NICE National Institute for Health and Care Excellence

For public (all confidential data redacted)

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

Multiple technology appraisal

Third appraisal committee meeting

Assessment Group: York CRD and York CHE

Technical team: Stephen O'Brien (chair), Verena Wolfram, Jamie Elvidge, Jasdeep Hayre

Companies: BTG, SIRTEX, Terumo Europe

4 August 2020

Key issue for ACM 3

Quality of life	Does the model capture all impacts on quality of life adequately?
	Do the utility values reflect differences in adverse events appropriately?
	Is it appropriate to apply QALY decrements for treatment related adverse events?

Appraisal Consultation Document (ACD): preliminary recommendation

- SIRTs are not recommended, within their CE marking, for treating hepatocellular carcinoma in adults.

Rationale

- for early and intermediate stage HCC:
  - not enough evidence
- for advanced HCC:
  - SIRTs are less effective and more costly than sorafenib

Other key points

- limited evidence of comparative effectiveness of QuiremSpheres and TheraSphere with other treatments
- not enough data to compare the effectiveness of the 3 SIRTs with each other
- unclear whether there is any comparative benefit regarding health-related quality of life
- limited evidence for subgroups
- model for advanced HCC assumed equal effectiveness of SIRTs

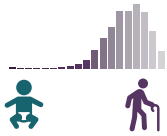
Background

Disease background

Hepatocellular carcinoma (HCC) is the most common form of liver cancer

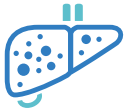
2,700 new cases of HCC in the England in 2017

Incidence is higher in men than women



Incidence increases with age

50% of people with HCC are diagnosed with advanced stage HCC and have poor prognosis with median survival of **less than 12 months**



HCC is commonly associated with cirrhosis

Common symptoms are:

- Pain in the upper right part of your belly
- A lump or feeling of heaviness in your upper belly
- Bloating or swelling in your belly

Selective internal radiation therapy (SIRT)

SIRT is a way of using radiotherapy to control cancers in the liver that can't be removed with surgery

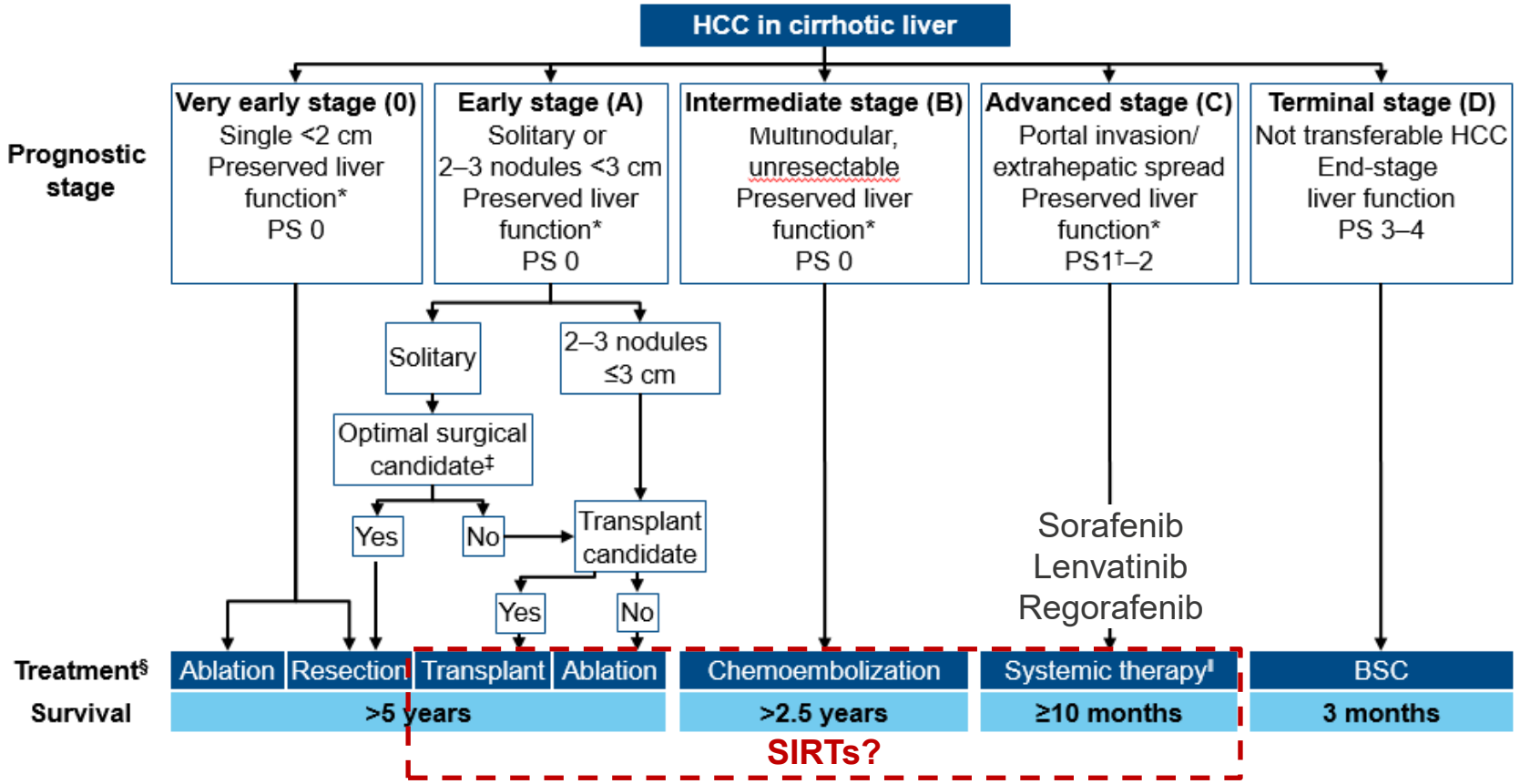
Internal radiotherapy using small radioactive beads that are injected into the tumour's blood supply and damage the tumour and the blood vessels it needs to survive

A work-up procedure including an angiogram is used to assess suitability for SIRT

SIRT is also called radioembolisation or transarterial radioembolisation (TARE)

Current UK treatment pathway

This appraisal considers selective internal radiation therapies for people with unresectable early (BCLC stage A), intermediate-stage (BCLC stage B) and advanced (BCLC stage C) HCC (with or without portal vein thrombosis/involvement).



Adults with unresectable HCC		
Eligible for transplant	Eligible for conventional transarterial therapies (CTT)	Ineligible for conventional transarterial therapies (CTT)

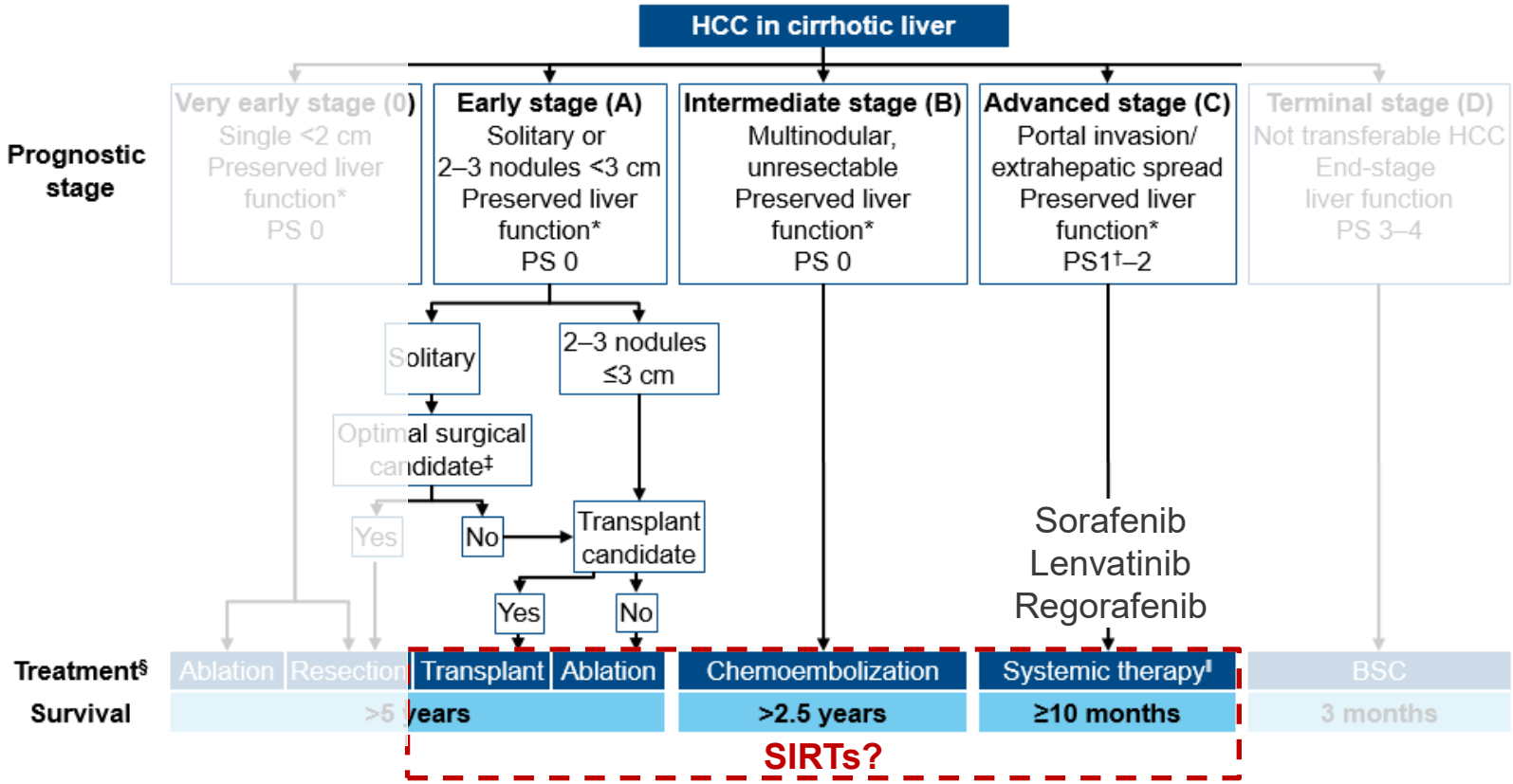
NICE *HCC EASL clinical practice guideline*
BCLC: Barcelona Clinical Liver Cancer

Summary

Appraisal Committee Meeting 1

November 2019

Committee considered 3 groups for the potential treatment with SIRTs



Adults with unresectable HCC		
Eligible for transplant	Eligible for conventional transarterial therapies (CTT)	Ineligible for conventional transarterial therapies (CTT)

There is enough clinical effectiveness evidence in the ineligible for CTT population for decision making

	Eligible for transplant	Eligible for CTT	Ineligible for CTT
Clinical evidence	QuiremSpheres – no evidence	QuiremSpheres – no evidence	QuiremSpheres – no evidence
	SIR-Spheres – no evidence	SIR-Spheres – RCT evidence (limited; 1 RCT n=24)	SIR-Spheres – RCT evidence (SARAH n=459 and SIRveNIB n=360, might not be generalisable), retrospective evidence
	TheraSphere – RCT evidence (limited; 2 RCTs n=45, 20), non-comparative evidence low quality and high risk of bias	TheraSphere – evidence (limited; 1 retrospective n=35), prospective comparative evidence low quality and high risk of bias	TheraSphere – evidence (limited; 2 retrospective n=90, 42)
Network meta-analysis	Not enough data available	Comparative effectiveness is very uncertain (weak links for SIR-Spheres and TheraSphere) – Not suitable for decision making	Comparative effectiveness is uncertain – BUT suitable for decision making

This evidence was included to calculate cost effectiveness for this group

	Eligible for transplant	Eligible for CTT	Ineligible for CTT
ICERs (including PASs)	Not performed	Not performed	Sorafenib dominated SIRTs in plausible scenarios SIRTs had fewer QALYs and were more costly in plausible scenarios Model assumed equal effectiveness of SIRTs
End of life criteria	Not met – life expectancy criteria not met	Not met – life expectancy criteria not met	Not met – extension of life ≥3 months not met

Committee also discussed the low tumour burden/ALBI 1 subgroup. It concluded there was not enough evidence for this subgroup.

Summary

Appraisal Committee Meeting 2

January 2020

Following stakeholders' comments the committee considered 4 themes at ACM2

At consultation BTG submitted results of dosimetry study; proposed patient access scheme for TheraSphere

Theme	Issues discussed	Committee discussion
Evidence	• Non-randomised evidence • UK real-world evidence and clinical experience • Dosimetry study	• Non-randomised evidence is associated with higher risk of bias; was used were appropriate • Considered dosimetry study
Subgroups	• People with portal vein thrombosis (PVT) • People with large tumour • People who are unable to tolerate sorafenib	• Limited or lack of evidence for these subgroups
Coverage with evidence generation	• Consideration of coverage with evidence generation for subgroups	• Noted by committee
Quality of life	• Patient expert testimonies • Impact on QoL	• Acknowledged that SIRTs might have a better safety profile than sorafenib

Health-related quality of life and side effects

Background

Utility values in original AG model

Health State	Utility values		
	SIRT	Systemic therapy	Work-up no SIRT
Progression-free survival	0.71	0.70	0.70
Progressive disease	0.67	0.66	0.66
Post-transplant*	0.71	0.71	0.71

*AG report scenarios 6 & 10 only

Stakeholder comments

- Quality of life data from the SARAH trial were favourable for SIRT (group effect p=0.0048) (EORTC-QLQ-C30 was collected every 3 months)
- Fewer and less severe side effects than other treatment options†
- One-off treatment with short lasting side effects†
- Sorafenib is long-term treatment with side effects; clinical experience suggest high discontinuation with sorafenib†
- Faster recovery time after SIRT when compared with TACE†

ACD:

- Committee noted that utility values were similar for SIRT and sorafenib
- Acknowledged that SIRTs are one-off interventions with short-term side effects
- Committee had not seen evidence comparing this benefit with relevant comparators

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†Included in model via adverse event rate or HRQoL data; †Not included in model as TACE is not included

Additional work requested by the committee at ACM2

Committee asked the AG to explore the evidence on quality of life relating to side effects

Questions addressed by the AG

1. Is it plausible that the model does not capture quality-of-life differences associated with side effects in full?
2. Can data from the clinical trials be used in the model to provide information on adverse event severity and duration?
3. Is there published real world evidence for adverse events that can be used?
4. Is it plausible to do scenario analyses with varying disutility values?

Differences in HRQoL might not impact domains in EQ-5D

Q1: Does the model fully capture differences in HRQoL due to side effects?

- EQ-5D is NICE's preferred measure of health-related quality of life
- EQ-5D utility values can be obtained
  - Directly from trials
  - Indirectly by mapping disease-specific utility measures onto EQ-5D

Direct elicitation

- SIRveNIB trial (SIR-Spheres versus sorafenib)

EQ-5D (direct)
SIR-Spheres = sorafenib

Indirect elicitation

- SARAH trial (SIR-Spheres versus sorafenib) used EORTC-QLQ-C30; company mapped data to EQ-5D

EORTC-QLQ-C30	EQ-5D (mapped)
SIR-Spheres > sorafenib	SIR-Spheres = sorafenib

- AG – important domains in HCC might not be represented in EQ-5D; algorithm not validated for people with HCC

Stakeholders: Small difference in QALYs between SIRTs and comparator (-0.076); lower adverse event QALY burden would reduce this difference.

Is QoL different for SIRTs and sorafenib?

SIRTs might have fewer adverse events than sorafenib but there is no evidence for difference in event duration

Q2: Can data from the clinical trials be used in the model to provide information on adverse event severity and duration?
Q3: Is there published real world evidence for adverse events that can be used?

Situation after ACM 2

- Committee acknowledges that SIRTs might have fewer adverse events than sorafenib
- The original model included grade 3 and 4 adverse events

Evidence provided for additional analysis

- Sirtex and BTG provided data on grade 1 and 2 events
- Sirtex provided data on event duration from SARAH
  - AG critiqued that data are averaged across arms and severity grades
- Stakeholders provided prospective and retrospective real world data
- Stakeholders highlighted ongoing French registry study

Are there fewer adverse events with SIRTs compared with sorafenib?
Is there a difference in how long adverse events last?
Is it reasonable to consider grade 1 and 2 adverse events in the model?

The AG provided scenario analyses to explore QALY losses resulting from adverse events

Q4: Is it plausible to do scenario analyses with varying disutility values?

Scenarios	TRAE QALY loss
AG base case – HRQoL effect of all AEs is captured by health state utility values	0.00
Grade 3+ AEs (SARAH): uniform 0.012 QALY loss per AE	Incremental: 0.006
Grade 3+ AEs (Kallini* & REFLECT†): uniform 0.012 QALY loss per AE	Incremental: 0.005
All grade AEs (SARAH): event-specific QALY loss	Incremental: 0.120
All grade AEs (SARAH): event-specific QALY loss, grade 1-2 AEs have a 50% lower reduction in HRQoL	Incremental: 0.070
All grade AEs (SARAH): event-specific QALY loss, grade 1-2 AEs have a 50% lower reduction in HRQoL and duration	Incremental: 0.047
All grade AEs (SARAH): event-specific QALY loss, grade 1-2 AEs have no effect on HRQoL	Incremental: 0.023

What is the most plausible scenario?

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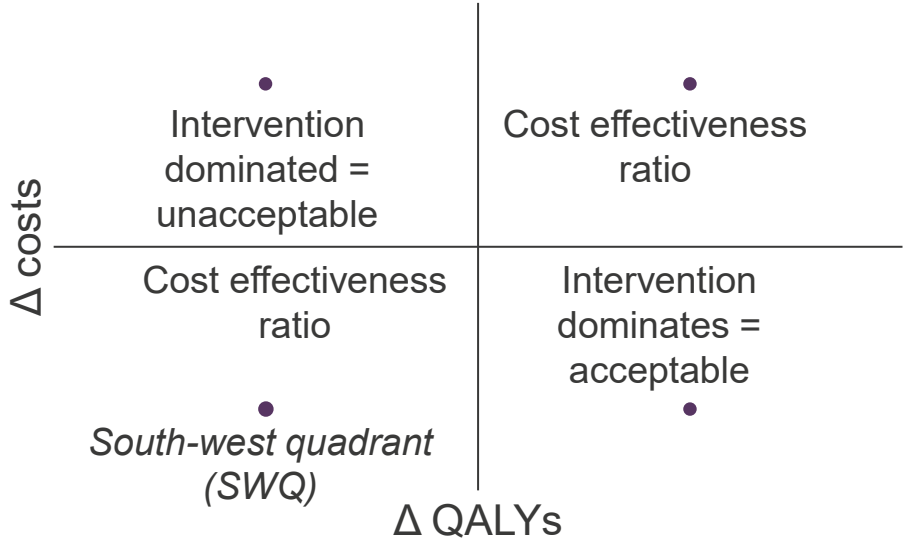
*compares adverse event profiles of TheraSphere with SIR-Spheres; †compares sorafenib with lenvatinib

AG revised base-case probabilistic results (not including PASs)

- Assumptions:
  - Efficacy of TheraSphere and QuiremSpheres equivalent to SIR-Spheres
  - All 3 SIRTs have identical procedure costs

	Costs	QALYs	Inc. cost	Inc. QALYs	ICER	NMB at £30K	% <£30K per QALY
SIR-Spheres	£30,885	0.765	-£4,074	-0.075	£54,068 (SWQ)	£1,824	72%
TheraSphere	£30,884	0.765	-£4,074	-0.075	£54,075 (SWQ)	£1,824	72%
QuiremSpheres	£32,872	0.765	-£2,086	-0.075	£27,683 (SWQ)	-£164	49%
Sorafenib	£34,958	0.84					

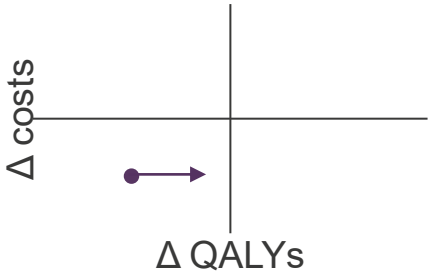


AG considered downstaging in a scenario analysis

Situation after ACM 2

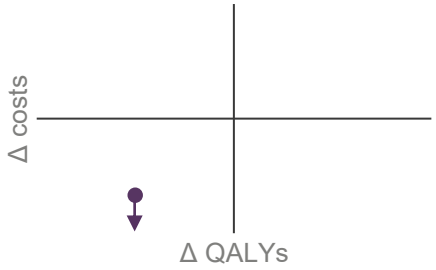
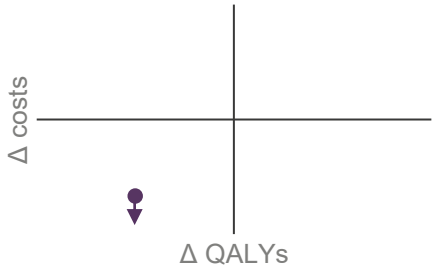
- Downstaging might have large impact on quality of life
- Downstaging is rare; proportion of people whose tumour downstages is unclear
- Limited data available for people whose tumour downstages
- Unclear whether people with advanced HCC would go on to curative treatment
- Highly uncertain whether SIRT technologies increase the proportion of patients whose tumour is downstaged

Proportion of people whose tumour downstaged and who receive curative treatment		
Source	**After SIR-Spheres**	**After sorafenib**
SARAH trial: ITT population	5.1%	1.4%
CIRT Registry	[redacted]	
Physician survey	5.6%	0.1%

Scenario	Impact on QALY difference	Impact on cost difference*	Impact on ICERs*
Downstaging included (companies consider excluding to be conservative)	Reduction in QALY difference (QALY difference 0.020)	No impact	

*Excluding PASs; not drawn to scale

AG also presented scenario analyses on regorafenib doses and duration in response to consultation

Scenario	Impact on QALY difference	Impact on cost difference*	Impact on ICERs*
Regorafenib treatment duration same approach as sorafenib	No impact	Small increase in costs for SIRTs and sorafenib; Larger impact on sorafenib costs	
Regorafenib dose interruption and adjustments allowed	No impact		

NICE *Excluding PASs; not drawn to scale

Results of the cost-effectiveness analyses containing comparator PASs will be presented in part 2

Companies reported ongoing studies for SIRT products

	SIR-Spheres	TheraSphere	QuiremSpheres
Company	SIRTEX	BTG	Terumo Europe
RCTs	None	STOP-HCC phase 3 trial comparing TheraSphere plus sorafenib and sorafenib alone	None
Non-RCTs	• European CIRSE Registry for SIR-Spheres Therapy (CIRT); CIRT-FR post-reimbursement • RESIN tumour registries in the USA and Taiwan • VESPRO patient data retrospective meta-analysis of patients from the SIRveNIB and SARAH trials • Patient preference study • 2 Phase II studies of SIRT plus nivolumab	BTG sponsored studies • LEGACY – retrospective study • TARGETA – retrospective study BTG supported studies • 10 prospective or retrospective studies	• HORA EST HCC • HEPAR primary – interventional phase 2 • Hope166 – observational