Selective internal radiation therapies for unresectable early-, intermediate- or advanced-stage hepatocellular carcinoma: systematic review, network meta-analysis and economic evaluation

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Scientific summary

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Scientific summary

Background

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma is the most common type of liver cancer.

Clinical management of hepatocellular carcinoma is complex; there is a range of treatment options available. The Barcelona Clinic Liver Cancer staging system is used to establish prognosis and enable the selection of appropriate treatment based on underlying liver dysfunction and cancer stage. Treatment options include surgery or ablation for early-stage disease, conventional transarterial therapies for intermediate-stage disease and systemic therapy for advanced-stage disease. Best supportive care is offered to patients when conventional transarterial therapy or systemic therapy is not available or appropriate, including patients with terminal-stage disease.

Selective internal radiation therapies deliver radiation to liver tumours via microspheres that are injected into the hepatic artery. There are three selective internal radiation therapies: TheraSphere™ [BTG Ltd, London, UK (now Boston Scientific, Marlborough, MA, USA)], SIR-Spheres® (Sirtex Medical Ltd, Woburn, MA, USA) and QuiremSpheres® (Quirem Medical BV, Deventer, the Netherlands).

Objective

To assess the clinical effectiveness and cost-effectiveness of selective internal radiation therapies for unresectable early-, intermediate- or advanced-stage hepatocellular carcinoma.

Methods

Methods of the clinical effectiveness review

A comprehensive search was undertaken to systematically identify clinical effectiveness literature relating to TheraSphere, SIR-Spheres and QuiremSpheres compared with each other, conventional transarterial therapy or established clinical management without selective internal radiation therapy, in patients with hepatocellular carcinoma. Randomised controlled trials were eligible for inclusion. Where randomised controlled trial evidence was insufficient to address the decision problem, non-randomised comparative studies and non-comparative studies were considered. In addition, a search for randomised controlled trials of comparator therapies was undertaken to strengthen the network of evidence.

Methods of network meta-analysis

A network meta-analysis was undertaken to estimate the relative effectiveness of the different treatments. Three network meta-analysis models were produced for the different populations of unresectable hepatocellular carcinoma patients: patients eligible for a transplant, patients ineligible for a transplant but eligible for conventional transarterial therapy and patients ineligible for conventional transarterial therapy.

The network meta-analysis in patients eligible for a transplant was not conducted. Clinical advice confirmed that there are short transplant waiting times in the UK, whereas these were much longer in the network trials. Therefore, the network may not be generalisable to UK practice. The network meta-analysis of patients eligible for conventional transarterial therapy was also not conducted because of the lack of good-quality evidence in this population.

Several network meta-analyses of patients who are ineligible for conventional transarterial therapy were conducted for both overall survival and progression-free survival outcomes in the per-protocol and intention-to-treat populations.

Methods of economic modelling

Owing to the limited clinical evidence in the early and intermediate patient groups, the focus of the Assessment Group's economic analysis was on an advanced hepatocellular carcinoma population, in which high-quality randomised controlled trial evidence was available.

The Assessment Group built a fully probabilistic de novo model, which compared the three selective internal radiation therapy treatments with the systemic therapies lenvatinib (Kisplyx®; Eisai Ltd, Tokyo, Japan) and sorafenib (Nexavar®; Bayer plc, Leverkusen, Germany). The model structure comprised a decision tree representing the outcome of the work-up procedure transitioning into a three-state partitioned survival model. The main model structure is similar to that adopted in previous appraisals in advanced hepatocellular carcinoma, consisting of health states representing progression-free survival, post progression and death. The time horizon was 10 years. Costs and benefits were discounted at a rate of 3.5% per annum. Costs were valued at 2017/18 prices.

The model drew on data from the SorAfenib versus Radioembolization in Advanced Hepatocellular Carcinoma (SARAH) [Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, *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] and Selective Internal Radiation Therapy Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB) (Chow PKH, 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) trials to estimate the relative effectiveness of selective internal radiation therapy and sorafenib; the base case assumed equivalence in efficacy for all selective internal radiation therapies. A hazard ratio derived from the network meta-analysis was applied to the sorafenib survival curve to estimate the efficacy of lenvatinib. Health state utilities were derived from the per-protocol subgroup of the SARAH trial for selective internal radiation therapy and systemic therapy patients. Resource use and cost inputs were derived primarily from the included trials, targeted literature searches, estimates presented in the companies' evidence submissions, and previous National Institute for Health and Care Excellence technology appraisals.

Confidential Patient Access Schemes are available for a number of modelled technologies, including the comparator therapies lenvatinib and sorafenib and also for QuiremScout® (Quirem Medical BV). All results in this report are based on list prices; separate analyses that include relevant Patient Access Scheme discounts are presented in *Appendix 17*.

Results were presented in terms of incremental net monetary benefit versus the least costly option in each scenario. Fully incremental cost-effectiveness ratios were also produced. Uncertainty was accounted for using probabilistic and deterministic sensitivity analyses. The base case was based on 20,000 model iterations using Monte Carlo sampling methods.

Results

Results of the clinical effectiveness review

Seven randomised controlled trials, seven prospective comparative studies, five retrospective comparative studies and one non-comparative case series were included in the review of clinical effectiveness.

Efficacy and safety of SIR-Spheres

Two large randomised controlled trials rated as being at a low risk of bias (SARAH and SIRveNIB) found no significant difference in overall survival or progression-free survival between SIR-Spheres and sorafenib, despite a statistically significantly greater tumour response rate in the SIR-Spheres arm of both trials (SARAH: 19% vs. 12%, $p = 0.0421$; SIRveNIB: 16.5% vs. 1.7%, $p < 0.001$). The SARAH trial reported a significant difference between groups in health-related quality of life, favouring SIR-Spheres; however, the proportion of patients who completed the questionnaires was low. There was no significant difference in health-related quality of life between groups in the SIRveNIB trial. Adverse events, particularly grade ≥ 3 events, were more frequent in the sorafenib group in both trials.

The Sirtex Medical Ltd (hereafter Sirtex) company submission selected a subgroup of patients from the SARAH trial with $\leq 25\%$ tumour burden and albumin–bilirubin 1 for its base-case analysis in the economic model; this is not a clinically recognised subgroup and was based on a post hoc analysis.

There were methodological differences between the trials; most notably, SARAH was conducted in France, whereas SIRveNIB was conducted in the Asia-Pacific region. Hepatocellular carcinoma in European patients is more likely to be caused by alcohol or hepatitis C, whereas in Asia it is more likely to be caused by hepatitis B. This has implications for the generalisability of the SIRveNIB trial results to the UK population, because the natural history of the disease and treatment options differ. In addition, the SARAH trial included patients with a poor prognosis who would be considered only for best supportive care in UK practice.

Three other randomised controlled trials of SIR-Spheres were included, comparing SIR-Spheres with transarterial chemoembolisation, or drug-eluting bead transarterial chemoembolisation and SIR-Spheres followed by sorafenib with sorafenib alone. Each of these small randomised controlled trials either were rated as being at a high risk of bias or caused some concerns regarding bias. The trials comparing SIR-Spheres with transarterial chemoembolisation or drug-eluting bead transarterial chemoembolisation appeared to favour conventional transarterial therapy over selective internal radiation therapy in terms of survival outcomes. The addition of SIR-Spheres to sorafenib did not appear to increase the number of treatment-emergent adverse events.

Efficacy and safety of TheraSphere

There were two small randomised controlled trials and seven prospective comparative studies of TheraSphere. One of the randomised controlled trials [Prospective Randomized study of chEmoeMbolization versus radIoEmbolization for the tReatment of hEpatocellular carcinoma (PREMIERE): Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, *et al.* Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2016;**151**:1155–63.e2] and all of the non-randomised controlled trial studies were rated as being at a high risk of bias, and the other randomised controlled trial caused some concerns regarding bias. PREMIERE compared TheraSphere with transarterial chemoembolisation as a bridge to transplant; outcomes were improved in the TheraSphere arm compared with the transarterial chemoembolisation arm. The other randomised controlled trial compared TheraSphere plus sorafenib with sorafenib alone as a bridge to transplant; outcomes were similar between treatment groups.

Efficacy and safety of QuiremSpheres

Only one very small case series of QuiremSpheres has been completed in patients with hepatocellular carcinoma. The available data are too limited to draw any conclusions about the safety or efficacy of QuiremSpheres.

Direct comparison of different selective internal radiation therapies

Five small retrospective comparative studies, all rated as being at a high or unclear risk of bias, compared SIR-Spheres with TheraSphere. Two studies included patients who had portal vein thrombosis and appear to have included some of the same patients. Overall survival was reported in four studies, including the

two studies of patients with portal vein thrombosis; overall survival was longer in the TheraSphere arm in three of the studies. One study assessed progression-free survival, which was longer with SIR-Spheres, and another study assessed time to progression, which was longer with TheraSphere (in patients with portal vein thrombosis). The tumour response rate was higher in the TheraSphere arm than in the SIR-Spheres arm in patients with portal vein thrombosis.

Clinical toxicities were generally more frequent with SIR-Spheres than with TheraSphere in one very small study. In a study of patients with portal vein thrombosis, there was no difference in the frequency of fatigue, but pain and nausea appeared to be more frequent with SIR-Spheres, and anorexia appeared to be more frequent with TheraSphere.

No studies that directly compared QuiremSpheres with either SIR-Spheres or TheraSphere were identified. An addendum was received from Terumo Europe NV (Leuven, Belgium) in August 2019 describing a very small pilot study with several methodological limitations.

Network meta-analysis results

The base-case network meta-analysis was in adults with unresectable hepatocellular carcinoma who were categorised as Child–Pugh class A and ineligible for conventional transarterial therapy in the per-protocol population. Three studies were included: two randomised controlled trials comparing SIR-Spheres with sorafenib (SARAH and SIRveNIB) and one randomised controlled trial comparing lenvatinib with sorafenib (REFLECT: 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). The results provided no evidence that the random-effects model should be preferred. Therefore, the results of the fixed-effects model were used for the base-case and scenario analyses.

There were no meaningful differences in overall survival between any of the three treatments in the per-protocol or intention-to-treat populations. In the per-protocol population, SIR-Spheres showed a non-significant marginal improvement in overall survival when compared with sorafenib (hazard ratio 0.94, 96% credible interval 0.77 to 1.14), although the credible interval indicates that this result is uncertain. SIR-Spheres was ranked as the most efficacious therapy, with a probability of being the best of 0.61. Sorafenib was ranked as the worst treatment, with a probability of being the best of 0.16. Lenvatinib was ranked as the second best, with a probability of being the best of 0.22.

To produce an efficacy estimate for TheraSphere, a sensitivity analysis included the only study that directly compared TheraSphere with SIR-Spheres for Child–Pugh class A patients ineligible for conventional transarterial therapy (Biederman DM, Titano JJ, Tabori NE, Pierobon ES, Alshebeeb K, Schwartz M, *et al.* Outcomes of radioembolization in the treatment of hepatocellular carcinoma with portal vein invasion: resin versus glass microspheres. *J Vasc Interv Radiol* 2016;**27**:812–21.e2). Adding this study had a substantial effect on the network meta-analysis results. In the per-protocol population, TheraSphere showed a significant improvement in overall survival when compared with SIR-Spheres (hazard ratio 0.44, 95% credible interval 0.20 to 0.84), sorafenib (hazard ratio 0.41, 95% credible interval 0.20 to 0.77) and lenvatinib (hazard ratio 0.40, 95% credible interval 0.18 to 0.78). However, these results may be biased and unreliable as the Biederman *et al.* study is a low-quality retrospective study reporting a very strong treatment effect on overall survival for TheraSphere compared with SIR-Spheres (hazard ratio 0.40, 95% credible interval 0.20 to 0.78). A sensitivity analysis excluding the Asia-Pacific SIRveNIB study from the network meta-analysis had very little impact on the results for overall survival in the per-protocol and intention-to-treat populations compared with the base case; there were no significant differences in treatment effects for any comparisons.

Results of economic modelling

The Sirtex and BTG Ltd (hereafter BTG) company submissions each present the methods and results of two separate economic evaluations that split the population potentially eligible for selective internal

radiation therapy into two groups: patients eligible for conventional transarterial therapy and patients ineligible for conventional transarterial therapy. In the corrected version of the BTG conventional transarterial therapy-eligible population, the probabilistic incremental cost-effectiveness ratio for selective internal radiation therapy compared with drug-eluting bead transarterial chemoembolisation was £24,647. In the corrected version of the BTG conventional transarterial therapy-ineligible population, the probabilistic incremental cost-effectiveness ratio for TheraSphere compared with regorafenib (Stivarga®, Bayer plc, Leverkusen, Germany) was £69,070. The economic assessment in the conventional transarterial therapy-eligible population submitted by Sirtex was a cost-minimisation analysis, and found that the costs of selective internal radiation therapy overlapped significantly with those of conventional transarterial therapy. The base-case economic analysis submitted for the conventional transarterial therapy-ineligible population by Sirtex was in a subgroup of patients with low tumour burden and preserved liver function. The results of the presented probabilistic analysis predicted that SIR-Spheres dominated sorafenib (lower costs and higher quality-adjusted life-years).

The results of the Assessment Group's base-case analysis (probabilistic) suggested that TheraSphere is cost-saving relative to both SIR-Spheres and QuiremSpheres. However, incremental costs between TheraSphere and SIR-Spheres were small, and pairwise net monetary benefit was close to zero (–£182). QuiremSpheres was associated with substantial incremental costs of £6615 relative to both TheraSphere and SIR-Spheres (exclusive of Patient Access Scheme). Pairwise net monetary benefit between QuiremSpheres and TheraSphere in the Assessment Group's base case was, therefore, negative, at –£6599. In analyses presented in *Appendix 17*, which include available Patient Access Scheme discounts, QuiremSpheres remained more costly than both TheraSphere and SIR-Spheres; thus, the pairwise net monetary benefit remained negative.

In a fully incremental analysis at list price, none of the three selective internal radiation therapies was predicted to be cost-effective at any willingness-to-pay threshold, being more costly and less effective than lenvatinib. The predicted net monetary benefit for lenvatinib compared with TheraSphere (the lowest-costing selective internal radiation therapy) was –£2154. In a pairwise comparison of sorafenib with TheraSphere, the incremental cost-effectiveness ratio for sorafenib was £31,974 per quality-adjusted life-year gained, with an estimated net monetary benefit of –£150 (implying that TheraSphere is cost-effective compared with sorafenib at a willingness-to-pay threshold of £30,000).

In a fully incremental analysis conducted including confidential Patient Access Scheme discounts, lenvatinib remained the most cost-effective therapy and dominated all selective internal radiation therapies, generating greater health benefits at lower costs. In pairwise comparisons of sorafenib with each selective internal radiation therapy, sorafenib also dominated all selective internal radiation therapies.

A number of scenarios were produced to explore the effect of using data from more restrictive but clinically effective subpopulations, downstaging to potentially curative therapy, different resource use, cost assumptions and data sources. When the modelled population was limited to only those with a low tumour burden and preserved liver function, the incremental cost-effectiveness ratios for TheraSphere and SIR-Spheres were £17,165 and £18,783, respectively, per quality-adjusted life-year gained versus the most cost-effective systemic therapy at list price. The most optimistic incremental cost-effectiveness ratios were produced when downstaging to curative therapy was permitted in this more selective population; incremental cost-effectiveness ratios for TheraSphere and SIR-Spheres decreased to £1440 and £2339, respectively. However, there was no scenario in which selective internal radiation therapy was predicted to be cost-effective at a willingness-to-pay threshold of £30,000 when confidential Patient Access Scheme discounts were included.

Discussion

The Assessment Group's analyses predicted lenvatinib to be the most cost-effective treatment in nearly all scenarios, and sorafenib was generally the most cost-effective alternative, producing more quality-adjusted life-years at a higher cost. The results of the Assessment Group's base-case analysis are robust to changes in a wide range of assumptions and across different scenarios.

Strengths of the Assessment Group model include:

- High-quality randomised controlled trial data were included to model the outcomes of the patient population most relevant to UK practice.
- Analyses included all appropriate comparators.
- There was independent modelling of the costs and outcomes of patients who receive work-up but were ineligible to receive selective internal radiation therapy.
- There was preserved randomisation and internal consistency with regard to the use of subsequent systemic and curative therapies.

Insurmountable limitations in the evidence base meant that the Assessment Group was unable to address the question of selective internal radiation therapy's cost-effectiveness in patients with early- and intermediate-stage hepatocellular carcinoma. The evidence for the use of TheraSphere and QuiremSpheres in advanced hepatocellular carcinoma patients was extremely limited, and a lack of head-to-head evidence prevented a meaningful comparison of SIR-Spheres, TheraSphere and QuiremSpheres with one another. This essentially limits this particular comparison to that of a cost minimisation, although a full comparison of the cost-effectiveness of selective internal radiation therapy versus sorafenib and lenvatinib was possible.

Conclusions

Implications for service provision

The existing evidence cannot provide decision-makers with clear guidance on the comparative effectiveness of treatments in early- and intermediate-stage hepatocellular carcinoma.

In the advanced-stage hepatocellular carcinoma population, two large randomised trials have assessed the comparative effectiveness of SIR-Spheres with sorafenib, showing that selective internal radiation therapy has effectiveness similar to that of sorafenib.

None of the selective internal radiation therapies is cost-effective at any willingness-to-pay threshold, being more costly and less effective than lenvatinib; this is the case both at list price and using Patient Access Schemes.

Suggested research priorities

No strong conclusions can be drawn in the early- and intermediate-stage hepatocellular carcinoma populations owing to considerable uncertainty in estimates of effectiveness and high risk of bias. A priority for further research is, therefore, the conduct of studies in these populations.

The low tumour burden/albumin–bilirubin 1 subgroup potentially represents a group of patients for whom selective internal radiation therapy may be beneficial when compared with sorafenib. Future work considering this subgroup may, therefore, be useful.

There is currently very limited evidence on the comparative effectiveness of alternative selective internal radiation therapies. Future high-quality studies evaluating alternative selective internal radiation therapies would be beneficial.

Study registration

This study is registered as PROSPERO CRD42019128383.

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This report

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