohort. Based on clinical experience this is a valuable population who have no other treatment options (both patients who are ineligible for sorafenib and patients who discontinue sorafenib due to adverse events). 1. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. (2019) Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 30:871-873. 2. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. (2017) Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 18:1624-1636.
5	**4: Patients with ALBI score 1 and tumour burden of ≤25%** A post-hoc analysis of the ITT population of the published SARAH trial,[1] by Palmer et al in Future Oncology,[2] suggested that this group of patients benefitted most from SIRT (compared with sorafenib in the SARAH trial). The authors acknowledged that this analysis is hypothesis generating only.

	A major problem with this subgroup is that ALBI is not used in most centres (Child-Pugh classification is more widely used), and so identification of these patients would not be routine. Furthermore, there is not a well-established correlate (e.g. among the Child-Pugh classification groups) for this population. In addition, patients with a tumour burden of ≤25% are not the patients most centres are selecting for SIRT. However, the ALBI score has been developed by leading UK clinicians (hepatology, oncology, surgery) and could easily be applied in the clinic setting to identify this subgroup of patients who were identified as best responders in this post-hoc analysis. 1. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. (2017) Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 18:1624-1636. 2. Palmer DH, Hawkins NS, Vilgrain V, Pereira H, Chatellier G, Ross PJ. (2020) Tumor burden and liver function in HCC patient selection for selective internal radiation therapy: SARAH post-hoc study. *Future Oncol* 16:4315-4325.
5	The groups defined above represent a small cohort of patients with HCC and we believe that the therapy will be cost-effective in these groups. A positive recommendation supporting the funding of SIRT in selected patients with the collection of real world data will enable us to deliver better survival outcomes and improved quality of life for patients with HCC whilst promoting innovation and delivering world-class care in the NHS. Similar precedents exist in the England such as funding for the use of SIRT in patients with metastatic colorectal cancer that cannot tolerate chemotherapy, or the use of radium-223 in cancer patients that cannot tolerate taxanes.

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1	**Proposed patient profiles and subgroups** *1. Patients with ALBI score 1 and tumour burden of ≤25%* This is the only evidence-based subgroup of patients who are most likely to benefit from SIRT. It is based on a post-hoc analysis of those with a tumour burden ≤25%, and who have an ALBI score of 1 (Palmer D et al 2019: dx.doi.org/10.1093/annonc/mdx369) (Palmer DH, Hawkins NS, Vilgrain V, Pereira H, Chatellier G, Ross PJ. (2019) Tumor burden and liver function in HCC patient selection for selective internal radiation therapy: SARAH post-hoc study. *Future Oncol*. DOI: 10.2217/fon-2019-0658). Patients with a tumour burden ≤25% of the liver volume, an ALBI grade 1 and dose of radiation ≥100 Gy to the tumours were the best responders to SIRT in the SARAH trial (Hermann A-L et al. J Hepatol. 2018 Apr 13;68:S13). Liver function has traditionally been measured with the Child-Pugh classification; however, it is considered that it does not adequately capture the hepatic functional reserve. Although the ALBI score is not currently a routinely undertaken and accepted measure it is based on a calculation using 2 routinely measured outcomes: bilirubin and albumin levels. The ALBI score was not developed at the time of the SARAH trial, however, bilirubin and albumin levels are routinely measured in clinical practice. A potential criticism is that ALBI is not currently used in most centres (Child-Pugh classification is more widely used) and so identification of these patients would not be routine. However, since ALBI has been developed by leading UK clinicians (oncology, surgery, hepatology) who know what is applicable in the clinic, clinicians who manage these patients agree that ALBI could be applied in the clinic if there was a clinical reason to do so. Both the tumour burden and the ALBI grade can be estimated using routine CT scans and routine lab tests (albumin and bilirubin). *2. In patients with portal vein thrombosis (PVT) as an alternative to transarterial chemoembolization (TACE)* This indication is based primarily on clinical experience and clinical need. Experts view that this is a valuable population to be treated with SIRT as effective treatment options are limited, but there is a lack of published evidence. This subgroup has previously been discussed by the NHSE HPB CRG and the committee agreed that this patient subgroup are currently inadequately treated with current available therapies, particularly sorafenib and TACE. To fill the gaps in the data, a single-arm Commissioning through Evaluation (CtE) programme should be advocated with this subgroup population. Patients with malignant/tumour thrombus have poorer outcomes than those with bland thrombus, and so some level of patient stratification may be needed in any CtE programme. An additional difficulty would be to find a control group. Sorafenib treatment is the current standard for this subgroup of patients, but there are no systematic data on the prognosis for this subgroup on sorafenib. These data on patients treated in routine clinical practice could be collected via the same UK Registry as the SIRT data.

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	3. As an alternative to sorafenib in patients unable to tolerate sorafenib This indication is also based primarily on clinical experience and clinical need. A significant sub-population of patients are ineligible for sorafenib or lenvatinib, or discontinue either of these drugs due to adverse events. They are currently not offered any alternative therapies, although it is possible that immunotherapy may be offered in the future depending on trial results and NICE review. A similar precedent exists in the UK such as funding for the use of SIRT in patients with metastatic colorectal cancer who cannot tolerate chemotherapy, or the use of radium-223 in metastatic prostate cancer patients that cannot tolerate taxanes. This subgroup would be a suitable patient group to assess via a CtE programme, and as for the subgroup discussed above, and a single CtE could include multiple subgroups in order to gather the necessary clinical data. Likely patient numbers for both subgroups were accurately estimated in the original NICE consultation document.

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Name of commentator person completing form:	Dr Teik Choon SEE

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Example 1	We are concerned that this recommendation may imply that ……..
1	The recommendation is based on limited evidence and primarily on two main RCTs (SARAH and SIRveNIB) which as we discussed cannot be generalised to the patient population in the UK. We have seen reports of the effectiveness of SIRT in HCCs and until we have a robust RCT in the UK it is not appropriate to exclude SIRT from the HCC treatment algorithm.
2	Clinically certain groups of patients will be disadvantaged particularly those who are in the intermediate and some in the advanced stage of the disease. The evidence may be weak but it should not be ignored.
3	Cost effectiveness may be improved by addressing the actual cost of the spheres.
4	Commissioning through Evaluation for SIRT in HCC could well be the model as was the case for SIRT in colorectal liver metastases.
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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	Helen Reeves Professor of Liver Cancer Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

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Example 1	We are concerned that this recommendation may imply that ……..
1	Has all of the relevant evidence been taken into account' **The answer is no – not because of any criticism of NICE and the AG, but because there is currently insufficient evidence from a representative UK population.** I think it is very important here to highlight again that 'the relevant evidence' is very poorly representative of the UK population patients – especially those managed in the North of England where the commonest cause of HCC is none alcoholic fatty liver disease (NAFLD). NAFLD-HCC patients are considerable older, with comorbidities – both of which exclude them from many 'standard' therapies. These patients have not been included in earlier trials of TACE, and are very poorly represented in later trials of medical therapies. Importantly – post hoc analyses of the SHARP and Asia pacific trials indicate very clearly that the benefit from sorafenib in 'non-HCV' patients is very small in deed. Furthermore, NAFLD-HCC do not tolerate the drug well. We desperately need treatments for our own patient cohort. Our experience with SIRT in Newcastle (approximately 70-80 patients treated) clearly indicates that there are those who do extremely well treated with SIRT – even patients who are cured. For these, where there are no good alternatives, it will be quite tragic to lose the option to use SIRT. As we have some experience, I have suggested below those patients in whom we might consider it, with evidence collection, in a 'real life UK cohort'. We could also provide evidence from our treated UK patients
2	Are the summaries of clinical and cost effectiveness reasonable interpretations These are reasonable. But please can I point out again a very important factor that I am sure you are all very much aware of already. The RCT analyses have all been done on an intention to treat basis. There are good reasons for this. BUT – as ~15% of patients are excluded from actually having SIRT AFTER randomisation to SIRT, because they have a technical issue such as shunting that excludes them, the analyses could be reconsidered. i.e. focus on patients after assessing eligibility for a treatment. Considering only those patients passing the pre-SIRT phase, focused only on those actually treated, would possibly yield different outcomes. It is also worth just noting again, that the superiority of SIRT in terms of tolerability and quality of life, should not be underestimated for these individuals. **MY OWN SUGGESTIONS** 1. SIRT could be considered as an alternative to TACE: - In patients with single lesions >7cm. TACE is tolerated poorly in these patients. It can shorten life rather than prolong it. On the other hand SIRT is tolerated well. This strategy is perhaps pertinent particularly for older non-cirrhotic patients (commonly seen in NAFLD cohort), who have ALBI 1 liver function and no other therapies proven benefit. - Some patients in this category may ultimately be downstaged to resection and cure 2. SIRT could be considered as an alternative to medical therapy, in those with preserved liver function, but with factors predicting a poor response to medical therapy. Namely: - Those with an etiology that is not HCV - Those with a partial portal vein thrombosis - Those with an elevated NLR. I do apologise for lack of references - consequent to my poor planning and lack of access right now to databases (travelling). If it would be helpful, I could provide these to the AG in advance of the meeting on 22nd.

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**LIVER4LIFE**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[NONE]
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	In discussion with my clinical colleagues, with regard to proposed patient profiles and subgroups, it was felt that some patient subgroups would benefit from treatment by SIRT;
2	*In patients with portal vein thrombosis (PVT) as an alternative to transarterial chemoembolization (TACE)* 1. Based primarily on clinical experience. 2. *Consultation group's viewpoint:* a. Based on clinical experience this is a valuable population to be treated with SIRT as effective treatment options are limited, but there is a lack of published evidence. b. To fill the gaps in the data, a single-arm Commissioning through Evaluation (CtE) programme may be useful with this subgroup population. c. A difficulty would be to find a control group. Sorafenib treatment may act as a control but often patients receiving SIRT may also receive sorafenib. d. Furthermore, patients with malignant/tumour thrombus may have poorer outcomes than those with bland thrombus, and so some level of patient stratification may be needed in any study/programme. e. Glass microspheres potentially have a better safety profile than resin microspheres in this setting as they have a lower embolic effect (due to the size of the spheres). f. A CtE would be better than trying to extract data from a published study such as SORAMIC,[3] as patient numbers are likely to be low in such subgroup analyses. g. It may be necessary to collect data (e.g., from a prospective registry) of outcomes in this group of patients who are treated based on local protocols (as some will not have access to SIRT). This would give some justification, and a control population, for any subsequent CtE. h. In conclusion, a CtE involving this patient subgroup (with stratification for malignant thrombus and bland thrombus) is recommended to provide further evidence for effectiveness of SIRT. A prospective registry to collect data on this subgroup being

	treated according to local protocols may be useful before a CtE. *In patients with ≥1 large tumour (>7 cm) ± PVT as an alternative to TACE* • Based upon data from the DOSISPHERE trial, from which interim data have been presented.[4] • *Consultation group's viewpoint:* o Based on clinical experience this is a valuable population to be treated with SIRT, but as for option 2, there is a lack of comparative clinical trial data. o As for option 2, a CtE programme may be useful with this subgroup population. It would be important to include the option of subsequent treatments if, for example, tumours became amenable to surgical resection. o A single CtE could include both patient subgroups (from option 2 and option 3). o The consultation group postulated that an alternative subgroup of patients would be those with tumours ≥5cm (±PVT as an alternative to TACE), as the 7 cm cut-off may be too restrictive and may exclude patients who could potentially benefit from SIRT. o In conclusion, the group recommend a CtE in this subgroup, but amended to include patients with at least one tumour ≥5cm in diameter, and this CtE could include this patient subgroup and the patient subgroup discussed in option 2. *4. As an alternative to sorafenib in patients unable to tolerate sorafenib* • Based primarily on clinical experience and the unmet need for more effective treatments in this setting. • *Consultation group's viewpoint:* o Based on clinical experience this is a valuable population (both patients who are ineligible for sorafenib and patients who discontinue sorafenib due to adverse events). o A perception may exist that although the SARAH trial[1] was not powered to demonstrate equivalence, the patients had similar outcomes with SIRT as with sorafenib. o Similar precedents exist in the UK such as funding for the use of SIRT in patients with metastatic colorectal cancer that cannot tolerate chemotherapy, or the use of radium-223 in cancer patients that cannot tolerate taxanes. o In conclusion, this would be a suitable subgroup to assess via a CtE programme, and as for the subgroups discussed in option 2 and 3, data may need to be gathered

(retrospective or prospective) to gain information on a suitable comparator population before initiating a CtE.

General and concluding comments

- The subgroups mentioned in options 2, 3 and 4 would benefit from a CtE programme.
- The consultation group could not prioritise these three subgroups: subgroup populations in options 3 and 4 may have the greatest clinical need, but the evidence for SIRT in the subgroup in option 2 is stronger.
- The group did not think they were in a position to give accurate estimates of the patient numbers in each of these subgroups in the UK.
- From the patient perspective, any treatment that avoids the side effects of other treatments of HCC is an important advantage.
- Furthermore, the quality of life data from the SARAH trial were favourable for SIRT,[1] and other studies and clinical experience show the potential for SIRT to down-size tumours for subsequent curative treatment. Both these aspects of SIRT should be considered alongside the efficacy data for SIRT.

References:

1. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. (2017) Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 18:1624-1636.
2. Palmer DH, Hawkins NS, Vilgrain V, Pereira H, Chatellier G, Ross PJ. (2019) Tumor burden and liver function in HCC patient selection for selective internal radiation therapy: SARAH post-hoc study. *Future Oncol*. DOI: 10.2217/fon-2019-0658
3. Ricke J, Klumpen HJ, Amthauer H, Bargellini I, Bartenstein P, de Toni EN, et al. (2019) Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. *J Hepatol* 71:1164-1174.
4. Garin E, Tselikas L, Guiu B, et al. A multicentric randomised study demonstrating the impact of MAA based dosimetry on tumour response with Y90 loaded glass microsphere SIRT for HCC: interim analysis of IIS Dosisphere. Global Embolization Cancer Symposium; 2019 May 9-12; New York.

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Assessment Group's Report

Selective internal radiation therapies (SIRTs) for treating hepatocellular carcinoma [ID1276]
Request to AG following 2nd committee meeting

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

Background

On 22 January, the Committee considered consultation responses for the multiple technology appraisals of SIRTs for treating hepatocellular carcinoma. The Committee understood from stakeholder comments that SIRTs might have fewer and less severe side effects than transarterial chemoembolisation (TACE) or sorafenib. Also, side effects persist only for a short period after a single SIRT treatment. The clinical expert and the patient expert explained that this might improve health related quality of life. However, the Committee noted the utility values, derived from EQ-5D, in the model were similar between SIRTs and systemic therapies (sorafenib or lenvatinib) for the following disease states: progression-free survival, progressive disease and post-transplant. There were only small differences in utilities between progression-free survival and progressive disease. There was no difference between the treatment options in quality of life.

Issue

The Committee considered that the potential difference in quality of life, in particular differences associated with side effects and adverse events, might not be captured in clinical trial results because quality-of-life data are collected at fixed time points.

Objectives

- Addendum to AG report including updated base case analysis and scenario analyses without PASs. The updated base case should be based on the Committee-preferred assumptions (see Appendix 1) and include:
    - Sorafenib duration from individual patient data
    - Similar work-up costs for the SIRTs
    - Contrast imaging for all SIRTs.
- Addendum confidential appendix including new base case analysis and scenario analyses with PASs.

Assessment Group response

Is it plausible that the model does not capture quality-of-life differences (QALY decrements) associated with side effects (adverse events) in full?

Quality of life in the AG's economic model was based on an analysis of health-related quality of life (HRQoL) data collected in the SARAH trial. In principle, the AG considers that the trial is likely to capture any disutility impact of AEs that are related to sorafenib, which is taken at daily intervals. The impact of any adverse events that occur would not be missed because of the trial design and schedule of questionnaires, although there will be a small proportion of patients who experience disease progression before 3 months whose HRQoL after baseline will not be captured. The trial may be less likely to capture the impact of AEs related to SIRT, as the first questionnaire is completed by the trial participant at 3 months, after which the majority of TRAEs are likely to have been resolved. Comparative HRQoL between sorafenib and SIRT in the SARAH trial is unclear because of the long interval between initiating of treatment and collection of data. A potential reason for the trial to not fully capture the impact of AEs may be that the patient with the AE would not complete the questionnaire, and would wait until the AE was resolved to complete it. However, this would impact both treatment arms, and is a common issue in all trial-based estimates of quality of life.

The mean health state utility values showed little difference between treatment arms. However, clinical experts consider that the toxicity profiles of the two treatments are sufficiently different that the difference in quality of life should be greater, and that improvement in HRQoL would result from the better safety profile of SIR-Spheres compared to sorafenib.

To explore this issue further, the AG considered how HRQoL varied over time in each of the treatment arms in the SARAH trial. As presented in Figure 1, the EORTC QLQ-C30 values for the SIRT arm appear relatively constant over the 12 months since randomisation, while patients in the sorafenib arm experienced a worsening in HRQoL over the first six months of treatment, with an improvement in mean QoL at approximately 9 months after randomisation (likely due to discontinuation of sorafenib due to disease progression). The observed trends in the SARAH EORTC data appear to support the assumption that sorafenib is associated with a poorer quality of life than SIRT, and that this is not captured in the mean health state values. A comparison of the EORTC time chart of utilities and the mapped EQ-5D values (Figure 2) suggests that this may be due to the insensitivity of the mapping algorithm used to translate EORTC values to EQ-5D values. This may be because the elements of the EORTC scale most affected by treatment with sorafenib were less important predictors of HRQoL as defined by EQ-5D. As the population used to map the

questionnaires comprised only multiple myeloma, breast cancer, and lung cancer patients, it may have been that QoL differences in HCC were not accurately translated across scores. In the mapped EQ-5D, the difference between arms is reduced, and sorafenib is actually associated with a higher mean EQ-5D value than SIRT at month 12.

Figure 1 EORTC-QLQ-C30 results from the SARAH trial (Fig 14, Sirtex submission)

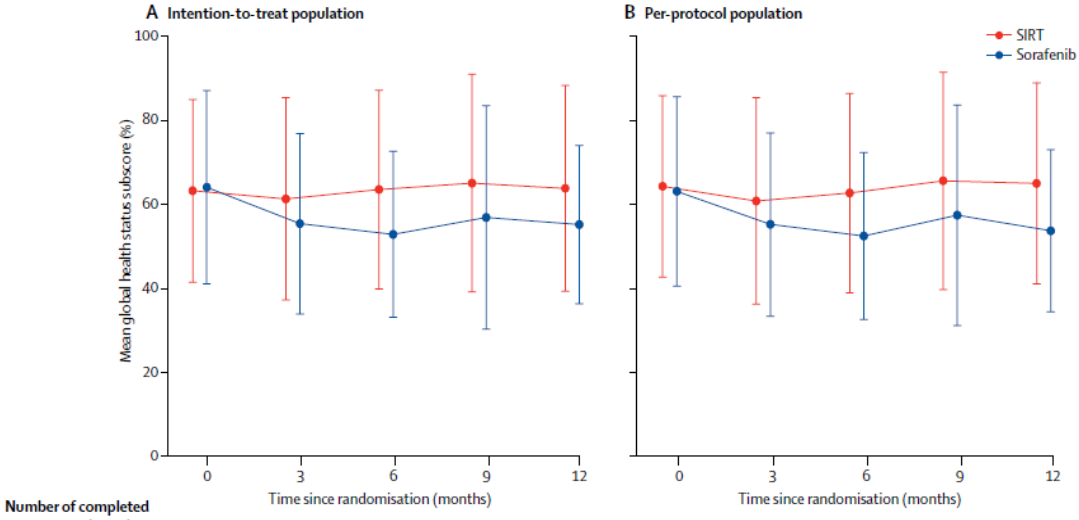
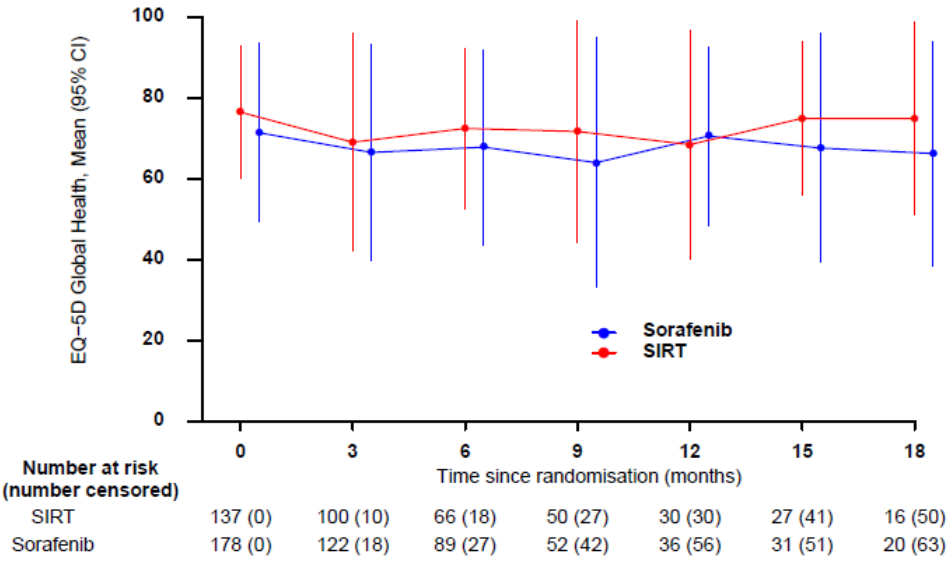


Figure 2. UK EQ-5D values by time (per protocol population) (Fig 36, Appendix G, Sirtex submission)



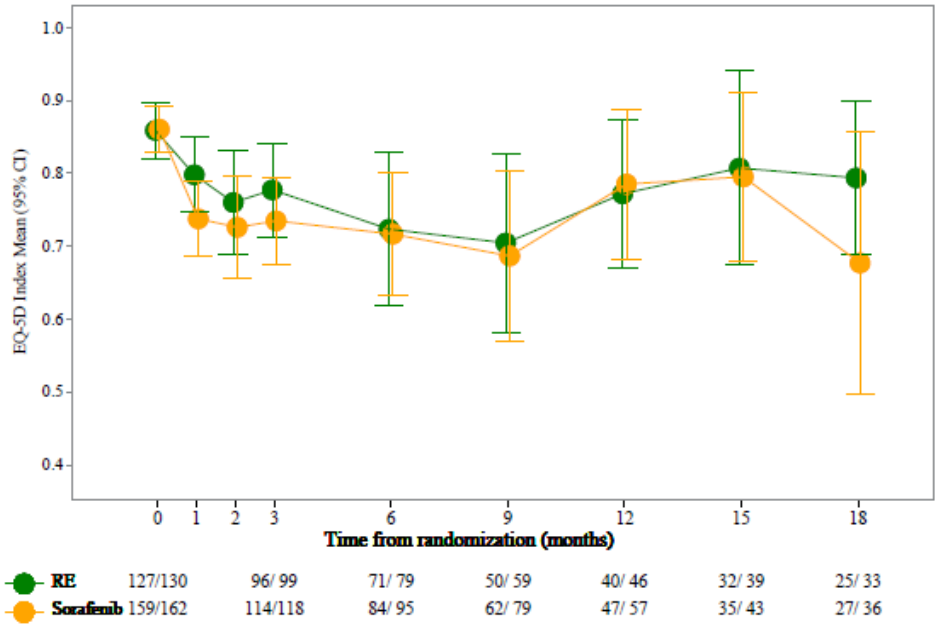
Sirtex, the funder of the SARAH trial, provided some explanation in their response to the Committee's request for data following the second Committee meeting. The company made reference to a published comparison of directly measured and imputed EQ-5D utilities (Crott et al),[1] which found that the external validity of a mapping algorithm when tested on a set of unrelated external data sets in other cancers proved to underestimate both the mean and variance of the mapped EQ-5D utilities. The mapping algorithm used to map SARAH EORTC data to EQ-5D was based on a dataset of 771 cancer patients, and Crott noted that the relationship between QLQ-C30 scores and EQ-5D values is not stable across the different data sets.

The company also considered that any variation in EQ-5D utility between treatments, that would have been observed had the EQ-5D questionnaire been employed, may be underestimated if mapping from another instrument (i.e. the EORTC) is used. This is because it is unlikely that the domains and measurement intervals in the EORTC instrument will completely cover the domains and measurement intervals included in the EQ-5D instrument, and so the mapping is unlikely to detect all variation in the EQ-5D instrument.

The AG considered the QoL reported in the SIRveNIB trial,[2] which collected EQ-5D data instead of EORTC, and so no mapping was required for this dataset. In this trial, there was an immediate decrease in QoL that was observed in both arms, although slightly greater in the sorafenib arm. However, after 6 months the EQ-5D values in both arms were very consistent with each other until at least 15 months after randomisation. While the population is not the same as the UK population due to different aetiology typically underlying HCC in Asia-Pacific patients, it does not seem unreasonable to assume that any differences in QoL due to the different safety profiles between the two arms would be captured in this dataset.

The Committee also asked the company whether the EQ-5D instrument would capture all HRQoL effects relevant to the current decision problem. The company highlighted a number of previous studies that have shown that the EQ-5D instrument may miss significant clinical changes in cancer patients, of which fatigue may be the most important aspect. Fatigue is one of the most commonly reported side effects of sorafenib, and it would follow that the EQ-5D would be less sensitive in capturing the disutility associated with this aspect of sorafenib treatment.

Figure 3 EQ-5D in SIRveNIB



In summary, analysis of the EORTC QLQ-C30 data from the SARAH trial suggests some difference in HRQoL between SIRT and sorafenib. However, this difference does not appear to translate to a difference between arms when translated to EQ-5D estimates of HRQoL. This may potentially be due to the insensitivity of the mapping algorithm. However, analysis of directly elicited EQ-5D data from the SIRveNIB trial also does not reveal a difference between SIRT and sorafenib. This may be because EQ-5D is insensitive to the type of AEs that typically differ between the two treatment arms. Generally, the data suggests that there may be a difference in HRQoL between SIRT and sorafenib, but it is likely that it is not very pronounced, and does not have much impact on the EQ-5D scale.

Can data from the clinical trials be used in the model to provide information on adverse event severity and duration?

The AG's economic analysis used data from the SARAH trial to model the cost impact of TRAEs for each treatment arm. Selected events were of Grade 3 and above, and either had an incidence of at least 5% or were considered significant.

Data on duration of AEs is not currently available in the public domain. In their response, Sirtex Medical provided the mean duration (days) for each event that occurred (see Table 1). Sirtex estimated a single duration for each type of AE, across study arms and across severity grades, in order to increase the sample size available per type of event. Assuming that Grade 3-4 events are both more severe and longer in duration, this will underestimate the duration of Grade 3-4 events and overestimate the duration of Grade 1-2 events. Since data is pooled across arms, it is not possible to comment on the clinical advisor's statement that "side effects persist only for a short period after a single SIRT treatment"; however, should this be the case, the pooling of data will also result in underestimated duration of AEs related to sorafenib and overestimated duration of AEs related to SIRT.

Table 1 Number of patients (%) experiencing treatment-related adverse events in the safety population (provided by Sirtex Medical)

Events	**SIR-Spheres (n= 226)**				**Sorafenib (n= 216)**				**Mean duration (days) for patients who had an event (SD)**
Grade	**1/2**	**3**	**4**	**5**	**1/2**	**3**	**4**	**5**	
Infection	6 (3)	2 (1)	0 (0)	1 (0)	16 (7)	8 (4)	0 (0)	2 (1)	[redacted]
Fever	13 (6)	0 (0)	0 (0)	0 (0)	17 (8)	3 (1)	0 (0)	0 (0)	[redacted]
Fatigue	81 (36)	20 (9)	0 (0)	0 (0)	123 (57)	41 (19)	0 (0)	0 (0)	[redacted]
Weight loss	14 (6)	0 (0)	0 (0)	0 (0)	40 (19)	6 (3)	0 (0)	0 (0)	[redacted]
Alopecia	0 (0)	0 (0)	0 (0)	0 (0)	35 (16)	0 (0)	0 (0)	0 (0)	[redacted]
Hand-foot skin reaction	0 (0)	1 (0)	0 (0)	0 (0)	37 (17)	12 (6)	0 (0)	0 (0)	[redacted]
Rash or desquamation	2 (1)	1 (0)	0 (0)	0 (0)	20 (9)	0 (0)	0 (0)	0 (0)	[redacted]
Pruritus	7 (3)	1 (0)	0 (0)	0 (0)	18 (8)	1 (0)	0 (0)	0 (0)	[redacted]
Dry skin	2 (1)	0 (0)	0 (0)	0 (0)	40 (19)	3 (1)	0 (0)	0 (0)	[redacted]
Other dermatological events	4 (2)	0 (0)	0 (0)	0 (0)	48 (22)	6 (3)	0 (0)	0 (0)	[redacted]
Anorexia	24 (11)	7 (3)	0 (0)	0 (0)	66 (31)	10 (5)	0 (0)	0 (0)	[redacted]
Diarrhoea	26 (12)	3 (1)	0 (0)	0 (0)	137 (63)	30 (14)	0 (0)	0 (0)	[redacted]
Nausea/Vomiting	25 (11)	1 (0)	0 (0)	0 (0)	47 (22)	5 (2)	0 (0)	0 (0)	[redacted]

Events	**SIR-Spheres (n= 226)**				**Sorafenib (n= 216)**				**Mean duration (days) for patients who had an event (SD)**
Grade	**1/2**	**3**	**4**	**5**	**1/2**	**3**	**4**	**5**	
Abdominal pain	43 (19)	6 (3)	0 (0)	0 (0)	57 (26)	13 (6)	0 (0)	1 (0)	[redacted]
GI ulceration	2 (1)	3 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	[redacted]
GI bleeding	1 (0)	5 (2)	0 (0)	4 (2)	6 (3)	7 (3)	0 (0)	1 (0)	[redacted]
Ascites	19 (8)	9 (4)	1 (0)	1 (0)	15 (7)	9 (4)	0 (0)	1 (0)	[redacted]
Liver dysfunction	28 (12)	16 (7)	2 (1)	7 (3)	30 (14)	27 (13)	0 (0)	0 (0)	[redacted]
Radiation hepatitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	[redacted]
Radiation pneumonitis	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	[redacted]
Hypertension	6 (3)	0 (0)	0 (0)	0 (0)	28 (13)	5 (2)	0 (0)	0 (0)	[redacted]
Cardiac failure congestive	25 (11)	2 (1)	0 (0)	1 (0)	24 (11)	11 (5)	0 (0)	0 (0)	[redacted]
Haemorrhage (non GI)	5 (2)	0 (0)	1 (0)	0 (0)	19 (9)	2 (1)	0 (0)	0 (0)	[redacted]
Pulmonary embolism	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	[redacted]
Hyperbilirubinemia	25 (11)	7 (3)	1 (0)	0 (0)	21 (10)	9 (4)	0 (0)	0 (0)	[redacted]
Other increased Liver values	53 (23)	19 (8)	1 (0)	0 (0)	46 (21)	16 (7)	0 (0)	0 (0)	[redacted]
Hematologic Biological abnormalities	41 (18)	22 (10)	1 (0)	0 (0)	53 (25)	28 (13)	1 (0)	1 (0)	[redacted]
Renal Dysfunction (Increased Creatinine)	23 (10)	2 (1)	0 (0)	2 (1)	32 (15)	8 (4)	1 (0)	3 (1)	[redacted]
Hyponatraemia	11 (5)	2 (1)	0 (0)	0 (0)	21 (10)	4 (2)	0 (0)	0 (0)	[redacted]

Evidence for TheraSphere

BTG, the manufacturer of TheraSphere, submitted additional evidence on safety from two RCTs that enrolled TheraSphere patients.[3,4] Neither RCT compared TheraSphere with sorafenib.

The Dosiphere trial compared patients receiving TheraSphere under standard dosimetry ([redacted]) with patients receiving personalised dosimetry ([redacted]).[3] BTG provided data for treatment-emergent AEs, defined as AEs that occurred on or after the first administration of TheraSphere or that were present prior to dosing but were exacerbated on or after the first TheraSphere administration indicating that most AEs are mild to moderate in severity. Events by severity were reported for all patients ([redacted]), presented in Table 2.

Table 2: Severity of the most frequently reported treatment-emergent AEs with TheraSphere in the Dosisphere study

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
[redacted]					

BTG also presented the safety results from an RCT published in 2011 comparing TheraSphere (n=123) with TACE (n=122), see Table 3.[4] It should be noted that this study enrolled a number of patients classed as Child-Pugh B and C, who are not eligible for sorafenib and so would not be included in the present analysis.

Table 3 Adverse events for TheraSphere and TACE, from Salem (2011)[3]

	TACE (n=122)	TheraSphere (n=123)	p
Fatigue	47 (38%)	68 (55%)	0.074
Abdominal pain	46 (38%)	18 (15%)	<0.001
Nausea/vomiting	25 (20%)	18 (15%)	NS
Anorexia	16 (13%)	13 (11%)	NS
Fever/chills	2 (2%)	10 (8%)	NS
Diarrhoea	10 (8%)	2 (2%)	NS

As the data from Dosisphere and Salem (2011) related only to TheraSphere, BTG compared the rates of AEs from these studies with those reported for sorafenib in the SARAH trial. BTG noted a number of key differences between TheraSphere and sorafenib. Firstly, there were no patients that received TheraSphere who had a hand-foot skin reaction (palmar-plantar erythrodysesthesia), which occurred as a Grade 3+ event in 6% of sorafenib patients in SARAH. Rates of abdominal pain, fatigue and diarrhoea were also higher for sorafenib in the SARAH trial than the rates for corresponding events for TheraSphere in the Dosisphere trial and Salem (2011), which is a consistent finding with SIR-Spheres compared with sorafenib in the SARAH trial (see Table 1). BTG note that fatigue with TheraSphere is transient; however, no evidence was provided to support this statement.

There are a number of drawbacks associated with the use of these two studies to establish a robust set of adverse event rates for TheraSphere. As noted above, neither compare TheraSphere to sorafenib or to SIR-Spheres. Dosisphere enrolled a smaller number of patients, so it would be more difficult to detect the less common AEs. Salem (2011) enrolled a number of patients classed as Child-Pugh B and

C, who are not eligible for sorafenib and so would not be included in the present analysis. The authors presented rates of AEs by Child-Pugh class, and found that those who were Child-Pugh A often had markedly different event rates to those who were Child-Pugh B/C. There were differences between some of the rates of events for SIR-Spheres from SARAH and for TheraSphere, e.g. the rate of Grade 3+ fatigue. BTG note that the rates for TheraSphere ranged from [redacted] (in the Dosisphere trial) to 57% (in Salem (2011)), all of which were grade 1 or 2 in severity. The rate of fatigue for SIR-Spheres in SARAH was 45% (of which 9% were of Grade 3 severity).

Is there published real world evidence for adverse events (rate, severity, duration) that can be used?

The companies were invited to submit additional real world evidence on the safety of the SIRTs. BTG, the manufacturer of TheraSphere submitted the following pieces of evidence on safety*:

- Adverse event (AE) data from a prospective longitudinal study from a single centre using TheraSphere (n=291).[5] In the prospective longitudinal study, the most frequent AE with TheraSphere was fatigue.
- Clinical opinion from clinicians using TheraSphere, stating that most patients receiving TheraSphere have mild to moderate AE, commonly fatigue, abdominal pain and nausea/vomiting, which are short in duration (lasting 2-3 days).

BTG also noted that a new non-comparative real world dataset using TheraSphere in patients with PVT will be available from a registry in France within 2 to 3 years. The study (PROACTIF) is now underway and will follow patients for 6 years (https://clinicaltrials.gov/ct2/show/NCT04069468).

Sirtex Medical did not present any additional real world evidence for the safety of SIR-Spheres.

* BTG also submitted additional data from a retrospective registry of SIRT patients in Newcastle (n=42). This reported on disease control measures and did not report any information on safety. The population in the Newcastle dataset does not appear to be relevant to the economic analysis, which considers a population that are ineligible for TACE. As such, this is not considered in this report on safety.

Is it plausible to do scenario analyses with varying disutility values?

Threshold analysis

This section presents a range of QALY losses associated with AEs, estimated under different scenarios (Table 4). Where event rates were estimated from SARAH, it was assumed that the event rates for TheraSphere were equivalent to those for SIR-Spheres.

Scenario 1 reflects the assumption in the AG's base case model, where the disutility impact was assumed to be captured in health state utility values. This assumption was also in line with the original economic analysis presented by Sirtex. Scenario 2 reflects a scenario presented in the AG's original analysis, where a QALY loss of 0.012 was applied to each event of Grade 3+ that occurred in the model, based on rates from the SARAH trial. The analysis presented by BTG (Scenario 3) also assumed a QALY loss of 0.012 for each event, citing "previous oncology submissions" (but no specific source of evidence), with AE rates for SIRTs from a systematic review of safety of SIRTs,[6] and AE rates for sorafenib from the REFLECT trial that compared lenvatinib to sorafenib.[7]

In their response, Sirtex Medical sourced event-specific disutility estimates through a review of recent NICE technology appraisals in oncology and a targeted literature search run in PubMed for literature reviews of cancer related utility values. Most disutility values were elicited for grade 3/4 AEs, and so Sirtex explored two scenarios to model the impact of Grade 1/2 events. In one, the disutility for grade 1/2 AEs was decreased by 50% (Scenario 5), and in the other it was assumed that these events would have the same disutility as the Grade 3/4 events (Scenario 4). The AG also conducted an additional scenario using Sirtex's disutility values on events of Grade 3+ only (Scenario 6). One final scenario conducted by the AG assumed that the disutility *and* the duration of grade 1/2 AEs was decreased by 50% (Scenario 7).

Table 4 QALY loss estimates for adverse events

Scenario		TRAE QALY loss
1	Assuming disutility impact captured in health state utility values	0.00
2	0.012 QALY loss for each event (Grade 3+, event rates from SARAH)	Sorafenib: 0.012 SIRT: 0.006 Incremental: 0.006
3	0.012 QALY loss for each event (Grade 3+, event rates from Kallini *et al.* and REFLECT)[6,7]	Sorafenib: 0.007 SIRT: 0.002 Incremental: 0.005
4	Event-specific QALY loss, event rates from SARAH (all grades of AE, QALY loss rate applied to all events)	Sorafenib: 0.2467 SIRT: 0.1294 Incremental: 0.12

5	Event-specific QALY loss, event rates from SARAH (assuming 50% reduction in QoL for grade 1/2 disutilities)	Sorafenib: 0.1508 SIRT: 0.0810 Incremental: 0.070
6	Event-specific QALY loss, event rates from SARAH (no QoL impact of Grade 1-2 AEs)	Sorafenib: 0.0558 SIRT: 0.0324 Incremental: 0.0233
7	Event-specific QALY loss, event rates from SARAH (assuming 50% reduction in QoL and in duration for grade 1/2 disutilities)	Sorafenib: 0.1037 SIRT: 0.0567 Incremental: 0.0470

Base case results of the economic analysis

The results of the economic analysis under the Committee-preferred assumptions (see Appendix 1) are presented in Table 5. These analyses are exclusive of the confidential PAS discounts that are associated with sorafenib, QuiremSpheres and TheraSphere. **Cost-effective results and threshold analyses based on the QALY losses in Table 4, with the confidential PAS discounts applied, are presented in a confidential appendix.**

In the base case scenario in Table 5, SIR-Spheres, TheraSphere and QuiremSpheres are associated with lower costs and fewer QALYs than sorafenib.

Under the current set of assumptions, the efficacy of TheraSphere and QuiremSpheres is assumed to be equivalent to SIR-Spheres, and all three SIRTs have identical procedure-related administration costs. When the PASs are not included, SIR-Spheres, QuiremSpheres and TheraSphere are in the southwest quadrant of the cost-effectiveness plane, producing fewer QALYs compared with sorafenib, but at lower cost.

Table 5 Base case results of the economic analysis, under Committee-preferred assumptions (no PAS applied)

	Costs	**QALYs**	**Inc. cost**	**Inc. QALYs**	**ICER**
SIR-Spheres	£31,070	0.764	-£4,589	-0.076	£60,089 (SWQ)
TheraSphere	£31,070	0.764	-£4,589	-0.076	£60,089 (SWQ)
QuiremSpheres	£33,050	0.764	-£2,609	-0.076	£34,159 (SWQ)
Sorafenib	£35,659	0.841	-	-	-

References

1. Crott R, Versteegh M, Uyl-de-Groot C. An assessment of the external validity of mapping QLQ-C30 to EQ-5D preferences. Qual Life Res. 2013 Jun;22(5):1045–54.
2. Chow PK, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018;36:1913-21.
3. Biotrial. Dosisphere safety results (Radiotherapie interne vectorisee des carcinomes hepatocellulaires avec les microspheres de verre marquees a l'yttrium 90: Dosimetrie optimisee versus dosimetrie standard), 2019.
4. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2011; 140(2): 497-507.e2.
5. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010; 138(1): 52-64.
6. Kallini JR, Gabr A, Thorlund K, Balijepalli C, Ayres D, Kanters S, et al. Comparison of the adverse event profile of therasphere with sir-spheres for the treatment of unresectable hepatocellular carcinoma: a systematic review. *Cardiovasc Intervent Radiol* 2017;40:1033-43.
7. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163-73.

Appendix A – Committee-preferred model assumptions

Table 6 Key features of model

Model Component	Description
Population	• People with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, o for whom any conventional transarterial embolisation therapies (TAE, TACE, DEB-TACE) are inappropriate, o with or without macroscopic vascular invasion, without extrahepatic disease.
Intervention	• SIR-Spheres Y-90 resin microspheres • TheraSphere Y-90 glass microspheres • QuiremSpheres Ho-166 PLLA microspheres
Comparator	• Sorafenib
Analysis type	• Cost-effectiveness (cost-utility) analysis
Economic outcome	• Incremental cost per QALY gained, incremental net monetary benefit
Perspective	• NHS and PSS
Time horizon	• Lifetime (10 years)
Discount rate	• Annual rate of 3.5% applied to costs and QALYs

Table 7 Sources of input parameters for the base case economic model

Model parameters	Evidence source
OS	*As per AG proposed base case:* Weibull fitted to pooled OS data from the SARAH and SIRveNIB trials for both SIR-spheres (per protocol) and sorafenib (intention-to-treat). OS for patients who received work-up but were ineligible to receive SIRT use KM data from SARAH.
PFS	*As per AG proposed base case:* Weibull fitted to pooled PFS data from the SARAH and SIRveNIB trials for both SIR-spheres and sorafenib.
Health utilities	*As per AG base case:* Utilities from SARAH trial data, and applied by treatment class (SIRT/systemic therapy)
Proportion receiving SIRT	*As per AG base case:* Proportion receiving SIRT after work-up based on the full SARAH trial population. Number of administrations of SIRT based on the SARAH trial.
SIRT costs	*As per AG base case:* Acquisition cost: Sirtex CS, BTG CS, Terumo CS Work-up costs: BTG-elicited values from The Christie NHS Foundation Trust Procedure costs: NHS Reference Costs 2017-18 *Additionally:* Equal administration costs for all SIRTs Imaging costs to be included for all SIRTs
Systemic therapies costs	*As per AG base case:* Sorafenib: BNF Dosing of sorafenib: SARAH trial *Additionally:* Duration of sorafenib: SARAH trial individual patient data
Subsequent treatment costs	*As per AG base case:* BNF, eMIT, TA555 (regorafenib)
AE costs	*As per AG base case:* AEs ≥5% of the population were modelled with rates drawn from the SARAH and REFLECT trials.

	Costs were drawn NHS Reference Costs, with cost categories based on NICE TA474, and 551
Health state costs	*As per AG base case:* Sirtex survey of clinical experts and NHS reference costs 2017/2018
Downstaging	*As per AG base case:* Not to be included because robust data are not available

Multiple Technology Appraisal (MTA)
Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]
Response to AG report completed after the second Committee meeting

Overview

We would like to thank the ERG for their work in assessing whether the health related quality of life (HRQoL) data collected during SIRT clinical trials reflect the true HRQoL differences between sorafenib and SIRT, taking into account the differing treatment-related adverse event (TRAE) profiles of the two treatments.

We have a number of specific concerns around the work carried out by the ERG, which are listed below and in Table 3, to be found at the end of this document.

However, as noted below, BTG/Boston Scientific is not suggesting that TheraSphere is used in patients who are able to take sorafenib, therefore, the relevance of the work carried out by the ERG is somewhat academic.

BTG/Boston Scientific believe that SIRT is best placed as a treatment option for people with hepatocellular carcinoma (HCC) unable to use the current standard of care. There are three such sub-populations:

1. Patients with large (≥5 cm) tumours (with or without portal vein thrombosis [PVT]), this subgroup are unable to receive conventional transarterial therapies (TACE).
2. Patients with PVT, this subgroup are unable to receive TACE.
3. Patients who are unable to receive or tolerate sorafenib, which is the systemic therapy standard of care.

As discussed in our earlier correspondence, this represents around 200 people in England.

We are also disappointed that our evidence using personalised dosimetry (PDA) appears not to have been considered.

To reiterate:

PDA, where the dose of radiation is tailored to the patient providing an optimised dose to the tumour, is a relatively new technique and has shown to result in improved survival outcomes compared to standard dosimetry (SDA). Data from both TheraSphere and SIR-Spheres have demonstrated survival benefit with PDA, with comparable AE profiles between the two approaches[1-5]. A recent expert recommendation consensus paper (Salem 2019) reflects on the benefits of PDA and stated that '*As new prospective trials are designed, incorporation of a refined and personalized dosimetry model will be essential for improved outcomes'*[5].

Further comments on the executable model will be submitted by 1700 on 30th June 2020 as agreed with Project Manager, Louise Jafferally.

Critique of Assessment Group report

The work undertaken by the Assessment Group focusses on the impact of TRAEs on HRQoL and magnitude of benefit (as expressed via lifetime quality adjusted life years [QALYs]) associated with each treatment. Consequently, the impact of these alterations has no impact on the lifetime costs of each treatment.

We would like to take this opportunity to remind the Committee that when the agreed BTG commercial arrangement is in place, TheraSphere becomes the least costly of the interventions assessed in these patient groups. For convenience, we reproduce the table of lifetime costs from the Assessment Group additional report below and note that all these values exclude patient access scheme (PAS) discounts.

Table 1: Table 5 from AF report Base case results of the economic analysis, under Committee-preferred assumptions (no PAS applied)

	Costs	QALYs	Inc. cost	Inc. QALYs	ICER
SIR-Spheres	£31,070	0.764	-£4,589	-0.076	£60,089 (SWQ)
TheraSphere	£31,070	0.764	-£4,589	-0.076	£60,089 (SWQ)
QuiremSpheres	£31,070	0.764	-£4,589	-0.076	£60,089 (SWQ)
Sorafenib	£35,659	0.841			

In light of the additional work undertaken by the Assessment Group, we would like to reiterate that the incremental lifetime QALYs generated (-0.076) is both small and conservative since it assumes no differential impact on HRQoL of treatment. To put this value into context, 0.076 QALYs represent approximately 3.5 quality adjusted weeks.

The Assessment Group present four scenarios for inclusion of differential TRAE-related utility loss into their model (see Assessment Group report Table 4) but as the results of these analyses were deemed commercially confidential we were not able to see the outputs from these. In particular, we were unable to see whether or not the 95% credible intervals from these analyses crossed zero (suggesting no evidence of any difference between the two treatments).

However, the application of common logic would dictate that the incremental benefit of sorafenib over TheraSphere would be reduced in all of these scenarios and hence the difference in incremental benefit would be less than 3 quality adjusted weeks.

Thus, regardless of which of the Assessment Group scenarios the Committee feel most plausible (see below), when compared to sorafenib, TheraSphere will be in either the south west or south east quadrant of the cost-effectiveness plane. In the absence of actual results from the scenario analyses, we can only present our view of the impact of these as per the table below. In the first of these, the likelihood of TheraSphere being cost-effective is increased as a result of the increased ICER in the first of these scenarios. In the second scenario, TheraSphere is the dominant treatment and hence cost-effective.

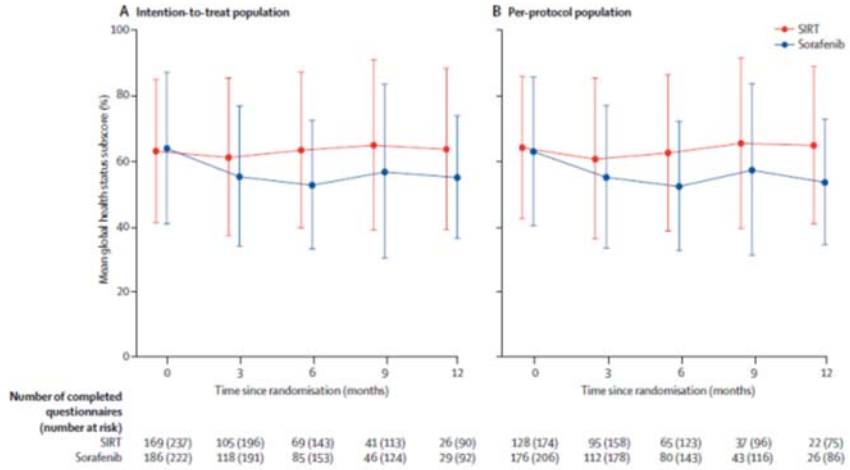
Table 2: Scenarios for TheraSphere

Scenario	Incremental cost impact	Incremental QALY impact	Impact on ICER
TheraSphere remains in the south west quadrant following application of the Assessment Group scenario	None	Between -0.07 and 0.00	Increases beyond the £60,089 reported in the Assessment Group addendum
TheraSphere moved to the south east quadrant following application of the Assessment Group scenario	None	Greater than 0.00	TheraSphere becomes the dominant therapy

Alternatively, the Committee might view the additional work as not robust enough on which to make a decision. In such a situation, we would request that the Committee view the products as clinically similar and base their decision making on a cost-minimisation approach (taking into account the BTG commercial agreement).

It should also be noted that the PAS for TheraSphere includes [redacted]

Table 3: Comments on the Assessment Group's Report Selective internal radiation therapies (SIRTs) for treating hepatocellular carcinoma [ID1276] Request to AG following 2nd committee meeting

Page 3/4	In SARAH, EORTC was mapped to EQ-5D using a dataset of 711 cancer patients none of whom had HCC. The Assessment Group note that '*As the population used to map the questionnaires comprised only multiple myeloma, breast cancer, and lung cancer patients, it may have been that QoL differences in HCC were not accurately translated across scores*' This has not been taken into consideration in the Assessment Group's final conclusion.
Page 5	In SIRveNIB, which collected HRQoL data using EQ-5D, there was no difference in HRQoL between SIRT and sorafenib. However, the Assessment Group report notes that '*… a number of previous studies that have shown that the EQ-5D instrument may miss significant clinical changes in cancer patients, of which fatigue may be the most important aspect. Fatigue is one of the most commonly reported side effects of sorafenib, and it would follow that the EQ-5D would be less sensitive in capturing the disutility associated with this aspect of sorafenib treatment'.* This has not been taken into consideration in the Assessment Group's final conclusion.
Page 6	The Assessment Group report states that '*Generally, the data suggests that there may be a difference in HRQoL between SIRT and sorafenib, but it is likely that it is not very pronounced, and does not have much impact on the EQ-5D scale'* We accept and acknowledge that was challenging for the Assessment Group to come to any definitive conclusions around the impact of any differential TRAE profiles. However, the Assessment Group were confident that such a difference is likely to exist. The basis for this is the comparison of the EORTC QLQ-C30 data from SARAH, and again we have reproduced the key plot from the Assessment Group report below for convenience. 

	The Assessment Group also tabulated key clinical events observed in the SARAH study (Assessment Group addendum report Table 1). Focussing on severe TRAEs (grade III/IV) there were notable differences in events that would be expected to impact on HRQoL. Examples include: • Infection (sorafenib 4%, SIR-Spheres 1%) • Fatigue (sorafenib 19%, SIR-Spheres 9%) • Diarrhoea (sorafenib 14%, SIR-Spheres 1%) • Hypertension (sorafenib 2%, SIR-Spheres 0%) Thus, it is fair to assume that these differences would lead to a difference in HRQoL, but the magnitude of this impact is unknown. There was considerable discussion at the Committee meeting around how HRQoL scales do not adequately capture the differences in AE between sorafenib and SIRTs. The key differences in TRAE between the two treatments are in duration and severity of TRAE. • TRAE with SIRT are transient (2-3 days maximum) and mild to moderate in severity. • TRAE with sorafenib are long-lasting (for as long as treatment is continued) and can be severe (In SARAH, grade 3 AE reactions were seen with fatigue: 25% of patients, diarrhoea:18%, hand-foot skin reaction:24% and abdominal pain: 18%). We accept that evidence for these clinically important differences is not available from randomised controlled trials (RCT), however, we urge the Committee to take a pragmatic approach to this issue, given the potential benefits to patients.
Page 9	*BTG note that fatigue with TheraSphere is transient; however, no evidence was provided to support this statement.* This is incorrect, in our response of 11 March, we provide evidence from two sources • *Advice from clinical experts working in the field in the UK, including feedback at the first Committee Meeting, supports these findings and confirms that most patients receiving TheraSphere have mild to moderate AE, commonly fatigue, abdominal pain and nausea/vomiting, which are short in duration (lasting 2-3 days).* Page 6 of our 11 March response. • *In the prospective longitudinal study the most frequent AE with TheraSphere was transient fatigue[6], reflecting the short-term nature of AE with TheraSphere*. Page 4 of our 11 March response.
Page 10 Footnote	*BTG also submitted additional data from a retrospective registry of SIRT patients in Newcastle (n=42). This reported on disease control measures and did not report*

	any information on safety. The population in the Newcastle dataset does not appear to be relevant to the economic analysis, which considers a population that are ineligible for TACE. As such, this is not considered in this report on safety. Given the paucity of data, the Newcastle data is helpful in that it indicates that [redacted][7].

References

1. Garin E, Rolland Y, Edeline J, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. *J Nucl Med* 2015; **56**(3): 339-46.
2. Garin E, Rolland Y, Pracht M, et al. High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with (90) Y-loaded glass microsphere radioembolization. *Liver Int* 2017; **37**(1): 101-10.
3. Garin E, Tselikas L, Guiu B. Major impact of personalized dosimetry on the targeted tumor response using 90Y loaded glass microspheres SIRT in HCC : preliminary results of a prospective multicentric randomized study. European Conference on Interventional Oncology; 2019; Amsterdam
4. Hawkins N, Ross P, Palmer D, Chatellier G, Pereira H, Vilgrain V. Overall survival of patients with hepatocellular carcinoma receiving sorafenib versus selective internal radiation therapy with predicted dosimetry in the SARAH trial (poster). European Society for Medical Oncology 2019; Barcelona
5. Salem R, Padia SA, Lam M, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. *Eur J Nucl Med Mol Imaging* 2019; **46**(8): 1695-704.
6. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010; **138**(1): 52-64.
7. Reicher J, Reeves HL, Manas DM, Priona, Jackson GR, Littler P. Preliminary experience of Selective Internal Radiation Therapy (SIRT) for Hepatocellular Carcinoma (HCC) at Newcastle Upon Tyne Hospitals NHS Foundation Trust. (unpublished data), 2020.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

June 2020

Issue 1 Duration of TRAE-related decrement and Assessment Group error in interpreting the original brief from Committee

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
It appears that the method of applying any TRAE-related decrement has been included in the following manner: • Setting of a check button on Worksheet "Controls" (row 43) • Use of event specific decrements on Worksheet "Adverse Events" (Cells I40:I65) • Use of a range of TRAE rates spread across multiple Worksheets ("Adverse Events" D40:H65 via "Adverse Events" D8:J33 which in turn comes from "Data tables" A137:K162) • Treatment specific weighted average calculations on each of the Engine sheets (cell B11 on each sheet) • The application of this weighted average value only in the first 2-week cycle (see column AR on each of the engine sheets) We are concerned that the decrements have only been applied for the first model cycle when it was clear from the conversation at the last Committee meeting	TRAE-related decrements should applied for the first 2 weeks for TheraSphere, but for the duration of treatment for sorafenib. This would take into account the transient nature of AE with TheraSphere versus the continual nature of AE with sorafenib. Importantly, the error in applying TRAE-related decrements means that the AG have not correctly interpreted the brief that they were given and as a result, the information being presented to the Committee on the impact of TRAEs on HRQoL will be misleading. Boston Scientific are most concerned about this issue.	Unfortunately, we were unable to amend the model we were sent in a meaningful way.

that one of the potential benefits of TheraSphere over sorafenib was that the HRQoL disutility would be transient (i.e. the effects should last longer than 2 weeks for those on sorafenib but not TheraSphere).		

Issue 2 Discrepancy between total lifetime QALYs in the model and the Assessment Group report

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model reports total lifetime QALYs for TheraSphere and Sorafenib of 0.679 and 0.841 respectively when the model is opened (Worksheet "Results" cells E12 and E15) The AG report has values of 0.764 and 0.841 for these two products in Table 5. • This discrepancy cannot be explained by any redaction as this should only have applied to costs and not benefits • It cannot be explained by the TRAE decrements as this is less than 0.01 for TheraSphere	Boston Scientific would like to note that while we see a way to amend the model to use the information listed in Table 4 of the AG report, given the discrepancy between the lifetime QALYs in the model and the report we would be unable to come to any position as to the relative impact of the changes.	Unfortunately, we were unable to amend the model we were sent in a meaningful way.

Issue 3 Missing all grade AE data used to inform scenarios 4-7

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The all grade AE event data used to inform scenarios 4 to 7 is missing. The master AE data table (Data tables A136:K162) only contains information on grade III/IV data.	Please confirm where the all grade AE event data can be found.	Unfortunately, we were unable to amend the model we were sent in a meaningful way.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Selective internal radiation therapies for treating hepatocellular carcinoma (ID1276)
Request to AG following 2nd committee meeting

Sirtex response to NICE

June 2020

File name	Version	Contains confidential information	Date
Sirtex response to NICE 2020 06 25	1.0	Redacted	25.06.2020

Sirtex response to the Assessment Group Report

Sirtex appreciates this opportunity to comment on the additional analyses. NICE requested additional analyses from the Assessment Group (AG) on 2nd March 2020, following the second committee meeting on the appraisal of selective internal radiation therapies (SIRTs) for treating hepatocellular carcinoma [ID1276]. These analyses are intended to address the issue that "*The committee considered that the potential difference in quality of life, in particular differences associated with side effects and adverse events), might not be captured in clinical trial results because quality-of-life data are collected at fixed time points*".

Sirtex welcomes the revision of the base case to reflect the appropriate SIRT and sorafenib costs. In the additional report shared by NICE, the AG revised the base case by including the duration of sorafenib based on individual patient data from the SARAH trial and excluding additional imaging costs for SIR-Spheres. The AG also presented various scenario analyses regarding the disutility consequences of the different adverse event (AE) profiles.

Despite these changes, the revised base case nevertheless represents a "worst-case" scenario for SIRT because it assumes:

a) no down-staging for SIRT contrary to the Committee recommendation (point 3.30 in the Appraisal Consultation Document) and to direct evidence from the SARAH trial (1,2) supported by observational studies(3–6) and expert opinion.

b) no patient selection despite evidence that it is possible to select a better responding subpopulation based on tumour morphology and liver function, with an increased rate of potentially curative therapies with SIRT, which could lead to improved effectiveness (2) (See Sirtex Submission Sections 6.2, 7.2.1.1 and 7.1.4.2)

c) bilobar disease treated in separate procedures as mandated by the protocol of the SARAH trial, contrary the real word experience of single administration of SIR-Spheres observed in the ENRY study for 96% of patients(7), and the single session used in 88% of bilobar cases in the European CIRSE Registry(6)

d) cost of administration of SIRT same as for TACE, while clinical experts stressed the increasing use of outpatient administration (see Sirtex Submission Section 7.2.4.1.1)

However, even using this “worst-case” scenario, in the AG revised base case SIR-Spheres results in lower costs (incremental costs: -£4,589) and very similar QALYs (incremental QALYs: -0.076), leading to sorafenib not being cost-effective (ICER of sorafenib vs. SIRT: £60,382). Assuming a large (40%) discount for the sorafenib patient access scheme, the differences between SIR-Spheres and sorafenib are minor for both QALYs and costs (incremental QALY: -0.076, incremental costs: £1,911).

When changing the revised base case according to above points, including the evidence-based AE scenarios and correcting for factual inaccuracies in the cost of subsequent regorafenib, the incremental QALYs for SIRT vary between -0.076 (AG base case) and 0.251 (selected patient population, including downstaging), while the incremental costs vary between -£,977 (bilobar tumours treated in one procedure) and -£1,762 (selected patient population with no downstaging). The incremental costs assuming a 40% discount for sorafenib are -£477 - £4,738 (Figure 1). Detailed results are available in the appendix.

Given these small differences between sorafenib and SIRT in the AG base case, the accepted differences in AE profiles, the evidence that treatment with SIR-Spheres is associated with a higher likelihood of subsequent treatment with curative intent, and the option of better patient selection offering better health outcomes, it would seem reasonable that individual patients (and their clinicians) should have the option to receive SIR-Spheres treatment based on their preferences regarding adverse events, quality of life and potential outcomes. The heterogeneity of individual preferences means, that certain AEs are unacceptable to some individuals, especially given the difficult patient journey of this population. For these patients, the availability of another treatment option with a very different mechanism of action, but similar health outcomes and costs at population level is invaluable.

Additionally, we encourage the Committee to take into account the lack of evidence on the comparative efficacy and safety of SIR-Spheres, TheraSphere and QuiremSpheres. All efficacy and safety data used in the economic model are obtained from the randomised controlled trials of SIR-Spheres. However, the hypotheses of equal efficacy and safety

between the SIRT technologies should be reassessed because of the differences between these products, including their dosage, administration mode and – for QuiremSpheres – their radioactive isotope. We encourage the Committee to consider that there is significantly less uncertainty associated with SIR-Spheres compared to all other SIRT devices, that lack comparative data for this patient population.

Figure 1. Results of the different scenarios

1 Factual inaccuracies in the calculation of subsequent regorafenib use after sorafenib

The AG model assumes the use of regorafenib after sorafenib to be 12.04% (sheet 'Cost Inputs', cell E95). The source reported in the model is the Sirtex model (sheet 'Cost Inputs', cells B95 and E95). However, the Sirtex model has used the mean percentage from the resource use survey after SIRT use: 18.95%. The correction of this error results in minor change, increasing in the AG model the cost of sorafenib.

Sirtex also welcomes the revision of treatment duration for sorafenib based on individual patient data from the SARAH trial in the AG model (sheet 'Comparator Costs', cell I16). However, the initial AG assumption for sorafenib is still used to inform the treatment duration for regorafenib (sheet 'Comparator Costs', cell I18), together with the assumption for the regorafenib mean daily dose (sheet 'Comparator Costs', cell G18), although the source for these parameters is described as being the regorafenib STA, i.e. NICE TA555 (sheet 'Comparator Costs', cell M18). Published mean treatment duration and mean daily dose data from the RESORCE trial(8), which was the source of clinical evidence used in TA555, could be used to replace these assumptions with validated data in a similar clinical setting. Substituting the assumptions with the data from the pivotal RESORCE trial(8), increases the duration of treatment from 123 days to 5.9 months reported in the publication (179.58 days). The mean dose meanwhile decreases from 160mg to 144.1mg.. Using these values together with the percentage change in the use of regorafenib increases the SIRT costs by £194 and the sorafenib costs by £2,853 compared to those in the revised AG base case.

While these changes are minor, these emphasise the cost-saving with SIR-Spheres using list prices and, using various assumed discount rates for sorafenib, result in even smaller cost differences between the treatments. Using the AG revised base case, beside the similar QALYs, the incremental cost was -£7,248 using list prices (SIR-Spheres resulting in cost-savings), and -£748 (SIR-Spheres still resulting in cost-savings) assuming a 40% discount for sorafenib.

2 The AG scenario analyses should use evidence-based disutilities

The accepted difference in the adverse event profile between sorafenib and SIRT are an important aspect of patients' choice. The most common AEs of sorafenib(9–11), fatigue, diarrhoea and skin disorders, have been reported to have the biggest impact on the health-related quality of life of patients receiving sorafenib (12). Furthermore the HRQoL analysis of the SARAH trial found that the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) global health status subscore was significantly better in the SIRT group (group effect p=0.0048) than for

sorafenib. It is therefore important to incorporate this effect in the cost-effectiveness analyses.

Sirtex welcomes the AG's exploration of this effect in multiple scenarios and has submitted disutility values for the relevant AEs sourced from the literature and previous NICE technology appraisals in oncology. The scenarios exploring the use of these are informative and helpful. However, the inclusion of scenarios that are not based on data, only an assumption of QALY loss (QALY loss of 0.012 for each AE) skews the realistic range of scenarios and should not be taken into account.

3 The revised AG base case presents a worst-case scenario

a) Downstaging

The ACD published on 05 December 2019 on the NICE website states that "… the base-case model should include downstaging" (Appraisal consultation document, paragraph 3.30, page 23). However, Table 7 in the AG report states that downstaging was not included "because robust data are not available".

However, downstaging was demonstrated in the SARAH phase III randomised trial which showed that patients in the SIRT group received subsequent treatments with curative intent more frequently than in the sorafenib group, in both the intention-to-treat population and more selected population. This benefit is confirmed for patients with HCC in the large CIRSE Registry for SIR-Spheres Therapy in Europe(6), a retrospective analysis (P4S study)(3) and two additional prospective studies(4,5) that unequivocally support the role of SIR-Spheres in downstaging patients to treatments with curative intent. It is also supported by expert opinion as presented in the Sirtex Submission (See section 7.2.1.3.3). The proportion of patients receiving subsequent curative therapies depends on the selection criteria of patients for SIR-Spheres(1,2).

The survival benefit of downstaging is not captured in the SARAH trial outcomes, as 13 out of 15 downstaged patient were alive and censored at the end of the follow-up period. Having the tumour downstaged to being able to undergo a potentially curative treatment in an otherwise unresectable population is an important benefit to patients. Its exclusion underestimates the benefits of SIR-Spheres.

b) Patient selection

We are concerned that the population of patients with a low tumour burden (≤25% of the liver volume) and an Albumin-Bilirubin (ALBI) grade 1 liver function(2) was dismissed not only as a the base case, but also as a scenario analysis for the revised results, given the evidence and the clinical expert opinion elicited in the open session of the Committee meeting on 6th November 2019.

The clinical plausibility of this subgroup is well established. Tumour burden is routinely assessed and the ≤25% criterion is already used by NHS England to determine the eligibility for SIRT of patients with colorectal liver metastases. The components of the ALBI grade are also routinely collected, and the score itself was developed in England and validated against UK cohorts of patients(13). It was reported to outperform the Child-Pugh score as a predictor of overall survival following SIRT(14,15) and is recommended in European clinical guidelines(16,17).

Although this is a post-hoc analysis, pre-determined analyses were not possible since the formula used to determine the ALBI grade was only published(13) immediately after the enrolment period of the SARAH trial (from 05/12/2011 to 19/02/2015).

c) Bilobar disease

The SARAH trial protocol mandated the sequential treatment of patients with bilobar HCC (disease affecting both lobes of the liver): using this approach, the contralateral liver lobe is treated during a separate hospital admission, 30-60 days after the first. However, SIR-Spheres is the only SIRT, that can be administered to both lobes of the liver during a single treatment session, with multiple infusions of the same source vial being performed selectively and in different arteries during the same procedure (see Sirtex Submission Section 2.2). This is specific to SIR-Spheres, therefore clinicians using TheraSphere would have to perform separate administrations.

Clinical practice for SIR-Spheres has evolved since the SARAH trial. Single administration of SIR-Spheres to patients with bi-lobar disease was observed in the ENRY study(7) (141/147 [95.9%] of whole-liver treatments were performed in a single session through one or more injections) and in the European CIRSE Registry for SIR-Spheres Therapy(6), in which [redacted] patients ([redacted]) with bi-lobar disease received a single treatment.

d) SIRT administration

While traditionally, SIRT work-up and procedure required on overnight stay in the hospital, clinicians in the UK have reported increasing use of a transradial vascular approach instead of the transfemoral approach. This allows for patients to receive outpatient care (see Sirtex Submission Section 2.1).

This shift towards outpatient care, together with the reduction of hospitalisations compared to sorafenib in the pre-progression period, not only saves costs, but also reduces the strain on NHS resources (especially in a peri-/post-COVID-19 setting).

4 Differences between the SIRT devices and lack of data for the equal efficacy assumption

Although SIR-Spheres and TheraSphere carry the same radioactive isotope yttrium-90, there are differences between the products in both dosage and administration methods which are likely to result in differences in their clinical efficacy and toxicity profiles (cf. Sirtex Submission, section 2.2, pages 23-25). QuiremSpheres use a different radioactive isotope than SIR-Spheres and TheraSphere, with different radioactive half-life and dosage. Higher amounts of injected radioactivity(18) and of tumour-absorbed dose are also recommended for the administration of TheraSphere compared to SIR-Spheres(19,20) due to the 50-fold difference between the products in the amount of radioactivity carried by each microsphere at their calibration time. This suggests different toxicity profiles, because of the correlation between higher radiation doses to the non-tumoural liver cells and the risk of complications of SIRT(20,21). Equal efficacy and safety can therefore not be assumed between these devices or with QuiremSpheres.

The AG initial assessment report stated that “equivalence is assumed between the SIRT technologies due to a lack of randomised evidence on the relative effectiveness of each SIRT”. However, we believe that the assumption of equivalence on the grounds of a lack of comparative evidence is unprecedented in previous NICE MTAs.

We therefore encourage the AG and Committee to reassess the equal efficacy assumption and, to consider that TheraSphere and QuiremSpheres are associated with additional uncertainty in terms of clinical outcomes and to reflect this uncertainty in the economic model and recommendations.

References

1. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux G-P, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017;18(12):1624–36.

2. Palmer DH, Hawkins NS, Vilgrain V, Pereira H, Chatellier G, Ross PJ. Tumor burden and liver function in HCC patient selection for selective internal radiation therapy: SARAH post-hoc study. Future Oncol Lond Engl. 2020 Jan;16(1):4315–25.

3. Pardo F, Sangro B, Lee R-C, Manas D, Jeyarajah R, Donckier V, et al. The Post-SIR-Spheres Surgery Study (P4S): Retrospective Analysis of Safety Following Hepatic Resection or Transplantation in Patients Previously Treated with Selective Internal Radiation Therapy with Yttrium-90 Resin Microspheres. Ann Surg Oncol. 2017 Sep;24(9):2465–73.

4. Iñarrairaegui M, Pardo F, Bilbao JI, Rotellar F, Benito A, D'Avola D, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2012 Jul;38(7):594–601.

5. Regnault H, Perrin C, Amaddeo G, Chalaye J, Tacher V, Luciani A, et al. P07-06 yttrium -90 trans arterial radioembolisation (tare) is an effective treatment for the downstaging of patients with hepatocellular carcinoma: a monocentric experience in a tertiary center. In Lisbon, Portugal: EASL; 2019.

6. CIRSE Registry for SIR-Spheres Therapy. CIRSE Registry for SIR-Spheres Therapy (CIRT): preliminary data on patients with HCC. 2019.

7. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatol Baltim Md. 2011 Sep 2;54(3):868–78.

8. Bruix J, Qin S, Merle P, Granito A, Huang Y-H, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Lond Engl. 2017 07;389(10064):56–66.

9. Marrero JA, Kudo M, Venook AP, Ye S-L, Bronowicki J-P, Chen X-P, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol. 2016;65(6):1140–7.

10. Ganten TM, Stauber RE, Schott E, Malfertheiner P, Buder R, Galle PR, et al. Sorafenib in Patients with Hepatocellular Carcinoma-Results of the Observational INSIGHT Study. Clin Cancer Res Off J Am Assoc Cancer Res. 2017 Oct 1;23(19):5720–8.

11. King J, Palmer DH, Johnson P, Ross P, Hubner RA, Sumpter K, et al. Sorafenib for the Treatment of Advanced Hepatocellular Cancer - a UK Audit. Clin Oncol R Coll Radiol G B. 2017;29(4):256–62.

12. Gill J, Baiceanu A, Clark PJ, Langford A, Latiff J, Yang P-M, et al. Insights into the hepatocellular carcinoma patient journey: results of the first global quality of life survey. Future Oncol Lond Engl. 2018 Jul;14(17):1701–10.

13. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol Off J Am Soc Clin Oncol. 2015 Feb 20;33(6):550–8.

14. Ali R, Yang Y, Antkowiak M, Gabr A, Mora R, Abouchaleh N, et al. Prognosticating Survival in Hepatocellular Carcinoma with Elevated Baseline Alpha-fetoprotein Treated with Radioembolization Using a Novel Laboratory Scoring System: Initial Development and Validation. Cardiovasc Intervent Radiol. 2019 May;42(5):700–11.

15. Antkowiak M, Gabr A, Das A, Ali R, Kulik L, Ganger D, et al. Prognostic Role of Albumin, Bilirubin, and ALBI Scores: Analysis of 1000 Patients with Hepatocellular Carcinoma Undergoing Radioembolization. Cancers. 2019 Jun 24;11(6).

16. Vogel A, Cervantes A, Chau I, Daniele B, Llovet J, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2018 01;29(Suppl 4):iv238–55.

17. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.

18. Kennedy A, Nag S, Salem R, Murthy R, McEwan AJ, Nutting C, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007 May 1;68(1):13–23.

19. Pasciak AS, Bourgeois AC, Bradley YC. A Microdosimetric Analysis of Absorbed Dose to Tumor as a Function of Number of Microspheres per Unit Volume in 90Y Radioembolization. J Nucl Med Off Publ Soc Nucl Med. 2016;57(7):1020–6.

20. Walrand S, Hesse M, Jamar F, Lhommel R. A hepatic dose-toxicity model opening the way toward individualized radioembolization planning. J Nucl Med Off Publ Soc Nucl Med. 2014 Aug;55(8):1317–22.

21. Sangro B, Martínez-Urbistondo D, Bester L, Bilbao JI, Coldwell DM, Flamen P, et al. Prevention and treatment of complications of selective internal radiation therapy: Expert guidance and systematic review. Hepatol Baltim Md. 2017;66(3):969–82.

Appendix: Results of the scenarios

Table 1. Incremental cost/QALY results using list price

Scenario	iCosts	iQALYs
AG Revised base case	-£4,589	-0.076
AG Disutility scenario 4 (all AEs)	-£4,589	0.044
AG Disutility scenario 5 (50% QoL for grade 1/2)	-£4,589	-0.006
AG Disutility scenario 5 (only grade 3/4)	-£4,589	-0.053
AG Disutility scenario 5 (50% QoL and length for grade 1/2)	-£4,589	-0.029
AG Revised base case with subsequent tx. revised	-£7,248	-0.076
AG Disutility scenario 4 (all AEs) with subsequent tx. revised	-£7,248	0.044
AG Disutility scenario 5 (50% QoL for grade 1/2) with subsequent tx. revised	-£7,248	-0.006
AG Disutility scenario 5 (only grade 3/4) with subsequent tx. revised	-£7,248	-0.053
AG Disutility scenario 5 (50% QoL and length for grade 1/2) with subsequent tx. revised	-£7,248	-0.029
AG Revised base case: Selected patient population	-£1,762	0.117
AG Revised base case: Including downstaging	-£5,255	-0.019
AG Revised base case: Selected patient population and including downstaging	-£4,147	0.251
AG Revised base case: Bilobar disease treated in one procedure	-£5,318	-0.076
AG Revised base case: Selected patient population with subsequent tx. revised	-£4,421	0.117
AG Revised base case: Including downstaging with subsequent tx. revised	-£7,914	-0.019
AG Revised base case: Selected patient population and including downstaging with subsequent tx. revised	-£6,806	0.251
AG Revised base case: Bilobar disease treated in one procedure with subsequent tx. revised	-£7,977	-0.076

AG: Assessment Group; AE: adverse event; QoL: quality of life; tx.: treatment; iCosts: incremental costs; iQALYs: incremental quality-adjusted life-years

Table 2. Incremental cost/QALY results assuming a 40% discount for sorafenib

Scenario	iCosts	iQALYs
AG Revised base case	£1,911	-0.076
AG Disutility scenario 4 (all AEs)	£1,911	0.044
AG Disutility scenario 5 (50% QoL for grade 1/2)	£1,911	-0.006
AG Disutility scenario 5 (only grade 3/4)	£1,911	-0.053
AG Disutility scenario 5 (50% QoL and length for grade 1/2)	£1,911	-0.029
AG Revised base case with subsequent tx. revised	-£748	-0.076
AG Disutility scenario 4 (all AEs) with subsequent tx. revised	-£748	0.044
AG Disutility scenario 5 (50% QoL for grade 1/2) with subsequent tx. revised	-£748	-0.006
AG Disutility scenario 5 (only grade 3/4) with subsequent tx. revised	-£748	-0.053
AG Disutility scenario 5 (50% QoL and length for grade 1/2) with subsequent tx. revised	-£748	-0.029
AG Revised base case: Selected patient population	£4,738	0.117
AG Revised base case: Including downstaging	£1,245	-0.019
AG Revised base case: Selected patient population and including downstaging	£2,353	0.251
AG Revised base case: Bilobar disease treated in one procedure	£1,182	-0.076
AG Revised base case: Selected patient population with subsequent tx. revised	£2,079	0.117
AG Revised base case: Including downstaging with subsequent tx. revised	-£1,414	-0.019
AG Revised base case: Selected patient population and including downstaging with subsequent tx. revised	-£306	0.251
AG Revised base case: Bilobar disease treated in one procedure with subsequent tx. revised	-£1,477	-0.076

AG: Assessment Group; AE: adverse event; QoL: quality of life; tx.: treatment; iCosts: incremental costs; iQALYs: incremental quality-adjusted life-years

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

June 2020

Issue 1 Input for the proportion of patients receiving regorafenib after sorafenib

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
On sheet 'Cost Inputs', in cell E95, the model assumes 12.04% of patients to receive regorafenib after sorafenib. The source reported in a comment is "Sirtex assumption". However the Sirtex model uses the mean value of regorafenib use after sorafenib from the survey conducted among UK clinicians (Sirtex submission Table 23, Sirtex model, 'Resource use' sheet, cell H26): 18.94%.	Sirtex recommends revising the proportion of patients receiving regorafenib after sorafenib from 12.04% to 18.94%.	This increases the sorafenib total costs by £1,490. As this change affects only the sorafenib arm, it decreases the incremental cost of SIR-Spheres also by £1,490.

Issue 2 Input for the length of treatment for regorafenib

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The length of treatment for regorafenib provided on sheet 'Comparator Costs', cell I18 linked from 'Data tables' sheet, cell B172 is 122.95 days. The source provided seems to be the Lenvatinib STA (TA555) on the first sheet and the SARAH trial on the second. However the length of treatment seems to be assumed to be the same as the initial assumption for the length of treatment with sorafenib, that was subsequently revised	Sirtex recommends revising of the length of treatment for subsequent regorafenib from 122.95 days to 5.9 months reported in the regorafenib publication (179.58 days).	This change affects both treatment arms: • SIRT arm: total costs increase by £291 • Sorafenib arm: total costs increase by £1,300 As a result, the incremental cost of SIR-Spheres decreases by £1,009.

by the Assessment Group at the request of the NICE Committee. Published mean duration of regorafenib after sorafenib is available from the RESORCE trial (Bruix et al. Lancet Lond Engl. 2017 07;389(10064):56–66) which was the source of clinical evidence used in TA555. This could be used to replace these assumptions with validated data in a similar clinical setting.		

Issue 3 Input for the dose of regorafenib

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The dose of regorafenib provided on sheet 'Comparator Costs', cell G18 is 160 mg. The source provided seems to be the Lenvatinib STA (TA555). This is the recommended dose of regorafenib. However, published mean dose of regorafenib (144.1 mg) is available from the RESORCE trial (Bruix et al. Lancet Lond Engl. 2017 07;389(10064):56–66) which was the source of clinical evidence used in TA555. The recommended dose should be replaced with validated data of the actual dose from a similar clinical setting.	Sirtex recommends revising the dose of subsequent regorafenib from 160 mg to 144.1 mg reported in the regorafenib publication.	Due to the wastage calculation, this amendment, on its own, does not change the results, as the number of packs used remains 6.

Selective Internal Radiation Therapies (SIRT) for treating unresectable hepatocellular carcinoma [ID1276]

Response to the AG response to points raised following the 2nd ACD

TERUMO EUROPE/QUIREM MEDICAL

GENERAL

We would like to thank the NICE Committee for requesting this additional report from the Assessment Group. The Committee's discussions in November – reflected in the ACD - highlighted the anticipated benefit in HRQoL between a systemic agent (such as sorafenib) vs a one-off treatment (such as SIRT). The ACD also noted that this benefit may not be appropriately reflected and captured by the QoL results of the relevant RCTs. This additional research confirms this (page 6) "*Generally, the data suggests that there may be a difference in HRQoL between SIRT and sorafenib, but it is likely that it is not very pronounced, and does not have much impact on the EQ-5D scale*."

COMMENT 1

We are concerned that we haven't had access to all results available and presented in the confidential annex. The *AG response to points raised following the 2nd ACD (AG report)* presents in Table 4 pg 11-12 a range of 7 scenari looking at QALY losses from treatment-related adverse events. However results presented in Table 5 are only for Scenario 1. We do not understand why results generated by the different scenari have to remain confidential, especially as they could have a significant impact on the final ICER.

COMMENT 2

The report confirms that there may be a difference in HRQoL between SIRT and sorafenib. The difference in HRQoL could "move" SIRT from its current south-west quadrant (*cheaper/less effective*) to the dominant quadrant (*cheaper/more effective*). Considering the uncertainty around this critical aspect, we believe that NICE should recommend SIRT as a treatment option in the limited patient group identified*. This would offer patients the choice of which treatment they wish to receive (between SIRT and sorafenib) and fully exercise shared decision-making. Indeed, patients may have a preference for a "one-off" loco-regional therapy such as SIRT to a systemic therapy. Considering the very unusual situation of the "south-west quadrant" (ie choosing SIRT wouldn't "break the bank"), and the tangible difference between a loco-regional treatment and a systemic agent for patients, it could be a very empowering decision.

People with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, for whom any conventional transarterial embolisation therapies (TAE, TACE, DEB-TACE) are inappropriate, with or without macroscopic vascular invasion, without extrahepatic disease. (appendix A page 14)

There is a large amount of published literature on shared decision-making (SDM), especially in the field of cancer. In 2019, LeBlanc stated that "SDM is the gold standard approach to cancer treatment decision-making in the 21st century" (https://pubmed.ncbi.nlm.nih.gov/31759817/)

In 2019, Laryionava et al wrote that "Eliciting and integrating patients' preferences in decision-making in palliative oncology is an important criterion for the quality of end-of-life care." (https://www.karger.com/Article/FullText/496120)

COMMENT 3

We are pleased that the AG report confirms that the efficacy of TheraSphere and QuiremSphere is equivalent to SIR-Spheres, and that the procedure costs of all three SIRTs are identical.

The results presented in Table 5 of the Assessment group report illustrate the cost effectiveness results with the above assumption, with an equivalent ICER for all SIRTs.

We are concerned that with the recent PAS proposed by one of the SIRT technologies, the procedure costs, and ICER, of the three SIRTs will differ. We appreciate that PAS proposals are confidential and therefore the appendix for the cost-effectiveness results and threshold analyses, inclusive of the PAS discounts, could not be shared. However it would be very concerning if one technology was favoured in the recommendation because of a last-minute PAS. Before a recommendation is made, would all manufacturers have the opportunity to engage with the Patient Access Liaison Unit so this difference in cost can be discussed? It is important for the Committee to note that price for medical devices is not fixed by NHS England but responds to the market competitive forces. All previous MTAs for medical devices have assumed equal effectiveness and also an "average" price across the technologies.

Assessment Group's report – SIRT for treating hepatocellular carcinoma (ID1276) (Request to AG following 2nd committee meeting) – response from the British Liver Trust on behalf of patients

Thank you for the opportunity to comment on the Assessment Group report. We appreciate the AG's effort to focus on quality of life and the side effects of treatments. The British Liver Trust has contacted patients through its online forum, Nurse-led Helpline and via direct telephone interview with supporters.

Side effects are a key concern for patients with advanced HCC who have often received previously unsuccessful treatments and have a limited life expectancy. They are prepared to "put up" with these side effects as there are usually no other options. However, some patients report that the side-effects of sorafenib can severely restrict their ability to perform daily tasks and have a pronounced impact on social activities. Examples of comments from patients who are taking or have taken sorafenib are below:

"Diarrhoea is the most constant side effect for me. I also feel sick and get some hand cramps. I take ginger chews for the sickness and Imodium for the diarrhoea but it means that I cannot leave the house at all."

"I was classed as terminal with no hope of transplant and I had 3 years on Sorafenib in the TACE 2 drug trial that was abruptly closed at a later point. I suffered badly from side effects and after 3 months my dose was halved. The side effects were still considerable on the half dose but luckily, I was able stand them, I know that there were people on the trial that couldn't. I was lucky in the fact that after the trial the tables were turned and I went on to have a transplant. I suppose that they have to try these treatments when there is little or no alternative and they don't know until tried if the patient will respond to the treatment or not."

"I have been on every treatment that there is – sorafenib was by far the worst for me – I felt nauseous and was sometimes violently sick and had diarrhoea. My elderly mother had to come first and look after me and after this my sister has had to take leave from her job and is now staying with me. I am so luck to have a supportive family but I feel a burden to them."

"My brother has been taking Sorafenib tablet for 2 weeks now but has had to stop because it's made him lose a considerable amount of weight, has become dehydrated and also has incontinence and diarrhoea. He has lost the ability to walk which really worries me."

Whilst we recognise that not every patient has these side effects, for those that do it has a significant effect. We would ask that the Committee consider the differences in side effects between SIRT and sorafenib as extremely relevant and disagree with the AG that these differences are likely "not very pronounced". The side effects make a difference whether patients can continue living a relatively normal life or not.

Patients treated with SIRT can receive their treatment, go home and maintain their activity and independence. They are less at risk of being stuck home in bed or readmitted to the hospital because of severe side effects. This is a major advantage for patients especially in the current context of COVID-19. By contrast [redacted] has experienced SIRT (as well as sorafenib and TACE) felt "a little bit tired" after SIRT but recovered swiftly.

"SIRT was a game changer. It undoubtedly extended my life. As a treatment type it has proven to be non-invasive, with limited and very tolerable side effects. I was fit enough to start running 2-3 weeks after hospital discharge. Six weeks later I ran nearly 150 miles along the Grand Union Canal from Birmingham to London. Sorafenib for me is an awful drug – it made me feel extremely unwell - I felt unbelievably sick and could not get out of bed."

It is possible that differences in quality of life are not captured using standard measures because most patients with HCC also have cirrhosis or other comorbidities: they therefore may not be rating their health as excellent, even when they are not affected by side effects. However, patients with HCC would not normally have diarrhoea, fatigue or hand-foot skin reaction therefore any reduction in the frequency and severity of these side effects is extremely relevant for them. This is particularly true considering the difficult prognosis that patients with HCC are facing.

In conclusion, we argue that patients with HCC should be offered the choice between SIRT and sorafenib depending on their individual preferences, the exact characteristics of their disease and in consultation with their medical specialists. SIRT is a minimally invasive procedure and usually performed as a one-off treatment and allows the patients to continue a somewhat normal life. SIRT should therefore be an option for patients - especially for those who are unable to tolerate sorafenib.

The British Society of Interventional Radiology

26th June 2020

Response on behalf of The British Society of Interventional Radiology

We thank the Committee and the Assessment Group for the opportunity to comment on the addendum to the AG report.

We appreciate the AG attempts to model the impact of adverse events on quality of life as this is a crucial consideration for patients with HCC. In our experience, SIRT is much better tolerated than sorafenib: this results in improved quality of life for patients and a reduced pressure on the NHS to manage and treat sorafenib toxicities.

SIRT had a statistically significant (p=0.0048) benefit over sorafenib in terms of quality of life using the EORTC QLQ-C30 questionnaire in the ITT analysis of the SARAH trial. We argue this benefit should be captured in the economic model. The Committee should consider scenarios where adverse event rates and duration are based on the SARAH trial because safety data from that trial is the most transferable to the UK population of patients with HCC.

We disagree with the AG model that downstaging is "not to be included because robust data are not available" (Table 7, page 15). Downstaging is a relevant benefit of SIRT over sorafenib. The SARAH trial has shown that more patients in the SIRT group received subsequent surgery or ablation than in the sorafenib group: this is evidence from a Phase III randomised trial in a European population with mostly advanced HCC. The evidence that SIRT can result in downstaging of advanced HCC is confirmed in other observational studies (Regnault H et al. Abstract P07-06 HCC Summit 2019; Iñarrairaegui MP et al. Eur J Surg Oncol. 2012;38(7):594-601), while this is extremely rare in clinical practice for patients receiving sorafenib.

In UK clinical practice, SIRT would not replace sorafenib but would be used as an alternative for some patients based on individual patient and clinician choices. HCC is a complex disease and it is important that clinicians are able to access the full 'toolbox' of liver directed therapies to allow us to deliver the most appropriate/personalized treatment to achieve the best outcomes for patients.

Dr Teik Choon See

Consultant Interventional Radiologist

Cambridge University Hospitals NHS Foundation Trust

Assessment Group's Report comments

SIRT for treating HCC ID1276

Quality of life differences

Pages 3 & 4, Figure 1:

- The EORTC QLQ-C30 values for the sorafenib arm improved at 9 months after randomisation, likely due to withdrawal of sorafenib. This is an important observation as continuation of sorafenib will most probably show a greater difference in QoL between SIRT and sorafenib.

Pages 3 & 4, Figure 2:

- It is possible that QoL differences in HCC treatments were not truly reflected due to variability of the mapping algorithm

Pages 5 & 6, Figure 3:

- It is technically very difficult to compare AEs of two different treatments with some different AEs, and certainly not possible to differentiate this fairly without a certain weighting.

Adverse event severity and duration

Page 7, Table 1

- It would appear from Table 1 that patients received sorafenib had more prolonged duration of AE at Grade 3 compared to the SIRT cohort

Page 9, Table 2

- Table 2 figures obscured

Page 10, real world evidence for adverse events

- The UK 'real world' evidence for adverse events post SIRT in colorectal liver cancer may be considered: *Analysis of a National Programme for Selective Internal Radiation Therapy for Colorectal Cancer Liver Metastases. J White et al. Clin Oncol (R Coll Radiol) . 2019 Jan;31(1):58-66.*

The Newcastle upon Tyne Hospitals NHS
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Professor Helen Reeves
26th June 2020

Helen Knight
Programme Director Centre for Health Technology Evaluation
National Institute for Health Care and Excellence

Dear Helen

Assessment Group's report – SIRT for treating hepatocellular carcinoma (ID1276) (Request to AG following 2nd committee meeting)

Thank you for sharing the report. I think that overall this is comprehensive and well explained.

I have one comment to make and would like to stress the importance of it.

The AG acknowledges that the UK population is not 'the same' as that of the Asia-Pacific patients, as there are different aetiologies typically. In reference to trial data, the AG goes on to state 'it does not seem unreasonable to assume that any differences in QoL due to the different safety profiles would be captured'.

Comment. Indeed, there is no reason to think that the incidence of side effects would be different based on an 'etiology of disease'. The consequences though, may be very different. This is because the patient profile that goes with the etiology is very different. Patients with HBV or HCV are likely to be 55-65 years of age and fit. These – or fit patients like them with another etiology -are the patients in the trials. They tolerate side effects well. Typical patients in much of the UK are very different. Patients with non-alcoholic fatty liver disease (NAFLD), which is now the commonest case in Northern England - are much older (70-85 years), with comorbidities. What is not captured in the available studies, are the really quite devastating consequences that side effects can have in these more typical patients. An elderly self caring patient with an excellent quality of life, who gets out and about daily – perhaps with a stick, taking their time because of arthritis, or breathlessness or a previous stroke – can have their independence and the quality of their life destroyed by side effects like diarrhoea, increasing tiredness or hand foot syndrome. A 'one off' treatment with minimal side effects is just so much better for some.

The assumption that the QoL due to different safety profiles can be translated from a study population so different the typical patients we see in our clinics, is flawed. An adjustment would be appropriate.

With Best wishes

Helen L Reeves
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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

June 2020

Issue 1

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
There is an assumption that the patients in the analysed trials adverse events, consequences and costs would be similar, regardless of etiology of disease, to patients in our clinics. As typical UK patients are older with more comorbidities than typical trial patients, the costings attributed to various adverse events may not be accurately translated to real practice	If possible, it would be helpful to run a model with a more 'matched ' patient group. Eg. 75-85 year old patients with ALD/NAFLD, who typically have type 2 diabetes and other complications of the metabolic syndrome.	I don't know if this can be done with the data you have. But I would expect – based on clinical experience – that the cost saving using SIRT - in carefully selected patients, would be much greater than calculated – compared to those patients who gain little tumour benefit from sorafenib (non-HCV, large tumours, PVT) but in whom the side effects can have a much greater and more costly impact

Issue 2

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Give full details of the problem detected, if necessary, with explanation of why the issue is considered to be a problem.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 3

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Give full details of the problem detected, if necessary, with explanation of why the	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate,

issue is considered to be a problem.		describe your expectations of how the problem might have an impact on the result

(please cut and paste further tables as necessary)

CONFIDENTIAL UNTIL PUBLISHED

Selective internal radiation therapies (SIRTs) for treating hepatocellular carcinoma [ID1276]

Assessment Group's Addendum following 2nd committee meeting

Including addendum update in response to consultation

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

Addendum in response to request to AG following 2nd committee meeting

Background

On 22 January, the Committee considered consultation responses for the multiple technology appraisals of SIRTs for treating hepatocellular carcinoma. The Committee understood from stakeholder comments that SIRTs might have fewer and less severe side effects than transarterial chemoembolisation (TACE) or sorafenib. Also, side effects persist only for a short period after a single SIRT treatment. The clinical expert and the patient expert explained that this might improve health related quality of life. However, the Committee noted the utility values, derived from EQ-5D, in the model were similar between SIRTs and systemic therapies (sorafenib or lenvatinib) for the following disease states: progression-free survival, progressive disease and post-transplant. There were only small differences in utilities between progression-free survival and progressive disease. There was no difference between the treatment options in quality of life.

Issue

The Committee considered that the potential difference in quality of life, in particular differences associated with side effects and adverse events, might not be captured in clinical trial results because quality-of-life data are collected at fixed time points.

Objectives

- Addendum to AG report including updated base case analysis and scenario analyses without PASs. The updated base case should be based on the Committee-preferred assumptions (see Appendix A) and include:
    - Sorafenib duration from individual patient data
    - Similar work-up costs for the SIRTs
    - Contrast imaging for all SIRTs.
- Addendum confidential appendix including new base case analysis and scenario analyses with PASs.

Assessment Group response

Is it plausible that the model does not capture quality-of-life differences (QALY decrements) associated with side effects (adverse events) in full?

Quality of life in the AG's economic model was based on an analysis of health-related quality of life (HRQoL) data collected in the SARAH trial. In principle, the AG considers that the trial is likely to capture any disutility impact of AEs that are related to sorafenib, which is taken at daily intervals. The impact of any adverse events that occur would not be missed because of the trial design and schedule of questionnaires, although there will be a small proportion of patients who experience disease progression before 3 months whose HRQoL after baseline will not be captured. The trial may be less likely to capture the impact of AEs related to SIRT, as the first questionnaire is completed by the trial participant at 3 months, after which the majority of TRAEs are likely to have been resolved. Comparative HRQoL between sorafenib and SIRT in the SARAH trial is unclear because of the long interval between initiating of treatment and collection of data. A potential reason for the trial to not fully capture the impact of AEs may be that the patient with the AE would not complete the questionnaire, and would wait until the AE was resolved to complete it. However, this would impact both treatment arms, and is a common issue in all trial-based estimates of quality of life.

The mean health state utility values showed little difference between treatment arms. However, clinical experts consider that the toxicity profiles of the two treatments are sufficiently different that the difference in quality of life should be greater, and that improvement in HRQoL would result from the better safety profile of SIR-Spheres compared to sorafenib.

To explore this issue further, the AG considered how HRQoL varied over time in each of the treatment arms in the SARAH trial. As presented in Figure 1, the EORTC QLQ-C30 values for the SIRT arm appear relatively constant over the 12 months since randomisation, while patients in the sorafenib arm experienced a worsening in HRQoL over the first six months of treatment, with an improvement in mean QoL at approximately 9 months after randomisation (likely due to discontinuation of sorafenib due to disease progression). The observed trends in the SARAH EORTC data appear to support the assumption that sorafenib is associated with a poorer quality of life than SIRT, and that this is not captured in the mean health state values. A comparison of the EORTC time chart of utilities and the mapped EQ-5D values (Figure 2) suggests that this may be due to the insensitivity of the mapping algorithm used to translate EORTC values to EQ-5D values. This may be because the elements of the EORTC scale most affected by treatment with sorafenib were less important predictors of HRQoL as defined by EQ-5D. As the population used to map the questionnaires comprised only multiple myeloma, breast cancer, and lung cancer patients, it may have been that QoL differences in HCC were not accurately translated across scores. In the mapped EQ-

5D, the difference between arms is reduced, and sorafenib is actually associated with a higher mean EQ-5D value than SIRT at month 12.

Figure 1 EORTC-QLQ-C30 results from the SARAH trial (Fig 14, Sirtex submission)

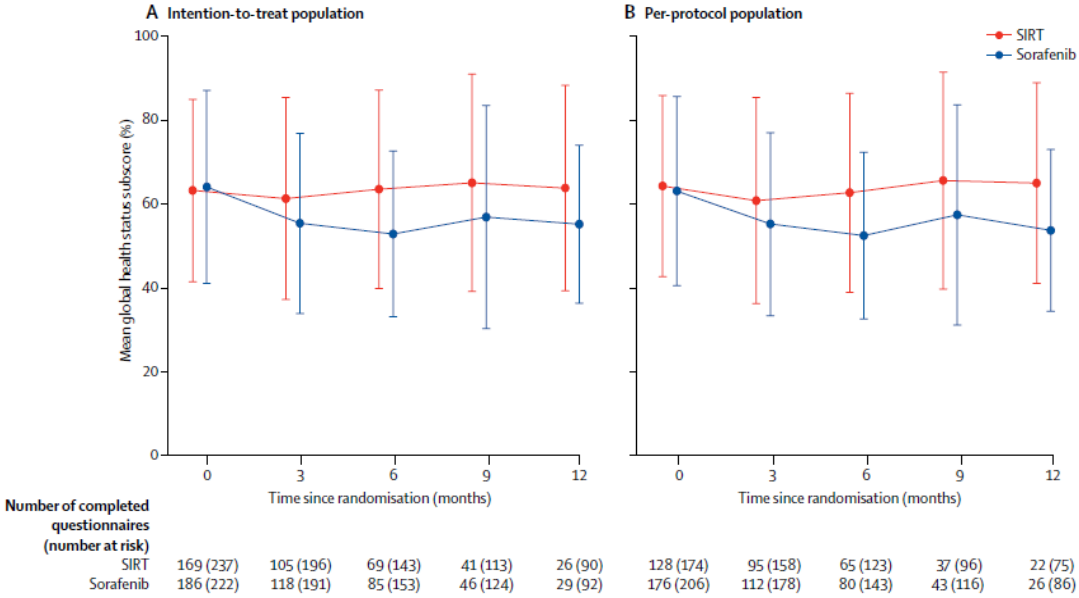
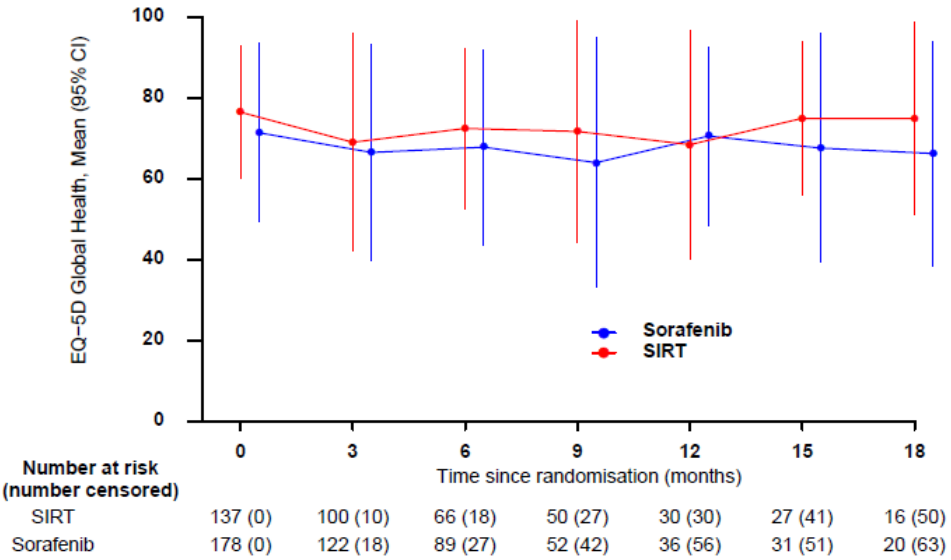


Figure 2. UK EQ-5D values by time (per protocol population) (Fig 36, Appendix G, Sirtex submission)



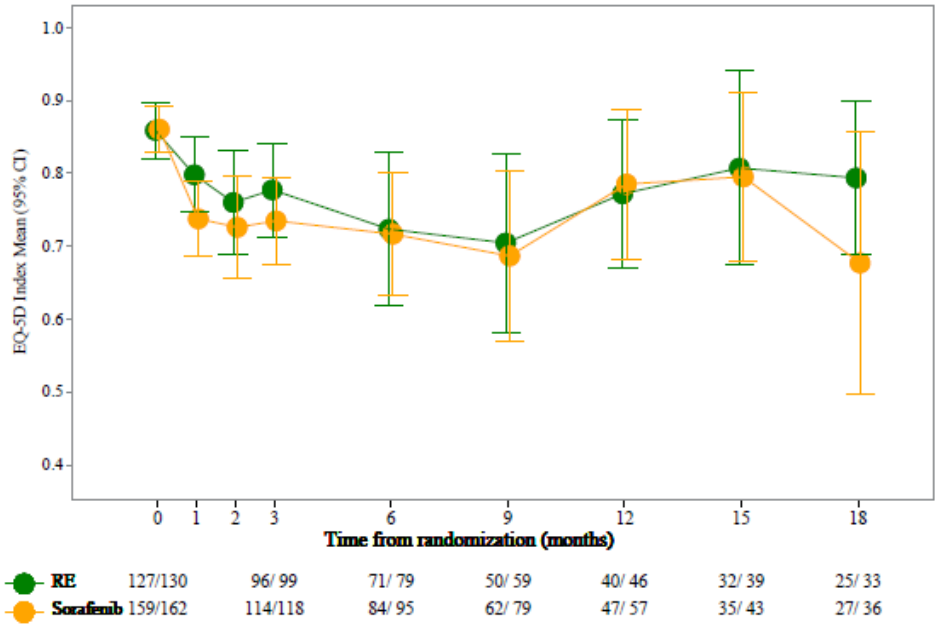
Sirtex, the funder of the SARAH trial, provided some explanation in their response to the Committee's request for data following the second Committee meeting. The company made reference to a published comparison of directly measured and imputed EQ-5D utilities (Crott et al),[1] which found that the external validity of a mapping algorithm when tested on a set of unrelated external data sets in other cancers proved to underestimate both the mean and variance of the mapped EQ-5D utilities. The mapping algorithm used to map SARAH EORTC data to EQ-5D was based on a dataset of 771 cancer patients, and Crott noted that the relationship between QLQ-C30 scores and EQ-5D values is not stable across the different data sets.

The company also considered that any variation in EQ-5D utility between treatments, that would have been observed had the EQ-5D questionnaire been employed, may be underestimated if mapping from another instrument (i.e. the EORTC) is used. This is because it is unlikely that the domains and measurement intervals in the EORTC instrument will completely cover the domains and measurement intervals included in the EQ-5D instrument, and so the mapping is unlikely to detect all variation in the EQ-5D instrument.

The AG considered the QoL reported in the SIRveNIB trial,[2] which collected EQ-5D data instead of EORTC, and so no mapping was required for this dataset. In this trial, there was an immediate decrease in QoL that was observed in both arms, although slightly greater in the sorafenib arm. However, after 6 months the EQ-5D values in both arms were very consistent with each other until at least 15 months after randomisation. While the population is not the same as the UK population due to different aetiology typically underlying HCC in Asia-Pacific patients, it does not seem unreasonable to assume that any differences in QoL due to the different safety profiles between the two arms would be captured in this dataset.

The Committee also asked the company whether the EQ-5D instrument would capture all HRQoL effects relevant to the current decision problem. The company highlighted a number of previous studies that have shown that the EQ-5D instrument may miss significant clinical changes in cancer patients, of which fatigue may be the most important aspect. Fatigue is one of the most commonly reported side effects of sorafenib, and it would follow that the EQ-5D would be less sensitive in capturing the disutility associated with this aspect of sorafenib treatment.

Figure 3 EQ-5D in SIRveNIB



In summary, analysis of the EORTC QLQ-C30 data from the SARAH trial suggests some difference in HRQoL between SIRT and sorafenib. However, this difference does not appear to translate to a difference between arms when translated to EQ-5D estimates of HRQoL. This may potentially be due to the insensitivity of the mapping algorithm. However, analysis of directly elicited EQ-5D data from the SIRveNIB trial also does not reveal a difference between SIRT and sorafenib. This may be because EQ-5D is insensitive to the type of AEs that typically differ between the two treatment arms. Generally, the data suggests that there may be a difference in HRQoL between SIRT and sorafenib, but it is likely that it is not very pronounced, and does not have much impact on the EQ-5D scale.

Can data from the clinical trials be used in the model to provide information on adverse event severity and duration?

The AG's economic analysis used data from the SARAH trial to model the cost impact of TRAEs for each treatment arm. Selected events were of Grade 3 and above, and either had an incidence of at least 5% or were considered significant.

Data on duration of AEs is not currently available in the public domain. In their response, Sirtex Medical provided the mean duration (days) for each event that occurred (see Table 1). Sirtex estimated a single duration for each type of AE, across study arms and across severity grades, in order to increase the sample size available per type of event. Assuming that Grade 3-4 events are both more severe and longer in duration, this will underestimate the duration of Grade 3-4 events and overestimate the duration of Grade 1-2 events. Since data is pooled across arms, it is not possible to comment on the clinical advisor's statement that "side effects persist only for a short period after a single SIRT treatment"; however, should this be the case, the pooling of data will also result in underestimated duration of AEs related to sorafenib and overestimated duration of AEs related to SIRT.

Table 1 Number of patients (%) experiencing treatment-related adverse events in the safety population (provided by Sirtex Medical)

Events	**SIR-Spheres (n= 226)**				**Sorafenib (n= 216)**				**Mean duration (days) for patients who had an event (SD)**
Grade	**1/2**	**3**	**4**	**5**	**1/2**	**3**	**4**	**5**	
Infection	6 (3)	2 (1)	0 (0)	1 (0)	16 (7)	8 (4)	0 (0)	2 (1)	[redacted]
Fever	13 (6)	0 (0)	0 (0)	0 (0)	17 (8)	3 (1)	0 (0)	0 (0)	[redacted]
Fatigue	81 (36)	20 (9)	0 (0)	0 (0)	123 (57)	41 (19)	0 (0)	0 (0)	[redacted]
Weight loss	14 (6)	0 (0)	0 (0)	0 (0)	40 (19)	6 (3)	0 (0)	0 (0)	[redacted]
Alopecia	0 (0)	0 (0)	0 (0)	0 (0)	35 (16)	0 (0)	0 (0)	0 (0)	[redacted]
Hand-foot skin reaction	0 (0)	1 (0)	0 (0)	0 (0)	37 (17)	12 (6)	0 (0)	0 (0)	[redacted]
Rash or desquamation	2 (1)	1 (0)	0 (0)	0 (0)	20 (9)	0 (0)	0 (0)	0 (0)	[redacted]
Pruritus	7 (3)	1 (0)	0 (0)	0 (0)	18 (8)	1 (0)	0 (0)	0 (0)	[redacted]
Dry skin	2 (1)	0 (0)	0 (0)	0 (0)	40 (19)	3 (1)	0 (0)	0 (0)	[redacted]
Other dermatological events	4 (2)	0 (0)	0 (0)	0 (0)	48 (22)	6 (3)	0 (0)	0 (0)	[redacted]
Anorexia	24 (11)	7 (3)	0 (0)	0 (0)	66 (31)	10 (5)	0 (0)	0 (0)	[redacted]
Diarrhoea	26 (12)	3 (1)	0 (0)	0 (0)	137 (63)	30 (14)	0 (0)	0 (0)	[redacted]
Nausea/Vomiting	25 (11)	1 (0)	0 (0)	0 (0)	47 (22)	5 (2)	0 (0)	0 (0)	[redacted]

Events	**SIR-Spheres (n= 226)**				**Sorafenib (n= 216)**				**Mean duration (days) for patients who had an event (SD)**
Grade	**1/2**	**3**	**4**	**5**	**1/2**	**3**	**4**	**5**	
Abdominal pain	43 (19)	6 (3)	0 (0)	0 (0)	57 (26)	13 (6)	0 (0)	1 (0)	[redacted]
GI ulceration	2 (1)	3 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	[redacted]
GI bleeding	1 (0)	5 (2)	0 (0)	4 (2)	6 (3)	7 (3)	0 (0)	1 (0)	[redacted]
Ascites	19 (8)	9 (4)	1 (0)	1 (0)	15 (7)	9 (4)	0 (0)	1 (0)	[redacted]
Liver dysfunction	28 (12)	16 (7)	2 (1)	7 (3)	30 (14)	27 (13)	0 (0)	0 (0)	[redacted]
Radiation hepatitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	[redacted]
Radiation pneumonitis	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	[redacted]
Hypertension	6 (3)	0 (0)	0 (0)	0 (0)	28 (13)	5 (2)	0 (0)	0 (0)	[redacted]
Cardiac failure congestive	25 (11)	2 (1)	0 (0)	1 (0)	24 (11)	11 (5)	0 (0)	0 (0)	[redacted]
Haemorrhage (non GI)	5 (2)	0 (0)	1 (0)	0 (0)	19 (9)	2 (1)	0 (0)	0 (0)	[redacted]
Pulmonary embolism	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	[redacted]
Hyperbilirubinemia	25 (11)	7 (3)	1 (0)	0 (0)	21 (10)	9 (4)	0 (0)	0 (0)	[redacted]
Other increased Liver values	53 (23)	19 (8)	1 (0)	0 (0)	46 (21)	16 (7)	0 (0)	0 (0)	[redacted]
Hematologic Biological abnormalities	41 (18)	22 (10)	1 (0)	0 (0)	53 (25)	28 (13)	1 (0)	1 (0)	[redacted]
Renal Dysfunction (Increased Creatinine)	23 (10)	2 (1)	0 (0)	2 (1)	32 (15)	8 (4)	1 (0)	3 (1)	[redacted]
Hyponatraemia	11 (5)	2 (1)	0 (0)	0 (0)	21 (10)	4 (2)	0 (0)	0 (0)	[redacted]

Evidence for TheraSphere

BTG, the manufacturer of TheraSphere, submitted additional evidence on safety from two RCTs that enrolled TheraSphere patients.[3,4] Neither RCT compared TheraSphere with sorafenib.

The Dosiphere trial compared patients receiving TheraSphere under standard dosimetry ([redacted]) with patients receiving personalised dosimetry ([redacted]).[3] BTG provided data for treatment-emergent AEs, defined as AEs that occurred on or after the first administration of TheraSphere or that were present prior to dosing but were exacerbated on or after the first TheraSphere administration indicating that most AEs are mild to moderate in severity. Events by severity were reported for all patients ([redacted]), presented in Table 2.

Table 2: Severity of the most frequently reported treatment-emergent AEs with TheraSphere in the Dosisphere study

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
[redacted]					

BTG also presented the safety results from an RCT published in 2011 comparing TheraSphere (n=123) with TACE (n=122), see Table 3.[4] It should be noted that this study enrolled a number of patients classed as Child-Pugh B and C, who are not eligible for sorafenib and so would not be included in the present analysis.

Table 3 Adverse events for TheraSphere and TACE, from Salem (2011)[3]

	TACE (n=122)	TheraSphere (n=123)	p
Fatigue	47 (38%)	68 (55%)	0.074
Abdominal pain	46 (38%)	18 (15%)	<0.001
Nausea/vomiting	25 (20%)	18 (15%)	NS
Anorexia	16 (13%)	13 (11%)	NS
Fever/chills	2 (2%)	10 (8%)	NS
Diarrhoea	10 (8%)	2 (2%)	NS

As the data from Dosisphere and Salem (2011) related only to TheraSphere, BTG compared the rates of AEs from these studies with those reported for sorafenib in the SARAH trial. BTG noted a number of key differences between TheraSphere and sorafenib. Firstly, there were no patients that received TheraSphere who had a hand-foot skin reaction (palmar-plantar erythrodysesthesia), which occurred as a Grade 3+ event in 6% of sorafenib patients in SARAH. Rates of abdominal pain, fatigue and diarrhoea were also higher for sorafenib in the SARAH trial than the rates for corresponding events for TheraSphere in the Dosisphere trial and Salem (2011), which is a consistent finding with SIR-Spheres compared with sorafenib in the SARAH trial (see Table 1). BTG note that fatigue with TheraSphere is transient; however, no evidence was provided to support this statement.

There are a number of drawbacks associated with the use of these two studies to establish a robust set of adverse event rates for TheraSphere. As noted above, neither compare TheraSphere to sorafenib or to SIR-Spheres. Dosisphere enrolled a smaller number of patients, so it would be more difficult to detect the less common AEs. Salem (2011) enrolled a number of patients classed as Child-Pugh B and

C, who are not eligible for sorafenib and so would not be included in the present analysis. The authors presented rates of AEs by Child-Pugh class, and found that those who were Child-Pugh A often had markedly different event rates to those who were Child-Pugh B/C. There were differences between some of the rates of events for SIR-Spheres from SARAH and for TheraSphere, e.g. the rate of Grade 3+ fatigue. BTG note that the rates for TheraSphere ranged from [redacted] (in the Dosisphere trial) to 57% (in Salem (2011)), all of which were grade 1 or 2 in severity. The rate of fatigue for SIR-Spheres in SARAH was 45% (of which 9% were of Grade 3 severity).

Is there published real world evidence for adverse events (rate, severity, duration) that can be used?

The companies were invited to submit additional real world evidence on the safety of the SIRTs. BTG, the manufacturer of TheraSphere submitted the following pieces of evidence on safety*:

- Adverse event (AE) data from a prospective longitudinal study from a single centre using TheraSphere (n=291).[5] In the prospective longitudinal study, the most frequent AE with TheraSphere was fatigue.
- Clinical opinion from clinicians using TheraSphere, stating that most patients receiving TheraSphere have mild to moderate AE, commonly fatigue, abdominal pain and nausea/vomiting, which are short in duration (lasting 2-3 days).

BTG also noted that a new non-comparative real world dataset using TheraSphere in patients with PVT will be available from a registry in France within 2 to 3 years. The study (PROACTIF) is now underway and will follow patients for 6 years (https://clinicaltrials.gov/ct2/show/NCT04069468).

Sirtex Medical did not present any additional real world evidence for the safety of SIR-Spheres.

* BTG also submitted additional data from a retrospective registry of SIRT patients in Newcastle (n=42). This reported on disease control measures and did not report any information on safety. The population in the Newcastle dataset does not appear to be relevant to the economic analysis, which considers a population that are ineligible for TACE. As such, this is not considered in this report on safety.

Is it plausible to do scenario analyses with varying disutility values?

Threshold analysis

This section presents a range of QALY losses associated with AEs, estimated under different scenarios (Table 4). Where event rates were estimated from SARAH, it was assumed that the event rates for TheraSphere were equivalent to those for SIR-Spheres.

Scenario 1 reflects the assumption in the AG's base case model, where the disutility impact was assumed to be captured in health state utility values. This assumption was also in line with the original economic analysis presented by Sirtex. Scenario 2 reflects a scenario presented in the AG's original analysis, where a QALY loss of 0.012 was applied to each event of Grade 3+ that occurred in the model, based on rates from the SARAH trial. The analysis presented by BTG (Scenario 3) also assumed a QALY loss of 0.012 for each event, citing "previous oncology submissions" (but no specific source of evidence), with AE rates for SIRTs from a systematic review of safety of SIRTs,[6] and AE rates for sorafenib from the REFLECT trial that compared lenvatinib to sorafenib.[7]

In their response, Sirtex Medical sourced event-specific disutility estimates through a review of recent NICE technology appraisals in oncology and a targeted literature search run in PubMed for literature reviews of cancer related utility values. These are presented in Appendix B. Most disutility values were elicited for grade 3/4 AEs, and so Sirtex explored two scenarios to model the impact of Grade 1/2 events. In one, the disutility for grade 1/2 AEs was decreased by 50% (Scenario 5), and in the other it was assumed that these events would have the same disutility as the Grade 3/4 events (Scenario 4). The AG also conducted an additional scenario using Sirtex's disutility values on events of Grade 3+ only (Scenario 6). One final scenario conducted by the AG assumed that the disutility *and* the duration of grade 1/2 AEs was decreased by 50% (Scenario 7).

Table 4 QALY loss estimates for adverse events

Scenario		TRAE QALY loss
1	Assuming disutility impact captured in health state utility values	0.00
2	0.012 QALY loss for each event (Grade 3+, event rates from SARAH)	Sorafenib: 0.012 SIRT: 0.006 Incremental: 0.006
3	0.012 QALY loss for each event (Grade 3+, event rates from Kallini *et al.* and REFLECT)[6,7]	Sorafenib: 0.007 SIRT: 0.002 Incremental: 0.005
4	Event-specific QALY loss, event rates from SARAH (all grades of AE, QALY loss rate applied to all events)	Sorafenib: 0.2467 SIRT: 0.1294 Incremental: 0.12

5	Event-specific QALY loss, event rates from SARAH (assuming 50% reduction in QoL for grade 1/2 disutilities)	Sorafenib: 0.1508 SIRT: 0.0810 Incremental: 0.070
6	Event-specific QALY loss, event rates from SARAH (no QoL impact of Grade 1-2 AEs)	Sorafenib: 0.0558 SIRT: 0.0324 Incremental: 0.0233
7	Event-specific QALY loss, event rates from SARAH (assuming 50% reduction in QoL and in duration for grade 1/2 disutilities)	Sorafenib: 0.1037 SIRT: 0.0567 Incremental: 0.0470

Base case results of the economic analysis

The results of the economic analysis under the Committee-preferred assumptions (see Appendix A) are presented in Table 5. These analyses are exclusive of the confidential PAS discounts that are associated with sorafenib, QuiremSpheres and TheraSphere. **Cost-effective results and threshold analyses based on the QALY losses in Table 4, with the confidential PAS discounts applied, are presented in a confidential appendix.**

In the base case scenario in Table 5, SIR-Spheres, TheraSphere and QuiremSpheres are associated with lower costs and fewer QALYs than sorafenib.

Under the current set of assumptions, the efficacy of TheraSphere and QuiremSpheres is assumed to be equivalent to SIR-Spheres, and all three SIRTs have identical procedure-related administration costs. When the PASs are not included, SIR-Spheres, QuiremSpheres and TheraSphere are in the southwest quadrant of the cost-effectiveness plane, producing fewer QALYs compared with sorafenib, but at lower cost.

Table 5 Base case results of the economic analysis, under Committee-preferred assumptions (no PAS applied)

	Costs	**QALYs**	**Inc. cost**	**Inc. QALYs**	**ICER**
SIR-Spheres	£31,070	0.764	-£4,589	-0.076	£60,089 (SWQ)
TheraSphere	£31,070	0.764	-£4,589	-0.076	£60,089 (SWQ)
QuiremSpheres	£33,050	0.764	-£2,609	-0.076	£34,159 (SWQ)
Sorafenib	£35,659	0.841	-	-	-

Note: incremental results for each SIRT are versus sorafenib.

Addendum update (July 2020)

Following consultation on the AG addendum addressing the committee's concerns regarding the modelling of the quality of life impact due to adverse events, NICE received feedback from stakeholders. This addendum update presents the AG response to the consultation feedback and the results of additional scenario analyses requested by the NICE technical team. The addendum includes the following sections:

- Additional scenario analyses with downstaging assumptions;
- Probabilistic results of the economic analysis;
- The cost of regorafenib use after sorafenib;
- Potential errors in the AG calculation of adverse event related disutilities.

Results of the economic analysis with downstaging assumptions

Sirtex, in their response, argued that the Committee-preferred scenario, whereby patients are not assumed to downstage to curative therapy is overly conservative and represents a "worst-case" scenario. Further, they highlight that downstaging was demonstrated in the SARAH trial which showed that patients in the SIRT group were successfully downstaged to curative treatment more frequently than patients in the sorafenib group. Sirtex highlighted that the ACD following the first Committee meeting in December 2019 concluded that the base-case model should consider downstaging. However, following further discussion at the second Committee meeting in January 2020, the Committee considered that downstaging should not be included in the base-case analysis due to a lack of robust evidence.

In light of these comments and at NICE's request, the AG therefore provides results for a scenario where downstaging to curative therapies is permitted. The AG considers these results to represent a "best case" scenario, clinical advice received by the AG suggests that it is unlikely that a substantive proportion of patients would receive curative treatment in practice. Further, the AG notes the significant uncertainty associated with data from the SARAH trial and note that the trial was not powered to reflect differences in the proportion of patients being downstaged to curative treatments.

The results of the economic analysis under the Committee-preferred assumptions, with downstaging to curative therapies permitted, are presented in Table 6. These analyses are exclusive of all confidential PAS discounts. **Cost-effective results and threshold analyses based on the QALY losses in Table 4, with the confidential PAS discounts applied, are presented in a confidential appendix.**

In the scenario in Table 6, SIR-Spheres, TheraSphere and QuiremSpheres are associated with lower costs and fewer QALYs than sorafenib, although the incremental QALY difference between each SIRT and sorafenib is smaller than in the scenario without downstaging (Table 5).

Under the current set of assumptions, the efficacy of TheraSphere and QuiremSpheres is assumed to be equivalent to SIR-Spheres, and all three SIRTs have identical procedure-related administration costs. SIR-Spheres, QuiremSpheres and TheraSphere are in the southwest quadrant of the cost-effectiveness plane, producing fewer QALYs compared with sorafenib, but at lower cost.

Table 6 Results of the economic analysis, under Committee-preferred assumptions – scenario with downstaging to curative therapies permitted (no PAS applied)

	Costs	**QALYs**	**Inc. cost**	**Inc. QALYs**	**ICER**
SIR-Spheres	£30,126	0.842	-£5,300	-0.020	£263,651 (SWQ)
TheraSphere	£30,126	0.842	-£5,300	-0.020	£263,651 (SWQ)
QuiremSpheres	£32,106	0.842	-£3,320	-0.020	£165,159 (SWQ)
Sorafenib	£35,426	0.862	-	-	-

Note: incremental results for each SIRT are versus sorafenib

Probabilistic results of the economic analyses

To represent the uncertainty in the cost-effectiveness estimated generated by the economic model, the AG has conducted a probabilistic sensitivity analysis for the base-case scenario under Committee-preferred assumptions (i.e. without downstaging), and for the scenario with downstaging to curative therapy permitted. Probabilistic results have the benefit of allowing the Committee to consider the parameterised uncertainty associated with a decision.

Results are presented in Table 7 and Table 8 for the two scenarios, respectively. The probability of being cost-effective is based on the number of iterations resulting in either an ICER less than £30,000 or the treatment being dominant. **Cost-effective results and threshold analyses based on the QALY losses in Table 4, with the confidential PAS discounts applied, are presented in a confidential appendix.**

In the base case scenario without downstaging, the majority of cost-effectiveness estimates for each SIRT compared to sorafenib were in the south-west quadrant of the cost-effectiveness plane (i.e. they produced lower costs but fewer QALYs than sorafenib). For SIR-Spheres and Therasphere, the proportion of estimates was 77% and 78% respectively. For QuiremSpheres, 64% of estimates were in the south-west quadrant of the cost-effectiveness plane and 16% were dominated by sorafenib. When downstaging was permitted, the majority of cost-effectiveness estimates for each SIRT compared to sorafenib were in the south-west quadrant of the cost-effectiveness plane (58%, 58% and 53% for SIR-Spheres, TheraSphere and QuiremSpheres, respectively).

Table 7 Probabilistic results of the base-case scenario under Committee-preferred assumptions, without downstaging (without PAS)

	Mean total costs	Mean total QALYs	Inc. cost	Inc. QALYs	Mean ICER	P(cost-effective)
SIR-Spheres	£30,885 (£22.42)	0.765 (0.001)	-£4,074	-0.075	£54,068	72%
TheraSphere	£30,884 (£22.43)	0.765 (0.001)	-£4,074	-0.075	£54,075	72%
QuiremSpheres	£32,872 (£24.91)	0.765 (0.001)	-£2,086	-0.075	£27,683	49%
Sorafenib	£34,958 (£21.33)	0.840 (0.001)	-	-	-	-

Note: mean and standard error; incremental results for each SIRT are versus sorafenib; SWQ south west quadrant

Table 8 Probabilistic results of the base-case scenario under Committee-preferred assumptions, with downstaging (without PAS)

	Total costs	Total QALYs	Inc. cost	Inc. QALYs	ICER	P(cost-effective)
SIR-Spheres	£29,912 (£22.15)	0.842 (0.001)	-£4,802	-0.021	£228,005	90%
TheraSphere	£29,911 (£22.15)	0.842 (0.001)	-£4,803	-0.021	£228,042	90%
QuiremSpheres	£31,895 (£24.74)	0.842 (0.001)	-£2,820	-0.021	£133,875	76%
Sorafenib	£34,714 (£21.22)	0.863 (0.001)	-	-	-	-

Note: mean and standard error; incremental results for each SIRT are versus sorafenib; SWQ south west quadrant

Cost of regorafenib use after sorafenib

Sirtex noted some potential inaccuracies or inconsistencies in the estimation of the cost of regorafenib use after sorafenib in the AG economic model. These are discussed in turn below.

Proportion receiving regorafenib treatment

The AG model assumes the use of regorafenib after sorafenib to be 12.04%. The source reported in the model is the Sirtex model; however, the Sirtex model has used the mean percentage from the resource use survey after SIRT use (18.95%).

The labelling of the source for the proportion receiving regorafenib after sorafenib within the executable AG model was an error, and the source of the assumption was the SARAH trial, as referenced correctly in the AG report. The modelled assumption is based on the proportion of patients in the sorafenib arm who received chemotherapeutic and systemic agents after sorafenib (26/216 patients, 12.04%). While the AG acknowledges that the patients in the SARAH trial will not have received regorafenib, the AG considers this a reasonable estimate of the proportion of patients who would go onto receive regorafenib, reflecting the fact that the chemotherapeutic and systemic agents administered to patients following sorafenib in the SARAH trial have now been displaced in practice by regorafenib, or are otherwise no longer in use.

As such, the AG maintains that their original assumption of 12.04% receiving regorafenib is appropriate, and that the use of data from SARAH rather than Sirtex's resource use survey is preferable as it is more consistent with the efficacy data for sorafenib.

Treatment duration for regorafenib treatment

In the original AG base-case, time on regorafenib treatment was modelled as being equal to time spent on sorafenib. This was done as no data were available from the trial evidence to support alternative assumptions. Sirtex, however, note that time on regorafenib treatment was not updated to reflect revisions to time on sorafenib treatment accepted at the previous committee meeting. Further Sirtex highlights that data on duration of regorafenib treatment are available from the RESORCE trial, which was the source of clinical evidence used in TA555.

The AG considers that the updated mean time on treatment estimate for sorafenib is a more appropriate assumption for the time on regorafenib treatment and that the RESORCE trial does not represent an appropriate source of data to inform this parameter. As noted by the Committee in TA555 the proportion of patients continuing treatment with regorafenib despite disease progression was high in RESORCE and is unlikely to reflect UK practice where the majority of patients will stop treatment upon disease progression. Clinical expert advice received by the Committee suggested only 20% of patients receive treatment beyond progression. In this regard the AG notes the modelled assumption of a median of 3.3 months regorafenib treatment better approximates the median time to progression for regorafenib in RESORCE (3.1 months). The AG therefore presents a revised scenario, where the time on regorafenib treatment is assumed to be equal to the updated sorafenib time on treatment (Table 9).

Dose of regorafenib

The mean dose of regorafenib in the AG analysis is based on full pack dosing, i.e. 160mg, which assumed that any medication not used as a result of dose interruptions and adjustments is not used for another patient. This represents the most conservative scenario with regards to regorafenib pricing. When dose interruptions and adjustments are considered, the mean dose decreases from 160mg to 144.1mg. An analysis based on the adjusted figure represents the most optimistic scenario with regards to regorafenib pricing, and assumes that any medication not used does not incur a cost. As discussed by the Committee in TA555, clinical practice is likely to be somewhere between these two extremes and although wastage could be minimised, evidence provided by the company suggested that it could not be eliminated entirely. Results are presented for a scenario using a mean regorafenib dose of 144.1mg to provide the Committee with a scenario based on the lower estimate of regorafenib cost (Table 9).

Results of scenario analysis for regorafenib cost

Results of the scenarios for time on regorafenib treatment and mean regorafenib dose are presented in Table 9. Varying the cost of regorafenib in these scenarios has minimal impact to the cost-

effectiveness results. Cost-effective results with the confidential PAS discounts applied, are presented in a confidential appendix.

Table 9 Results of cost-effectiveness scenarios for regorafenib costing (without PAS)

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
No downstaging, time on regorafenib after sorafenib is 146.1 days, mean dose is 160mg					
SIR Spheres	£31,167	0.764	-£4,925	-0.076	£64,492 (SWQ)
TheraSphere	£31,167	0.764	-£4,925	-0.076	£64,492 (SWQ)
QuiremSpheres	£33,147	0.764	-£2,945	-0.076	£38,563 (SWQ)
Sorafenib	£36,092	0.841	-	-	-
Downstaging permitted, time on regorafenib after sorafenib is 146.1 days, mean dose is 160mg					
SIR Spheres	£30,217	0.842	-£5,637	-0.020	£280,369 (SWQ)
TheraSphere	£30,217	0.842	-£5,637	-0.020	£280,369 (SWQ)
QuiremSpheres	£32,197	0.842	-£3,656	-0.020	£181,877 (SWQ)
Sorafenib	£35,854	0.862	-	-	-
No downstaging, time on regorafenib after sorafenib is 146.1 days, mean dose is 144.1mg					
SIR Spheres	£31,097	0.764	-£4,683	-0.076	£61,318 (SWQ)
TheraSphere	£31,097	0.764	-£4,683	-0.076	£61,318 (SWQ)
QuiremSpheres	£33,077	0.764	-£2,702	-0.076	£35,388 (SWQ)
Sorafenib	£35,780	0.841	-	-	-
Downstaging permitted, time on regorafenib after sorafenib is 146.1 days, mean dose is 144.1mg					
SIR Spheres	£30,151	0.842	-£5,394	-0.020	£268,317 (SWQ)
TheraSphere	£30,151	0.842	-£5,394	-0.020	£268,317 (SWQ)
QuiremSpheres	£32,131	0.842	-£3,414	-0.020	£169,824 (SWQ)
Sorafenib	£35,546	0.862	-	-	-

Note: Incremental results and ICERs are each versus sorafenib

Potential error in the model calculations of adverse event-related disutility

Boston Scientific (BTG) noted a number of potential errors and discrepancies in the estimation of adverse event-related disutilities that the AG presented in the original analysis (Table 4, Table 5). The AG can reassure BTG that the model does not contain the errors that they were concerned about. The model has been thoroughly validated throughout the appraisal process, and we appreciate that the redaction of key clinical data makes it more challenging for stakeholders to validate.

The AG, however, did detect a single error in the application of adverse event disutilities for a single scenario (Scenario 3), and this has been amended in the relevant table in the confidential appendix.

- **The utility decrements for adverse event-related have only been applied for the first model cycle, while the analysis should account for the transient nature of AE with TheraSphere versus the continual nature of AE with sorafenib.**

BTG suggested that the method of applying a TRAE-related utility decrement made use of a function in the economic model. This function was used on a version of the model in the early stages of development, and is now defunct and should have been removed. The AG estimated the total adverse event-related QALY loss for each treatment arm in the model, using the rates of each adverse event and their associated disutility. This was then included in the calculation of total QALYs.

In the AG analysis, the adverse event rates were based on the total proportion of patients who experienced the adverse event in question, from the SARAH trial. The duration of each adverse event was based on the total number of days that the patient experienced the event, and were provided by Sirtex Medical. The AG noted the limitations associated by this approach, as highlighted by Sirtex, who estimated a single duration for each type of AE, across study arms and across severity grades, in order to increase the sample size available per type of event. As acknowledged in the original response, this may result in underestimated duration of AEs related to sorafenib and overestimated duration of AEs related to SIRT.

- **There is a discrepancy between the total lifetime QALYs for TheraSphere in the redacted model and the figure reported by the AG, but not for the total lifetime QALYs for sorafenib. This discrepancy cannot be explained by any redaction, as this should only have applied to costs and not benefits**.

This is because the data on which sorafenib is based were not removed from the redacted model as they were estimated from data in the public domain. However, the number of QALYs estimated for each SIRT treatment was based on two sources of data: one which estimated the number of QALYs for patients who received treatment with SIRT, and the other for those who did not receive SIRT and received either BSC or sorafenib. The latter source of evidence was provided by a stakeholder and was omitted from the redacted model.

- **The all grade AE event data used to inform scenarios 4 to 7 (Table 4) is missing.**

This is provided in Appendix B.

References

1. Crott R, Versteegh M, Uyl-de-Groot C. An assessment of the external validity of mapping QLQ-C30 to EQ-5D preferences. Qual Life Res. 2013 Jun;22(5):1045–54.

2. Chow PK, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018;36:1913-21.

3. Biotrial. Dosisphere safety results (Radiotherapie interne vectorisee des carcinomes hepatocellulaires avec les microspheres de verre marquees a l'yttrium 90: Dosimetrie optimisee versus dosimetrie standard), 2019.

4. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2011; 140(2): 497-507.e2.

5. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010; 138(1): 52-64.

6. Kallini JR, Gabr A, Thorlund K, Balijepalli C, Ayres D, Kanters S, et al. Comparison of the adverse event profile of therasphere with sir-spheres for the treatment of unresectable hepatocellular carcinoma: a systematic review. *Cardiovasc Intervent Radiol* 2017;40:1033-43.

7. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163-73.

Appendix A – Committee-preferred model assumptions

Table 10 Key features of the economic model

Model Component	Description
Population	• People with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, o for whom any conventional transarterial embolisation therapies (TAE, TACE, DEB-TACE) are inappropriate, o with or without macroscopic vascular invasion, without extrahepatic disease.
Intervention	• SIR-Spheres Y-90 resin microspheres • TheraSphere Y-90 glass microspheres • QuiremSpheres Ho-166 PLLA microspheres
Comparator	• Sorafenib
Analysis type	• Cost-effectiveness (cost-utility) analysis
Economic outcome	• Incremental cost per QALY gained, incremental net monetary benefit
Perspective	• NHS and PSS
Time horizon	• Lifetime (10 years)
Discount rate	• Annual rate of 3.5% applied to costs and QALYs

Table 11 Sources of input parameters for the base case economic model

Model parameters	Evidence source
OS	*As per AG proposed base case:* Weibull fitted to pooled OS data from the SARAH and SIRveNIB trials for both SIR-spheres (per protocol) and sorafenib (intention-to-treat). OS for patients who received work-up but were ineligible to receive SIRT use KM data from SARAH.
PFS	*As per AG proposed base case:* Weibull fitted to pooled PFS data from the SARAH and SIRveNIB trials for both SIR-spheres and sorafenib.
Health utilities	*As per AG base case:* Utilities from SARAH trial data, and applied by treatment class (SIRT/systemic therapy)
Proportion receiving SIRT	*As per AG base case:* Proportion receiving SIRT after work-up based on the full SARAH trial population. Number of administrations of SIRT based on the SARAH trial.
SIRT costs	*As per AG base case:* Acquisition cost: Sirtex CS, BTG CS, Terumo CS Work-up costs: BTG-elicited values from The Christie NHS Foundation Trust Procedure costs: NHS Reference Costs 2017-18 *Additionally:* Equal administration costs for all SIRTs Imaging costs to be included for all SIRTs
Systemic therapies costs	*As per AG base case:* Sorafenib: BNF Dosing of sorafenib: SARAH trial *Additionally:* Duration of sorafenib: SARAH trial individual patient data
Subsequent treatment costs	*As per AG base case:* BNF, eMIT, TA555 (regorafenib)
AE costs	*As per AG base case:* AEs ≥5% of the population were modelled with rates drawn from the SARAH and REFLECT trials.

	Costs were drawn NHS Reference Costs, with cost categories based on NICE TA474, and 551
Health state costs	*As per AG base case:* Sirtex survey of clinical experts and NHS reference costs 2017/2018
Downstaging	*As per AG base case:* Not to be included because robust data are not available

Appendix B – Estimation of adverse event disutilities

Table 12 Disutilities for adverse events (reproduced from Sirtex response to NICE request for additional information, March 2020)

AEs	Disutility	Source	Comment
Abdominal pain	-0.07	Paracha 2018 (Doyle 2008)	
Alopecia	-0.06	Hall 2019	
Anorexia	-0.081	Hagiwara 2018	Disutilities for grade 2 were included
Ascites	-0.05	TA510	Assumed same as abdominal distention
Blood bilirubin increase	-0.218	Wehler 2018 (Stein 2017)	
Cardiac failure, congestive	-0.108	Beaudet 2014	Assumed same as heart failure
Diarrhoea	-0.24	Hall 2019	
Dry skin	-0.202	TA595	Assumed same as rash
Fatigue	-0.1	Hall 2019	
Fever	-0.09	TA592	
Gastrointestinal bleeding	-0.25	Paracha 2018 (Nafees 2016)	
Haematological biological abnormalities	-0.108	TA592	Assumed same as thrombocytopenia
Haemorrhage (non-gastrointestinal)	-0.131	Wehler 2018 (Lachaine 2015)	
Hand-foot skin reaction	-0.202	TA595	Assumed same as rash
Hypertension	-0.0003	Paracha 2018 (Nafees 2016)	
Hyponatraemia	0	Wehler 2018	
Infection	-0.218	Wehler 2018 (Stein 2017)	
Liver dysfunction	-0.218	Wehler 2018 (Stein 2017)	Assumed same as liver toxicity
Nausea or vomiting	-0.23	Hall 2019	
Other dermatological events	-0.12	TA592	Assumed same as skin infection
Other increased liver values	-0.218	Wehler 2018 (Stein 2017)	Assumed same as increased bilirubin
Pruritus	-0.202	TA595	Assumed same as rash
Rash	-0.202	TA595	
Renal dysfunction (increased creatinine)	-0.048	Beaudet 2014	
Weight loss	-0.081	Hagiwara 2018	Assumed same as anorexia

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Article type : Original

Liver Transplantation Following Yttrium-90 Radioembolization: 15-year Experience in 207-Patient Cohort

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/hep.31318

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Conflict of Interest: SM, AR, KD, TB, RJL and RS are advisors to Boston Scientific.

Word count: Abstract: 287; Manuscript including tables & references: 5709

Key words: downstaging, transplantation, radioembolization, survival

Acknowledgements: We would like to thank Nina Kay for her compassionate care of these patients.

Abbreviations: HCC: hepatocellular carcinoma; **LT:** Liver transplantation **Y90:** Yttrium-90 radioembolization; **MELD**: Model of endstage liver disease; **BCLC:** Barcelona Clinic Liver Cancer; **cTACE:** conventional chemoembolization; **LRT**: locoregional therapy; **OS**: Overall survival; **RFS**: Recurrence-free survival; **TTP:** time-to-progression. **TTR:** Time-to-recurrence; **DSM:** Disease-specific-mortality; **MRI:** gadolinium-enhanced magnetic resonance imaging; **CT:** triphasic contrast-enhanced computerized tomography; **CP:** Child-Pugh; **IQR:** Interquartile range; **KM:** Kaplan-Meier analysis **CI:** 95% Confidence Interval; **ECOG:** Eastern Cooperative Oncology Group; **UNOS:** United Network for Organ Sharing; **AFP:** Alpha fetoprotein; **CTCAE:** Common terminology criteria for adverse events; **DCD:** Donor after cardiac death; **LLD:** Living Liver Donor; **DBD:** Donation after brain death. **ETOH:** Alcoholic cirrhosis; **NASH:** Non-alcoholic steatohepatitis; **PBC:** Primary biliary cirrhosis; **PSC:** Primary sclerosing cholangitis; **HCV:** Hepatitis C virus infection; **HBV:** Hepatitis B virus infection

ABSTRACT

Radioembolization (Y90) is used in hepatocellular carcinoma (HCC) as a bridging as well as downstaging liver directed therapy to curative liver transplantation. In this study we report long-term outcomes of liver transplantation (LT) for HCC patients bridged/downstaged by

Y90. Patients undergoing LT following Y90 between 2004-2018 were included, with staging by United Network of Organ Sharing (UNOS) TNM at baseline pre-Y90 and pre-LT. Post-Y90 toxicities were recorded. Histopathological data of HCC at explant were recorded. Long-term outcomes including overall survival (OS), recurrence-free survival (RFS), disease-specific mortality (DSM) and time-to-recurrence (TTR) were reported. Time-to-endpoint analyses were estimated using Kaplan-Meier. Uni/multivariate analyses were performed using log-rank test and Cox proportional hazards model, respectively. During the 15-year period, 207 patients underwent LT after Y90. OS from LT was 12.5 years, with median time to LT of 7.5 months (IQR: 4.4-10.3). 169 patients were bridged while 38 were downstaged to LT. 94 (45%), 60 (29%) and 53 (26%) patients showed complete, extensive and partial tumor necrosis on histopathology. Three, five and ten-year OS rates were 84%, 77%, and 60% respectively. Twenty-four patients developed recurrence, with median RFS of 120 (95%CI: 69-150) months. DSM at 3, 5 and 10 years was 6%, 11% and 16% respectively. There were no differences in OS/RFS for bridged or downstaged patients. RFS was higher in patients with complete/extensive versus partial tumor necrosis ($p<0.0001$). For UNOS T2 patients treated during the study period, 5.2% dropped out due disease progression. **Conclusion:** Y90 is an effective treatment for HCC in the setting of bridging/downstaging to LT. Patients who achieved extensive or complete necrosis had better RFS, supporting the practice of neoadjuvant treatment prior to LT.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, 5th most common malignancy in males, and the 2nd most common cause of cancer-related mortality.(1) Liver transplantation (LT) is the most effective treatment for HCC and is curative.(2) Mazzaferro has demonstrated 75% 4-year survival following LT and established the Milan criteria(3),(4).

Given the risk of dropout in case of progression beyond T2 stage, many centers have adopted locoregional therapy (LRT) to control HCC and prolong time-to-progression (TTP). Yttrium-90 radioembolization (Y90) has emerged over the past decade as a locoregional therapy with favorable efficacy, safety profile, and quality-of-life outcomes.(5-7) While conventional transarterial chemoembolization (cTACE) is the most commonly used treatment in this setting, there is little data on LT following Y90. A recent phase 2 randomized controlled trial demonstrated significantly longer TTP (>26 months) with Y90 compared to cTACE (6.8 months) (P=0.0012). This was the first level I evidence establishing improved TTP with Y90 over cTACE, and this has led to adoption of Y90 as standard arterial therapy for HCC.(8, 9)

In this study, we report the 15-year follow-up of efficacy and long-term survival of 207 HCC patients undergoing LT after Y90, the largest reported to date.

METHODS

This study was approved by the Northwestern University institutional review board and Health Insurance Portability and Accountability Act compliant. Between 2004 and 2018, 207 patients with unresectable HCC underwent LT after being treated with Y90 radioembolization as part of a bridging or downstaging care pathway. A comprehensive analysis of baseline characteristics at Y90 and LT were performed. Imaging and survival outcomes were also assessed.

Evaluation/Staging

A multidisciplinary team comprised of hepatology, oncology, transplant surgery, and interventional radiology reviewed all patients considered for LT and triaged to Y90 as was the deliberate practice and expertise of the institution. Routine contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) were performed, with HCC diagnosis by guidelines.(10) Liver function was assessed by Child-Pugh (CP) and tumor staging was performed by UNOS and Barcelona Clinic Liver Cancer classification (BCLC).

Y90 Radioembolization

Pretreatment mesenteric angiography and macroaggregated albumin scans were performed to assess vascularity, gastrointestinal flow, and lung shunting fraction. The device used was glass-based (Boston Scientific, Minneapolis, MN); this brachytherapy device approved by the Food and Drug Administration for HCC with or without PVT.(11) Planned administered dose was 120-150 Gy for lobar infusions and >190 Gy for segmental injections.(12, 13)

Follow-up

All patients were followed for any Y90 related toxicities following the National Cancer Institute Common Terminology Criteria v4.0 for 6 months or until LT, and subsequently by transplant hepatology following transplantation.[14] High-risk patients (ex: >T2) were followed with MRI every 6 months for 5 years and non-contrast chest CT every year.

Imaging Analysis

Baseline imaging reads were initially performed by diagnostic radiology. Confirmatory imaging review and tumor staging at Y90 and LT was assessed by interventional radiology (blinded). UNOS staging was based solely on size regardless of enhancement. RECIST 1.1 response status (index lesion) at transplant was included in uni/multivariate analyses to assess its prognostic value in post-transplant outcomes.

Bridging/Downstaging

Bridging was defined as the use of Y90 for tumor control and limiting progression of T1/T2 disease until an organ became available. Downstaging was defined as treatment of >T2 patients (outside the Milan criteria) with the intent of reducing tumor burden to ≤T2 (Milan criteria) at LT.

Liver Transplantation

Given the dearth of published data on transplantation in livers exposed to Y90, surgical parameters encountered intra-operatively were documented, including intra-operative blood loss, organ cold ischemia, and transfusions. Patients underwent post-transplant imaging follow-up per our institutional guidelines, which included ultrasonography and doppler scanning within the first 24 hours post-transplant, then at 14 days, 3, 6, 9, 12 months, followed by yearly scans thereafter. If deemed necessary, CT chest was performed concurrently with other abdominal imaging. Date and site (intra/extrahepatic) of HCC recurrence, when present, were documented.

Liver Explant Analysis

Explant pathology analysis was performed following LT prior to sequestering the liver per our institutional radiation safety expert's policies. Hepatic parenchymal architecture was examined for the presence fibrosis and/or cirrhosis, with all nodules encountered reported as grades 1, 2 and 3 for well, moderately and poorly differentiated HCC, respectively. Necrosis was reported as complete (no viable HCC), extensive (50-99% necrosis) and partial necrosis (<50%).

Overall/Recurrence-free Survival

Overall survival (OS) was calculated from LT until death or last date of follow-up using Kaplan-Meier (KM). Recurrence-free survival (RFS) was calculated from date of LT until date of tumor recurrence, metastases or death. Disease-specific mortality rate (DSMR: defined as death post-LT due to HCC recurrence) was calculated from the day of LT until death from recurrent HCC or metastases or until last follow-up. Time-to-recurrence (TTR) was also estimated using KM. Median follow-up time was calculated using reverse KM.(15, 16)

Uni/Multivariate Analyses

KM univariate analysis was conducted for OS, RFS, DSMR, and TTR with Log-rank test to compare factors including age, sex, Milan Criteria, bridging vs downstaging, and tumor necrosis at transplant. Multivariate analysis (Cox proportional hazards) was conducted for OS and RFS. All statistical analyses were conducted using MedCalc Statistical Software Versions 19.2.1 (Ostend, Belgium), with significance set at $p<0.05$.

RESULTS

Baseline Characteristics at Y90

Table 1 lists the baseline characteristics at the time of Y90. Median age was 60 years (IQR: 56-65). 99 (48%), 91 (44%) and 17 (8%) patients were CP Class A, B and C, respectively. 192 (93%) patients showed imaging signs of cirrhosis, while 15 (7%) were confirmed by biopsy. 9 (4%), 160 (77%), 22 (11%), 12 (6%) and 4 (2%) patients were stage T1, T2, T3, T4a and T4b stages, respectively. 164 (79.5%) patients were treatment-naïve.

Outcomes/Toxicities Following Y90

117 (57%) patients were listed for LT at Y90; while 90 (43%) were listed following Y90 treatment. The majority [167 (81%)] received one Y90 treatment before LT; 40 (19%) received ≥2 sessions. 37 (18%) patients received lobar treatment with a median dose of 124 Gy (IQR: 132-146), while 170 (82%) received radiation segmentectomy at a median dose of 260 Gy (IQR: 235-350). In patients with elevated AFP >13 ng/dl (n=93), the median percent AFP reduction following Y90 was 77% (IQR 51-95). In the 45-patient subset with baseline AFP >100, the median AFP reduction following Y90 was 93% (IQR 77-97) (**Supplementary Table 1**). 7 patients exhibited grade 3 albumin toxicities; all but 1 was pre-existing prior to Y90. 27 exhibited grade 3 bilirubin toxicities; all but 9 were pre-existing prior to Y90. At the time of transplant, 132 (64%) had normal AFP (≤13), while 62 (30%) exhibited AFP >13-100, and 13 (6%) had AFP (>100).

Baseline Characteristics at Transplantation

Table 2 shows baseline characteristics at LT, with a median age of 62 years (IQR: 57-66) for recipients and 48 for donors (IQR: 27-63). Eighty-seven (42%) patients were blood group A, 24 (11%), 90 (43%) and 6 (4%) were blood groups B, O and AB, respectively. The majority 102 (49%) had chronic hepatitis C virus infection as the main predisposing factor; 22 (10%) had chronic hepatitis B virus infection, while 30 (14%) and 13 (6%) had alcohol cirrhosis and

non-alcoholic steatohepatitis (NASH), respectively. Seventeen (8%) patients received live donor, 155 (75%) received liver donation after brain death (DBD) while 35 (17%) patients received donation after circulatory death (DCD). On pathological examination of liver explants, 94 (45%), 60 (29%) and 53 (26%) demonstrated complete, extensive and partial necrosis, respectively.

Tumor Stage at Y90 and at LT

Supplementary Table 2 summarizes UNOS stage at Y90 and at LT:

a) **Bridging within Milan:** 169 (82%) patients were within Milan (≤T2) at Y90. 166 (98%) patients were still within Milan criteria at LT, while 3 (2%) progressed to T3.

b) **Downstaging to T2:** 38 (19%) patients were beyond Milan before Y90, 18 (47%) were downstaged to T2, while 20 (53%) were transplanted with >T2 stage. Fourteen T3 were downstaged to T2 (64%). Two patients with T4a showed nodule resolution and downstaged to T2. Two T4b patients displayed complete resolution of their tumor thrombus and downstaged to T2.

c) Downgrading: One and four T1 and T2 patients, respectively, displayed resolution of treated hepatomas on cross sectional imaging to T0. 47 (23%) patients were downgraded from T2 to T1. 4 (2%) patients were downgraded from T4a to T3.

Intention-to-Treat Bridging UNOS T2 to Transplant Analysis

During the study time period, 362 HCC T2 patients underwent Y90. 150 patients were not listed due to: advanced age (N=50), cardiovascular and pulmonary comorbidities (N=23), concurrent malignancies (N=12), obesity (N=2), lack of psycho-social support (N=4), alcohol and/or drug abuse (N=12), non-compliance with transplant evaluation protocol (N=8), lack of follow-up (N=9), Bombay blood group (N=1), declined LT (N=15) and opted for resection (N=14). Of 212 listed T2 patients, at the time of data closure, 160 successfully underwent LT, 12 were still on the wait list, and 40 were delisted. Reasons for delisting included progressive disease (N=11), death from variceal bleed (N=1), development of systemic illness (N=8: cardiovascular disease, pulmonary hypertension, renal failure, septicemia), development of other malignancies (N=3), relocating to another state (N=2), and drug abuse (N=2). 13 patients refused transplant and were delisted after initially agreeing to being listed. This translates to 19% (40 of 212) dropping off the transplant list. Specifically, due to progressive disease, 5.2% (11 of 212) dropped off.

Median intention to treat OS of all T2 patients (N=362) was 94.4 months (CI: 79.2-120.0) from date of Y90 (**Figure 1**). Median OS of the 160 transplanted T2 patients was not reached, with 5- and 10-year survival rates of 82% and 56%, respectively. Median OS of the 202 non-transplanted T2 patients was 34.5 months (CI: 29.0-47.3), with better survival when stratified by CP class [67.5 months (CI: 40.0-80.2), 21.3 months (CI: 16.3-29.0), 6.0 months (CI: 4.0-11.3) for CP A (N=121), B (N=70) and C (N=11), respectively] (**Figure 2**).

Long-term Outcomes Following Transplantation

1-Overall Survival (OS): From date of Y90, the median OS of the 207 transplanted patients was 13 years (95%CI: 120-157) from Y90. From LT, median OS was 12.5 years (95%CI: 120-150), with survival rates at 3-, 5- and 10-years of 84%, 77% and 60%, respectively (**Figure 3**). Stratifying patients by age (<65 vs ≥65), patients <65 had significantly longer survival rates (P=0.003); median was not reached at 150 months with 3-, 5-, and 10-year

survival of 88%, 85% and 71% respectively. Liver-recipients ≥65 exhibited median OS of 12.5 years, with 3-, 5-, and 10-year survival rates of 73%, 58% and 43% respectively (**Table 3**). Of note, the 17 BCLC D (CP C) patients that received segmental Y90 and subsequently transplanted exhibited a 5-year survival of 91.5% (one death).

2-Tumor Recurrence: 24 (11.5%) patients developed tumor recurrence. **Supplementary Table 3** provides granular detail on the 24 recurrence cases. 10 (42%) patients were beyond Milan criteria at Y90, while 6 (25%) were beyond Milan criteria at LT. 17 (70%) of the 24 recurrences died at a median 29 (range: 5-83) months after LT, while 7 (30%) patients are alive at their last follow up at 8, 16, 72, 110, 111, 114 and 154 months. Recurrence-free probability was 76% at 10-years post LT (**Supplementary Figure 1**).

3-Mortality Rate: At time of data closure, 44 (21%) had died, with causes of death including cardiac decompensation (n=12, 6%) renal failure (n=2, 1%), infection (n=8, 4%), recurrent HCC (n=17, 8%), cerebrovascular disease (n=1, 0.5%) and other malignancies (n=4, 2%).

4-DSMR: No median was reached at 13 years for mortality rate from HCC recurrence. At 3-, 5- and 10 years post-LT, DSMR were 6%, 11% and 16%, respectively (**Supplementary Figure 2**).

5-RFS: Median RFS was 120 (95%CI: 69-150) months, with 3-, 5- and 10-year RFS rates of 77%, 65% and 43%, respectively (**Supplementary Figure 3**).

Univariate Analyses (Table 4)

1-OS: Univariate analyses for OS, showed only age to be a significant prognostic factor of survival. Median hazard ratio (HR) for patients ≥65 was 2.8 when compared to patients <65 (p=0.003). Different tumor stage at either Y90 or LT did not prove any significant effect on survival after LT. There was a trend towards better OS in patients achieving complete or

extensive tumor necrosis compared to <50% necrosis (p=0.056). A trend was noticed in patients achieving response by RECIST 1.1 (P=0.06).

2-RFS: Univariate analyses for RFS showed similar results to those of OS, supporting that age remains a significant prognosticator. Complete/extensive tumor necrosis demonstrated better RFS (p=0.0056).

3-DSMR: Patients within Milan at Y90 showed lower risk for DSMR compared those >T2 (HR: 0.21, *P* = 0.01). Similarly, patients who were within Milan criteria at LT had better DSMR (HR: 0.19, p = 0.02). Tumor necrosis showed strong significance on DSMR (P=0.0009). Patients with normal AFP (≤ 13 ng/dL) exhibited lower DSMR (HR: 0.23, P=0.0036).

4-TTR: Univariate analyses showed tumor characteristics to be strong predictors of recurrence. Patients within Milan at Y90 and LT had lower rates of recurrence (P=0.003 and 0.01, respectively). Tumor necrosis proved strongly associated with lower recurrence (P<0.0001), as was normal AFP (≤13 ng/dL) (P=0.0009). It should be noted that for the aforementioned analysis, we used largest lesional diameter (RECIST 1.1), not enhancement (mRECIST), thereby providing the most conservative imaging assessment. As an example, a completely necrotic 2 cm lesion that did not change in size was categorized as a persistent 2 cm tumor.

Multivariate Analysis

Multivariate analyses using Cox proportional-hazards regression was conducted for OS and RFS. Multivariate analysis was not conducted for DSMR and TTR endpoints due to insufficient endpoints. Age, tumor necrosis (>50%) and treatment response showed better OS outcomes (P=0.0048, 0.03 and 0.015, respectively). Similarly, RFS was significantly impacted by age (P=0.05), extensive tumor necrosis (>50%) (p=0.005), complete (100%) tumor necrosis (P=0.007), and normal AFP at transplant and (P=0.016) (**Table 5**).

Analysis of Tumor Recurrence by Necrosis

HCC recurrence was more commonly observed in patients with less necrosis on explant histo-pathology. Of 94 and 60 patients with complete and extensive necrosis, 2 (2%) and 4 (6.7%) developed recurrence after LT, respectively. In contradistinction, 18 out of 53 (34%) patients who had partial pathological response to Y90 developed recurrence (Chi-squared=35.5, $p<0.0001$). **Supplementary Figure 4** demonstrates an example of complete pathologic necrosis in an explant specimen.

DISCUSSION

LT is considered the most effective treatment for BCLC A cirrhotic, nonresectable HCC patients(17), providing 5-year OS approaching 75%.(4) Over the last decade, there has been a rise in the use of LRT prior to LT, with TACE remaining the most commonly used bridging/downstaging modality(18). Despite this, Y90 experience continues to grow, with our group first reporting long-term outcomes in 291 patient cohort, followed subsequently by a 1000-patient analysis.(7),(19) Also, while early retrospective comparative analyses found longer TTP for Y90 than TACE, these findings were subsequently confirmed in a prospective randomized trial(20). In totality, these results favor Y90 over TACE for early HCC awaiting LT.(8) Our center initiated the Y90 program in 2003, with the first case of LT post Y90 in 2004. The promising response, TTP, and downstaging prompted the shift in practice towards Y90 being the first-line arterial modality for HCC patients.(21) Since then, 207 patients underwent LT after Y90. We herein present the long-term outcomes and largest series published on the topic.

Overall Survival: OS was comparable to what is observed in non-HCC and non-Y90 LT patients.(22) While the majority were bridged, some downstaged patients also proceeded to LT after local board approval. While limiting recurrence could be attributed to disease control by LRT, there are conflicting data supporting this mechanism. In a recent study by Oligane, OS after LT was significantly longer in patients who underwent bridging LRT vs those that did not (75.9 vs 53.1 months, respectively; $P<0.001$).(23) In our cohort, 3, 5 and 10-year OS rates of 86%, 80% and 60% represent excellent outcomes, similar to LT for non-malignant liver disease.

At LT date, 184 patients were within Milan criteria ($\leq$T2), while 23 patients were beyond (>T2). The net OS for 207 patients was higher than currently reported results of long-term

outcomes of LT after HCC. (24) OS was not affected by tumor stage at Y90 or tumor stage at LT, with age of the recipient proving to have significant impact on survival.

Current evidence suggests that Milan criteria is a significant prognosticator for OS after LT.(25) There are many questions which have emerged, including whether imaging assessment and subsequent staging of patients after LRTs should include size of the entire lesion, or solely the enhancing portion? Evolving data support the notion that necrosis (decreased enhancement) following LRT correlates with complete pathologic necrosis following Y90.(26) Furthermore, certain studies suggest tumor response predicts better survival outcomes.(27, 28) This is consistent with a recent transplant multicenter consortium analysis of 3601 patients.(29) Similarly, our data show that tumor necrosis and RECIST response translated to better OS.

Recurrence-Free Survival: With a median recurrence-free survival of 10 years, LT after Y90 proves to be a definitive curative therapy for HCC. It should be also noted that neither HCC stage (≤T2 vs >T2) at Y90 nor at LT was of significant prognostic value for RFS [HR=0.9 at Y90 (p=0.69); HR=1.2 at LT (p=0.57)]. RFS has always been an ambiguous endpoint in HCC due to the confounding factor of underlying liver function on survival. While in liver transplantation RFS overcomes the confounding factor of cirrhosis on OS, it does not overcome other confounders such as age, comorbidities and other issues unique to transplantation. Since OS and RFS were more significantly affected by age than tumor stage, we focused on DSMR and time-to-recurrence as endpoints reflective of the effect of LRTs prior to LT.

HCC Recurrence: With 24 (12%) cases of post-LT HCC recurrence over a 13-year period,(30) LT proves to be an effective treatment for HCC. This low rate of recurrence is hypothesized to be attributed to Y90 providing tumor control and downstaging.(31) In our 207-patient cohort, there were 58 LT patients with tumors ≤T1. Of those, 51 initially presented as T2, and they were subsequently downstaged to T1 (n=47) or T0 (n=4). This highlights the importance of treating solitary 2-3 cm tumors, since those are likely to be

downstaged to T1, translating to a lowered recurrence rate post-LT. Explant tumor necrosis associated lower risk of recurrence (P<0.0001).

Disease-Specific Mortality: DSMR analysis was undertaken in order to assess the impact of Y90 and LT on survival. Of the 44 patients who reached their death endpoint, only 17 patients died of tumor recurrence, while the other 27 died from cardiac or infectious etiologies. DSMR was also significantly impacted by tumor stage prior to Y90 and LT, as well as degree of tumor necrosis at explant.

Alpha-fetoprotein: Treatment with Y90 was associated with significant reductions in AFP and in several cases, complete normalization. Normal AFP at transplant was associated lower recurrence and DSMR compared to those with elevated AFP. This is potentially attributable to better tumor biology (normal AFP) and/or achieving complete response to treatment with normalization of AFP.(32) However, this did not translate to improvement in survival.

Impact of Y90: While studying the impact of bridging LRT by intention-to-treat has been challenging, several studies show that bridging LRT is associated with favorable post-LT outcomes.(33) Oligane et al. reported that bridging LRT resulted in lower recurrence and longer OS when compared to patients who underwent LT without prior LRT. (23) Agopian et al. showed that patients with complete pathological response had better RFS. However, patients who received ≥3 LRT before transplant exhibited worse RFS.(29) Hence, the authors considered the increasing need for LRT as potential surrogate for aggressive tumor biology. Most recently, an Intention-to-treat analysis by Lai et al. suggested that LRT served as a protective factor, providing better outcomes post-LT, while tumor progression and ≥4 LRTs were strong prognostic factors of poor outcomes (aggressive tumor biology).(34) In our study, we conducted an independent intention-to-treat analysis of 362 T2 HCC patients treated over a 15-year period. Despite being within Milan criteria, only 212 were eligible for listing, of whom 160 underwent successful LT. The drop-out due to disease progression or

death occurred in few patients (5.2%). Therefore, Y90 appears to provide a high degree of disease stability/response, usually achieved by one treatment, resulting in few progressors. This finding was observed in a recent prospective randomized trial.(8) Despite this, patients who did not undergo LT for any reason still exhibited favorable OS, particularly those with CP A disease (67.5 months).

Also, the impact of pathologic necrosis was evident for all endpoints (OS, RFS, DSMR, TTR), with complete/extensive necrosis demonstrating significant OS benefit when compared to partial necrosis, leading to two different hypotheses. First, Y90 use prior to LT has its own significant impact on tumor recurrence, DSMR and OS after LT. Second, patients with partial necrosis + stable RECIST findings are at higher risk of developing recurrence, necessitating repeat treatment and conversion to extensive/complete necrosis + RECIST response prior to LT. Indeed, failure to achieve at least extensive necrosis may represent a de facto marker of aggressive tumor biology.(29)

Strengths and Limitations: This study is subject to strengths and limitations. It represents the largest cohort of transplanted patients treated with Y90 to date, with median time from Y90 to LT of 7.5 months. UNOS stages at Y90 and LT not being confined to Milan criteria reveal the effect of Y90 prior to LT at the pathology level. In order to provide more insight into the variable multifactorial nature of listing/unlisting with ultimate organ transplantation and the role of Y90, we generated an intention-to-treat analysis of UNOS T2 patients. RECIST 1.1 was used, demonstrating the continued importance of size criteria in assessing response in HCC. Limitations include the retrospective nature and well-known selection bias inherent to the transplantation process. Given the recent modifications to wait times prior to being transplanted, findings demonstrating longer TTP in the bridging setting are now more relevant.(8) Downstaging is only dealt with on a case-by-case basis in our region, preventing us from performing an ITT analysis without influence of the regional board.

CONCLUSION

Y90 is an effective treatment for early stage HCC in cirrhotic patients being bridged or downstaged to LT. Long-term OS outcomes are comparable to previously reported outcomes for non-malignant conditions. RFS is not different between patients bridged versus downstaged, or within versus beyond Milan criteria. Tumor recurrence and disease specific mortality are significantly affected by tumor stage and degree of necrosis. LRT with Y90 should be considered one of the standard treatment options prior to LT.

REFERENCES

1. Global Burden of Disease Cancer C, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al. The Global Burden of Cancer 2013. JAMA Oncol 2015;1:505-527.
2. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698-711.
3. Ringe B, Pichlmayr R, Wittekind C, Tusch G. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. World J Surg 1991;15:270-285.
4. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-699.
5. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. J Vasc Interv Radiol 2006;17:1251-1278.
6. Salem R, Gilbertsen M, Butt Z, Memon K, Vouche M, Hickey R, Baker T, et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. Clin Gastroenterol Hepatol 2013;11:1358-1365.e1351.
7. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 2010;138:52-64.
8. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, Mulcahy MF, et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology 2016;151:1155-1163.e1152.

9. Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, Hickey R, et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. Hepatology (Baltimore, Md.) 2018;68:1429-1440.
10. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.
11. Salem R, Lewandowski RJ, Sato KT, Atassi B, Ryu RK, Ibrahim S, Nemcek AA, Jr., et al. Technical aspects of radioembolization with 90Y microspheres. Tech Vasc Interv Radiol 2007;10:12-29.
12. Riaz A, Gates VL, Atassi B, Lewandowski RJ, Mulcahy MF, Ryu RK, Sato KT, et al. Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. Int J Radiat Oncol Biol Phys 2011;79:163-171.
13. Salem R, Lewandowski RJ, Gates VL, Nutting CW, Murthy R, Rose SC, Soulen MC, et al. Research reporting standards for radioembolization of hepatic malignancies. J Vasc Interv Radiol 2011;22:265-278.
14. Common Terminology Criteria for Adverse Events (CTCAE). In; 2009.
15. Clark TG, Altman DG, Stavola BLD. Quantification of the completeness of follow-up. The Lancet 2002;359:1309-1310.
16. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Controlled Clinical Trials 1996;17:343-346.
17. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421-430.
18. Oligane HC, Close ON, Xing M, Kim HS. Bridging locoregional therapy: Longitudinal trends and outcomes in patients with hepatocellular carcinoma. Transplant Rev (Orlando) 2017.
19. Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, Hickey R, et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. Hepatology 2017.

20. Salem R, Lewandowski RJ, Kulik L, Wang E, Riaz A, Ryu RK, Sato KT, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2011;140:497-507.e492.

21. Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, Ibrahim SM, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009;9:1920-1928.

22. Jain A, Reyes J, Kashyap R, Dodson SF, Demetris AJ, Ruppert K, Abu-Elmagd K, et al. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. Ann Surg 2000;232:490-500.

23. Oligane HC, Xing M, Kim HS. Effect of Bridging Local-Regional Therapy on Recurrence of Hepatocellular Carcinoma and Survival after Orthotopic Liver Transplantation. Radiology 2017;282:869-879.

24. Yoo HY, Patt CH, Geschwind JF, Thuluvath PJ. The outcome of liver transplantation in patients with hepatocellular carcinoma in the United States between 1988 and 2001: 5-year survival has improved significantly with time. J Clin Oncol 2003;21:4329-4335.

25. Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, Mariani L. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl 2011;17 Suppl 2:S44-57.

26. Riaz A, Kulik L, Lewandowski RJ, Ryu RK, Giakoumis Spear G, Mulcahy MF, Abecassis M, et al. Radiologic-pathologic correlation of hepatocellular carcinoma treated with internal radiation using yttrium-90 microspheres. Hepatology 2009;49:1185-1193.

27. Riaz A, Gabr A, Abouchaleh N, Ali R, Al Asadi A, Mora R, Kulik L, et al. Radioembolization for hepatocellular carcinoma: Statistical confirmation of improved survival in responders by landmark analyses. Hepatology 2018;67:873-883.

28. Memon K, Kulik L, Lewandowski RJ, Wang E, Riaz A, Ryu RK, Sato KT, et al. Radiographic response to locoregional therapy in hepatocellular carcinoma predicts patient survival times. Gastroenterology 2011;141:526-535.e522.

29. Agopian VG, Harlander-Locke MP, Ruiz RM, Klintmalm GB, Senguttuvan S, Florman SS, Haydel B, et al. Impact of Pretransplant Bridging Locoregional Therapy for Patients With Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation: Analysis of 3601 Patients From the US Multicenter HCC Transplant Consortium. Ann Surg 2017;266:525-535.

30. Zimmerman MA, Ghobrial RM, Tong MJ, Hiatt JR, Cameron AM, Hong J, Busuttil RW. Recurrence of hepatocellular carcinoma following liver transplantation: a review of preoperative and postoperative prognostic indicators. Arch Surg 2008;143:182-188; discussion 188.

31. Yao FY, Kinkhabwala M, LaBerge JM, Bass NM, Brown R, Jr., Kerlan R, Venook A, et al. The impact of pre-operative loco-regional therapy on outcome after liver transplantation for hepatocellular carcinoma. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2005;5:795-804.

32. Agopian VG, Harlander-Locke MP, Markovic D, Zarrinpar A, Kaldas FM, Cheng EY, Yersiz H, et al. Evaluation of Patients With Hepatocellular Carcinomas That Do Not Produce α-Fetoprotein. JAMA Surg 2017;152:55-64.

33. Mehta N, Sarkar M, Dodge JL, Fidelman N, Roberts JP, Yao FY. Intention to treat outcome of T1 hepatocellular carcinoma with the "wait and not ablate" approach until meeting T2 criteria for liver transplant listing. Liver Transpl 2016;22:178-187.

34. Lai Q, Vitale A, Iesari S, Finkenstedt A, Mennini G, Onali S, Hoppe-Lotichius M, et al. The Intention-to-Treat Effect of Bridging Treatments in the Setting of Milan Criteria-In Patients Waiting for Liver Transplantation. Liver Transpl 2019;25:1023-1033.

FIGURE LEGEND

Figure 1: Post-Y90 Intention-to-Treat OS analysis of 362 T2 patients.

Figure 2: Post-Y90 OS of 202 T2 patients who did not undergo subsequent liver transplant.

Figure 3: Post-LT OS survival of 207 HCC patients treated with Y90.

Table 1: Baseline Characteristics at Y90

		Median [IQR] N (%)
Age (years)	60 [56-65]	
Sex	Male	156 (75%)
	Female	51 (25%)
ECOG	0	145 (70%)
	1	61 (29.5%)
	2	1 (0.5%)
Child-Pugh	A	99 (48%)
	B	91 (44%)
	C	17 (8%)
BCLC	A	106 (51%)
	B	20 (10%)
	C	64 (31%)
	D	17 (8%)
UNOS TNM	T1	9 (4%)
	T2	160 (77%)
	T3	22 (11%)
	T4a	12 (6%)
	T4b	4 (2%)
Imaging Cirrhosis	Present	192 (91%)
	Absent	15 (9%)
AFP (ng/dL)	<13 (normal)	114 (55%)
	13-100	48 (23%)
	>100	45 (22%)
	Range	0.8-15735
Prior Liver therapy	Surgical Resection	8 (3.5%)
	Prior HCC LRT	35 (17%)
	Treatment Naïve	164 (79.5%)
Listing	Prior to Y90	117 (57%)
	After Y90	90 (43%)
Y90 treatments prior to LT	1	167 (81%)
	2	33 (16%)

	3	6 (3%)
	4	1 (0.5%)
Y90 Administration	Lobar	37 (18%)
	Segmental	170 (82%)
Y90 Dose (Gy)	Lobar	124 [132-146]
	Segmental	260 [235-350]

Table 2: Baseline Characteristics at LT

		Median [IQR] *N(%)*	
Recipient	Age (years)	62 [57-66]	
	MELD-Na Score	13 [10-17]	
	Wait-list time (months)	7 [4-10]	
	Time from Y90 (months)	7.5 [4.4-10.3]	
	Etiology of HCC	Autoimmune hepatitis	3 (1.5%)
		Alpha 1 antitrypsin	1 (0.5%)
		Biliary Atresia	1 (0.5%)
		Cryptogenic	13 (6%)
		ETOH	30 (14%)
		HCV + ETOH	11 (5%)
		HCV	102 (49%)
		HBV	22 (10%)
		NASH	13 (6%)
		PBC	7 (3%)
		Wilson's	1 (0.5%)
		PSC	1 (0.5%)
		Hemochromatosis	2 (1%)
	AFP (ng/dL)	<13 (normal)	132 (64%)
		13-100	62 (30%)
		>100	13 (6%)
		Range	0.8-13774
	Blood Group	A	87 (42%)
		B	24 (11%)
		O	90 (43%)
		AB	6 (4%)
	Organs Transplanted	Liver Only	197 (95%)

		Liver & Kidney	10 (5%)
Donor	Age	48 [27-63]	
	Donor State	Living donor	17 (8%)
		DBD	155 (75%)
		DCD	35 (17%)
Surgical Parameters	Cold Ischemic Time (Hours)	7 [6-8]	
	RBCs (units)	7 [4-14]	
	Fresh Frozen Plasma (units)	8 [5-14]	
	Platelets (units)	2 [2-4]	
Explant	Liver Parenchyma	Cirrhosis	202 (97.5%)
		Bridging Fibrosis	5 (2.5%)
	Tumor Grade	Grade 1	37 (18%)
		Grade 2	69 (33%)
		Grade 3	6 (3%)
		Fibrolamellar	1 (0.5%)
		Mixed HCC-cholangiocarcinoma	4 (2%)
		Unable to identify due to extensive necrosis	90 (43.5%)
	Tumor Necrosis	Complete (100%)	94 (45%)
		Extensive (51-99%)	60 (29%)
		Partial (<50%)	53 (26%)

MELD-Na: New Model of end-stage liver disease-Sodium; HCV: Hepatitis C virus infection; HBV: Hepatitis B virus infection; ETOH: Alcoholic cirrhosis; NASH: Non-alcoholic steatohepatitis; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis; DCD: Donor after cardiac death

Table 3: Survival and Recurrence Outcomes

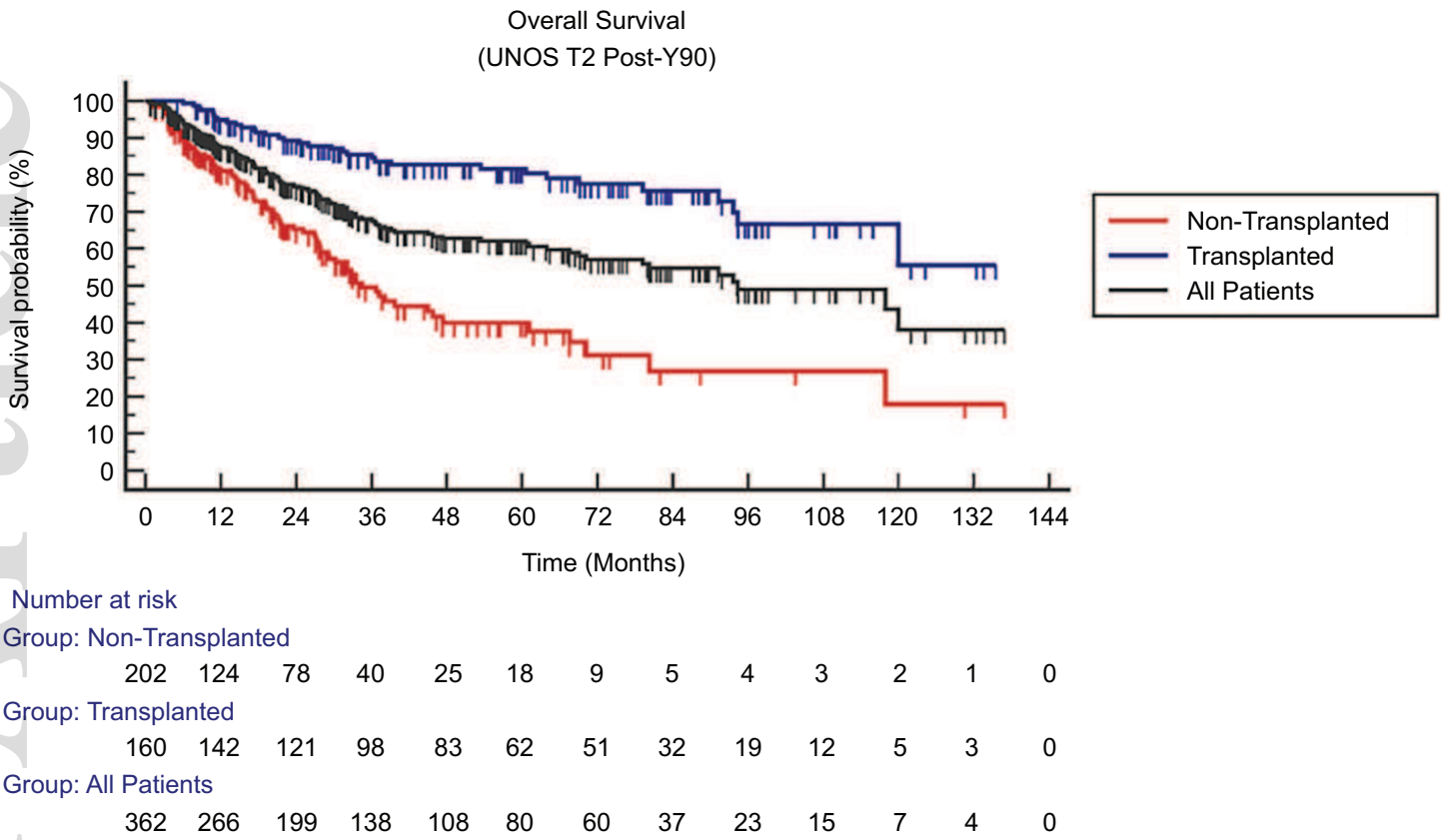
	Median	3-year	5-year	10-year
Overall Survival from Y90	157 mo. (13.1 years) [CI: 120-157]	87%	80%	62%
Overall Survival from LT	150 mo (12.5 years) [CI: 120-150]	84%	77%	60%
Recurrence-Free Survival from LT	120 mo (10.0 years) [CI:69-150]	77%	65%	43%
Disease-Specific Mortality Rate	Not Reached	6%	11%	16%
Time-to-Recurrence (Recurrence-Free Probability)	Not Reached	88%	79%	76%

Table 4: Univariate Analyses

Factor		N	Overall Survival		Recurrence-free Survival		Disease-Specific Mortality		Time-to-Recurrence	
			HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	<65	145	1	**0.003**	1	**0.04**	1	0.11	1	0.5
	>65	62	2.8 (1.4-5.6)		1.78 (0.96 - 3.3)		2.47 (0.82-7.49)		0.75 (0.3-1.8)	
Sex	M	155	1.54 (0.8-3)	0.2	1.8 (1-3.4)	0.08	1.65 (0.57-4.78)	0.36	2.1 (0.88-5)	0.16
	F	52	1		1		1		1	
Milan at Y90	≤T2	169	1.1 (0.5-2.3)	0.87	0.9 (0.5-1.73)	0.71	0.21 (0.06-0.73)	**0.01**	0.2 (0.07-0.58)	**0.003**
	>T2	38	1		1		1		1	
Milan @ LT	≤T2	184	1.01 (0.42-2.46)	0.98	0.8 (0.36-1.82)	0.57	0.19 (0.04-0.82)	**0.02**	0.2 (0.06-0.69)	**0.01**
	>T2	23	1		1		1		1	
Bridging vs Downstaging vs Neither	Bridged	166	1	0.99	1	0.85	1	0.055	1	**0.02**
	Downstaged	18	1 (0.4-2.8)		0.98 (0.4-2.4)		2 (0.35-13)		2.3 (0.5-10.7)	
	Neither	23	0.99 (0.4-2.3)		1.2 (0.5-2.8)		3.4 (0.8-14.7)		3.3 (0.9-11)	
Donor	DBD	155	1	0.34	1	0.18	1	0.23	1	0.56
	DCD	35	1.7 (0.7-3.87)		1.78 (0.8-4)		2 (0.5-8.4)		1.7 (0.5-5.4)	
	LLD	17	1.05 (0.4-2.9)		0.79 (0.3-1.9)		2.4 (0.47-12.7)		1.4 (0.4-5.2)	
Tumor Necrosis	Complete	94	0.53 (0.26-1.1)	0.056	0.46 (0.2-0.8)	**0.0056**	0.1 (0.03-0.3)	**0.0009**	0.07 (0.03-0.19)	**<0.0001**
	Extensive	60	0.43 (0.2-0.9)		0.36 (0.17-0.76)		0.3 (0.09-1.1)		0.2 (0.07-0.61)	
	Partial	53	1		1		1		1	
RECIST 1.1 Response @ LT	Response	92	0.35 (0.11-1.11)	0.06	0.53 (0.19-1.5)	0.34	0.8 (0.12-5.5)	0.42	1.7 (0.35-8.2)	0.75
	Stable	97	0.52 (0.16-1.64)		0.59 (0.21-1.65)		1.59 (0.23-11.8)		2.03 (0.42-9.7)	
	Progression	18	1		1		1		1	
AFP	≤13	132	0.69 (0.37-1.28)	0.24	0.6 (0.34-1.1)	0.07	0.23 (0.09-0.61)	0.0036	0.25 (0.11-0.57)	0.0009
	>13	75	1		1		1		1	

Table 5: Multivariate Analyses

Parameter			OS		RFS	
		N	HR (CI)	P	HR (CI)	P
Age	≤65	145	1		1	
	>65	62	2.41 (1.31-4.44)	**0.0048**	1.79 (1-3.2)	**0.05**
Sex	M	155	1		1	
	F	52	0.62 (0.28-1.37)	0.24	0.49 (0.23-1.04)	0.063
RECIST 1.1	Response	92	0.31 (0.12-0.8)	**0.015**	0.44 (0.17-1.07)	0.07
	Stable	97	0.44 (0.18-1.1)	0.07	0.45 (0.18-1)	0.08
	Progression	18	1		1	
AFP	≤13	132	1		1	
	>13	75	1.67 (0.89-3.13)	0.11	2.03 (1.14-3.62)	**0.016**
Tumor Necrosis	Complete	94	0.5 (0.2-1.1)	0.07	0.41 (0.21-0.79)	**0.007**
	Extensive	60	0.4 (0.18-0.9)	**0.03**	0.33 (0.15-0.71)	**0.005**
	Partial	56	1		1	



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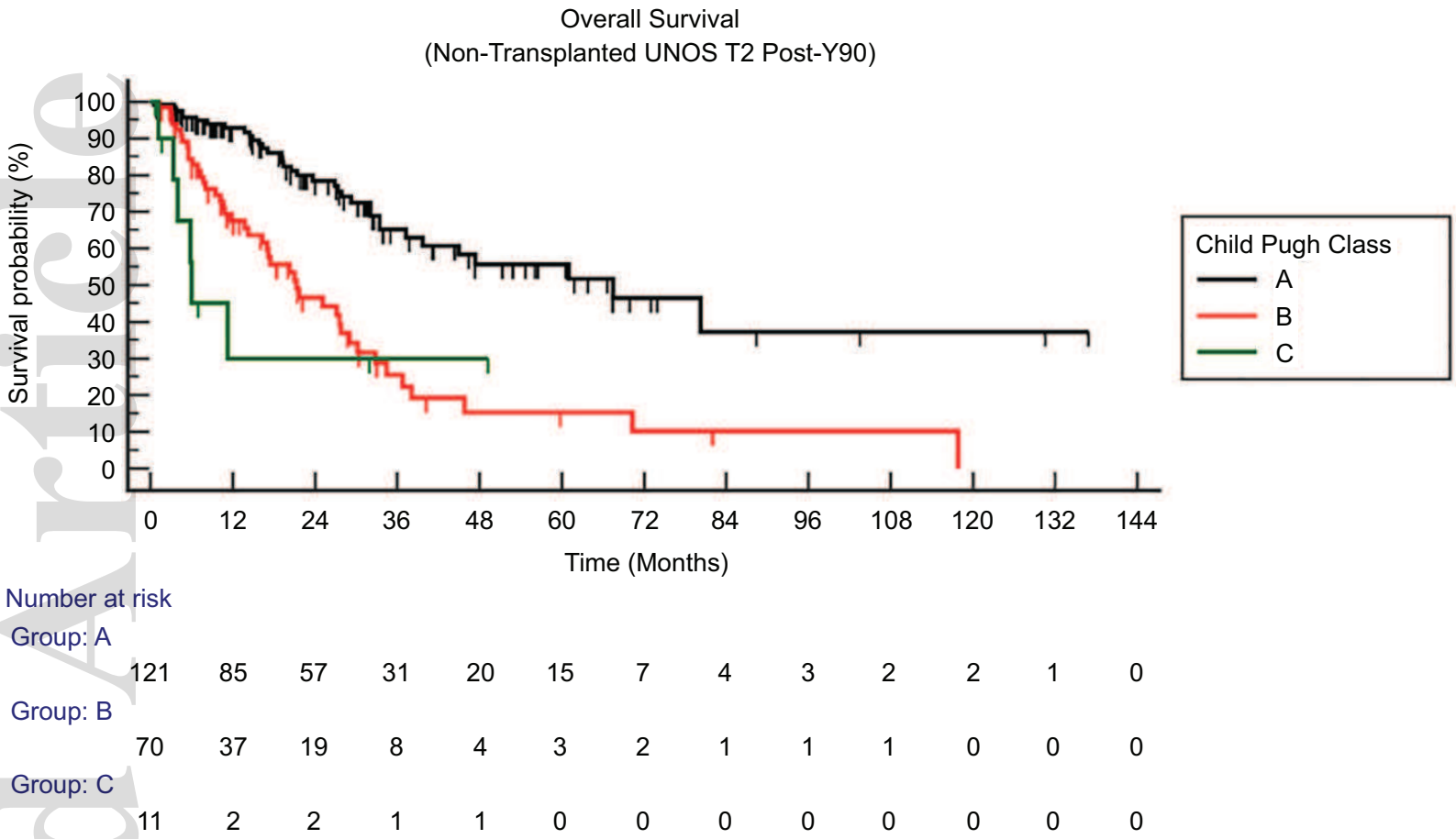

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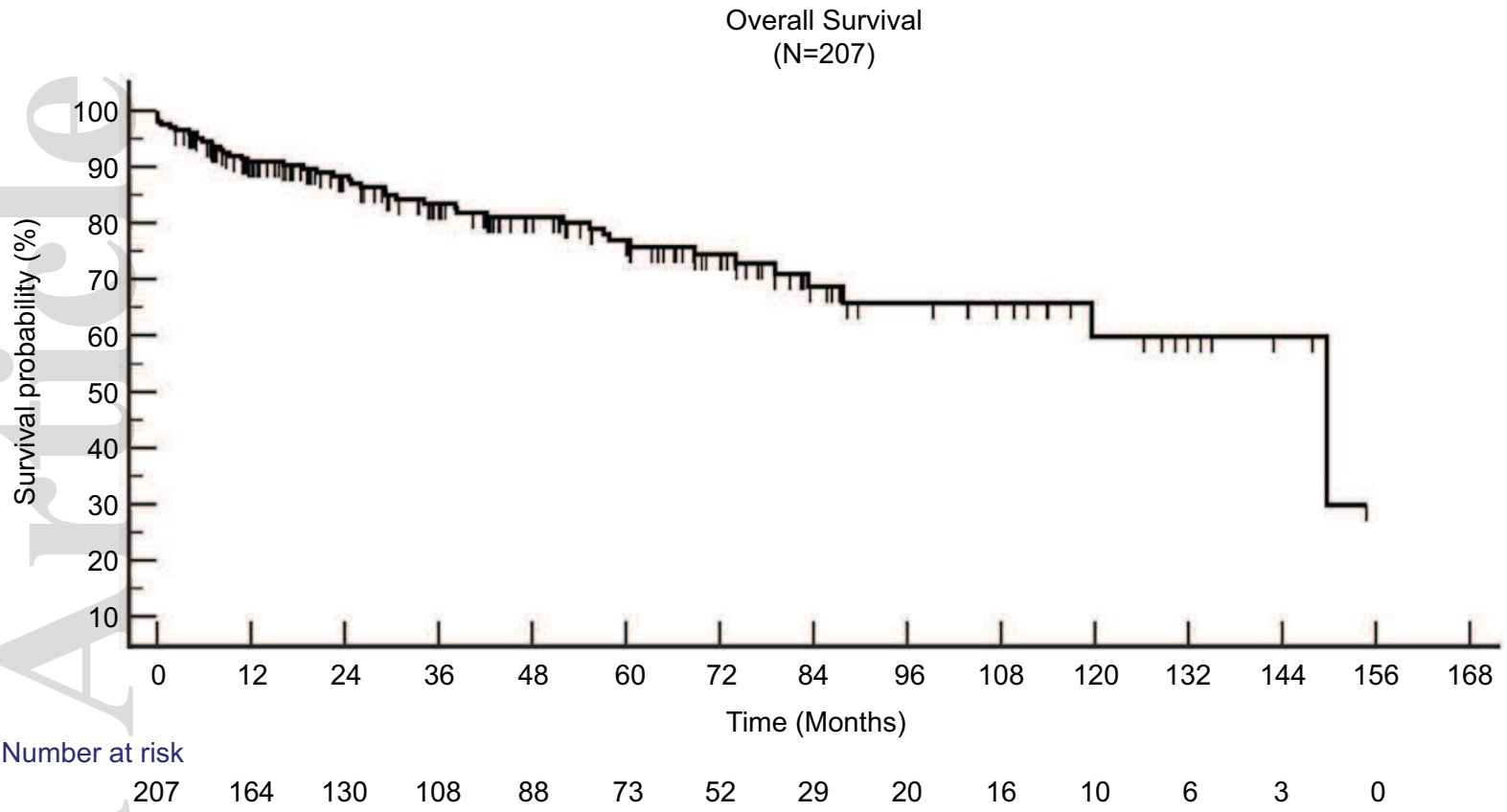

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SUPPLEMENTARY FIGURE LEGEND

Supplementary Figure 1: Time-to-recurrence.

Supplementary Figure 2: Disease-Specific Mortality rate.

Supplementary Figure 3: Recurrence-Free-Survival.

Supplementary Figure 4: High magnification histopathology slide showing completely necrotic tumor with Y90 microspheres in the background.

Supplementary Table 1: AFP Change in Patients with Baseline >100 ng/dL

Patient No.	AFP at Y90	AFP at LT	Absolute AFP Change post Y90	Percent Change post Y90
1	293.8	43.8	-250	-85.2%
2	2838	1436.1	-1401.9	-49.4%
3	9165.5	1208.8	-7956.7	-86.8%
4	452.9	99.3	-353.6	-78.1%
5	277.7	2.4	-275.3	-99.1%
6	142.6	33.2	-109.4	-76.7%
7	446.4	8.5	-437.9	-98.1%
8	809.4	17.4	-792	-97.9%
9	562.5	3.5	-559	-99.4%
10	2144.8	171.7	-1973.1	-92.0%
11	529.1	39.1	-490	-92.6%
12	1468.1	399.6	-1068.5	-72.8%
13	192.3	94.1	-98.2	-51.1%
14	2826.6	132.4	-2694.2	-95.3%
15	402.2	5.3	-396.9	-98.7%
16	610.9	17.4	-593.5	-97.2%
17	1076.4	292.8	-783.6	-72.8%
18	1728.6	42.5	-1686.1	-97.5%
19	14201.7	13774.1	-427.6	-3.0%
20	2290.7	2374.3	+83.6*	+3.7%*
21	3777	29.9	-3747.1	-99.2%
22	374.8	55.5	-319.3	-85.2%
23	155	7.6	-147.4	-95.1%
24	350.9	11.3	-339.6	-96.8%
25	1146.1	46.7	-1099.4	-95.9%
26	458.9	3.5	-455.4	-99.2%
27	378	7.6	-370.4	-98.0%
28	364.7	2.7	-362	-99.3%
29	616.5	27.6	-588.9	-95.5%
30	287	60	-227	-79.1%
31	110.8	12.2	-98.6	-89.0%
32	123.4	93.1	-30.3	-24.6%
33	284.2	349.6	+65.4*	+23.0%*
34	133.7	5.6	-128.1	-95.8%
35	15735.3	11.6	-15723.7	-99.9%
36	1053.7	70.5	-983.2	-93.3%
37	311.5	279	-32.5	-10.4%
38	205	13	-192	-93.7%

39	478	28	-450	-94.1%
40	166	28	-138	-83.1%
41	114	28	-86	-75.4%
42	800	21	-779	-97.4%
43	146	22	-124	-84.9%
44	255	21	-234	-91.8%
45	464	16	-448	-96.6%

Supplementary Table 2: UNOS Stages at Y90 and LT

Stage at Y90		Stage at Transplantation					
-	-	T0	T1	T2	T3	T4a	T4b
T1	9	1	6	2	-	-	-
T2	160	4	47	106	3	-	
T3	22	-	-	14	7	1	-
T4a	12	-	-	2	4	6	
T4b	4	-	-	2	1	-	1

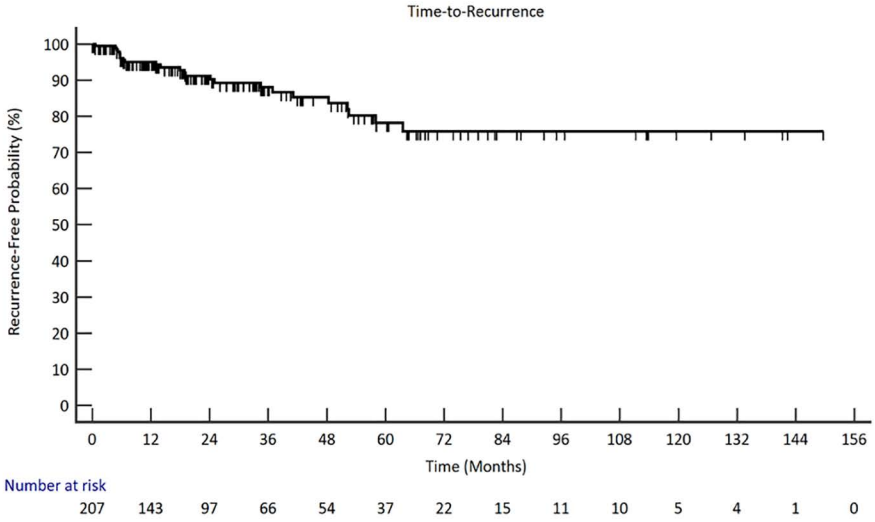
Supplementary Table 3: Tumor Recurrence after LT (N=24)

	Stage at Y90	Stage at LT	Liver Donor	Time between Y90 and LT	Time to first recurrence	Type of recurrence	Survival
1	T3	T3	DCD*	6 months	24 months	Lung (Treated with resection)	Alive at 154 months
2	T4b	T4b	Living Donor	9 months	4 months	Liver, bone, brain	Died at 5 months
3	T2	T2	DBD (liver and kidney)	10 months	19 months	Liver, lung	Died at 83 months
4	T4a	T4a	Living Donor	3 months	13 months	Liver, lung, bones	Died at 38 months
5	T4b	T3	Living Donor	2 months	6 months	liver	Died at 12 months
6	T2	T2	DBD	2 months	34 months	liver	alive at 114 months (F/U at Outside Hospital)
7	T3	T2	DBD	19 months	25 months	Liver, lung	Died at 38 months
8	T3	T2	DBD (liver and kidney)	7 months	6 months	Liver, lung	Died at 26 months
9	T2	T2	DBD	8 months	19 months	Lung	Died at 30 months
10	T2	T2	DBD	4 months	6 months	Bone	Died at 8 months
11	T2	T2	DBD	5 months	63 months	Liver	Died at 74 months
12	T2	T2	DBD	4 months	58 months	Chest wall (Treated with resection)	Alive at 110 months

13	T3	T3	DBD	11 months	37 months	Bone	Died at 42 months
14	T2	T1	DBD	9 months	48 months	Liver	Alive at 72 months
15	T2	T2	DCD	6 months	7 months	Lung, bone	Died at 8 months
16	T4a	T4a	DCD	18 months	41 months	Lung	Died at 55 months
17	T2	T2	DBD	12 months	6 months	Liver, bone	Died at 7 months
18	T2	T2	DCD	1 months	18 months	Liver	Died at 21 months
19	T2	T2	DCD	3 months	14 months	Lung	Died at 29 Months
20	T3	T4a	DCD	8 months	1 month	Liver, lymph nodes	Alive at 16 months
21	T3	T2	DBD	15 months	52 months	Lung (Treated with resection)	Alive at 111 months
22	T2	T2	DBD	3 months	33 months	Liver and Adrenal gland	Died at 58 Months
23	T2	T2	DBD	8 months	5 months	Liver	Died at 9 months
24	T2	T2	DBD	10 months	6 months	Lymph nodes	Alive at 8 months

*DCD: Donation after circulatory death.

**DBD: Donation after brain death.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72
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96
108
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Time (Months)
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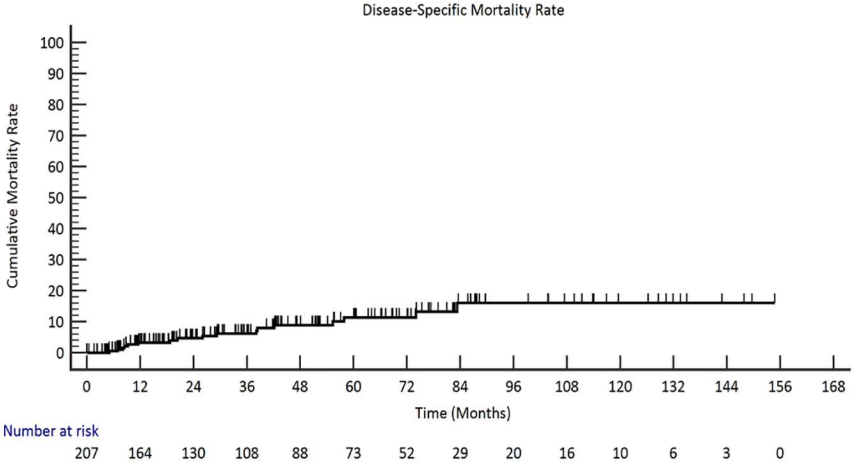
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Cumulative Mortality Rate
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132
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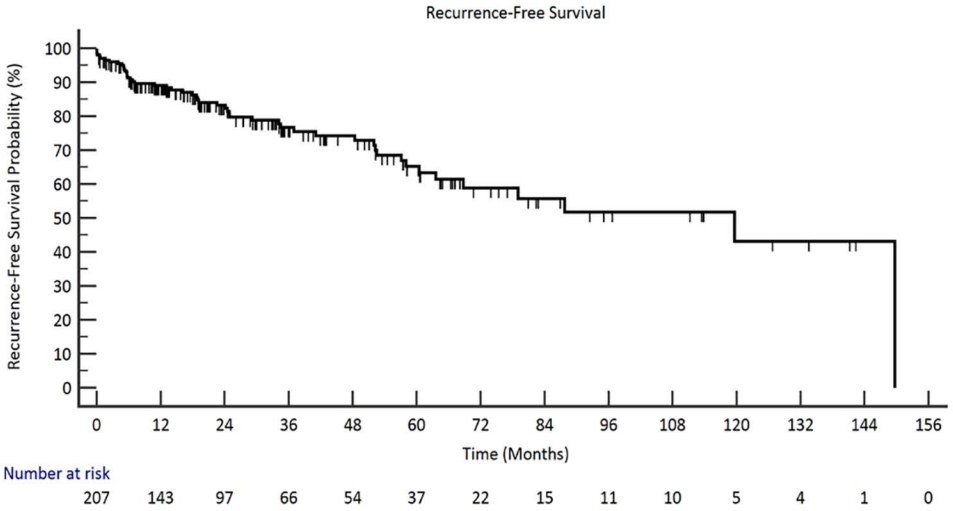
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Recurrence-Free Survival Probability (%)
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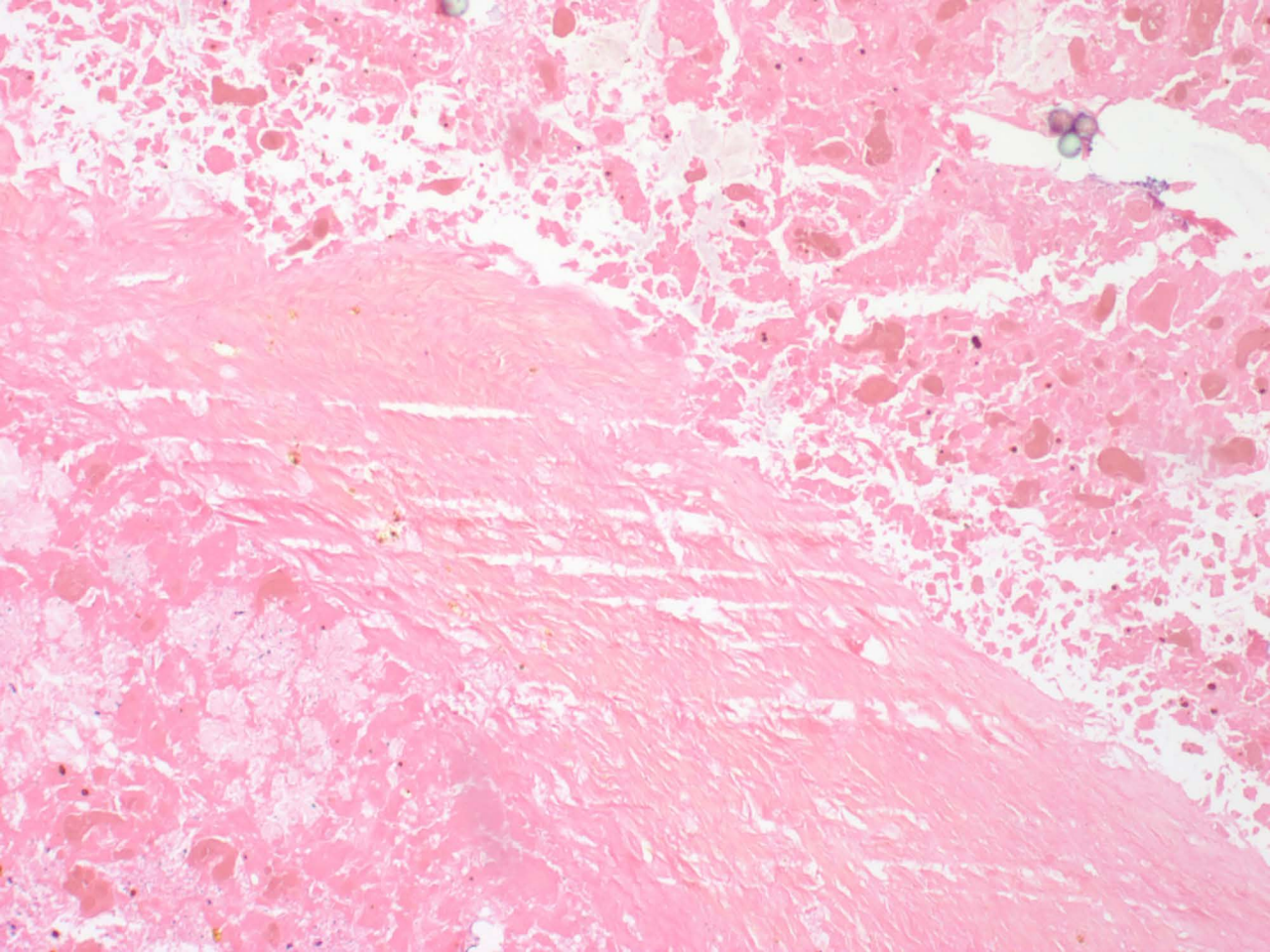

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-020-04976-8

SHORT COMMUNICATION

Correlation of Y90-absorbed radiation dose to pathological necrosis in hepatocellular carcinoma: confirmatory multicenter analysis in 45 explants

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Received: 13 June 2020 / Accepted: 27 July 2020

Abstract

Purpose To study the correlation between absorbed perfused liver dose using Y90 radioembolization and degree of hepatocellular carcinoma (HCC) necrosis in liver explants in a multicenter cohort analysis

Methods A retrospective analysis of 45 HCC patients treated between 2014 and 2017 is presented. Inclusion criteria were treatment-naïve solitary HCC ≤ 8 cm and Child-Pugh A liver status using the radiation segmentectomy approach. All patients underwent liver resection or transplantation (LT). Liver explants were examined per institutional routine protocols to assess histopathological viability of HCC. Tumor pathological necrosis was classified into complete (100% necrosis), extensive (> 50% and ≤ 99%) necrosis, and partial (< 50%) necrosis. Absorbed perfused liver doses were estimated using MIRD calculations. Associations between dose and degree of necrosis were studied.

Results Thirty-four (76%) patients underwent LT, and 11 (24%) patients underwent hepatic resection. Median radiation dose was 240 (IQR: 136–387) Gy. Thirty (67%) patients had complete pathologic necrosis (CPN) at explant, while 10 (22%) and 5 (11%) had extensive and partial necrosis, respectively. There were significant differences among perfused liver doses that exhibited partial, extensive, and complete necrosis ($p = 0.001$). Twenty-four out of twenty-eight (86%) patients who had dose > 190 Gy achieved CPN, while 11/17 (65%) who had < 190 Gy did not (Fisher's exact test; $p = 0.001$). Using binary logistic regression, only absorbed radiation dose was significantly associated with CPN ($p = 0.01$), while tumor size was not ($p = 0.35$). All patients receiving > 400 Gy exhibited CPN.

Conclusion Radiation segmentectomy for early HCC with ablative dosing > 400 Gy results in CPN. This represents the new standard target dose for radiation segmentectomy.

Keywords Yttrium-90 · Transplantation · Radiation segmentectomy

Editor:

This article is part of the Topical Collection on Oncology - General

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Yttrium-90 (Y90) radioembolization has been established as an effective liver-directed therapy (LDT) in bridging hepatocellular carcinoma (HCC) patients to liver transplantation and resection [1]. Successful bridging entails disease control by achieving tumor response and delaying tumor progression. Among patients who have been successfully bridged to liver transplantation or resection, histopathological exams of liver explants have revealed high rate of complete necrosis of treated HCC [2, 3]. While post-treatment complete resolution of tumor arterial enhancement by mRECIST has been correlated to complete necrosis, the need for a predictive biomarker remains. A study by Vouche et al. found that radiation dose > 190 Gy was associated with a high rate of complete tumor necrosis [4].

Published online: 04 August 2020

In this study, we present a 45 patient multicenter analysis of individuals who underwent Y90 from 2014 to 2017 and subsequently transplanted or resected. Inclusion criteria included solitary HCC ≤ 8 cm, no previous history of LDT, preserved liver function (Child-Pugh class A) and treatment using radiation segmentectomy (RS). All patients received Y90 glass microspheres, with dosimetry performed using the Medical Internal Radiation Dose (MIRD) scheme, where dose absorbed by a specific volume of interest is computed using the equation:

$$\text{Dose (Gy)} = \frac{\text{Administerd Activity (Gbq)x (1−Lung Shunt Fraction) x 50}}{\text{Mass of Perfused Liver Volume (Kg)}}.$$

In this analysis, the mass of the perfused liver volume is that of the radiated tumor-bearing segment. This is usually obtained using cone-beam CT, where the microcatheter is placed in the target segment, and the perfused tissue from there is the targeted area for RS. The liver explant was evaluated grossly and histologically. Histopathologic slides were examined after hematoxylin and eosin staining of 0.5–1-cm slice thickness of explanted liver to assess for tumor viability. The treated target lesion was examined for the presence of viable neoplastic tissue by the attending pathologist. The degree of necrosis was classified as follows: (1) complete pathological necrosis (CPN) (100%): no viable tumor; (2) extensive (50–99%) necrosis: significant necrosis with presence of minimal viable tissue; and (3) partial necrosis: defined as minimal necrosis encompassing < 50% of the treated tumor. The degree of necrosis was correlated to the absorbed Y90 radiation dose in the treated segment.

Forty-five patients met the inclusion criteria; 37 were treated at Northwestern Memorial Hospital, 5 at Mount Sinai Hospital, and 3 at University of Washington Hospital. Table 1 summarizes baseline tumor sizes, absorbed doses, and degree of necrosis in all 45 patients. Thirty-four (76%) patients underwent LT and 11 (24%) underwent hepatic resection. Median radiation dose was 240 (IQR: 136–387) Gy. Thirty (67%) patients demonstrated complete tumor necrosis at explant, while 10 (22%) and 5 (11%) had extensive and partial necrosis, respectively. There were no biliary complications, and no surgical difficulties were observed during transplantation or resection [5].

There were notable differences in radiation doses among the different degrees of necrosis achieved; complete necrosis patients received a median dose of 287 (IQR: 198–507) Gy, extensive necrosis patients received a median dose of 135 (IQR: 113–271) Gy, while partial necrosis patients received a median dose of 118 (IQR: 90–134) Gy (Fig. 1). Using independent samples Kruskal-Wallis test, there were significant differences in dose received by the tumor-bearing segments that exhibited partial, extensive, and complete necrosis ($p < 0.001$), with the significance being maintained

Table 1 Summary of baseline tumor sizes, absorbed doses, and degree of necrosis in all 45 patients

Patient	Degree of necrosis	Dose (Gy)	Tumor size (cm)
1	Complete	412	2.6
2	Extensive	114	3.1
3	Complete	244	2
4	Partial	86	4.6
5	Complete	188	2.2
6	Complete	219	2.1
7	Extensive	120	2.1
8	Extensive	284	2.1
9	Complete	176	2.4
10	Partial	134	2
11	Complete	138	3.8
12	Complete	207	2.8
13	Complete	164	2.2
14	Extensive	361	2.7
15	Complete	251	2.5
16	Complete	240	2.1
17	Extensive	146	2
18	Complete	359	2
19	Complete	463	4.2
20	Complete	102	2.1
21	Complete	200	3.7
22	Partial	94	2.5
23	Extensive	111	2.2
24	Partial	133	2.1
25	Complete	352	2
26	Extensive	266	2.5
27	Complete	253	2
28	Complete	549	2.8
29	Extensive	209	3.9
30	Complete	276	4.4
31	Complete	193	2.7
32	Complete	357	2.2
33	Complete	142	2
34	Complete	465	3.2
35	Partial	118	8
36	Extensive	102	2.8
37	Extensive	123	5.1
38	Complete	1355	2.0
39	Complete	1038	3.6
40	Complete	493	2.4
41	Complete	755	1.3
42	Complete	553	2.2
43	Complete	969	3.7
44	complete	645	2.3
45	Complete	297	2.7

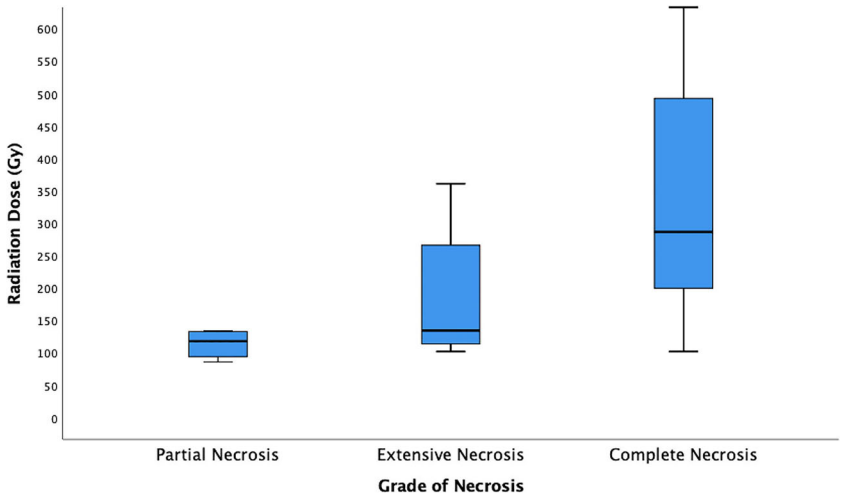

Fig. 1 Box and whisker plot showing ranges of radiation doses among different degrees of tumor necrosis. All cases having > 800 Gy achieved complete necrosis (these are outliers exceeding the upper *y*-axis limit and not displayed)

between complete and partial ($p = 0.001$), extensive ($p = 0.009$), but not between partial and extensive ($p = 0.189$). Further stratification by complete vs incomplete (partial + extensive) necrosis showed that radiation dose was significantly higher in the completely necrotic (mean: 402 Gy) versus incompletely necrotic (mean: 160 Gy) ($p < 0.001$).

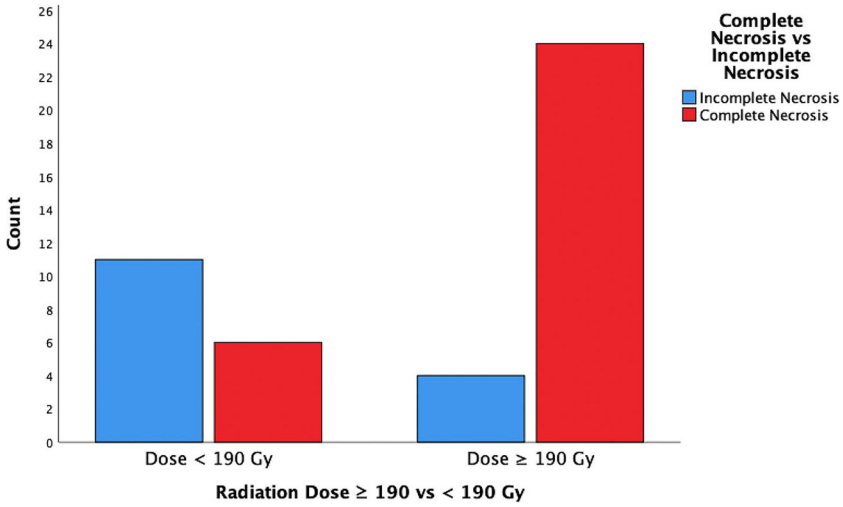

Fig. 2 Distribution of complete and incomplete necrosis among patients receiving > 190 and < 190 Gy

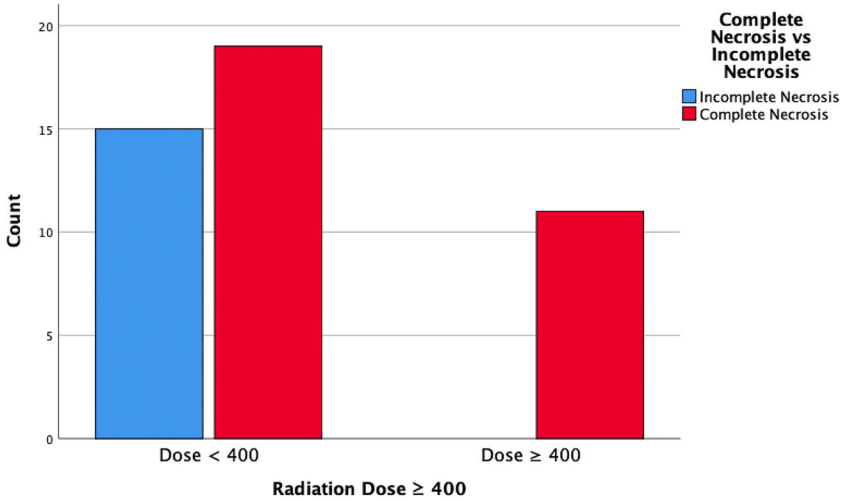

Fig. 3 Distribution of complete and incomplete necrosis among patients receiving > 400 and < 400 Gy

In order to validate the prior Vouche RS study initially proposing the 190-Gy threshold for CPN [4], we stratified patients by ≥ 190 ($n = 28$) and < 190 Gy ($n = 17$). Twenty-four out of twenty-eight (86%) patients who had absorbed radiation dose > 190 Gy achieved CPN, while 11/17 (65%) who had < 190 Gy did not (Fisher's exact test; $p = 0.001$), thereby validating the Vouche finding (Fig. 2). Median tumor size was 2.5 cm (range: 1.3–8). A binary logistic regression model was used to test for association between baseline tumor size and absorbed radiation dose of the segment and CPN. Only absorbed radiation dose was significantly associated with CPN ($p = 0.01$), while tumor size was not ($p = 0.35$).

The results of this multicenter analysis confirm the relationship between absorbed radiation dose of the tumor-bearing segment and CPN. Radiation segmentectomy, defined as the super selective administration of high dose to the tumor-bearing segment, has been shown effective in early-stage HCC. With high response rate and long survival outcomes (comparable to ablation, resection), RS has been shown to be potentially curative and can now be performed in select cases without the lung shunt study [6–8]. In this analysis, all patients had a solitary tumor that received selective injections of Y90. The results confirm the relationship between ablative dosimetry (> 190 Gy or above) and CPN. This finding further supports the technical adoption of radiation segmentectomy as the mainstay Y90 in the treatment of early-stage HCC, with dosing of at least 190 Gy. While this is consistent with current recommendations of 250–300 Gy, given the findings from this analysis, we recommend 400 Gy as the new contemporary threshold dose to achieve CPN [9] (Fig. 3). This is also of importance given the long-term survival imparted when CPN is achieved in transplant patients [5].

In conclusion, radiation segmentectomy with ablative dosing of Y90 for early-stage HCC is associated with CPN. The new threshold dose > 400 Gy is recommended to maximize the percent of patients achieving CPN.

Compliance with ethical standards

Conflict of interest All authors are advisors to Boston Scientific.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Northwestern University, University of Washington, Mount Sinai) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. Hepatology. 2017. https://doi.org/10.1002/hep.29691.
2. Riaz A, Kulik L, Lewandowski RJ, Ryu RK, Giakoumis Spear G, Mulcahy MF, et al. Radiologic-pathologic correlation of hepatocellular carcinoma treated with internal radiation using yttrium-90 microspheres. Hepatology. 2009;49:1185–93. https://doi.org/10.1002/hep.22747.
3. Vouche M, Kulik L, Atassi R, Memon K, Hickey R, Ganger D, et al. Radiological-pathological analysis of WHO, RECIST, EASL, mRECIST and DWI: imaging analysis from a prospective randomized trial of Y90 ± sorafenib. Hepatology. 2013;58:1655–66. https://doi.org/10.1002/hep.26487.
4. Vouche M, Habib A, Ward TJ, Kim E, Kulik L, Ganger D, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology. 2014;60:192–201. https://doi.org/10.1002/hep.27057.
5. Gabr A, Kulik L, Mouli S, Riaz A, Ali R, Desai K, et al. Liver transplantation following Yttrium-90 radioembolization: 15-year experience in 207-patient cohort. Hepatology. 2020. https://doi.org/10.1002/hep.31318.
6. Lewandowski RJ, Gabr A, Abouchaleh N, Ali R, Al Asadi A, Mora RA, et al. Radiation segmentectomy: potential curative therapy for early hepatocellular carcinoma. Radiology. 2018;287:1050–8. https://doi.org/10.1148/radiol.2018171768.
7. Biederman DM, Titano JJ, Bishay VL, Durrani RJ, Dayan E, Tabori N, et al. Radiation segmentectomy versus TACE combined with microwave ablation for unresectable solitary hepatocellular carcinoma up to 3 cm: a propensity score matching study. Radiology. 2017;283:895–905. https://doi.org/10.1148/radiol.2016160718.
8. Gabr A, Ranganathan S, Mouli SK, Riaz A, Gates VL, Kulik L, et al. Streamlining radioembolization in UNOS T1/T2 hepatocellular carcinoma by eliminating lung shunt estimation. J Hepatol. 2020;72:1151–8. https://doi.org/10.1016/j.jhep.2020.02.024.
9. Salem R, Padia SA, Lam M, Bell J, Chiesa C, Fowers K, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging. 2019;46:1695–704. https://doi.org/10.1007/s00259-019-04340-5.

Discussion on the LEGACY study and additional supportive studies

LEGACY: **L**ocal radio**E**mbolization using **G**lass microspheres (TheraSphere™) for the **A**ssessment of Tumor **C**ontrol with **Y**-90) study

October 7, 2020

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FORWARD: This supplemental document describes results of the LEGACY study recently presented at CIRSE 2000. Additional sub-group and secondary endpoint analyses will be presented at future congresses. In addition to LEGACY, data from 2 studies recently published by Gabr et al, which included LEGACY patients, are discussed. The results of these studies substantiate results of the LEGACY study and add to our knowledge around the use of TheraSphere in the treatment of HCC.

As a backdrop to the LEGACY study, the administration techniques used therein, and the importance of the new threshold dose suggested by LEGACY, previous relevant literature is included to provide historical perspective and support for the LEGACY results.

1.1 BACKGROUND INFORMATION ON THE USE OF THERASPHERE IN THE LEGACY STUDY

UNMET NEED FOR THERASPHERE AS A TREATMENT FOR HCC

HCC is the most common form of liver cancer accounting for approximately 70% of all primary liver cancers (1). The incidence of HCC is anticipated to continue increasing due to increasing incidence of hepatitis C-related cirrhosis, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD) and hepatitis B (5). The fastest increasing incidence of HCC is seen amongst men aged 55-64 years (5) (6).

The Barcelona Clinical Liver Cancer (BCLC) staging system provides treatment recommendations for HCC based on disease staging (7). Treatment and optimal therapy selection are often complicated by the concomitant existence of underlying liver cirrhosis (evaluated using the Child Pugh (CP) score) making the treatment of HCC unique amongst cancers (8). Patients must be assessed individually for best treatment options as there is great heterogeneity in disease characteristics within BCLC stages. Therefore, recommended treatment by the BCLC algorithm may not be suitable for an individual patient. Best outcomes are achieved when disease is treated in the early stages, tumor burden and spread is limited and treatment impact on normal liver tissue is minimized. Liver transplantation, ablation or resection are the currently recommended curative therapies for HCC but are suitable for only less than 20% of HCC patients at diagnosis (9). Although these 'curative' therapies offer the best outcomes, recurrence remains a risk with an approximate recurrence rate of 20% post transplantation within 2 years, up to 70% within 5 years post resection and up to 39% post ablation in lesions <5 cm (10) (11) (12) (13). Where curative measures are not appropriate or possible, (e.g., for patients with unresectable disease due to one or more of the following: lesions near critical structures, disease too advanced, poor surgical candidate due to age, co-morbidities, performance status or personal preference), locoregional liver-directed treatments may be an option. In these patients, TheraSphere can provide localized tumor control as **standalone** therapy. Curative treatment is the goal of HCC treatment and when TheraSphere is administered as neoadjuvant therapy to curative therapy, this goal can be achieved in some patients.

EVIDENCE SUPPORTING THE USE OF THERASPHERE AS EITHER NEOADJUVANT OR STANDALONE THERAPY FOR THE TREATMENT OF HCC

Selective liver treatment with TheraSphere is preferred over lobar treatment when HCC is limited to ≤2 segment(s) of the liver. **Radiation segmentectomy** is a technique whereby a high absorbed dose of radiation is administered to ≤2 tumor-containing liver segments effectively ablating or killing the tumor and normal tissue within the perfused segment. Ablative radioembolization often leads to complete pathological necrosis within the treated area, while sparing non-perfused normal tissue from radiation exposure. First described by Rhee et al, many others have since reported on the effectiveness and safety of radiation segmentectomy and the positive effect on tumor response, time to progression (TTP) and overall survival (OS) (14) (15) (16) (17) (18) (19) (20) (11). With time, outcomes have improved with smaller catheters, better imaging modalities (i.e., cone beam CT) and the identification of a threshold absorbed tumor dose of >190 Gy (recent literature supports a higher target of >250 Gy to the perfused volume). These improvements have

led to outcomes using radiation segmentectomy that are comparable to those attained with curative therapies (11) (21). Radiation segmentectomy is the best example of TheraSphere's ability to preserve liver function as minimal normal liver tissue is exposed to radiation while delivering a high ablative radiation dose to a limited treatment volume. Preservation of liver function is critical in patients with underlying cirrhosis as it allows patients and physicians to preserve other treatment options.

TheraSphere may be used as a **bridge to transplant** therapy providing durable tumor control in order to maintain transplant eligibility to within Milan criteria or as a downstaging therapy to meet Milan criteria (15) (22) (23) (24). Current recommendations note a waiting period prior to transplantation in order to establish the tumor biology wherein locoregional therapies, such as TheraSphere, may be administered as neoadjuvant treatment for tumor control. Response to neoadjuvant therapy, along with tumor biology, assists in identifying the best patients for the limited organ supply (25).

TheraSphere may be used as neoadjuvant therapy before resection. At presentation, some HCC patients may require hypertrophy of the future liver remnant (FLR) to become a resection candidate. Liver resection is limited in the setting of chronic liver disease by potential hepatic insufficiency due to a small FLR, the amount of liver which would remain post resection, incapable of sustaining adequate liver function. For patients with unilobar disease and good underlying liver function but with inadequate FLR, lobar administration of TheraSphere can provide localized tumor control resulting in atrophy of the treated lobe while concomitantly causing hypertrophy in the contralateral lobe, a procedure referred to as **Radiation Lobectomy**. This procedure has been well documented and makes curative resection a possibility for some HCC patients (26) (27) (28) (29) (30) (31) (32) (33) (34) (35). Gabr et al recently reported on a refinement of Radiation Lobectomy, called **Modified Radiation Lobectomy**. This administration technique combines a segmental administration (>190 Gy) with a lobar administration (80-120 Gy) to create this atrophy-hypertrophy response (26). Providing durable localized tumor control, stimulating FLR hypertrophy, evaluation of tumor biology and establishing a demarcation line for surgical resection have all been demonstrated for TheraSphere using Radiation Lobectomy as part of **bridge to resection** therapy.

An added advantage of bridging or downstaging therapy is the biological test of time inherent with these procedures, during which a patients' tumor biology can be evaluated. Patients responding to locoregional treatment using for bridging or downstaging therapy , including TheraSphere, are typically considered as being more favorable for curative therapy since these patients tend to experience better and long-lasting outcomes post-transplant or resection than non-responders (24) (26). In patients with more aggressive disease, often characterized by a lack of therapy response, this waiting time prevents patients undergoing a surgical procedure that would not provide long-term benefit.

SAFETY OF THERASPHERE

The safety profile of TheraSphere has been well established over 20 years of use and with this use it has become clear that with optimal patient selection, pre-treatment angiography, imaging, catheterization technique, and optimal dosing, treatment efficacy is improved, and toxicity is

mitigated. Amongst the most frequently reported TheraSphere-related non-serious, side effects are fatigue, nausea, vomiting, anorexia and abdominal pain collectively characterized as post radioembolization syndrome. These side effects are usually not serious enough to warrant hospitalization and typically last 7-10 days (15) (36) (37). Transient increases in serum bilirubin and other liver function parameters are seen; however, in the face of underlying cirrhotic disease, this is not unexpected and are generally transient and, in most patients, return to normal without medical intervention. Many patients experience sustained lymphopenia but these laboratory changes usually are without clinical sequelae and do not require medical intervention. Maintaining existing liver function on any treatment, is a critical safety indicator for an effective HCC treatment. Patients with underlying cirrhosis will decompensate as a natural progression of their disease therefore, any effective HCC treatment must balance the benefits of HCC treatment with potential impact on normal liver function. Changes in CP score, ECOG status, increases in blood bilirubin and decreased albumin levels can indicate decreasing liver function with liver decompensation representing a poorer prognosis. In a 1,000 patient retrospective study of TheraSphere including patients undergoing radiation segmentectomy, none of the 190 patients with limited disease (UNOS T1/T2) and CP A reported Grade 3/4 increased toxicity from baseline or new bilirubin or albumin toxicities within 6 weeks post treatment (38).

THE IMPORTANCE OF DOSE

Published evidence confirms that for TheraSphere, achieving a threshold absorbed tumor dose (while limiting exposure of normal tissue within the perfused volume to below a threshold level) is the major determinant for good clinical outcomes across the BCLC staging system (19) (11) (39) (40) (41) (42) (43) (44). Early studies with TheraSphere used single-compartment dosimetry and lobar treatments to achieve neoadjuvant to curative treatment or as a palliative treatment. Single compartment dosimetry, using the MIRD schema, has widely been used to determine the dose delivered to the perfused liver volume. This dosimetry method assumes homogenous distribution of microspheres and thus absorbed dose within the perfused tumor and normal tissue volume, which is not the case as hypervascular tumors will have preferential vascular uptake of microspheres compared to normal perfused tissue. As experience with TheraSphere has increased, personalized treatment options have developed. Personalized options include selective treatment to limit normal tissue exposure, multiple catheter placements to personalize the absorbed dose to tumor and normal tissue, evaluation of multi-compartment dosimetry to adjust the tumor and normal tissue absorbed dose and targeting portal vein tumor (PVT), all which help to provide optimal individual patient outcomes.

As noted above, selective ablative radiation is preferred when HCC is limited to ≤2 liver segments, however, the principles of achieving a threshold absorbed dose apply to all tumors. Multi-compartment dosimetry (also based on the MIRD schema) measures the absorbed dose of each volume of interest e.g., tumor volume or normal parenchyma volume. By virtue of the hypervascularity of HCC tumors, preferential distribution of TheraSphere typically occurs in tumors where the recently reported tumor:normal tissue ratio range was 1.4 to 14.7 (39). Other factors affecting absorbed dose to tumor and normal tissue include 1) the activity infused, 2) the perfused liver volume and 3) the volume ratio of tumor to normal tissue. Multi-compartment dosimetry takes each of these factors into account in order to personalize the tumor and normal tissue absorbed dose for each patient and to assess PVT targeting, when present. A number of

retrospective studies have evaluated these treatment factors and their contribution to improved overall survival (OS) (40) (41) (42). Prolonged OS was noted for patient treatment factors of multi-compartment TheraSphere dosimetry when a threshold tumor absorbed dose was achieved, good PVT targeting was achieved, normal tissue absorbed dose was below a maximum threshold and a minimum FLR (treatment naïve normal tissue volume) was preserved (42).

One of the most compelling multi-compartmental studies published to date is the phase 2 randomized, multi-center DOSISPHERE-01 study in intermediate and advanced HCC patients who typically receive lobar treatment (43). This study compares outcomes using single compartmental dosimetry to determine the absorbed TheraSphere dose within the perfused liver volume (planned absorbed dose was 120±20 Gy) with outcomes obtained from multi-compartment (personalized) dosimetry (planned absorbed dose was ≥205 Gy to the index lesion, 250-300 Gy if possible; with ≤120 Gy to the perfused normal liver tissue which was ≥30% FLR). Tc-99m MAA SPECT/CT was used to calculate the planned absorbed dose for multi-compartment dosimetry and to assess PVT targeting of Tc-99m MAA, which served as a surrogate for TheraSphere. This study clearly demonstrated that with multi-compartment dosing and good PVT targeting superior clinical outcomes in terms of index lesion objective response rate (ORR) and OS were attained compared to single-compartment dosimetry (71.4% vs 35.7%, and median OS of 26.6 months vs 10.7 months, respectively).

In summary, the literature supports the role of TheraSphere used either as primary, typically standalone therapy, or neoadjuvant bridging therapy for HCC patients. Regardless of the treatment intent, the cumulative body of evidence on TheraSphere confirms that optimal clinical outcomes are achieved when the dosimetry is optimized based on individual patient cirrhosis status and HCC characteristics.

PURPOSE OF LEGACY

The purpose of LEGACY was to expand on the body of evidence with TheraSphere by confirming TheraSphere provides effective and durable localized tumor control treatment for unresectable HCC patients. The study is robust and comprehensive by virtue of the following study characteristics:

- First study to report the perfused volume absorbed dose necessary to achieve an optimal and durable tumor response
- Study reported more outcome data than many previously published TheraSphere studies:
    - Many endpoints evaluated using 3 tumor response criteria (localized mRECIST, mRECIST, RECIST 1.1)
    - 19 secondary safety and efficacy endpoints
    - 13 different subgroups analyzed for both primary and secondary endpoints
    - Descriptive data on additional parameters of interest e.g. type of subsequent treatments

In addition, robustness was ensured by virtue of:

- Multi-center study
- Data from 162 patients collected sequentially at each center

- Blinded Independent Review Committee (BICR) assessed images for primary endpoints data
- 2 primary endpoints required to be met for study success
- Tumor response (CR of PR) at the first timepoint required confirmation at a second timepoint > 4 weeks from the first noted response assessed by BICR
- Statistical sensitivity analyses were performed for primary and secondary endpoint to confirm primary statistical analyses

1.2 LEGACY STUDY DESIGN

LEGACY is a retrospective, single-arm, multi-center study conducted at 3 sites in the U.S. Data from 162 consecutive eligible patients treated with TheraSphere between January 2014 and December 2017 from all 3 sites was included.

Eligibility criteria for the study are as follows:

Inclusion criteria:

- ≥ 18 years of age
- confirmed unresectable HCC (by histology or imaging) of any etiology
- patients with an unresectable solitary HCC lesion ≤ 8 cm at largest diameter measured using mRECIST
- BCLC A with ECOG 0 or BCLC C with ECOG 1
- Child Pugh A disease
- Has received lobar (150 ± 20 Gy) or selective TheraSphere administration
- has received either lobar (up to 180 Gy) or selective TheraSphere treatment
- pre (multi-phase contrast enhanced CT or contrast enhanced MRI within 60 days prior to TheraSphere- if >60 days, confirmatory image must be taken at time of angiography) and post treatment imaging available (multi-phase contrast enhanced CT or contrast enhanced MRI).

Exclusion Criteria:

- no prior liver transplantation, surgical resection, locoregional or systemic therapy for HCC
- no portal vein thrombus (PVT
- no extrahepatic disease (EHD)
- no clinically evident ascites or on diuretics for ascites
- no hepatic encephalopathy
- no synchronous diagnosis of additional malignancy besides HCC

OTHER STUDY DESIGN CONSIDERATIONS

In order to minimize bias with respect to response evaluations, radiologic response assessments were conducted by a trained BICR. Images were assessed separately by two independent reviewers, on a timepoint by timepoint basis blinded to visit sequence. Once all visits were completed for a patient, a further unblinded overall patient review was performed where

reviewers could amend their initial evaluation. Adjudication was implemented where differences between reviewer assessments occurred and this adjudication was considered final.

Localized mRECIST was used to evaluate both primary endpoints in LEGACY. The use of mRECIST, an evaluation tool specific for HCC, has been used in many HCC publications for diagnosis, treatment and recurrence due to increased sensitivity and specificity (16) (45) (46) (47). Using localized mRECIST to evaluate localized tumor response provides the most precise evaluation of the tumor response to a single locoregional therapy and minimizes confounding factors, for example, new tumors outside the treated area, pseudo-progression noted on imaging, or inclusion of non-viable scar tumor tissue in response measurements. Both RECIST 1.1 and mRECIST were used in secondary endpoint evaluations in LEGACY. Generally, these evaluation tools result in lower response rates than localized mRECIST as they consider not only localized tumor response, but also liver and extrahepatic response, and disease progression. For HCC, RECIST 1.1 is limited in HCC as a response assessment since a decrease in tumor size does not occur in all patients and if present, may lag behind the time window noted for mRECIST. As a consequence, evaluations using RECIST 1.1 generally have the lowest response rates amongst the 3 evaluation tools due to fewer and slower changes in size.

1.2.1 Primary Objectives: Localized Tumor Control and Duration of Response within Treatment Area

The two primary endpoints of the study were:

1) Objective response rate (ORR) defined as the percentage of patients with a confirmed response (complete response (CR) or partial response (PR)) as determined by localized modified RECIST (mRECIST); and

2) Duration of response (DOR) defined as the duration between the confirmed first response (CR or PR) and the first observation of progressive disease (PD) by localized mRECIST

Note: Localized mRECIST measures tumor response within the treatment area, including the entirety of any tumor that is either partially or completely within the treatment area using mRECIST.

The study success criteria were:

1) Lower limit of 95% confidence interval (CI) for ORR by localized mRECIST >40%; and

2) DOR by localized mRECIST ≥6 months for ≥60% of responders

To be considered a successful study, both criteria had to be met.

1.3 LEGACY Results

1.3.1 Patient Characteristics

The following table lists patient characteristics of interest.

Table 1: Patient Characteristics

Patient Characteristics	Treated Population (N=162), N (%)	Patient Characteristics	Treated Population (N=162), N (%)
Median age (range), years	66 (21-90)	**Median Tumor Size (range), cm**	2.6 (0.9-8.1)
≥ 18 to < 65	69 (42.6)	**Initial Y-90 Treatment Goal**	
≥ 65 to < 75	64 (39.5)	Radiation segmentectomy	104 (64.2)
≥ 75	29 (17.9)	Radiation lobectomy	8 (5.0)
Gender, male	123 (75.9)	Bridge to liver transplantation	36 (22.2)
HCC Etiology		Other	1 (0.6)
HCV	112 (69.1)	Unknown	13 (8.0)
Alcohol	48 (29.6)	**Type of Infusion**	
NASH	23 (14.2)	Selective	155 (95.7)
HBV	15 (9.3)	Lobar	3 (1.9)
Other/unknown	5 (3.1)	Mixed	4 (2.5)
ECOG Status		**Absorbed dose to perfused liver volume (Gy), median, (IQR)**	410.1 (199.7, 797.7)
0	98 (60.5)	**Number of TheraSphere Treatments**	
1	64 (39.5)	1	130 (80.2)
BCLC Status		≥2	32 (19.8)
A	98 (60.5)		
C	64 (39.5)		
AFP ≥ 200 ng/mL	24 (14.8)		

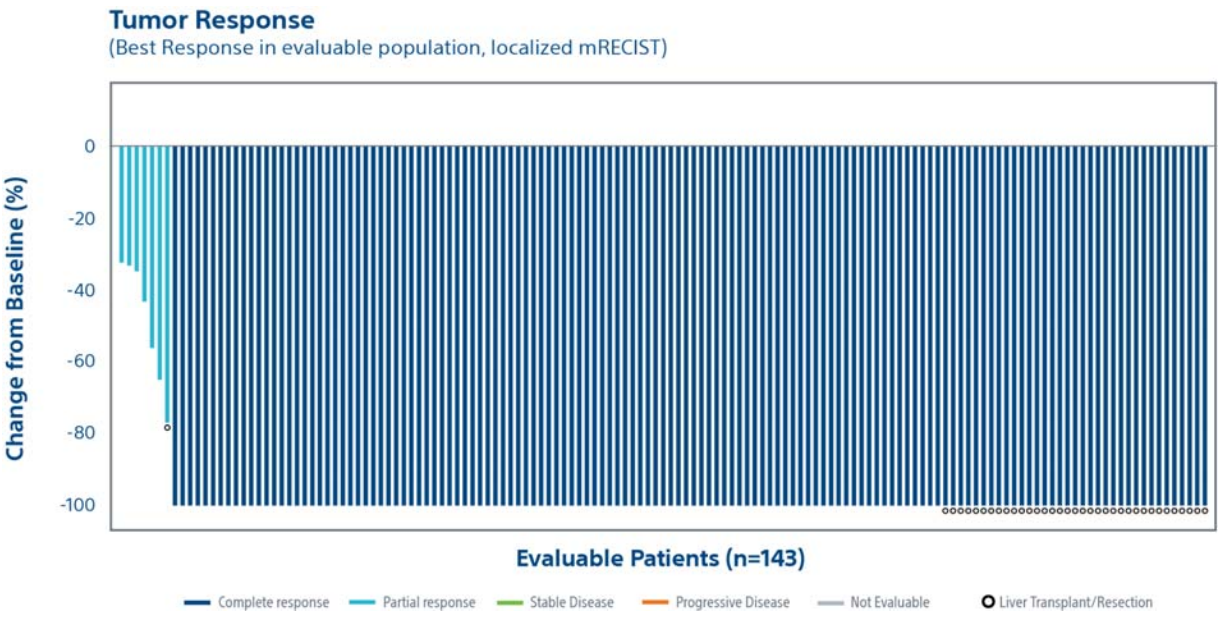
1.2.2.1 OBJECTIVE RESPONSE RATE AND LOCALIZED TUMOR RESPONSE

Objective response rate using localized mRECIST ORR was 72.2% (95% CI: 64.9, 78.5) in the Treated Population (n=162) of which 115 evaluable patients (71.0%) had a confirmed response

of CR and 2 patients (1.2%) had a confirmed response of PR. To be deemed evaluable, patients must have had a confirmatory image > 4 weeks after the first occurrence of CR of PR as evaluated by BICR. There were no patients with SD or PD response as per localized mRECIST. Notably, 20 patients were not evaluable for ORR as they underwent liver transplantation or resection which led to lack of confirmed response imaging or to lack of imaging assessments within the pre-defined windows.

Figure 1 shows the waterfall plot of the best response in the evaluable population (n=143) using localized mRECIST. Best response is what is typically reported in the literature and does not require confirmatory imaging response at a second timepoint. The response rate in this population was 88.3% with 84% (n=136) reporting a best response of CR and 4.3% (n=7) reporting a best response of PR. The median time to best response was 3.9 months (95% CI: 3.5, 4.1 months) by Kaplan-Meier (KM) analysis and using localized mRECIST. This best response was attained with only 1 TheraSphere treatment in 96.8% of patients, with 100% of patients attaining their best response after 2 treatments, assessed by localized mRECIST.

Figure 1: Best Tumor Response



The ORR results in LEGACY are consistent with published literature demonstrating excellent response rates of solitary lesions treated with TheraSphere. Lewandowski et al demonstrated an ORR in solitary lesions ≤5cm of 90% using European Association for the Study of the Liver (EASL) criteria (enhancement) and 71% using WHO criteria (size) in patients who did not undergo transplantation (11). LEGACY enhancement criteria too reported a higher response rate; ORR using mRECIST was 68.8% (95% CI: 61.0, 75.2) and using RECIST 1.1. was 46.3% (95% CI: 38.8, 54.0) following TheraSphere treatment. Vouche et al similarly examined response rate of unresectable solitary lesions ≤5cm and demonstrated an ORR of 87% using mRECIST (19). Biederman et al reported a CR rate of 82.9% in patients with lesions ≤3cm treated with

TheraSphere (18). In a Landmark analysis using data from TheraSphere-treated patients, fewer responders and a longer time to achieve response were noted for RECIST 1.1 versus the tumor/tissue enhancement criteria EASL. mRECIST provides early and better predictability than RECIST 1.1 of tumor response correlation to OS for locoregional therapy in general, and for TheraSphere specifically (20).

The importance of achieving good tumor response, as was seen in LEGACY, is highlighted in a publication by Riaz et al who demonstrated a positive correlation between tumor response to TheraSphere treatment (CR or PR) and OS in a Landmark analysis (20). They demonstrated that responders survived longer than non-responders regardless of CP score or tumor size, that tumor response can predict survival and concluded that attaining a CR should be the treatment goal with TheraSphere. The ORR and OS relationship was further supported by recent data from Garin et al in the DOSISPHERE-01 study. In this study large HCC index lesions (≥7cm) were treated with TheraSphere using standard dosimetry resulting in an ORR of 35.7% in the mITT (in the modified intention to treat population used for the primary endpoint) using EASL and a corresponding median OS of 10.6 months in the intention to treat (ITT) population (43). In the comparison group, using multi-compartment dosimetry, an ORR of 71.4% and a corresponding median OS of 26.7 months was achieved. These 2 studies demonstrate the criticality of attaining good tumor response with TheraSphere and the resultant OS advantage. Notably, a relationship between tumor response and OS was not observed in the SARAH or SIRveNIB studies using resin microspheres (SIR-Spheres®).

1.2.2.2 DURATION OF RESPONSE

Not only is ORR important in assessing efficacy, DOR is also of paramount importance as most HCC patients die due to HCC disease progression (48). Regardless which HCC therapy a patient receives, recurrence remains a risk. For unresectable HCC with limited treatment options, longer therapeutic effectiveness translates into a longer time to progression (TTP), extending the period before additional therapy is required. Reducing the number of treatments may also reduce the impact on normal liver function, decreasing the rate of liver decompensation due to cirrhosis. In patients awaiting surgical interventions, a more durable response provides time to assess the aggressiveness of the disease; essentially a biological test of time. This determination is beneficial to assess which patients may benefit most from transplantation or resection as patients with aggressive disease are more likely to experience recurrence (25). In addition, a longer DOR allows the opportunity to extend the organ procurement wait time while remaining within Milan transplant criteria.

In LEGACY, 89 of the 117 responders (76.1%) had a DOR by localized mRECIST of ≥6 months, exceeding the boundary for success, namely DOR ≥60%. Through 24 months after the first TheraSphere treatment, no patient had disease progression by localized mRECIST. Using RECIST 1.1 and mRECIST, 72% and 74.8% of patients respectively, had DOR ≥6 months consistent with the 76.1% achieved using localized mRECIST.

Time to best response is of interest in any malignant disease but in HCC is especially important for the following reasons: 1) in LEGACY all responses were either CR or PR by localized mRECIST which, as reported by Riaz et al, can translate into longer OS (20); 2) the sooner a best

response is attained, the sooner an evaluation regarding the patients' eligibility with respect to curative therapy can be made; given the unpredictability of available transplant organs, timing can be critical; 3) the disease-free interval and time to subsequent HCC treatment is extended by an early response to treatment and 4) although not examined in the LEGACY study, some aspects of quality of life have been shown to improve post TheraSphere treatment thus an early response to therapy is desired (49). As mentioned above, median time to best response by KM analysis by localized mRECIST was 3.9 months (95% CI: 3.5, 4.1 months) and this short response interval as well as the long DOR (all responders were without disease progression at 24 months) makes TheraSphere an attractive option for the treatment of HCC.

In summary, the ORR and DOR results met the study success criteria; thus the study was deemed a success. Both primary endpoint results were consistent across all subgroups based on demographics, disease characteristics, and treatment parameter analyses. The results indicate that TheraSphere provides durable localized tumor control in patients with unresectable HCC.

1.2.2 Other Indicators of Response and Durability of Response to TheraSphere (Secondary Endpoints)

The table below lists the secondary endpoint data collected in the LEGACY study. Results of several of the most important endpoints are presented below.

Table 2: Secondary Endpoints in LEGACY

	Tumor Response Criteria		
Endpoint	**Localized mRECIST**	**mRECIST**	**RECIST 1.1**
ORR and DoR		√	√
Disease Control Rate (CR+PR+SD)	√	√	√
Duration of disease control	√	√	√
Time to best response within the treatment area	√		
Hepatic time to progression (hTTP)		√	√
TTP	√	√	√
Progression free survival (PFS)	√	√	√
• Overall Survival (OS) • % of patients maintaining or improving baseline CP A status • % of patients maintaining or improving baseline ECOG status • % of patients attaining and/or maintaining Milan transplant criteria • % of patients with pre-specified % decrease in baseline AFP levels • # of TheraSphere treatments to achieve best tumor response			

- Absorbed dose to perfused liver volume and the association with tumor response and toxicities
- Characterization of SAEs and AEs within 60 days post treatment and of at least possibly related events until 12 month post treatment. Radiation-specific events until patient completes the study

1.2.2.1 HEPATIC TIME TO PROGRESSION ((H)TTP) AND (HEPATIC) PROGRESSION FREE SURVIVAL ((H)PFS)

Figure 2 below shows the time to localized tumor progression in the treated population when assessed using the 3 tumor response criteria. Median TTP was not reach in many analyses, therefore the percentage of patients without tumor progression at 24 months is reported. Using localized mRECIST, mRECIST or RECIST 1.1, the percentage of patients without localized tumor progression at 24 months was 100%, 84.1% and 82.0%, respectively. The study demonstrated a local recurrence rate within the localized treated area (using localized mRECIST) of 5.6% (9/162).

Figure 2: Time to Progression

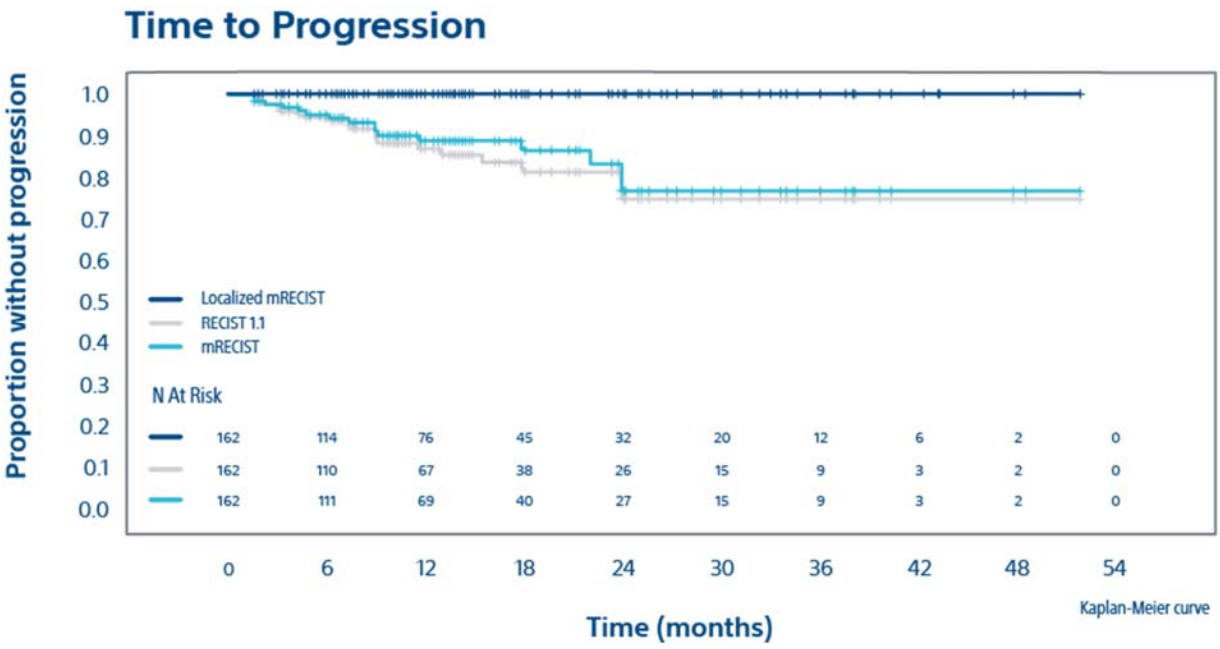
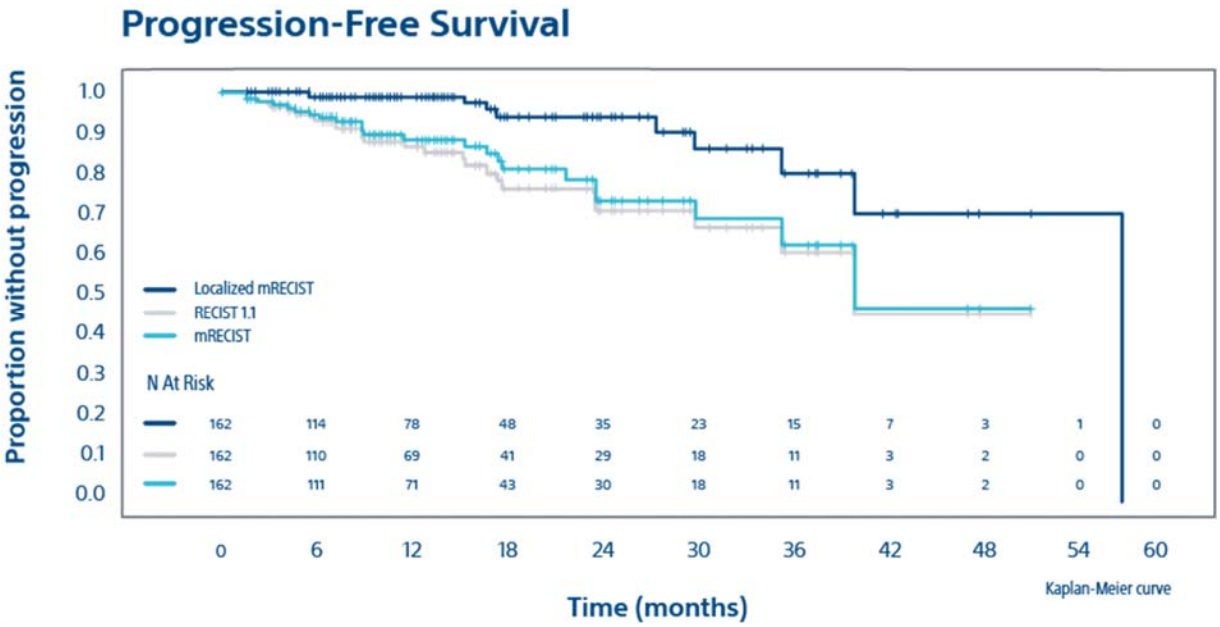


Figure 3 below, shows PFS in the treatment population using 3 response criteria. At 24 months, the percentage of patients alive and without disease progression was 93.9%, 78.8% and 76.6% using localized mRECIST, mRECIST and RECIST 1.1, respectively. These data demonstrate a long duration of response to localized treatment with TheraSphere.

Figure 3: Progression Free Survival



Several studies have reported TTP and PFS outcomes for single lesions treated with TheraSphere using radiation segmentectomy. Biederman et al reported a median TTP of 11.1 months (95% CI: 8.8, 25.6 months) in a retrospective study including 41 patients with lesions ≤3 cm treated with TheraSphere (18). Vouche et al reported a median time to disease progression of 33.1 months (IQR: 10-35 months) in 102 patients with lesions ≤5 cm treated with TheraSphere (19). Both studies included BCLC A and C patients. Lewandowski reported a median TTP of 2.4 years (95% CI: 2.1, 5.7 years) in 70 patients with single lesions ≤5 cm and BCLC A disease, of which 72% of patients had no target lesion progression at 5 years (11). None of these 3 studies reported on PFS.

Collectively, these data demonstrate that patients who received TheraSphere as standalone treatment experienced a long disease-free interval post TheraSphere treatment.

1.2.2.2 ABILITY TO MAINTAIN LIVER FUNCTION AND PERFORMANCE STATUS

The goal of any liver cancer treatment is to treat the liver lesion without compromising underlying liver function or overall performance status. Both CP and ECOG are used to evaluate a patient's overall response to therapy, overall well-being which may affect quality of life and ability to tolerate future treatments. In LEGACY, all patients had baseline well compensated liver function (CP A) and good performance status (ECOG of 0 or 1). Of the 77 patients with CP data at 6 months post TheraSphere, 72.7% (n=56) either maintained or improved their CP score from baseline. At 12, 18 and 24 months, 73.2% (30/41), 80.0% (16/20) and 84.6% (11/13) respectively, patients with baseline CP data at those specific time points, either maintained or improved their CP score from baseline.

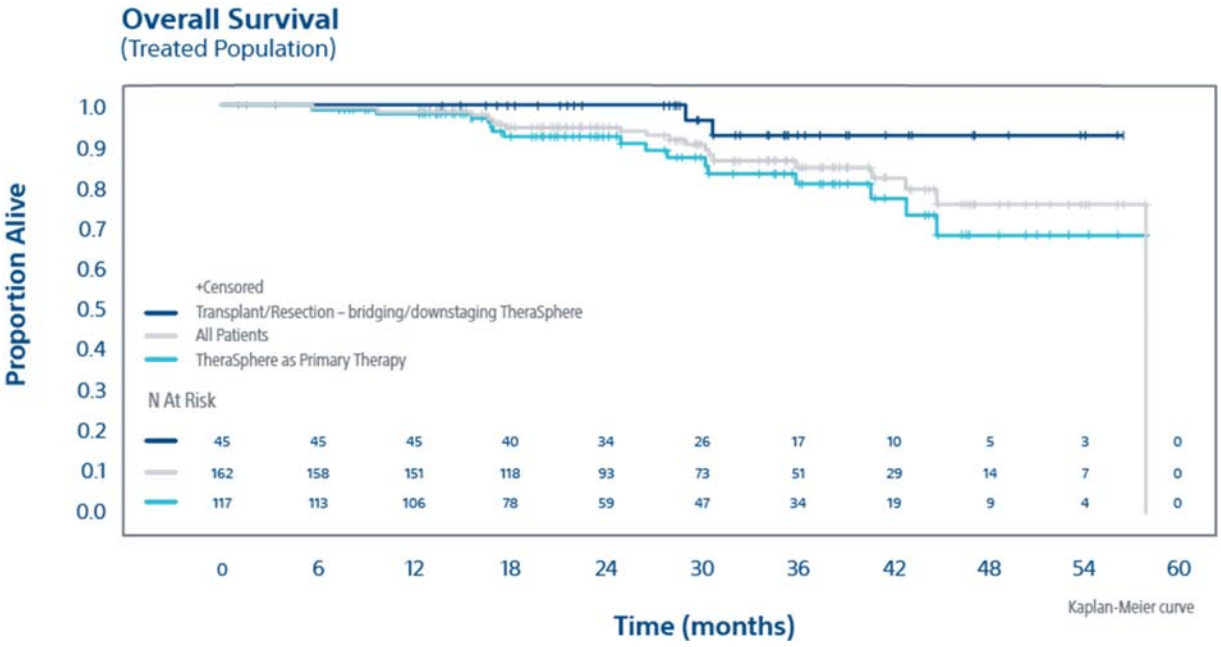
Similarly, of the 77 patients with ECOG data at 6 months post TheraSphere, 89.6% (n=69) either maintained or improved their ECOG Performance Status. At 12, 18 and 24 months, 87.2%, 85.2% and 82.4% of patients with ECOG data at the specified time point either maintained or improved their ECOG status from baseline.

These data support the use of a locoregional therapy to treat HCC lesions and without incurring any detrimental long-term consequence to liver function or overall well-being in the majority of patients. Notably, since LEGACY is a retrospective study, some CP score and ECOG data were missing at the assessment timepoints, however, the long follow-up, OS data and CP scores in LEGACY attest to the notion that liver decompensation was likely minimal.

1.2.2.3 EFFECT OF THERASPHERE ON OVERALL SURVIVAL

Figure 4 shows the OS curves for the treated population for 1) all treatment patients 2) patients receiving TheraSphere for neoadjuvant therapy and 3) patients who received TheraSphere as their primary treatment (e.g. did not go on to be transplanted/resected).

Figure 4: Overall Survival



At 24 months post treatment, 94.8%, of all treated patients (n=162), 100% of transplanted/resected patients (n=45) and 92.5% of patients (n=117) who received TheraSphere as their primary treatment were alive. At 36 months post treatment, 86.6%, of all treated patients (n=162), 92.8% of transplanted/resected patients (n=45) and 83.5% of patients (n=117) who received TheraSphere as their primary treatment were alive.

The importance of achieving durable tumor response and its relationship with OS, is highlighted in a publication by Riaz et al who demonstrated a positive correlation between tumor response (CR or PR) and OS in a Landmark analysis (20). They demonstrated that responders survived longer than non-responders regardless of CP score or tumor size, that tumor response can predict

survival and concluded that attaining a CR status should be the treatment goal with TheraSphere. The ORR and OS relationship was further supported by recent data from Garin et al in the DOSISPHERE-01 study in which a large index lesion (≥7 cm) treated with TheraSphere and using standard dosimetry had an ORR of 35.7% and a corresponding median OS of 10.6 months (included 1 resected patient) (43). In the comparison group, using multi-compartment dosimetry, an ORR of 71.4% and a corresponding median OS of 26.7 months was achieved (included 10 resected patients. These 2 highlighted studies demonstrate the criticality of attaining tumor response with TheraSphere in order to attain prolonged OS. In both LEGACY and DOSISPHERE-01 the targeted tumor absorbed dose is based on achieving a threshold and with which a high tumor response is achievable the importance of which is further discussed below.

The OS results reported in LEGACY are consistent with data reported by two recent TheraSphere studies. The first by Gabr et al, who reported a median OS of 13 years from TheraSphere treatment in patients (BCLC A through D) who received neoadjuvant TheraSphere as a bridge or downstaging to liver transplantation (n=207) (54). The second study reported by Lewandowski et al in solitary tumor BCLC stage 0 or A patients (n=70) who did not undergo liver transplantation showed a longer median OS of 6.7 years (95% CI; 31, 6.7), 12 month survival of 98% and 36 month survival of 66% (11). Using the same comparative studies Lewandowski et al used in their publication and using solitary tumors ≤5 cm data as the most conservative approach, table 3 below provides the publication results referenced within Lewandowski et al and OS results from LEGACY (11).

Table 3: Overall survival from published data using curative therapies and from LEGACY

Publication	**1-year Survival (%)**	**3-year Survival (%)**
Resection		
Chen et al (55)	93%	73%
Radiofrequency ablation		
Lencioni et al (56)	100%	89%
Chen et al (55)	94%	69%
Transplantation		
Llovet et al (57)	84%	74%
Jonas et al (58)	90%	Not stated
LEGACY* Study	**98%**	**83%**

* excludes patients who received a transplant or resection

Comparing the survival rates across these curative treatments to those attained in LEGACY patients who did not receive transplant or resection, namely 1 year and 3 year rates of 98.2% and 83.5%, the results suggest that TheraSphere can achieve survival rates comparable to those reported for curative therapies.

LEGACY patients who were transplanted or resected or patients who received TheraSphere as primary therapy, had a 3-year survival rate of 92.8% and 86.6% respectively, reflecting in part the degree to which HCC and the underlying cirrhotic liver disease is removed from the patient and no longer contributes to new disease lesion development. Gabr et al reported a median OS from

transplant in the 207 patient cohort of 12.5 years (54). In this study, 3-year survival post-transplant was 84% which compares favorably with the 92.8% 3-year survival rate reported in LEGACY in patients transplanted post TheraSphere.

As noted in LEGACY, the patient cohort bridged to a curative treatment option, such as liver transplantation, achieved a longer median OS; however, TheraSphere as the primary therapy also demonstrated a comparable, long median OS.

As mentioned earlier within this document, tumor response, OS and absorbed tumor dose within the perfused volume, are critical to attaining good outcomes and there is a clear interdependency between these parameters. This relationship is further discussed in later within this document.

1.4 THERASPHERE AS STANDALONE THERAPY IN THE ELDERLY

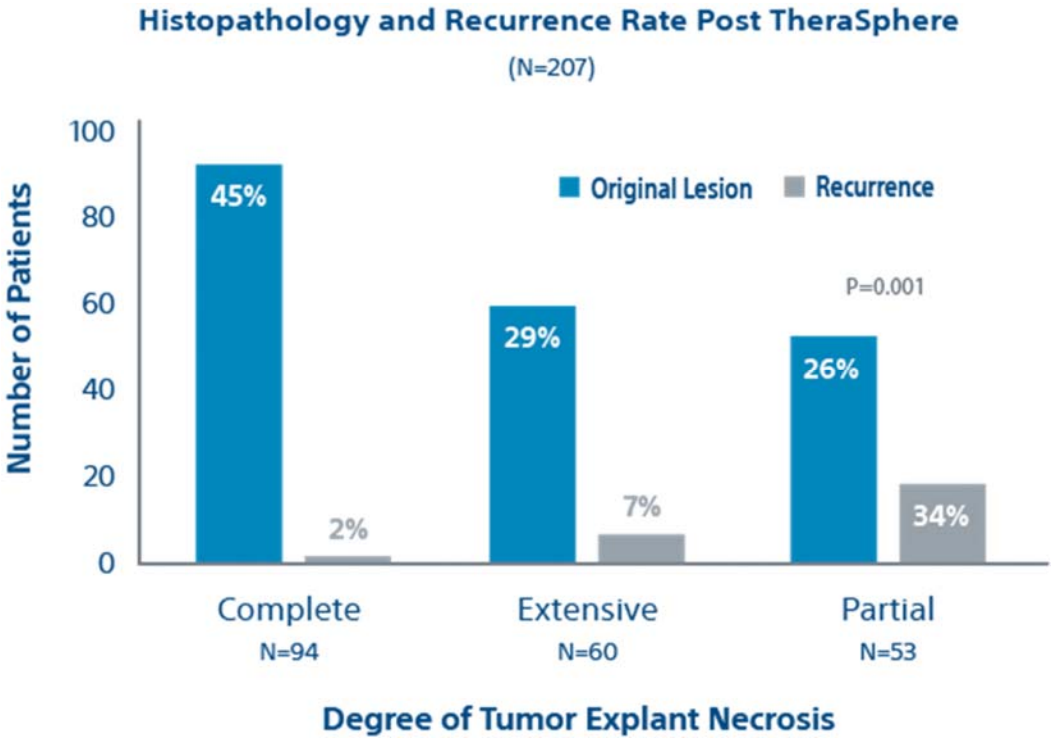
The effectiveness of TheraSphere as a standalone therapy is particularly relevant for patients ≥75 years of age who may be less likely to be considered good candidates for liver transplantation or resection, both with inherent surgical risks in a population with a higher prevalence of comorbidities. For later stage HCC, systemic therapies are recommended but may be associated with serious side effects consistent with chronic treatment (sorafenib; intolerance of therapy is high), or require multiple and ongoing treatments (immunotherapies; may not be suitable for liver transplantation and immune suppression) and require strict compliance. In LEGACY, this geriatric population represented 18% of the Treated Population, who without TheraSphere may have been relegated to receiving systemic therapies or best supportive care. Treatment with TheraSphere offers these patients an effective, durable and minimally invasive treatment, usually requiring only 1 treatment and performed on an out-patient basis.

1.5 THE IMPORTANCE OF DOSE

The goal of TheraSphere treatment is to deliver at minimum a tumoricidal absorbed dose and where normal parenchyma exposure is to an expendable liver volume an ablative radiation absorbed dose to tumor and normal tissue (≤2 liver segments) while achieving favorable clinical outcomes. The threshold dose for radiation segmentectomy was determined using single-compartment dosimetry by Vouche et al who showed that significantly more excised post-transplant tumors treated using >190 Gy had complete necrosis than treated with <190 Gy, thereby establishing a threshold ablative dose used in radiation segmentectomy (P=0.03) (19). Abiding by this threshold dose in their study, Riaz et al reported that OS was extended in solitary tumor BCLC 0 and A patients who were responders to treatment compared to non-responders, emphasizing the importance of achieving a CR (20).

In a recent study examining long-term outcomes in 207 patients receiving a liver transplant post TheraSphere (120 – 150 Gy for lobar infusions and >190 Gy for selective infusions), complete (no viable HCC) and extensive (50-99% necrosis) tumor necrosis in explants was associated with a significantly lower mortality due to HCC (p=0.0009), longer recurrence free survival (P=0.0056), longer time to recurrence (p<0.0001) and lower recurrence rate (p=0.0001) compared to patients with partial necrosis (<50% necrosis) (54) as shown in Figure 5 below.

Figure 5: Histopathology and Recurrence Rate post TheraSphere



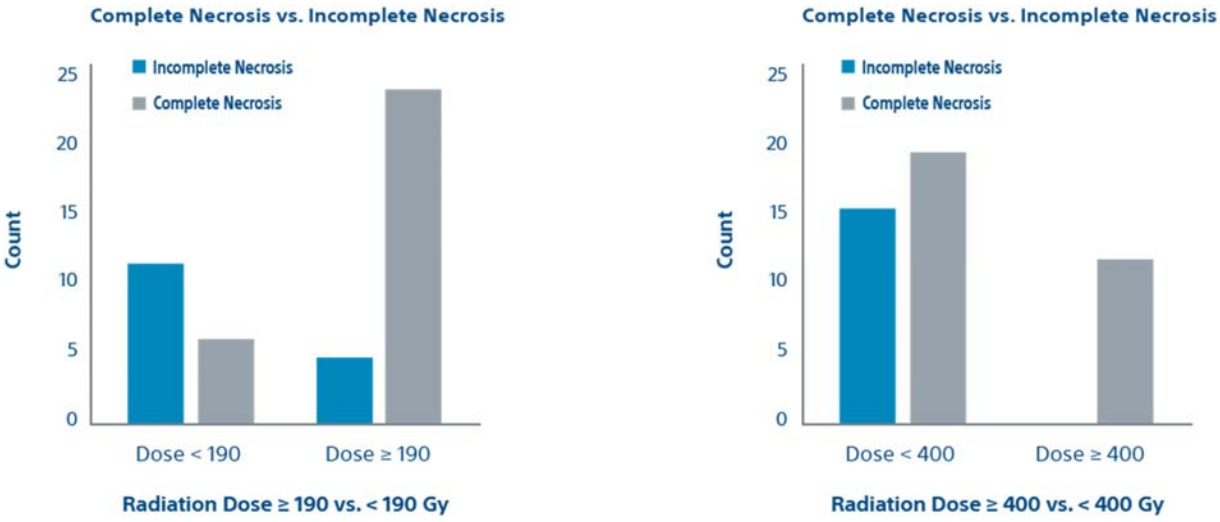
Lewandowski et al demonstrated that TheraSphere administered in early BCLC 0 and A patients at a dose of >190 Gy (with a target of >250 Gy) to the perfused volume, can result in clinical outcomes comparable to curative therapies, namely ablation, resection or transplantation (11). These studies emphasize the importance of administering above a threshold dose to achieve good clinical outcomes in patients.

In LEGACY, the median absorbed dose to the perfused liver volume was 410.10 Gy (IQR: 199.69-797.71 Gy). Dosing in this manner resulted in an ORR of 72.2% by localized mRECIST with 76.1% of responders having a DOR ≥6 months, indicating that treatment was highly effective. The data from 3 centers established a higher perfused volume absorbed dose threshold with acceptable tolerability. Taken with the context of achieving complete pathologic necrosis being correlated to the perfused volume absorbed dose, a higher target is warranted for TheraSphere administration to ≤2 liver segments. In the context of lobar treatment, the objective of local tumor control may use a similar perfused volume absorbed dose when tumor is within ≤2 liver segments and administer a lobar absorbed dose to stimulate contralateral lobe hypertrophy as a bridge to resection.

Recently, Gabr et al published histopathology data using post-explant tumors from 45 patients treated with TheraSphere and included in LEGACY. As seen in the figure below, more patients who received an absorbed dose to the perfused volume of ≥ 190 Gy had complete tumor necrosis compared to patients receiving <190 Gy. These results support earlier results of Vouche et al

(16). In LEGACY patient tumor explants, all patients receiving an absorbed dose ≥400 Gy to the perfused volume had complete necrosis of the tumor. Thus, this histopathology data supports a new absorbed dose threshold dose of 400 Gy established in LEGACY.

Figure 6: Histopathology Correlation with Absorbed Dose



Collectively, these data emphasis the importance of administering an optimal and personalized dose for a patient in order to ensure optimal outcomes.

The LEGACY study used single-compartmental dosimetry but more recent studies have explored the use of multi-compartmental dosimetry. While neoadjuvant TheraSphere treatment is the goal for a subset of unresectable HCC patients single-compartment dosimetry may not be the preferred dosimetry method. Advancements in knowledge of the importance of tumor and normal tissue absorbed dose has led to clinical research into multi-compartment dosimetry.

Multi-compartment dosimetry takes into account the higher concentrations of microspheres deposited within the tumor vasculature compared to normal tissue within the perfused volume based on tumor hypervascularity. Research in this area has primarily been published by Garin et al who demonstrated the relationship between tumor absorbed dose, tumor response and OS using a multi-compartment dosimetry model for lobar treatment based on Tc-99m MAA SPECT/CT pretreatment planning dosimetry (40) (41) (42). Their body of work established a threshold absorbed dose to the tumor of ≥205 Gy (with a target of 250-300 Gy) which resulted in tumor response in most patients. A maximum threshold for acceptable exposure to normal tissue was also established. When the tumor absorbed dose threshold was not achieved (e.g. in larger, more vascular tumors), and normal tissue absorbed dose was acceptable the administered activity was increased and described as “boosting” or “dose intensification” resulting in improved outcomes.

Most recently, Garin et al in a prospective, randomized, multicenter phase 2 study (DOSISPHERE-01) compared the use of multi-compartment dosimetry (≥205 Gy absorbed dose to the index lesion, and if possible 250-300 Gy) to use of single-compartment dosimetry (delivering 120±20 Gy to the perfused liver). A normal perfused liver absorbed dose maximum was also noted at ≤120 Gy with a ≥30% hepatic reserve. This study enrolled intermediate to advanced HCC patients with at least 1 lesion ≥7cm and included patients with PVT (pre-selected for good uptake) or without PVT, where TheraSphere was administered mostly as lobar treatment. Significantly better tumor response rates were achieved using multi-compartment dosimetry compared to single-compartment dosimetry (ORR: 64.7% vs 31.7% respectively, P=0.0095). More striking are the OS results which demonstrated that median OS can be extended by 16 months when multi-compartment dosimetry was used (median OS: 26.7 months for multi-compartment vs 10.6 months for single-compartment, P=0.0096).

Publications from other institutions support the use of multi-compartment dosimetry used in attaining optimal tumor absorbed dose and clinical outcomes (39) (68) (44). Insights from the publications discussed in this section led to the publication of clinical and dosimetric recommendations for the treatment of HCC across the BCLC staging system (21). Dosing recommendation for radiation segmentectomy using single compartment dosimetry suggests an absorbed dose to the treatment volume of >190 Gy for radiation segmentectomy (with a target of 250-300 Gy) and with no stated upper limit. For lobar treatment use of multicompartmental dosimetry is preferred using a threshold tumor absorbed dose of >200 Gy and a maximum of <75 Gy absorbed normal tissue dose (based on the entire normal liver tissue; treated and untreated) recommended in patients with no PVT. Based on Garin et al, patients requiring lobar treatment and with good PVT targeting, multi-compartment dosimetry is advised with a tumor absorbed dose of >205 Gy in these guidelines.

This collective body of evidence emphasizes the importance of tumor and normal tissue absorbed dose in achieving excellent clinical outcomes. Whether to utilize single-compartment or multi-compartment dosimetry is primarily driven by normal tissue absorbed dose when larger treatment volumes are involved. When an expendable liver volume, i.e., ≥2 liver segments, or when the objective is to cause atrophy in the treated lobe and hypertrophy in the untreated lobe the tumor absorbed dose is the driving factor as long as ≥30% of hepatic reserve is available and the patient's CP score is A5 or A6. In both the single-compartment and multi-compartment dosimetry studies the tumor absorbed dose noted are consistent. Ablative radiation in ≤2 liver segments occurs for TheraSphere >190 Gy, with increased thresholds based on clinical experience. Recent clinical recommendations were >250 Gy with no upper limit and LEGACY supports safety and efficacy with a median of 410.10 Gy again with no upper limit established. LEGACY represents the first study where perfused volume absorbed dose and tumor response were evaluated by BICR.

An expendable liver volume can be administered an ablative radiation absorbed dose to tumor and normal tissue within a perfused liver volume, i.e., radiation segmentectomy, with results similar to surgical resection. When normal tissue preservation is warranted published data support a tumor absorbed dose of ≥205 Gy, with a target of 250-300 Gy (21) (43). The LEGACY study confirmed a dose of 400 Gy to perfused liver volume provides ablative radioembolization. Preservation of a ≥30% hepatic reserve is key to patient selection to ensure clinical benefit. The

tumor absorbed dose ranges for single-compartment and multi-compartment overlap and demonstrate that the objective is to reach a prescribed threshold to achieve tumor response. In the multiple studies discussed above demonstrating a high tumor response a demonstration of correlation to OS, the primary objective of cancer therapy, is confirmed.

1.6 SUMMARY OF SAFETY IN LEGACY

The safety profile in the Treated Population in LEGACY was consistent with the known profile of use with this device to treat HCC and as documented in the risk management documentation for this product. There was only one Grade 4 adverse event (AE), worsening lymphopenia, that was deemed possibly related to TheraSphere. There were 19 deaths during the study, none of which were attributed to the device. In all, 16 patients (9.9%) reported serious adverse events (SAEs) in the Treated Population most of which occurred within 60 days post TheraSphere treatment. In LEGACY, 75% of AEs resolved and >80% required no treatment amongst which fatigue, and non-specific flu-like symptoms were common, in line with published literature (15). The most frequently reported laboratory events included lymphocyte count decrease, blood bilirubin increase, white blood cell count decrease and platelet count decrease. There was no impact of absorbed dose to the perfused liver volume on the occurrence of SAEs. Higher absorbed tumor dose, which was to a lower perfused liver volume, did lower the occurrence of Grade ≥3 AEs due to less radiation distribution in normal liver parenchyma (toxicity to normal liver tissue results in AEs).

1.7 OVERALL SUMMARY OF LEGACY RESULTS:

LEGACY demonstrated the following:

- 88.3% ORR (best response): 84.0% CR and 4.3% PR (localized mRECIST)
- Durable response with 76.1% of responders having a DoR ≥ 6M with a local recurrence rate of 5.6%
- Safe and effective stand-alone therapy in elderly patients (≥75 years) who may not be candidates for surgical options
- Preserved liver function (CP status), ECOG status thus not limiting subsequent therapy options
- OS compared favorably between patients receiving Y-90 glass microspheres as stand-alone therapy and those receiving Y90 as neoadjuvant to transplant/resection
- 96.8% achieved their best response with a single Y-90 glass microsphere treatment
- No new safety signals were identified

- High perfused volume absorbed dose (median 410 Gy) was well tolerated and effective as a selective ablative treatment

In conclusion,

- The multicenter LEGACY study demonstrated the safety and efficacy of Y-90 (TheraSphere) as a therapy for both early and advanced hepatocellular carcinoma
- The use of Y-90 as neoadjuvant to transplant, resection, or as a stand-alone treatment
- LEGACY study as well as supportive histopathology data supports the use of a perfused volume absorbed dose of > 400 Gy

1.8 REFERENCES

1. Massarweh NN, El-Serag HB. Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Cancer Control. 2017; 24: p. 1-11.

2. Kim H, El-Serag HB. The epidemiology of hepatocellular carcinoma in the USA. [Online].; 2019 [cited 2020 June 5. Available from: https://doi.org/10.1007/s11894-019-0681-x.

3. White DL, Thrift AP, Kanwal F, et al. Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. Gastroenterology. 2017; 152: p. 812-820.

4. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391: p. 1301-1314.

5. Villanueva A , Toffanin S, Llovet J. Linking molecular classification of hepatocellular carcinoma and personlized medicine: preliminary steps. Curr Opin Oncol. 2008; 20: p. 444-453.

6. Lin S, Hoffmann K, Schemmer P. Treatment of Hepatocellular carincoma: a systematic review. Liver Cancer. 2012; 1: p. 144-158.

7. Zhang JA, Kwee SA, Wong LL, et al. Late recurrence of hepatocellular carcinoma after liver transplantation. Hepatoma Res. 2017; 3: p. 58-66.

8. Lewandowski RJ, Gabr A, Abouchaleh N, et al. Radiation Segmentectomy: Potential curative therapy for early hepatocellular carcinoma. Radiology. 2018; 287: p. 1050-1058.

9. Tiong L, Maddern GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. Br J Surg. 2011; 98: p. 1210-1224.

10. Cho YK, Rhim H, Noh S. Radiofrequency ablation versus surgical resection as primary treatment of hepatocellular carcinoma meeting the Milan criteria: a systematic review. J Gastroenterol Hepatol. 2011; 26: p. 1354-1360.

11. Rhee TK, Lewandowski RJ, Liu DM, et al. 90Y radioembolization for metastatic neuroendocrine liver tumors. Ann Surg. 2008; 247: p. 1029-1035.

12. Kulik LM, Attasi B, Van Holsbeeck L, et al. Yttrium-90 microspheres (TheraSphere). Treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. J Surg Oncol. 2006; 95: p. 572-586.

13. Biederman DM, Titano JJ, Korff RA, et al. Radiation segmentectomy versus selective chemoemoblization in the treatment of early-stage hepatocellular carcinoma. J Vasc Interv Radiol. 2018; 29: p. 30-37.

14. Padia S, Johnson GE, Horton KJ, et al. Segmental yttrium-90 radioembolization versus segmental chemoembolization for localized hepatocellular carcinoma: Results of a single-center, retrospective, propensity score-matched study. J Vasc Interv Radiol. 2017; 28: p. 777-785.

15. Biederman DM, Titano JJ, Bishay VL, et al. Radiation segmentectomy versus TACE combined with microwave ablation for unresectable solitary hepatocellular carcinoma up to 3 cm: A propensity score matching study. Radiology. 2017; 283: p. 895-905.

16. Vouche M, Habib A, Ward TJ, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: Multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology. 2014; 60: p. 192-201.

17. Riaz A, Gabr A, Abouchaleh N, et al. Radioembolization for hepatocellular carinoma: Statistical confirmation of improved survival. Hepatology. 2018; 67: p. 873-883.

18. Salem R, Padia SA, Lam M, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. Eur J Nucl Med MOl Imaging. 2019; 46: p. 1695-1704.

19. Tohme S, Sukato D, Chen H, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: A single-institution experience. J Vasc Interv Radiol. 2013; 24: p. 1632-1638.

20. Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2016; 15: p. 1155-1163.

21. Titano JJ, Voutsinas N, Kim E. The role of radioembolization in bridging and downstaging hepatocellular carcinoma to curative therapy. Semin Nucl Med. 2019; 49: p. 189-196.

22. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant. 2009; 9: p. 1920-1928.

23. Gabr A, Riaz A, Mouli S, et al. Modified radiation lobectomy: An evolving paradigm to convert patients to liver resection candidacy. Semin Intervent Radiol. 2019; 36: p. 343-348.

24. Lewandowski RJ, Donahue L, Chokechanachaisakul A, et al. 90Y radiation lobectomy: Outcomes following surgical resection in patients with hepatic tumors and small future liver remnant volumes. J Surg Oncol. 2016; 114: p. 99-105.

25. Gaba RC, Lewandowski RJ, Kulik LM, et al. Radiation lobectomy: Preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. Ann Surg Oncol. 2009; 16: p. 1587-1596.

26. Vouche M, Lewandowski RJ, Atassi R, et al. Radiation lobectomy: Time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. J Hepatol. 2013; 59: p. 1029-1036.

27. Teo JY, Goh BK. Contra-lateral liver lobe hypertrophy after unilobar Y90 radioembolization: An alternative to portal vein embolization? World J Gastroenterol. 2015; 21: p. 3170-3173.

28. Theysohn JM, Ertle J, Muller S, et al. Hepative volume changes after lobal selective internal radiation therapy (SIRT) of hepatocellular carcinoma. Clin Radiol. 2014; 69: p. 172-178.

29. Edeline J, Lenoir L, Boudjema K, et al. Volumetric changes after 90Y radioemboization for hepatocellular carcinoma in cirrhosis: an option to portal vein embolization in a preoperative setting? Ann Surg Oncol. 2013; 20: p. 2518-2525.

30. Gabr A, Abouchaleh N, Rehan A, et al. Outcomes of surgical resection after radioembolization for hepatocellular carcinoma. J Vasc Interv Radiol. 2018; 29: p. 1502-1510.

31. Palard X, Edeline J, Rolland Y, et al. Dosimetric parameters predicting contralateral liver hypertrophy after unilobar radioembolization of hepatocellular carcinoma. Eur J Nucl Med Imaging. 2018; 45: p. 392-401.

32. Van der Velden S, Braat MN, Labeur TA, et al. A pilot study on hepatobiliary scintigraphy to monitor regional liver function in yttrium-90 radioembolization. J Nucl Med. 2019; 60: p. 1430-1436.

33. Riaz A, Awais R, Salem R. Side effects of yttrium-90 radioembolization. Front Oncol. 2014; 4: p. 198.

34. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90mMicrospheres: A comprehensive report of long-term outcomes. Gastroenterology. 2010; 138: p. 52-64.

35. Salem R, Gabr A, Riaz A, et al. Institutional decision to adopt Y90 as primary treatment for HCC informed by a 1,000-patient 15-year experience. Hepatology. 2018; 68: p. 1429-1440.

36. Ho CL, Chen S, Cheung SK, et al. Radioembolization with (90)Y glass microspheres for hepatocellular carcinoma: significance of pretreatment (11)C-acetate and (18)F-FDG PET/CT and posttreatment (90)Y PET/CT in individualized dose prescription. Eur J Nucl Mol Imaging. 2018; 45: p. 2110-2121.

37. Garin E, Lenoir L, Edeline J, et al. Boosted selective internal radiation therapy with 90Y-loaded glass mcirospheres (B-SIRT) for hepatocellular carcinoma patients: a new personalized promising concept. Eur J Nucl Med Mol Imaging. 2013; 40: p. 1057-1068.

38. Garin E, Rolland Y, Edeline J, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged survival in hepatocellular carcinoma patients with portal vein thrombosis. J Nucl Med. 2015; 56: p. 339-346.

39. Garin E, Rolland Y, Pracht M, et al. High impact of macroaggregated albumin-based tumour dose on response and overall survival in heptaocellular carcinoma patients treated with 90Y-loaded glass mircrosphere radioembolization. Liver Int. 2017; 37: p. 101-110.

40. Garin, E; Tzelikas, L; Guiu, B; et al. Major impact of personalized dosimetry using 90Y loaded glass microspheres SIRT in hCC: final analysis, including overall survival, of a multicentre randomized Phase II study (DOSISPHERE-01). Oral Presentation at SIR 2020 June 14, 2020. [Online].; 2020. Available from: https://www.sirmeeting.org/index.cfm?do=abs.viewAbs&abs=2018.

41. Kappadath SC, Mikell J, Balagopal A, et al. Hepatocellular carcinoma tumor dose response after (90)Y-radioembolization with glass microspheres using (90)Y-SPECT/CT-based voxel dosimetry. Int J Radiat Oncol BIol Phys. 2018; 102: p. 451-461.

42. Lencioni R, Llovet JM. Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. Semin Liver Dis. 2010; 30: p. 52-60.

43. Biederman DM, Titano JJ, Lee KM. Yttrium-90 glass-based microsphere radioembolization in the treatment of hepatocellular carcinoma secondary to the hepatitis B virus: Safety, efficacy and survival. J Vasc Interv Radiol. 2015; 26: p. 1630-1638.

44. Bhangoo MS, Karnani DR, Hein PN, et al. Radioembolization with yttrium-90 microspheres for patients with unresectable hepatocellular carcinoma. J Gastrointest Oncol. 2015; 6: p. 469-478.

45. Couto OF, Dvorchik I, Carr BI. Causes of death in patients with unresectable hepatocellular carcinoma. Dig Dis Sci. 2007; 52: p. 3285-3289.

46. Salem R, Gilbertsen M, Butt Z, et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compare with chemoembolization. Clin Gastroenterol Hepatol. 2013; 11: p. 1358-1365.

47. Gabr A, Kulik L, Riaz A, et al. Liver transplantation following yttrium-90 radioembolization: 15 year experience in 207 patients cohort. Hepatology. 2020; doi: 10.1002/hep.31318.

48. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006; 243: p. 321-328.

49. Lencioni R, Cioni D, Crocetti L, et al. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology. 2005; 234: p. 961-967.

50. Llovet JM, Bruix J, Fuster J, et al. Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastasis classification dose not have prognostic power. Hepatology. 1998; 27: p. 1572-1577.

51. Jonas S, Bechstein WO, Steinmueller T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatology. 2001; 33: p. 1080-1086.

52. Chan K, Alessio A, Johnson G , et al. Prospective trial using internal pair-production positron emission tomography to establish the Yttrium-90 radioembolization dose required for response of hepatic tumors. Int J Radiat Oncol Biol Phys. 2018; 101: p. 358-365.

53. Khalaf N, Ying J, Mittal S, et al. Natural history of untreated hepatocellular carcinoma in a US cohort and the role of cancer surveillance. Clin Gastroenterol Hepatol. 2017; 15: p. 273-281.

54. Cabbibo G, Maida M, Genco C, et al. Natural history of untreatable hepatocellular carcinoma: a retrospective study. World J Hepatol. 2012; 4: p. 256-261.

55. Giannini EG, Farinati F, Ciccarese F, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology. 2015; 61: p. 184-190.

56. Riaz A, Ryu RK, Kulik LM, et al. Alpha-Fetoprotein response after locoregional therapy for heptocellular carcinoma: Oncologic marker of radiologic response, progression and survival. J Clin Oncol. 2009; 27: p. 5734-5742.

57. Mehta N, Dodge JL, Hirose R, et al. Increasing liver transplantation wait-list dropout for hepatocellular carcinoma with widening geographical disparities: Implications for organ allocation. Liver Transpl. 2018; 24: p. 1346-1356.

58. Memon K, Kulik L, Lewandowski RJ, et al. Alpha-fetoprotein response correlates with EASL response and survival in solitary hepatocellular carcinoma treated with trans-arterial therapies: A subgroup analysis. J Hepatol. 2012; 56: p. 1112-1120.

59. Tandon P, Garcia-Tsao G. Prognostic indicators in hepatocellular carincoma: A systematic review of 72 studies. Liver International. 2009; 29: p. 502-510.

60. Hilgard P, Hamami M, El-Fouly A, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Heptaology. 2010; 52: p. 1741-1749.

61. Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008; 47: p. 71-81.

62. Bayer Healthcare.com. [Online]. [cited 2020 June 4. Available from: http://labeling.bayerhealthcare.com/html/products/pi/Nexavar_PI.pdf.

63. Abouchaleh N, Gabr A, Ali R, et al. Y90 radioembolization for locally advanced hepatocellular carcinoma with portal vein thrombosis: Long-term outcomes in a 185-patient cohort. J Nucl Med. 2018; 59: p. 1042-1048.

64. BMS.com. [Online]. [cited 2020 June 5. Available from: http://packageinserts.bms.com/pi/pi_opdivo.pdf.

65. Carr BI. Hepatic artery chemoembolization for advanced stage HCC: experience of 650 patients. Hepatogastroenterology. 2002; 49: p. 79-86.

66. Mazzaferro V, Regalia E, Doci R, al e. LIver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996; 334: p. 693-699.

67. Carter RE, Huang P. Cautionary note regarding the use of CIs obtained from Kaplan-Meier survival curves. J Clin Oncol. 2009; 27: p. 174-175.

68. Piana PM, Bar V, Doyle L, al e. Early arterial stasis during resin-based yttrium-90 radioembolization: Incidence and preliminary outcomes. HPB (Oxford). 2014; 16: p. 336-341.

69. Salem R ea. Yttrium-90 glass microspheres in the treatment of hepatocellular carcinoma: The LEGACY study. CIRSE 2000 Virtual Summit, September 12-15 2020. .

Radioembolisation with personalised dosimetry: improving outcomes for patients with advanced hepatocellular carcinoma

Lancet Gastroenterol Hepatol 2020

Published Online November 6, 2020 https://doi.org/10.1016/S2468-1253(20)30306-X

See Online/Articles https://doi.org/10.1016/S2468-1253(20)30290-9

In *The Lancet Gastroenterology & Hepatology,* Etienne Garin and colleagues[1] report a randomised, multicentre, phase 2 trial comparing standard dosimetry (120 ± 20 Gy targeted to the perfused lobe) with personalised dosimetry (≥205 Gy targeted to the index tumour) in patients with unresectable, locally advanced hepatocellular carcinoma undergoing selective internal radiation therapy with yttrium-90 (^{90}Y)-loaded glass microspheres (TheraSphere, Boston Scientific, Marlborough, MA, USA). The personalised approach delivered higher tumour radiation doses, maintained a benign adverse event profile, and resulted in improved objective response rates and overall survival when compared with standard dosimetry (26·6 months [95% CI 11·7–not reached] in the personalised dosimetry group *vs* 10·7 months [6·0–16·8] in the standard dosimetry group, p=0·0096).[1]

The results of this trial[1] challenge outcomes from other recent randomised trials[2,3] of selective internal radiation therapy with ^{90}Y-loaded microspheres versus sorafenib, which failed to show an overall survival benefit of selective internal radiation therapy in patients with advanced hepatocellular carcinoma. The design of these previous studies had recognised limitations, with centres lacking technical experience in performing selective internal radiation therapy, a large number of participants who did not receive selective internal radiation therapy, and those who did receiving treatment after a substantial time-lag compared with patients in the control groups. By contrast, the study by Garin and colleagues[1] posits that, with proper techniques, experienced centres, and the implementation of personalised dosimetry, better outcomes can be achieved. This concept is supported by recent publications[4,5] of curative-intent selective internal radiation therapy with ^{90}Y-loaded microspheres for early-stage hepatocellular carcinoma, revealing superior outcomes with radiation doses above a similar threshold as that used in the study by Garin and colleagues (>190 Gy).[1]

The limitations of this study[1] should be highlighted, but contextualised. Although relatively small compared with pharmaceutical studies, the study sample size was similar to that of practice-changing chemoembolisation studies published in 2002.[6,7] The limitations inherent to a sample size of 60 patients were offset by the magnitude of the treatment effect, rendering this study both statistically significant and clinically meaningful. A control group in which patients received a standard dose of ^{90}Y is potentially controversial. However, the median overall survival of 10·7 months in this group is consistent with, if not better than, the overall survival of 8·1 months observed in subset analyses of patients with vascular invasion who received systemic therapy in a previous study.[8] Furthermore, even if this control group is considered by many to be unproven, ineffective, or placebo, increasing the dose of this so-called placebo more than doubled overall survival.

There are several strengths to the study.[1] First, it addresses an important unmet need for patients with hepatocellular carcinoma who have large index tumours, vascular invasion, and exhibit a Child-Pugh liver function class of A or B. The outcome measures are positive despite the severity of liver disease. Second, the granularity of detail provided about patient liver or tumour characteristics at baseline, such as tumour location, degree of vascular invasion, focality, unilobar or bilobar disease, and largest index lesion size, represent important clinical details often not provided in trials of systemic therapy. The mean size of index tumours in this study was more than 10 cm, which is universally considered as large and advanced by clinicians. Large tumours are often contraindicated for transarterial chemoembolisation, and a review of the published data would suggest that patients with such tumours are often excluded from trials of systemic therapy. Although reporting the index lesion size might initially seem unusual, it provides substantially more clinical context and information about tumour burden than reporting the sum of the size of multiple smaller lesions. A 10·0 cm lesion (with or without focal vascular invasion) is clearly different to four 2·5 cm nodules. In fact, part of trial data interpretation should distinguish broad trial inclusion criteria from that of patients who were actually enrolled; these are two

distinct concepts and often differ substantially. Third, the objective response in these large lesions (according to European Association for the Study of the Liver criteria), observed in 20 (71% [95% CI 51–87]) of 28 patients in the personalised dosimetry group compared with ten (36% [19–56]) of 28 patients in the standard dosimetry group, shows the substantial local antitumoral effect of selective internal radiation therapy with ^{90}Y-loaded microspheres; it is more difficult to achieve a response in a 10·0 cm lesion than in four 2·5 cm nodules. Fourth, the trial included patients with Child-Pugh liver function class A and B, with class A representing strict inclusion criteria in hepatocellular carcinoma trials, and class B representing an understudied group of patients. Finally, the study[1] further illustrates the concept of a right-to-left shift in staging (ie, downstaging) in a population often relegated to palliative therapies, as shown by the significantly higher proportion of patients who were able to undergo resection with curative intent in the personalised dosimetry group (ten [36%] of 28 patients) compared with the standard dosimetry group (one [4%] of 28 patients).

In conclusion, this study[1] challenges the evolving narrative that patients with advanced hepatocellular carcinoma should have systemic therapy at the expense of locoregional therapy. This notion is particularly true for patients with large tumours and local vascular invasion. In an era of individualised patient care, including granular detail of baseline patient characteristics in trials, such as index tumour size and distribution, and the location or degree of vascular invasion, is imperative. Personalised dosimetry (ie, reaching specific threshold radiation doses) is a natural evolution of selective internal radiation therapy with ^{90}Y-labelled microspheres, and should be incorporated into future trials of hepatocellular carcinoma. Rather than head-to-head comparisons advocated by guidelines, future studies should combine modern selective internal radiation therapy concepts with systemic therapies in a manner that reflects current practice patterns, recognising that patients with hepatocellular carcinoma naturally progress through various treatments in sequence and exhibit left-to-right and right-to-left (ie, upstaging) stage migration. These trials will be challenging, given the daunting task of showing overall survival superiority in an era of multiple available systemic drugs, and the inevitable confounding effect of treatment after progression, but necessary to achieve the goal of improving patient outcomes through a collaborative approach.

RJL reports personal fees from Boston Scientific, Bard, and ABK Biomedical outside the submitted work. RS reports personal fees from Boston Scientific, Eisai, Cook, Sirtex, and AstraZeneca; and grants and non-financial support from Boston Scientific and Genentech outside the submitted work.

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1 Garin E, Tselikas L, Guiu B, et al. Personalised versus standard selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. *Lancet Gastroenterol Hepatol* 2020; published online Nov 6. https://doi.org/10.1016/S2468-1253(20)30290-9.

2 Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2017; **18:** 1624–36.

3 Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018; **36:** 1913–21.

4 Gabr A, Riaz A, Johnson GE, et al. Correlation of Y90-absorbed radiation dose to pathological necrosis in hepatocellular carcinoma: confirmatory multicenter analysis in 45 explants. *Eur J Nucl Med Mol Imaging* 2020; published online Aug 4. https://doi.org/10.1007/s00259-020-04976-8.

5 Lewandowski RJ, Gabr A, Abouchaleh N, et al. Radiation segmentectomy: potential curative therapy for early hepatocellular carcinoma. *Radiology* 2018; **287:** 1050–58.

6 Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; **35:** 1164–71.

7 Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359:** 1734–39.

8 Raoul JL, Bruix J, Greten TF, et al. Relationship between baseline hepatic status and outcome, and effect of sorafenib on liver function: SHARP trial subanalyses. *J Hepatol* 2012; **56:** 1080–88.

Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial

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Summary

Background All randomised phase 3 studies of selective internal radiation therapy for advanced hepatocellular carcinoma published to date have reported negative results. However, these studies did not use personalised dosimetry. We aimed to compare the efficacy of a personalised versus standard dosimetry approach of selective internal radiation therapy with yttrium-90-loaded glass microspheres in patients with hepatocellular carcinoma.

Methods DOSISPHERE-01 was a randomised, multicentre, open-label phase 2 trial done at four health-care centres in France. Patients were eligible if they were aged 18 years or older and had unresectable locally advanced hepatocellular carcinoma, at least one measurable lesion 7 cm or more in size, a hepatic reserve of at least 30% after selective internal radiation therapy, no extrahepatic spread (other than to the lymph nodes of the hilum, with a lesion <2 cm in size), and no contraindications to selective internal radiation therapy, as assessed by use of a technetium-99m macroaggregated albumin scan. Patients were randomly assigned (1:1) by use of a permutated block method, with block sizes of four and without stratification, to receive either standard dosimetry (120±20 Gy) targeted to the perfused lobe; standard dosimetry group) or personalised dosimetry (≥205 Gy targeted to the index lesion; personalised dosimetry group). Investigators, patients, and study staff were not masked to treatment. The primary endpoint was the investigator-assessed objective response rate in the index lesion, according to European Association for the Study of the Liver criteria, at 3 months after selective internal radiation therapy in the modified intention-to-treat population. Safety was assessed in all patients who received at least one selective internal radiation therapy injection, and analysed on the basis of the treatment actually received (defined by central dosimetry assessment). The trial is registered with ClinicalTrials.gov, NCT02582034, and has been completed.

Findings Between Dec 5, 2015, and Jan 4, 2018, 93 patients were assessed for eligibility. Of these patients, 60 were randomly assigned: 31 to the personalised dosimetry group and 29 to the standard dosimetry group (intention-to-treat population). 56 (93%) patients (28 in each group) were treated (modified intention-to-treat population). In the modified intention-to-treat population, 20 (71% [95% CI 51–87]) of 28 patients in the personalised dosimetry group and ten (36% [19–56]) of 28 patients in the standard dosimetry group had an objective response (p=0·0074). In the safety analysis population, a least one serious adverse event was reported in seven (20%) of the 35 patients who received personalised dosimetry, and in seven (33%) of the 21 patients who received standard dosimetry. The most frequent (ie, occurring in >5% of patients) grade 3 or higher adverse events were ascites (one [3%] patient who received personalised dosimetry *vs* two [10%] patients who received standard dosimetry), hepatic failure (two [6%] *vs* none), lymphopenia (12 [34%] *vs* nine [43%]), increased aspartate aminotransferase concentrations (three [9%] *vs* two [10%]), increased alanine aminotransferase concentrations (three [9%] *vs* none), anaemia (two [6%] *vs* one [5%]), gastrointestinal haemorrhage (none *vs* two [10%]), and icterus (none *vs* two [10%]). One treatment-related death occurred in each group.

Interpretation Compared with standard dosimetry, personalised dosimetry significantly improved the objective response rate in patients with locally advanced hepatocellular carcinoma. The results of this study suggest that personalised dosimetry is likely to improve outcomes in clinical practice and should be used in future trials of selective internal radiation therapy.

Funding Biocompatibles UK, a Boston Scientific Group company.

Lancet Gastroenterol Hepatol 2020

Published Online November 6, 2020 https://doi.org/10.1016/S2468-1253(20)30290-9

See Online/Comment https://doi.org/10.1016/S2468-1253(20)30306-X

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for articles published in English between Jan 1, 2000, and May 1, 2020, focusing on publications of randomised studies for hepatocellular carcinoma using the search terms "selective internal radiation therapy" or "radioembolisation", and "personalised dosimetry". We identified no randomised studies. Only two retrospective studies of personalised dosimetry were identified, and the results suggested that personalised dosimetry was associated with a significant improvement in objective response rate and a favourable overall survival compared with standard dosimetry.

We also searched PubMed for articles published in English between Jan 1, 2000, and May 1, 2020, focusing on publications of large randomised studies, using the search terms "selective internal radiation therapy" or "radioembolisation", and "sorafenib", with sorafenib being the standard of care for locally advanced hepatocellular carcinoma. We identified three studies. All studies found no increase in the overall survival of patients treated with selective internal radiation therapy, alone or in combination with sorafenib, when compared with sorafenib alone. Reported median overall survival was 8·0–12·1 months in the selective internal radiation therapy groups and 9·9–11·4 months in the selective internal radiation plus sorafenib group and sorafenib only group. Personalised dosimetry was not used in any of these studies.

The present randomised multicentre study was designed to assess the potential superiority of selective internal radiation therapy with personalised dosimetry over standard dosimetry in terms of the objective response rate in patients with hepatocellular carcinoma.

Added value of this study

To our knowledge, this is the first randomised study to compare personalised dosimetry and standard dosimetry in patients with hepatocellular carcinoma. In patients with locally advanced hepatocellular carcinoma, the objective response rate was significantly higher in the personalised dosimetry group compared with the standard dosimetry group, with no increase in the toxicity profile. A meaningful improvement in overall survival was also observed in the personalised dosimetry group compared with the standard dosimetry group.

Implications of all the available evidence

These results suggest that personalised dosimetry could become the definitive standard-of-care method of administering selective internal radiation therapy, and also challenge the conclusions of previous negative randomised phase 3 studies of selective internal radiation therapy, in which no personalised dosimetry was used. This study provides a strong rationale for new randomised studies to compare selective internal radiation therapy using personalised dosimetry (alone or in combination with standard of care) with standard of care alone in patients locally advanced hepatocellular carcinoma, to try to improve patient outcomes.

Introduction

Hepatocellular carcinoma is the most common primary liver cancer and the third leading cause of cancer-related death worldwide, with around 745 000 deaths reported annually.[1] Most often, patients are not operable because of the extent of disease or underlying liver cirrhosis, and treatment is challenging.[2]

Sorafenib became the standard of care for patients with advanced hepatocellular carcinoma in 2008, with a median overall survival of 10·7 months versus 7·9 months with best supportive care (hazard ratio [HR] 0·69 [95% CI 0·55–0·87]).[3] Only recently (2020) has a treatment been shown to significantly improve overall survival when compared with sorafenib, with the combination of bevacizumab with atezolizumab expected to become the new standard of care for patients with advanced hepatocellular carcinoma (median overall survival not yet reached with the immunotherapy combination versus 13·2 months with sorafenib, HR 0·58, 95% CI 0·42–0·79).[4]

For more than 20 years, selective internal radiation therapy for hepatocellular carcinoma has used yttrium-90 (^{90}Y)-loaded glass microspheres (TheraSphere, Boston Scientific, Marlborough, MA, USA) or resin microspheres (SIR-Sphere, Sirtex Medical, Australia).[5,6] The microspheres are injected directly into the hepatic artery. Microsphere injection is always preceded by a diagnostic liver angiography, including a liver perfusion scintigraphy with intra-arterial injection of technetium-99m (^{99m}Tc) macro-aggregated albumin (a macro-aggregated albumin scan). The main objective of these screening tools is to identify patients with absolute contraindication to selective internal radiation therapy, such as those with a high risk of lung shunt or gastrointestinal shunt.[7,8]

Several guidelines consider selective internal radiation therapy as an option for patients with hepatocellular carcinoma.[9,10] Selective internal radiation therapy has shown promising results in terms of response, safety, and overall survival in cohort studies and phase 2 studies.[11,12] However, three randomised phase 3 trials[13–15] failed to show any improvement in overall survival with selective internal radiation therapy compared with sorafenib. The absence of a personalised dosimetry approach could potentially explain these negative results.[16] Indeed, despite the fact that selective internal radiation therapy is a radiation oncology approach, personalised dosimetry, especially with regards to the tumour absorbed dose, is not addressed in the instructions for use of the products,[7,8] and was not used in these three randomised studies.[13–15] This absence of a personalised dosimetry approach is inaccurate according to radiobiological rules, in which a

threshold tumour absorbed radiation dose needs to be reached to achieve an effect.[17]

A macro-aggregated albumin scan can be done before selective internal radiation therapy to evaluate the tumour absorbed dose, and it provides an accurate predictive tool of response and overall survival.[5,18,19] The threshold tumour absorbed dose reported for glass microspheres is 205 Gy.[18,19] The concept of personalised dosimetry targeting more than 205 Gy to hepatocellular carcinomas has been described with favourable outcomes.[20,21]

The aim of this randomised multicentre study was to compare the efficacy of a standard versus personalised dosimetry approach of selective internal radiation therapy with ^{90}Y-loaded glass microspheres in patients with hepatocellular carcinoma.

Methods

Study design and participants

DOSISPHERE-01 was a randomised, multicentre, open-label phase 2 trial done at four health-care centres in France. According to the main prespecified inclusion criteria, eligible patients were aged 18 years or older and had histologically confirmed hepatocellular carcinoma that was not amenable to surgery or local ablative treatment; an Eastern Cooperative Oncology Group performance status of 0 or 1; a Child-Pugh liver function class A (or B7 if bilirubin concentrations were <35 µmol/L); a Barcelona Clinic Liver Cancer classification of A, B, or C; at least one measurable lesion 7 cm in size or larger; a hepatic reserve (ie, untreated liver fraction) of at least 30% after selective internal radiation therapy; and mainly unilateral involvement (minimal bilateral involvement allowed only with a hepatic reserve of ≥30% after bilateral selective internal radiation therapy). The following criteria for biological parameters had to be met: haemoglobin concentrations of 8·5 g/dL or greater; granulocyte counts of 1500 cells per µL or greater; platelet counts of 50 000 platelets per µL or greater; bilirubin <35 µmol/L; aspartate aminotransferase or alanine aminotransferase concentrations five or less times the upper limit of normal; and creatinine ≤1·5 times the upper limit of normal. Previous treatment with sorafenib was allowed if it had been stopped at least 4 weeks before the diagnostic angiography. The main prespecified exclusion criteria were: extrahepatic spread (other than to the lymph nodes of the hilum, with a lesion <2 cm in size); more than 70% of the liver having tumour involvement; a history of chemoembolisation of the principal lesion (except for a nodular residual lesion measuring at least 7 cm in size, or progression after an initial response); severe underlying biliary pathology (ie, a bile duct abnormality, including cirrhosis of biliary origin); having received treatment for another cancer less than 1 year previously; pulmonary shunting leading to pulmonary dosimetry of more than 30 Gy; a digestive shunt not correctable by embolisation; and poor targeting of the tumour or a main portal vein thrombosis on ^{99m}Tc macro-aggregated albumin scintigraphy. A complete list of inclusion and exclusion criteria are provided in the appendix (p 3). To ensure eligibility for selective internal radiation therapy, patients were included in the trial only after the ^{99m}Tc macro-aggregated albumin scan.

During the screening period, a diagnostic angiography was done for arterial mapping, selection of catheter position for treatment, embolisation of gastrointestinal arterial branches (if necessary), and ^{99m}Tc macro-aggregated albumin injection (over 20–30 s). Specific recommendations were followed to preserve blood flow, including the preferential use of a floppy catheter to avoid spasm.[22] For the macro-aggregated albumin scan, planar images were acquired for lung shunt evaluation. For tumour and portal vein thrombosis dosimetry evaluation, single-photon emission CT combined with CT (SPECT/CT) scans were acquired. Tumour and portal vein thrombosis targeting were evaluated visually on macro-aggregated albumin SPECT/CT images, with poor targeting defined as a lower macro-aggregated albumin uptake in the tumour or in the portal vein thrombosis than the uptake in healthy liver tissue. Indeed, macro-aggregated albumin is used as a ^{90}Y-loaded microsphere surrogate, and macro-aggregated albumin uptake quantifcation with SPECT/CT is used to calculate the absorbed dose of ^{90}Y assuming that the distributions of macro-aggregated albumin and ^{90}Y-loaded microspheres are the same. Patients were discharged and readmitted for selective internal radiation therapy 1 or 2 weeks later if eligibility was confirmed.

Patients provided written informed consent before undergoing study-specific procedures. The study was done in accordance with the Declaration of Helsinki and approved by the ethics committee of the University Hospital La Cavalle Blanche (Brest, France; IRB-ID: 2015-A00894–45). The trial protocol is available online.

For the **DOSISPHERE-01 trial protocol** see http://www.centre-eugene-marquis.fr/etude-clinique-dosisphere/

Randomisation and masking

Eligible patients were randomly assigned (1:1) to two parallel groups, in which patients received either personalised dosimetry or standard dosimetry. The randomisation list was computer-generated by the permutated block method with a block size of four and without stratification. Once eligibility was confirmed, physicians were informed of the randomised treatment allocated to the patient by the clinical project research assistant. The funder, investigators, patients, and research staff were masked to the randomisation list but were not masked to treatment.

Procedures

Selective internal radiation therapy was done during a therapeutic angiography, and a lobar approach was used in the trial. Dosimetry was evaluated by investigators using local software (Volumetric analysis [Syngo Workstation, Siemens, Malvern, PA, USA] and PLANET Dose [DOSIsoft, Paris, France]); the target dose was based on

macro-aggregated albumin-based dosimetry. The dosimetry target for patients in the standard dosimetry group was to deliver 120±20 Gy to the perfused lobe (the standard targeted perfused liver dose at time of study design),[7] while not exceeding 30 Gy to the lungs. The dosimetry targets for patients in the personalised dosimetry group were to deliver: (1) at least 205 Gy to the tumour (tumour dose), and more than 250 Gy, if possible; (2) a dose of 120 Gy or less to the healthy perfused liver tissue; and (3) a dose of 30 Gy or less to the lungs.[20,21]

The activity of ^{90}Y-loaded glass microspheres needed to meet the dosimetry target was calculated by use of the following formula:[17]

$$D_{VOI} = \frac{A_{VOI} \times 50}{W_{VOI}}$$

where D_{VOI} is the mean absorbed dose (measured in Gy) in the volume of interest (ie, the perfused liver, tumour, or healthy perfused liver tissue), A_{VOI} is the activity of ^{90}Y-loaded microspheres (measured in GBq) in the volume of interest, and W_{VOI} is the weight of the volume of interest (measured in kg), with the weight equal to the volume (measured in L) multiplied by 1·03.

Volume of interest was evaluated by use of macro-aggregated albumin SPECT/CT scan images in the personalised dosimetry group, and by use of standard diagnostic imaging (CT scan, MRI, or cone beam CT, when available) and the Couinaud classification in the standard dosimetry group.[18,20]

In patients who had two arteries that required treatment (ie, in those with an anatomical variant or a central lesion vascularised by two arteries), two macro-aggregated albumin evaluations in two separate angiography procedures were done at least 24 h apart, as macro-aggregated albumin quantification is technically only evaluable for one macro-aggregated albumin injection (one vessel).

In patients with bilobar disease, selective internal radiation therapy was first used to treat the liver lobe with the largest tumour load. The treatment of the lobe with the smaller tumour load was left at the discretion of investigators; selective internal radiation therapy was permitted providing that at least 30% of the liver volume was spared from radiation after both selective internal radiation therapies. If the two treatments were not done during the same session, they had to be separated by a prespecified time interval of 5–8 weeks.

Patients were followed up until disease progression. Visits, including those for clinical examination, laboratory tests (haematological, blood liver, and blood biochemistry), and abdominal imaging (CT or MRI), were scheduled 4–6 weeks after selective internal radiation therapy, and at 3, 6, and 12 months.

Outcomes

The primary endpoint was the objective response rate, defined as the proportion of patients who had a complete or partial response in the index lesion (ie, the largest treated lesion ≥7 cm in size), according to European Association for the Study of the Liver (EASL) criteria (appendix p 3), which was evaluated by one unmasked investigator at 3 months after selective internal radiation therapy.[23] Patients with stable disease, or progressive disease, or those who had started systemic cancer therapy (or local therapy targeting the index lesion) before 3 months, or had not had a radiological evaluation at 3 months, were considered not to have had an objective response.

Tumour response was evaluated with CT scan imaging by site investigators at week 6 and at 3, 6, and 12 months after selective internal radiation therapy. 6-week and 3-month CT scan response assessments were centrally reviewed by two masked central reviewers to confirm the primary endpoint results.

The overall response rate, defined as the proportion of patients who had a complete or partial response in the index lesion and other lesions, was evaluated according to EASL criteria in a post-hoc analysis. Patients with an extension of portal vein thrombosis at 3 months were considered as non-responders, regardless of the response in the other lesions.

Post-hoc analysis of objective response in the index lesion and overall response response, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, was done centrally by one masked study investigator.

Macro-aggregated albumin-based dosimetry was assessed centrally using Simplicit^{90}Y software (Mirada Medical, Oxford, UK) by one reviewer who was masked to treatment and response.

Secondary endpoints were dose-response evaluation, safety, and time-to-event measures of progression-free survival and overall survival. Progression-free survival was defined as the time from randomisation to progressive disease or death; patients were censored for progression-free survival if they were lost to follow-up, had initiated a systemic treatment or surgery, or had no progression before the end of the study follow-up period (at the 12-month visit). Overall survival was defined as the time from randomisation to death from any cause. Secondary endpoints of the dose-toxicity association and post-treatment ^{90}Y dosimetry will be reported elsewhere.

Vital status was updated until database lock (Aug 21, 2019), and follow-up was censored if the patient was still alive. Adverse events were recorded from the time of written informed consent to 30 days after selective internal radiation therapy. The adverse event data collection period was extended to 3 months for liver events, and the entire study period for selective internal radiation therapy-related liver serious adverse events. Adverse events were coded according to the Medical Dictionary for Regulatory Activities version 20.1,[24] and severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse

Events version 4.03.[25] Radioembolisation-induced liver disease, as defined by Sangro and colleagues,[26] was analysed in a post-hoc analysis. Adverse event imputability to selective internal radiation therapy respected the following rule for liver adverse events: in patients with both a liver adverse event and no evidence of progression, the adverse event was attributed to selective internal radiation therapy; conversely, in patients with evidence of progressive disease on imaging, the adverse event was attributed to disease progression.

Statistical analysis

The study was designed to detect a 35% difference in objective response rate in the index lesion between the standard dosimetry and personalised dosimetry groups, with an expected objective response rate in the index lesion in the standard dosimetry group of 50%, a 5% two-sided type I error rate, and 80% power. An interim analysis was planned when 60 patients had been enrolled (allowing for 10% dropout after randomisation). If the estimated difference in objective response rate between standard dosimetry and personalised dosimetry groups was greater than 15% and the one-sided p value was less than 0·01348, the trial could be stopped and concluded as positive. Otherwise, the study could either be stopped early (with an estimated difference of <15% between the two groups) or the study could be continued in up to 254 patients.

All analyses were assessed in the modified intent-to-treat population, defined as all randomly assigned patients who received treatment. Sensitivity analyses were done in the intention-to-treat population, which included all randomly assigned patients. Safety was assessed in the safety analysis population, defined as all patients who received selective internal radiation therapy according to the treatment actually received, which was based on central dosimetry assessment. A patient in the standard dosimetry group was considered to have received personalised dosimetry if the perfused liver dose was more than 150 Gy (a perfused liver dose of >150 Gy represents a treatment intensification by definition),[20] and a patient in the personalised dosimetry group was considered to have received standard dosimetry if the index lesion dose was less than 205 Gy.

Statistical inferences were assessed at a two-sided 5% level of significance. Response rates with 95% CIs were presented by study group and compared by use of χ^2 or the Fisher's exact tests. Overall survival and progression-free survival were calculated with Kaplan-Meier estimators; product-limit estimates were presented by study group using median time, and 12-month, 18-month, and 24-month survival rates with the corresponding two-sided 95% CIs, which were derived using the log-log transformation of the survival function. Median follow-up and 95% CIs were calculated by use of the reverse Kaplan-Meier method.[27] Survival curves of the two study groups were compared by use of a log-rank test. The HR (95% CI) of the standard dosimetry group versus the personalised dosimetry group was computed by use of a univariable Cox regression approach. Pre-specified subgroup analyses were done to estimate HRs (personalised dosimetry *vs* standard dosimetry) in subpopulations defined by the following cofactors (using cutoff points frequently reported in the medical literature when applicable): sex, age (≤65 years *vs* >65 years), Child-Pugh score (A5 *vs* A6-B7), performance status (0 *vs* 1), cirrhosis (yes *vs* no), tumour distribution (unifocal *vs* multifocal), number of lobes affected (unilobar *vs* bilobar), portal vein thrombosis (yes *vs* no),

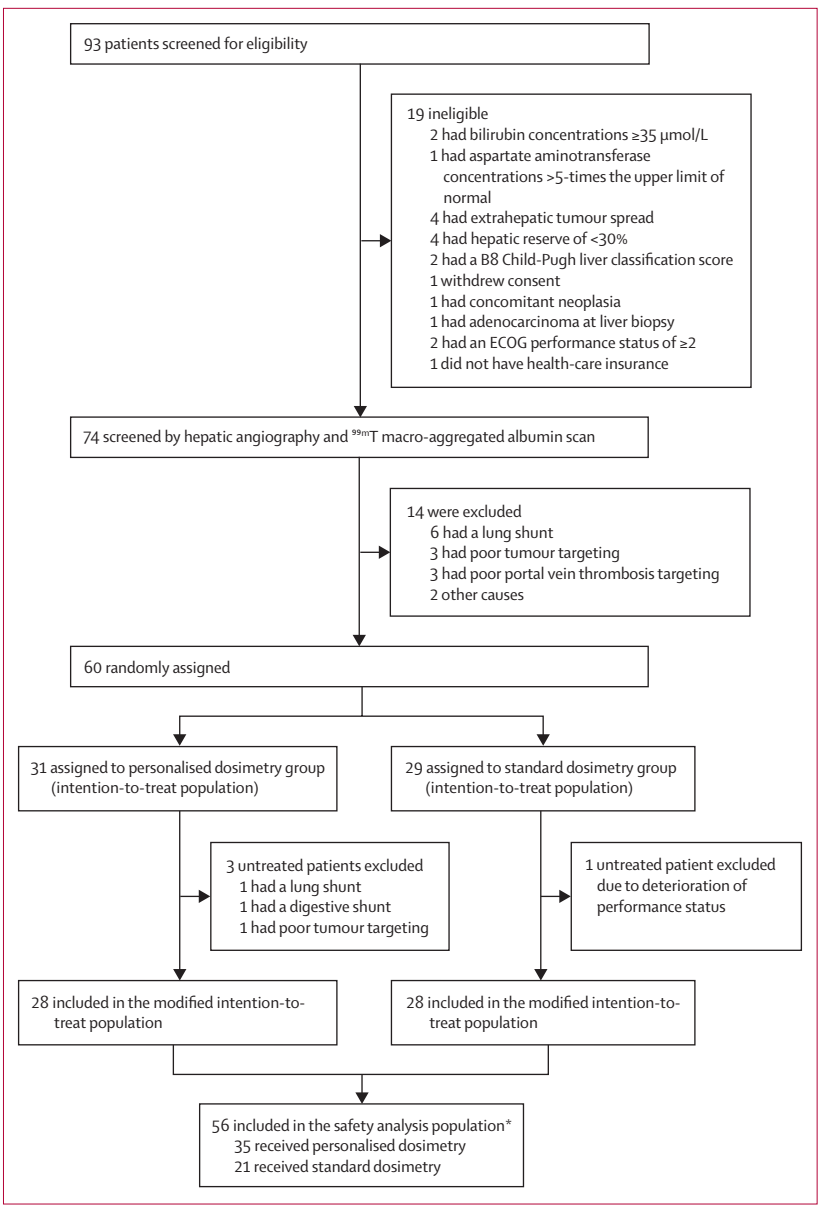

Figure 1: **Trial profile**
ECOG=Eastern Cooperative Oncology Group. ^{99m}Tc=technetium-99m. *Safety was measured according to treatment actually received, which was classified on the basis of central dosimetry review.

	Intention-to-treat population		Modified intention-to-treat population	
	Personalised dosimetry group (n=31)	Standard dosimetry group (n=29)	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)
Mean age, years	65·0 (10·1)	63·2 (13·4)	64·8 (10·1)	62·5 (13·1)
Sex				
Female	3 (10%)	2 (7%)	2 (7%)	2 (7%)
Male	28 (90%)	27 (93%)	26 (93%)	26 (93%)
Child-Pugh liver function classification				
A5	25 (81%)	23 (79%)	22 (79%)	22 (79%)
A6 or B7	6 (19%)	6 (21%)	6 (21%)	6 (21%)
ECOG performance status				
0	18 (58%)	14 (48%)	16 (57%)	13 (46%)
1	13 (42%)	15 (52%)	12 (43%)	15 (54%)
BCLC classification				
B	4 (13%)	3 (10%)	3 (11%)	2 (7%)
C	27 (87%)	26 (90%)	25 (89%)	26 (93%)
Portal vein invasion				
Absent	11 (36%)	8 (27%)	10 (36%)	7 (25%)
Present	20 (65%)	21 (72%)	18 (64%)	21 (75%)
Portal vein invasion location				
Segmental	10 (33%)	9 (31%)	8 (30%)	9 (32%)
Lobar or main	9 (30%)	12 (41%)	9 (33%)	12 (43%)
Unknown	1 (3%)	0	1 (4%)	0
Cause of cirrhosis				
Alcohol	9 (29%)	9 (31%)	9 (32%)	9 (32%)
Viral hepatitis	8 (26%)	9 (31%)	7 (25%)	9 (32%)
Haemochromatosis	1 (3%)	0	1 (4%)	0
Non-alcoholic steatohepatitis	3 (10%)	3 (10%)	3 (11%)	3 (11%)
Mixed (alcohol and other)	4 (13%)	3 (10%)	4 (14%)	3 (11%)
No cirrhosis	6 (19%)	5 (17%)	4 (14%)	4 (14%)
Treatment line				
First	21 (68%)	25 (86%)	20 (71%)	25 (89%)
Second and subsequent	8 (26%)	3 (10%)	8 (29%)	3 (11%)
Previous transarterial chemoembolisation	5 (16%)	0	5 (18%)	0
Unknown	2 (6%)	1 (3%)	0	0
Tumour distribution				
Unifocal	18 (58%)	12 (41%)	15 (54%)	12 (43%)
Multifocal	13 (42%)	17 (59%)	13 (46%)	16 (57%)
Lobes affected				
Unilobar disease	17 (55%)	12 (41%)	16 (57%)	12 (43%)
Bilobar disease	14 (45%)	17 (59%)	12 (43%)	16 (57%)
Number of lobes treated with selective internal radiation therapy				
One	25 (81%)	21 (72%)	25 (89%)	21 (75%)
Both	3 (10%)	7 (24%)	3 (11%)	7 (5%)
Neither	3 (10%)	1 (3%)	0	0
Tumoural involvement				
Mean	23·9% (14·4)	27·0% (15·8)	23·0% (13·9)	25·6% (14·1)
≥50%	3 (10%)	3 (10%)	2 (7%)	2 (7%)
<50%	27 (87%)	26 (90%)	26 (93%)	26 (93%)
Missing data	1 (3%)	0	0	0

(Table 1 continues on next page)

treatment line (first line *vs* subsequent line), largest diameter of the index lesion (<10 cm *vs* ≥10 cm), baseline α-fetoprotein concentrations (<200 µg/L *vs* ≥200 µg/L), and degree of tumour involvement (<50% *vs* ≥50%). Response and survival parameters were also estimated according to tumour dose (<205 Gy *vs* ≥205 Gy). Post-hoc subgroup analyses were also done to estimate HRs (personalised dosimetry *vs* standard dosimetry) in subpopulations defined by the location of portal vein thrombosis, the number of selective internal radiation therapy procedures done (unilobar or bilobar), and treatment centre.

Data were analysed using SAS software versions 9.4 and 7.1.

The trial is registered with ClinicalTrials.gov, NCT02582034, and has been completed.

Role of the funding source

The funder of the study validated the study design, but had no role in data collection, data analysis, or data interpretation. Editorial assistance for the report was funded by Boston Scientific. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 5, 2015, and Jan 4, 2018, 93 patients were screened, of whom 60 patients were found to be eligible and were randomly assigned to either the personalised dosimetry group (n=31) or to the standard dosimetry group (n=29; figure 1). Three patients in the personalised dosimetry group did not receive treatment due to major protocol deviations (one patient had a digestive shunt, one patient had a high lung shunt, and one patient had no macro-aggregated albumin targeting of a main portal vein thrombosis) and one patient in the standard dosimetry group did not receive treatment due to deterioration of his general condition (performance status of 2). Therefore, the modified intention-to-treat population comprised 56 patients (28 in each group). Patient characteristics were not statistically different between the two groups (table 1). The cutoff date for the primary analysis was Aug 21, 2019.

In the personalised dosimetry group, treatment was unilobar in 25 (81%) of 28 patients and bilobar in three (11%) patients. In the standard dosimetry group, treatment was unilobar in 21 (72%) of 28 patients and bilobar in seven (24%) patients (appendix p 4). The bilobar treatments were not a result of progression. In patients with bilobar disease, details of treatment of the second lobe (with minimal tumour involvement) are presented in the appendix (p 4).

The median prescribed activity was 3·6 GBq (IQR 2·4–4·8) in the personalised dosimetry group compared with 2·6 GBq (2·2–3·0) in the standard dosimetry group (p=0·0049). All patients received less than 150 Gy to the whole liver (consistent with the

instructions for use of the product),[7] except in one patient in the personalised dosimetry group who received 150·6 Gy in one treatment, without any grade 3 or higher liver adverse events of interest.

Dosimetry was evaluated in the 56 treated patients; however, the index lesion dose and normal perfused liver dose was not evaluable for four patients in each group who received two macro-aggregated albumin administrations during the pretreatment angiography. According to the investigator assessment, a significant difference in all pretreatment macro-aggregated albumin dosimetry parameters was observed between the personalised dosimetry and standard dosimetry groups (table 2). These differences included the proportion of patients with an absorbed dose to the index lesion that met or surpassed the threshold dose of 205 Gy and the proportion of patients with an absorbed dose of greater than 150 Gy to the perfused liver (table 2). Centralised assessments confirmed these significant differences (table 2).

According to investigator assessment, the objective response rate in the index lesions in the modified intention-to-treat population at 3 months was significantly higher in the personalised dosimetry group than in the standard dosimetry group, with 20 (71% [95% CI 51–87]) of 28 patients in the personalised dosimetry group had an objective response compared with ten (36% [19–56]) of 28 patients in the standard dosimetry group (p=0·0074; table 3). These results met the prespecified stopping criteria and the study was interrupted for efficacy. Centralised assessment confirmed these results (table 3). The effect of personalised dosimetry on objective response rate was consistent across prespecified subgroups based on baseline characteristics (appendix p 7). The overall response rate according to EASL criteria in patients in the modified intention-to-treat population at 3 months was significantly higher in the personalised dosimetry group than in the standard dosimetry group, with 14 (50% [31–69]) patients in the personalised dosimetry group who had an overall response compared with five (14% [4–33]) patients in the standard dosimetry group (p=0·0042). The objective response rate in the index lesions and objective response rate as per RECIST version 1.1 criteria are presented in the appendix (p 4).

Resection with curative intent after selective internal radiation therapy was done in ten (36%) of 28 patients in the personalised dosimetry group and in one (4%) of 28 patients in the standard dosimetry group (p=0·029; appendix p 5). Of these 11 patients, ten (91%) underwent R0 (microscopic tumour-free margins) surgical resection, and one (9%) patient had a complete histological response. Among 39 patients with portal vein thrombosis, resection after selective internal radiation therapy was done in eight (44%) of 18 patients in the personalised dosimetry group and in no patients in the standard dosimetry group.

Patients were followed up for a median of 27·2 months (IQR 33·9–18·7). During the study, 37 (62%) of 60 patients in the intention-to-treat population had died, including 14 (45%) of 31 patients in the personalised dosimetry group and 23 (79%) of 29 patients in the standard dosimetry group. Median overall survival in the intention-to-treat population was 26·6 months (95% CI 11·7–not reached [NR]) in the personalised dosimetry group compared with 10·7 months (6·0–16·8) in the standard dosimetry group (HR 0·421 [95% CI 0·215–0·826], p=0·0096; figure 2A). Overall survival estimates in the intention-to-treat population were 66·5% (95% CI 46·6–80·4) in the personalised dosimetry group versus 44·8% (26·5–61·6) in the standard dosimetry group at 12 months, 62·6% (42·5–77·3) in the personalised dosimetry group versus 26·8% (12·3–43·7) in the standard dosimetry group at 18 months, and 53·3% (32·8–70·1) in the personalised dosimetry group versus 22·3% (9·0–39·3) in the standard dosimetry group at 24 months. The significant difference in median overall survival between the two groups was maintained after censoring at the date of surgery (post-hoc analysis; appendix p 8).

Median overall survival in the modified intention-to-treat population was 26·6 months (95% CI 11·7–NR) in the personalised dosimetry group versus 10·7 months (6·0–14·8) in the standard dosimetry group (HR 0·38 [95% CI 0·19–0·83], p=0·0063; appendix p 9). The effect of personalised dosimetry versus standard dosimetry was consistent across prespecified subgroups based on baseline characteristics (appendix p 10), including in

	Intention-to-treat population		Modified intention-to-treat population	
	Personalised dosimetry group (n=31)	Standard dosimetry group (n=29)	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)
(Continued from pervious page)				
Index tumour size, cm				
Mean	10·6 (2·8)	11·1 (2·8)	10·5 (2·4)	10·9 (2·57)
≥10	17 (55%)	18 (62%)	15 (54%)	17 (61%)
<10	14 (45%)	11 (38%)	13 (46%)	11 (39%)
α-fetoprotein concentration, kU/L				
Mean	8580·3 (27059·2)	12559·3 (25833·1)	4052·0 (9920·7)	13007·8 (26192·0)
≥200	13 (42%)	12 (41%)	11 (39%)	12 (43%)
<200	18 (58%)	17 (59%)	17 (61%)	16 (57%)
Bilirubin concentration, μmol/mL				
Mean	13·6 (6·1)	14·2 (6·3)	14·0 (6·0)	14·3 (6·4)
<35	31 (100%)	29 (100%)	28 (100%)	28 (100%)
Treatment site				
Site 1	10 (32%)	5 (17%)	10 (36%)	5 (18%)
Site 2	5 (16%)	7 (24%)	3 (11%)	6 (21%)
Site 3	5 (16%)	3 (10%)	4 (14%)	3 (11%)
Site 4	11 (36%)	14 (48%)	11 (39%)	14 (50%)

Data are n (%) or mean (SD). ECOG=Eastern Cooperative Oncology Group. BCLC=Barcelona Clinic Liver Cancer.

Table 1: **Demographic and baseline characteristics of patients in the intention-to-treat and modified intention-to treat populations**

patients with portal vein thrombosis, in whom median overall survival was 22·9 months (95% CI 9·1–NR) in the personalised dosimetry group versus 9·5 months (5·3–17·6) in the standard dosimetry group (HR 0·39 [95% CI 0·17–0·90], p=0·023).

According to investigator assessment, progression events occurred in 34 (57%) of 60 patients in the intention-to-treat analysis population (17 [55%] of 31 patients in the personalised dosimetry group and 17 [59%] of 29 patients in the standard dosimetry group). Median progression-free survival in this population was 6·0 months (95% CI 3·5–11·6) in the personalised dosimetry group compared with 3·4 months (2·9–8·5) in the standard dosimetry group (HR 0·71 [95% CI 0·39–1·30], p=0·26; figure 2B). In the 34 treated patients with confirmed recurrence, progression events occurred in untreated areas (in the opposite lobe or a distant metastatic lesion) in 24 (71%) patients, and in the treated area in ten (29%) patients (appendix p 5).

After selective internal radiation therapy, 28 (50%) of 56 patients in the modified intention-to-treat population received at least one second-line treatment (appendix p 5).

In the safety analysis, 35 patients were considered to have received personalised dosimetry treatment and 21 were considered to have received standard dosimetry treatment on the basis of centralised dosimetry assessment (table 2). One patient in the personalised dosimetry group received a tumour dose of less than 205 Gy and was considered to have received standard dosimetry. Eight patients in the standard dosimetry group received a dose of greater than 150 Gy to the lobe (ie, they had treatment intensification by definition).[20] Among the 56 patients, 50 (89%) had 241 adverse events, 37 (66%) had 67 grade 3 or worse adverse events, 27 (48%) had 35 grade 3 or worse treatment-related adverse events, 14 (25%) had 20 serious adverse events, and six (11%) had seven serious treatment-related adverse events (table 4). At least one adverse event was reported in 31 (89%) of 35 patients who received personalised dosimetry and in 19 (90%) of 21 patients who received standard dosimetry. A breakdown of type and grades of adverse events, including treatment-related adverse events and serious adverse events, is shown in table 4. One treatment-related death was reported in each group (table 4). Frequent adverse events (ie, those that occurred in ≥5% of patients) are presented in table 5. The most frequent (ie, occurring in ≥5% of patients) grade 3 or higher adverse events were ascites (one [3%] patient who received personalised dosimetry *vs* two [10%] patients who

	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)	p value
Investigator assessment			
Perfused liver dose, Gy			
Mean	178·4 (59·9)	120·3 (15·2)	0·0001
>150	19 (68%)	1 (4%)	<0·0001
Absorbed tumour dose, Gy*			
Mean	331·1 (131·5)	221·3 (139·4)	0·0007
≥205	21 (88%)	9 (38%)	0·0008
Normal perfused liver dose, Gy*	92·8 (30·1)	64·5 (36·6)	0·0069
Centralised assessment			
Perfused liver dose, Gy			
Mean	213·7 (70·2)	155·2 (97·4)	0·0002
>150	21 (75%)	8 (29%)	0·0011
Absorbed tumour dose, Gy*			
Mean	332·1 (94·8)	225·0 (126·2)	0·0010
≥205	23 (96%)	10 (42%)	<0·0001
Normal perfused liver dose, Gy*	119·7 (67·3)	79·2 (56·9)	0·029

Data are mean (SD) or n (%). ^{99m}Tc=technetium-99m. *Evaluated in 48 patients (24 in each group), as tumour dose and normal perfused liver dose was not evaluable for eight patients (four in each group) due to these patients receiving two ^{99m}Tc macro-aggregated albumin injections during the same pretreatment angiography.

Table 2: **Investigator and centralised ^{99m}Tc macro-aggregated albumin dosimetry results in patients who received selective internal radiation therapy**

	Investigator evaluation			Centralised evaluation		
	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)	p value	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)	p value
Objective response	20 (71%)	10 (36%)	..	22 (79%)	12 (43%)	..
Complete response	6 (21%)	3 (11%)	..	5 (18%)	6 (21%)	..
Partial response	14 (50%)	7 (25%)	..	17 (61%)	6 (21%)	..
No response	8 (29%)	18 (64%)	..	6 (21%)	16 (57%)	..
Stable disease	4 (14%)	14 (50%)	..	3 (11%)	11 (39%)	..
Progressive disease	1 (4%)	0	..	0	1 (4%)	..
Other	3 (11%)*	4 (14%)†	..	3 (11%)*	4 (14%)†	..
Objective response rate (95% CI)	71% (51–87)	36% (19–56)	0·0074	79% (59–92)	43% (24–63)	0·0062

Data are n (%), unless otherwise stated. *Two patients were evaluated at 3 months after the introduction of systemic treatment, and one patient was not evaluated at month 3. †One patient was evaluated at 3 months after the introduction of systemic treatment, and three patients were not evaluated at 3 months, including two patients who had died due to progressive disease.

Table 3: **Objective response evaluation of the index lesion at 3 months by investigator and centralised review in the modified intention-to-treat population**

received standard dosimetry), hepatic failure (two [6%] *vs* none), lymphopenia (12 [34%] *vs* nine [43%]), increased aspartate aminotransferase concentrations (three [9%] *vs* two [10%]), increased alanine aminotransferase concentrations (three [9%] *vs* none), anaemia (two [6%] *vs* one [5%]), gastrointestinal haemorrhage (none *vs* two [10%]), and icterus (none *vs* two [10%]; table 5). The number of grade 3 or higher liver events of interest did not differ between the two dosimetry treatments, and were reported in four (12%) patients who received personalised dosimetry treatment and in five (24%) patients who received standard dosimetry treatment (appendix p 6). Clinically relevant radioembolisation-induced liver disease, which is a post-selective internal radiation therapy liver-specific complication characterised by jaundice and ascites,[26] occurred in five (9%) of 56 patients in the safety analysis population (in three [9%] of 35 patients who received personalised dosimetry treatment and in two [10%] of 21 patients who received standard dosimetry treatment).

In 30 patients who received a tumour dose of 205 Gy or higher, 23 (77%) patients had an objective response in the index lesion compared with four (22%) of 18 patients who received less than 205 Gy (p=0·0002), as per investigator assessment of dose and response. The mean index lesion absorbed dose was 337·6 Gy (SD 145·4) in patients with an objective response compared with 210·3 Gy (118·2) in those without an objective response (p=0·0021).

Median overall survival in the modified intention-to-treat population was 26·6 months (95% CI 13·5–NR) in patients who received a tumour dose of 205 Gy or higher compared with 7·1 months (95% CI 4·6–14·8) in those who received a tumour dose of less than 205 Gy (HR 0·33 [95% CI 0·15–0·71], p=0·0029; figure 2C).

Discussion

The multicentre, randomised DOSISPHERE-01 trial compared personalised dosimetry with standard dosimetry treatment in patients with advanced hepatocellular carcinoma. The results showed that the objective response rate, according to EASL criteria, was significantly higher in the personalised dosimetry group than in the standard dosimetry group, with 20 (71% [95% CI 51–87]) of 28 patients in the personalised dosimetry group and ten (36% [19–56]) of 28 patients in the standard dosimetry group having had an objective response in the target lesion at the interim analysis (p=0·0074). These results met the prespecified hypothesis, with a significant difference (p<0·01348) in the objective response rate in the index lesion observed between the standard dosimetry and personalised dosimetry groups, and the study was interrupted for efficacy. The overall response rate according to EASL criteria was also significantly higher in the personalised dosimetry group than in the standard dosimetry group, with 14 (50% [95% CI 31–69]) of 28 patients in the personalised dosimetry group who had an overall response compared with five (14% [4–33]) of 28 patients in the standard dosimetry group (p=0·0042).

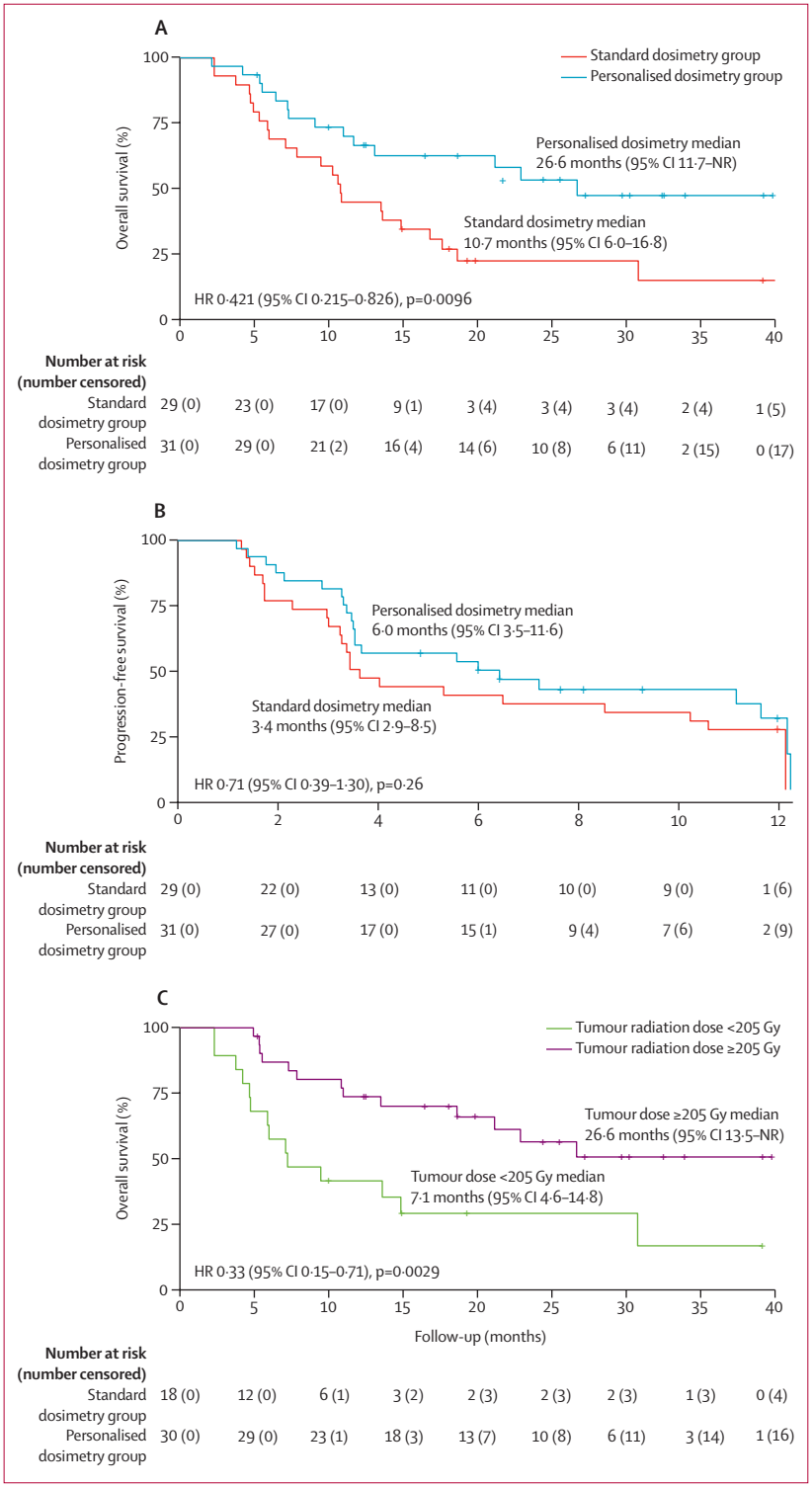

***Figure 2*: Kaplan-Meier survival curves**
Overall survival (A) and progression-free survival (B) in the intention-to-treat population. (C) Overall survival in the modified intention-to-treat population, according to tumour radiation dose (investigator assessment). Tumour radiation dose was not evaluable in eight patients (four in each group) because they received two technetium-99m macro-aggregated albumin injections during the same pretreatment angiography. NR=not reached. HR=hazard ratio.

	Personalised dosimetry treatment (n=35)		Standard dosimetry treatment (n=21)	
	Patients	Events	Patients	Events
Any adverse event	31 (89%)	158	19 (90%)	83
Grade 3	20 (57%)	30	14 (67%)	26
Grade ≥3	21 (60%)	36	16 (76%)	31
Grade 4	3 (9%)	3	2 (10%)	2
Grade 5	2 (6%)*	3	3 (14%)†	3
Any serious adverse event	7 (20%)	10	7 (33%)	10
Serious treatment-related adverse events				
Grade 3	14 (9%)	16	11 (67%)	16
Grade ≥3	16 (6%)	18	11 (52%)	17
Grade 4	1 (3%)	1	0	0
Grade 5	1 (3%)	1	1 (5%)	1
Serious treatment-related adverse events	3 (9%)	4	3 (14%)	3

Adverse events occurring in patients who reported one or more adverse event. 35 patients received personalised dosimetry treatment (>150 Gy to the perfused liver) and 21 patients received standard dosimetry treatment (<205 Gy to the index lesion). *One patient died due to hepatic failure (related to treatment) and the other patient died due to encephalopathy associated with deterioration of their general condition (unrelated to treatment; counted as two grade 5 events). †These patients died due to ascitis (related to treatment), spinal cord compression (unrelated to treatment), and cachexia (unrelated to treatment).

Table 4: **Adverse events in the safety analysis population**

The observed objective overall response rate in the personalised dosimetry group of 50% according to EASL criteria and 29% (eight of 28 patients) according to RECIST version 1.1 criteria is higher than that reported in previous studies of selective internal radiation therapy (36 [20%] of 190 according to RECIST criteria in the SARAH trial), and higher than that reported in studies of immunotherapy (108 [33%] of 325 according to modified RECIST criteria in the IMbrave150 study).[4,13] Tumour size is recognised as a strong prognostic indicator for response and overall survival after locoregional treatment.[19,28] Tumour size has also recently been suggested to have a strong negative impact on response to immunotherapy in different tumour types,[29,30] which could also be the case for hepatocellular carcinoma. Therefore, it is important to highlight the fact that the high objective response rate we observed was in selected patients who had at least one lesion larger than 7 cm in size, which was not an inclusion criterion in other previous studies, including the SARAH and IMbrave150 trials.[4,13,15]

Our study showed a meaningful effect of personalised dosimetry on overall survival, with a HR of death in the intention-to-treat population of 0·421 (95% CI 0·215–0·826, p=0·0096) when comparing personalised dosimetry with standard dosimetry. Of particular note, median overall survival was 26·6 months in patients in the personalised dosimetry group (intention-to-treat population), which is long considering that these patients had large lesions (ie, >7 cm in size) and that there was a high proportion of patients with portal vein thrombosis.

Our results compare favourably with the results of other randomised studies of selective internal radiation therapy. Median overall survival in the treated population was 9·9 months (95% CI 8·0–12·7) in the SARAH trial[13] and 11·3 months (9·2–13·6) in SIRveNIB trial.[14] It is important to observe that the median overall survival of 10·7 months (95% CI 6·0–16·8) observed in patients in the standard dosimetry group in the DOSISPHERE-01 trial is within the range of median overall survival observed in patients treated with selective internal radiation therapy in the SARAH[13] and SIRveNIB trials,[14] indicating that we did not select for patients with a better prognosis than in these previous studies.

Comparing the median overall survival observed in the DOSISPHERE-01 trial with studies of systemic drugs requires caution, as the study populations are not identical. Previous studies[2,3] of systemic drugs have included more patients with extrahepatic spread and therefore a poorer prognosis compared with the DOSISPHERE-01 trial, which only enrolled patients with large lesions and more patients with portal vein thrombosis. It should be noted that the prognosis of patients with portal vein thrombosis is not usually evaluated in studies of systemic therapy (in which patients with portal vein thrombosis and those with extrahepatic spread are evaluated together), except in the subgroup analysis of the SHARP study[31] of sorafenib, which showed that the prognosis of patients with portal vein thrombosis (median overall survival 4·9 months) was poorer than that of patients with extrahepatic spread (8·3 months) in the best supportive care group.[31] In the IMbrave150 study, median overall survival had not been reached at the time of the primary report, but is expected to be around 20 months in the atezolizumab plus bevacizumab group compared with 13·2 months in the sorafenib group (HR 0·58 [95% CI 0·42–0·79]).[4]

In our study, median overall survival in patients with portal vein thrombosis alone was longer in the personalised dosimetry group (22·9 months [95% CI 9·1–NR]) than in those in the standard dosimetry group (9·5 months [5·3–17·6]), and compares favourably with the overall survival of 8·1 months reported with sorafenib in the SHARP study.[31] The observation that eight (44%) of 18 patients with portal vein thrombosis in the personalised dosimetry group could undergo resection with curative intent after selective internal radiation therapy underscores the clinical benefit provided by personalised dosimetry, because surgery in patients with portal vein thrombosis is unusual after systemic therapy.

The effect of tumour dose on outcomes, as suggested in previous retrospective studies,[5,18–21] was prospectively confirmed in the DOSISPHERE-01 trial. Indeed, prospective dosimetry assessments done by investigators indicated that of the 30 patients who received a tumour dose of 205 Gy or higher, 23 (77%) patients had an objective response in the index lesion compared with four (22%) of 18 patients who received less than 205 Gy (p=0·0002), and median overall survival was 26·6 months (95% CI

	Personalised dosimetry treatment (n=35)				Standard dosimetry treatment (n=21)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Lymphopenia	4 (11%)	11 (31%)	1 (3%)	0	3 (14%)	9 (43%)	0	0
Asthenia	12 (34%)	1 (3%)	0	0	8 (38%)	1 (5%)	0	0
Ascites	3 (9%)	1 (3%)	0	0	6 (29%)	1 (5%)	0	1 (5%)
Increased blood bilirubin	5 (14%)	1 (3%)	0	0	5 (24%)	1 (5%)	0	0
Nausea	7 (20%)	0	0	0	3 (14%)	0	0	0
Abdominal pain	7 (20%)	0	0	0	2 (10%)	0	0	0
Increased aspartate aminotransferase	2 (6%)	3 (9%)	0	0	1 (5%)	1 (5%)	1 (5%)	0
Pyrexia	2 (6%)	0	0	0	2 (10%)	0	0	0
Anaemia	3 (9%)	2 (6%)	0	0	0	1 (5%)	0	0
Diarrhoea	5 (14%)	0	0	0	1 (5%)	0	0	0
Thrombocytopenia	5 (14%)	0	0	0	0	1 (5%)	0	0
Decreased weight	1 (3%)	0	0	0	2 (10%)	0	0	1 (5%)
Increased alanine aminotransferase increased	1 (3%)	3 (9%)	0	0	0	0	0	0
Constipation	4 (11%)	0	0	0	0	0	0	0
Increased blood alkaline phosphatase	1 (3%)	0	0	0	2 (10%)	0	0	0
Gastrointestinal haemorrhage	0	0	0	0	0	2 (10%)	0	0
Icterus	1 (3%)	0	0	0	0	2 (10%)	0	0
Cough	3 (9%)	0	0	0	0	0	0	0
Decreased appetite	3 (9%)	0	0	0	1 (5%)	0	0	0
Hepatic failure	1 (3%)	1 (3%)	0	1 (3%)	0	0	0	0
Vomiting	3 (9%)	0	0	0	1 (5%)	0	0	0
Acute kidney injury	2 (6%)	0	0	0	1 (5%)	0	0	0
Back pain	2 (6%)	0	0	0	0	0	0	0
Hypoalbuminaemia	2 (6%)	0	0	0	1 (5%)	0	0	0
Inflammation	2 (6%)	0	0	0	1 (5%)	0	0	0
Injection site haematoma	2 (6%)	0	0	0	0	0	0	0
Injection site pain	2 (6%)	0	0	0	0	0	0	0
Neutropenia	2 (6%)	0	0	0	0	0	0	0
Varices oesophageal	2 (6%)	0	0	0	0	0	0	0

One death related to treatment was reported in each group.

Table 5: **Adverse events occurring in 5% or more of patients**

13·5–NR) in those who received a tumour dose of more than 205 Gy compared with only 7·1 months (4·6–14·8) in those who received a tumour dose of less than 205 Gy (HR 0·33 [95% CI 0·15–0·71], p=0·0029). This point is of major interest and suggests that macro-aggregated albumin-based dosimetry can be used as standard practice in clinical sites to implement personalised dosimetry.

Progression-free survival did not differ significantly between the personalised dosimetry (6·0 months [95% CI 3·5–11·6]) and standard dosimetry groups (3·4 months [2·9–8·5]). However, due to the study design, progression-free survival had to be censored at the time of surgery because patients had to be withdrawn for resection. This censoring resulted in an important bias, as ten (35%) of 28 patients in the personalised dosimetry group had secondary resection compared with only one (4%) of 28 patients in the standard dosimetry group. With the low complete histological response, the importance of surgical resection in this population is highlighted. It seems that, given the high response rate in large lesions, selective internal radiation therapy with personalised dosimetry acts as a debulking agent for liver tumour load and has a positive effect on overall survival, even in patients with early recurrence. This debulking action of selective internal radiation therapy has already been described in a phase 2 study[32] done in patients with large non-operable intrahepatic cholangiocarcinoma, in which eight (30%) of 27 patients with unilobar disease underwent secondary resection.

Despite treatment intensification in 29 (83%) of 35 patients who received personalised dosimetry, safety was acceptable, with a similar proportion of liver adverse events of interest observed in the two groups in the safety analysis population. Clinically relevant radioembolisation-induced liver disease occurred in five (9%) of 56 treated patients, and occurred at a similar frequency in those who received personalised dosimetry (three [9%] of 35 patients) and standard dosimetry (two [10%] of 21 patients). These results are consistent with the 5–19% of patients with hepatocellular carcinoma who

developed radioembolisation-induced liver disease after selective internal radiation therapy in previous studies,[9,13] and is especially interesting for the patients who received personalised dosimetry in our study because they often underwent treatment intensification. This acceptable safety profile is probably the result of accurate patient selection, with the inclusion of patients with good liver function and a hepatic reserve of at least 30% after selective internal radiation therapy.

With regards to the design of the DOSISPHERE-01 trial, we used a multidisciplinary approach, with the input of oncologists, hepatologists, interventional radiologists, and nuclear medicine physicians, and personalised dosimetry to improve the efficacy of selective internal radiation therapy. Additionally, two other design elements were implemented. First, our study is the first to randomise patients only after determining whether they were able to receive selective internal radiation therapy (ie, by use of the macro-aggregated albumin scan to identify contra-indications, such as lung or digestive shunts). This reduces the number of patients who would otherwise have dropped out of the study after randomisation but before treatment. In the negative phase 3 trials, randomisation was done before the macro-aggregated albumin scan, [13,15] which led 22–28% of patients in the selective internal radiation therapy groups to not actually receive this treatment.[13,14] The second study design element relates to patient selection to preserve safety: patients were included only if they had good liver function and liver disease that had not spread too widely, with the possibility of sparing at least 30% of the liver from radiation. Furthermore, patients were excluded if they were poor candidates for selective internal radiation therapy due to poor targeting of the tumour or portal vein thrombosis.[20,21] All new selective internal radiation therapy trials should follow a similar design, in which the macro-aggregated albumin scan is used as a sort of biomarker for patient selection: randomisation after hepatic angiography and ^{99m}Tc macro-aggregated albumin scan simulation, personalised dosimetry, and more refined patient selection than has been used in previous studies, emphasising good tumour and main portal vein thrombosis targeting with macro-aggregated albumin.

Our study has some limitations. A small number of patients were included in the trial; however, this limitation resulted from the prespecified statistical criterion for stopping early for efficacy, and translated into a clinically meaningful benefit in overall survival. The use of macro-aggregated albumin as a surrogate for microspheres has been widely debated, and many confounding factors have been described.[17] However, this study showed that, at least in the case of hepatocellular carcinoma, and while taking care to limit the occurrence of spasm (which affects macro-aggregated albumin distribution), macro-aggregated albumin has sufficient accuracy for personalised dosimetry to be done with good clinical results. In addition, international recommendations from an expert group in the field supporting macro-aggregated albumin-based personalised dosimetry were published recently (2019).[33] Furthermore, we selected a specific population of patients for inclusion in the study. The generalisability of the results to patients with small lesions (ie, <7 cm) has yet to be evaluated. An improvement in the objective response rate and overall survival in these patients is expected, but the extent of this improvement compared with that observed in patients with large lesions would probably be lower, as the objective response rate in patients with small lesions treated with standard dosimetry is already higher than that observed in patients with large lesions. Even with the use of radiation segmentectomy,[34] the complete histological response rate is 66%, but might be improved with personalised dosimetry. The generalisability of DOSISPHERE-01 trial results to resin microspheres also needs to be evaluated. Theoretically, the concept of personalised dosimetry also applies to resin microspheres, but with a different hepatocellular carcinoma tumoricidal tumour dose of between 100 Gy and 120 Gy[5,35] compared with 205 Gy for glass microspheres. The effect of tumour dose on response and survival has already been described with resin microspheres; [5,34] however, the use of personalised dosimetry and its effects have not been analysed prospectively.

In summary, macro-aggregated albumin SPECT/CT-based personalised dosimetry is safe and leads to a meaningful improvement in the objective response rate and overall survival of patients with locally advanced hepatocellular carcinoma, with an acceptable toxicity profile and without increasing toxicity when compared with standard dosimetry. These results challenge the interpretation of the previously published negative phase 3 trials of selective internal radiation therapy, in which personalised dosimetry was not used. The promising results shown by the use of personalised dosimetry warrant further phase 3 randomised trials of selective internal radiation therapy with personalised dosimetry, either alone or in combination with newer agents.

Contributors

EG, BC-G, JE, and YR made substantial contributions to the conception and design of this study. All authors participated in acquiring the data, and EG, LT, BG, JC, JE, EA, YR, SL, and BC-G also contributed to data analysis and interpretation. EG, LT, BG, JC, JE, EA, YR, and BC-G wrote the manuscript. All authors contributed to the review and revision of the manuscript. All authors approved the final version of the manuscript and take responsibility for the accuracy and integrity of this work.

Declaration of interests

EG reports receiving a grant, personal fees, and non-financial support from Boston Scientific during the conduct of the study. LT reports personal fees from Boston Scientific, Sirtex, and GE Healthcare; grants from Terumo and the Bristol Myers Squibb Foundation; and non-financial support from GE Healthcare during the conduct of the study. BG reports personal fees from Boston Scientific during the conduct of the study. JE reports receiving a grant from Boston Scientific during the conduct of the study; personal fees from Boston Scientific, Bayer, Roche, Eisai, Merck Sharpe & Dohme, AstraZeneca, and Ipsen; grants and personal fees from Bristol Myers Squibb; and non-financial support from Amgen, outside the submitted work. TdB reports grants from Terumo; and personal fees from Guerbet and Terumo during the

conduct of the study. AH reports non-financial support from Servier, Incyte, and Lilly; and personal fees from Amgen, Eisai, and Gritstone Oncology, outside the submitted work. MK reports grants from DOSIsoft outside the submitted work. HR reports personal fees from Boston Scientific outside the submitted work. CR, XP, SLS, SL, BC-G, and YR report receiving a grant from Boston Scientific during the conduct of the study. All other authors declare no competing interests.

Data sharing

The study protocol, statistical analysis plan, and clinical study report can be obtained by contacting the corresponding author (EG). Individual participant data will not be made available.

Acknowledgments

This study was sponsored by the Cancer Institute Eugène Marquis of Rennes, France, and funded by Biocompatibles UK, a Boston Scientific Group company. The authors thank the patients who participated in the study and their families. Editorial support for the manuscript was provided by Tuli Ahmed (Accelera Communications), and funded by Boston Scientific Group.

References

1 Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136:** E359–86.

2 Balogh J, Victor D, Asham EH, et al. Hepatocellular carcinoma: a review. *J Hepatocell Carcinoma* 2016; **3:** 41–53.

3 Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359:** 378–90.

4 Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020; **382:** 1894–905.

5 Lau WY, Leung WT, Ho S, et al. Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study. *Br J Cancer* 1994; **70:** 994–99.

6 Dancey JE, Shepherd FA, Paul K, et al. Treatment of nonresectable hepatocellular carcinoma with intrahepatic 90Y-microspheres. *J Nucl Med* 2000; **41:** 1673–81.

7 Boston Scientific. Package insert: TheraSphere yttrium-90 glass microspheres. https://www.researchgate.net/publication/325791701_The_value_of_99mTc-MAA_SPECTCT_for_lung_shunt_estimation_in_90Y_radioembolization_a_phantom_and_patient_study/fulltext/5b23fba8458515270fd0ee83/The-value-of-99mTc-MAA-SPECT-CT-for-lung-shunt-estimation-in-90Y-radioembolization-a-phantom-and-patient-study.pdf (accessed Aug 12, 2020).

8 Sirtex Medical. SIR-Spheres microspheres (yttrium-90 microspheres). December, 2019. https://www.sirtex.com/au/clinicians/package-insert/ (accessed Aug 6, 2020).

9 Benson AB, D'Angelica MI, Abbott DE, et al. Guidelines insights: hepatobiliary cancers, version 2. 2019. *J Natl Compr Canc Netw* 2019; **17:** 302–10.

10 Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; **30:** 871–73.

11 Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010; **138:** 52–64.

12 Sangro B, Carpanese L, Cianni R, et al. European network on radioembolization with yttrium-90 resin microspheres (ENRY). Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; **54:** 868–78.

13 Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2017; **18:** 1624–36.

14 Chow PKH, Gandhi M, Tan S-B, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018; **36:** 1913–21.

15 Ricke J, Klümpen HJ, Amthauer H, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. *J Hepatol* 2019; **71:** 1164–74.

16 Garin E, Rolland Y, Campillo-Gimenez B, Edeline J. Negative phase 3 study of 90Y microspheres versus sorafenib in HCC. *Lancet Oncol* 2018; **19:** e70.

17 Garin E, Rolland Y, Laffont S, Edeline J. Clinical impact of 99mTc-MAA SPECT/CT-based dosimetry in radioembolization of liver malignancies with ^{90}Y-loaded microspheres. *Eur J Nucl Med Mol Imaging* 2016; **43:** 559–75.

18 Garin E, Lenoir L, Rolland Y, et al. Dosimetry based on 99mTc-macroaggregated albumin SPECT/CT based dosimetry accurately predicts tumour response and survival in hepatocellular patients treated with 90Y-loaded glass microspheres: preliminary results. *J Nucl Med* 2012; **53:** 255–63.

19 Garin E, Rolland Y, Pracht M, et al. High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with 90Y-loaded glass microsphere radioembolization. *Liver Int* 2017; **37:** 101–10.

20 Garin E, Lenoir L, Edeline J, et al. Boosted selective internal radiation therapy with 90Y-loaded glass microspheres (B-SIRT) for hepatocellular carcinoma patients: a new personalized promising concept. *Eur J Nucl Med Mol Imaging* 2013; **40:** 1057–68.

21 Garin E, Rolland Y, Edeline J, et al. Personalized dosimetry and intensification concept with 90Y-loaded glass microsphere radioembolization induce prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. *J Nucl Med* 2015; **56:** 339–46.

22 Garin E, Rolland Y, Edeline J. 90Y-loaded microsphere SIRT of HCC patients with portal vein thrombosis: high clinical impact of 99mTc-MAA SPECT/CT-based dosimetry. *Semin Nucl Med* 2019; **49:** 218–26.

23 Forner A, Ayuso C, Varela M, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer* 2009; **115:** 616–23.

24 Harrison J, Mozzicato P. MedDRA: the tale of a terminology: side effects of drugs essay. In: Aronson JK (ed). Side effects of drugs annual. Amsterdam: Elsevier, 2009: 33–51.

25 US Department of Health and Human Services. Common terminology criteria for adverse events (CTCadverse event) version 4.0. May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accessed Aug 6, 2020).

26 Sangro B, Gil-Alzugaray B, Rodriguez J, et al. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. *Cancer* 2008; **112:** 1538–46.

27 Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17:** 343–46.

28 Kadalayil L, Benini R, Pallan L, et al. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. *Ann Oncol* 2013; **24:** 2565–70.

29 Hopkins AM, Kichenadasse G, McKinnon RA, Rowland A, Sorich MJ. Baseline tumor size and survival outcomes in lung cancer patients treated with immune checkpoint inhibitors. *Semin Oncol* 2019; **46:** 380–84.

30 Joseph RW, Elassaiss-Schaap J, Kefford R, et al. Baseline tumor size is an independent prognostic factor for overall survival in patients with melanoma treated with pembrolizumab. *Clin Cancer Res* 2018; **24:** 4960–67.

31 Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012; **57:** 821–29.

32 Edeline J, Touchefeu Y, Guiu B, et al. Radioembolization plus chemotherapy for first-line treatment of locally advanced intrahepatic cholangiocarcinoma: a phase 2 clinical trial. *JAMA Oncol* 2020; **6:** 51–59.

33 Salem R, Padia SA, Lam, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. *Eur J Nucl Med Mol Imaging* 2019; **46:** 1695–704.

34 Vouche M, Habib A, Ward TJ, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. *Hepatology* 2014; **60:** 192–201.

35 Hermann AL, Dieudonne A, Ronot M, et al. Relationship of tumor radiation-absorbed dose to survival and response in hepatocellular carcinoma treated with transarterial radioembolization with ^{90}Y in the SARAH Study. *Radiology* 2020; **290:** 673–84.