



Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic exploration report number:	TER310
Topic:	Selective internal radiation therapy (SIRT) for adults with unresectable metastatic colorectal cancer that cannot be treated successfully with chemotherapy or surgery alone.
Summary of findings:	<p>Selective internal radiation therapy (SIRT) delivers radiotherapy treatment to internal tumours, usually in the liver, by injecting radioactive substances held in microspheres into arteries near the tumour. We searched for evidence on SIRT to treat adults with colorectal cancer that has metastasised to the liver and cannot be successfully treated with chemotherapy or surgery alone.</p> <p>A 2018 Clinical Commissioning Policy by NHS England included an evidence review and economic evaluation of SIRT. This used evidence from one randomised controlled trial, two observational studies and UK registry data to assess the clinical and cost effectiveness of SIRT for chemotherapy refractory/intolerant metastatic colorectal cancer. The policy states that adults with chemotherapy refractory or chemotherapy intolerant metastatic colorectal cancer are eligible for SIRT if their disease is limited to the liver and they meet other clinical criteria.</p> <p>We identified a number of other more recent evidence reviews or guidelines, which all broadly support SIRT but differ in the strength of their conclusions and the exact populations they consider. There may also be some newer primary studies that could inform an updated appraisal (although none use a randomised design).</p>

Introduction and aims

Around 25% of people diagnosed with colorectal cancer will develop metastatic disease, and in most cases this involves disease spread to the liver. SIRT can be used to deliver radiotherapy treatment to tumours in the liver, by injecting radioactive substances held in microspheres into arteries near the tumour. These then lodge in small blood vessels and irradiate the tumour. SIRT has been investigated as both a first-line treatment with curative aims, or for later, palliative use in more advanced disease. Health Technology Wales researchers searched for evidence on SIRT for treatment of adults with colorectal cancer that has metastasised to the liver and cannot be successfully treated with chemotherapy or surgery alone.

Evidence overview

Secondary evidence

NHS England published a clinical commissioning policy on SIRT for chemotherapy refractory/intolerant metastatic colorectal cancer in 2018. This was informed by two evidence reviews (that searched up to November 2017), and a Commissioning Through Evaluation study that reported results from a UK registry. Cost-effectiveness modelling was also done using outputs from the registry.

The two evidence reviews searched for comparative evidence of any design and identified three relevant studies comparing SIRT to other forms of care. One was a randomised controlled trial (Hendlisz, 2010) comparing SIRT plus fluorouracil chemotherapy (n =21) with fluorouracil chemotherapy alone (n = 23); two were observational studies that compared SIRT to current care (the reviews authors note that the exact nature of treatment received by controls was not clearly described). Almost all of the evidence used yttrium-90 based treatments; no evidence comparing holmium-166 based treatments to current care was found. The randomised controlled trial reported a significant benefit for SIRT and chemotherapy in controlling liver tumour growth compared to chemotherapy alone. The two non-randomised studies indicated that SIRT may improve overall survival compared to standard care. The review authors highlighted some concerns with the reliability of the evidence, the lack of well-designed comparative studies comparing SIRT to current care and a lack of evidence on quality of life.

The Commissioning Through Evaluation study collected data on the use of SIRT (using yttrium-90) in people with unresectable colorectal cancer liver metastases, which had progressed following standard chemotherapy. A total of 399 patients across 10 UK centres between 2013 to 2017 were included. Median overall survival was 7.6 months (95% CIs 6.9-8.3) and survival 12 months after SIRT was 30%. Median progression-free survival was 3.0 months (95% CIs 2.8-3.1) and median liver-specific progression-free survival was 3.7 months (95% CIs 3.2-4.3). Subgroup analyses identified absence of extrahepatic disease, fewer liver tumours, and smaller tumour to liver volume percentage, as factors associated with an increased survival benefit. Health related quality of life was measured using EQ-5D-5L and EQ-VAS and remained relatively high and constant before and after the SIRT procedure.

Outcomes from the Commissioning Through Evaluation study were used to inform a cost-effectiveness model comparing SIRT to best supportive care. The ICER for SIRT compared to best supportive care was £85,350 in the base case. Treatment with SIRT resulted in an increase in QALYs of 0.32 (0.58 vs 0.26). SIRT was £27,406 more expensive than BSC (£31,028 vs £3,623 discounted costs). The cost of the SIRT procedure and the length of overall survival were the main drivers in

the model. A scenario analysis used a longer survival estimate and a lower procedure cost, along with a longer time horizon, based on a previously published model by Pennington et al. (2015); this resulted in a lower ICER of £31,888.

NHS England's policy and evidence review closely matches the review question of interest, but is based on evidence up to 2017. We therefore also searched for other more recent sources of secondary evidence.

In 2020, NICE published Interventional Procedures Guidance (IPG472) on SIRT for unresectable colorectal metastases in the liver. This considered use of SIRT for any line of treatment but included evidence on chemotherapy-refractory colorectal cancer liver metastases. The comparative evidence identified was identical to the sources included in NHS England's evidence review. The review also included the UK registry data used by NHS England and two other uncontrolled case series (1,137 patients included across the two studies).

The NICE Guideline on colorectal cancer (NG151) was last updated in January 2020 and included a review of the evidence on treatments for patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent. This did not identify any new comparative evidence in addition to that described above and the recommendations made in the guideline on the use of SIRT were in line with those of NICE IPG472.

We identified one further evidence review that addressed the review question as part of guidelines produced by the Program in Evidence-Based Care (Karanicolas, 2021). This only included the randomised controlled trial by Hendlisz et al (2010) described above.

Primary studies

We searched for any comparative studies of SIRT in the population of interest published after the search dates of the secondary evidence described above. No new randomised controlled trials were found. One retrospective comparative study (Haber, 2021) found that in patients with hepatic metastases from colorectal cancer in salvage settings, the addition of SIRT to systemic therapy may improve survival. Median survival from the date of primary diagnosis was 38 months (95% CI 26 to 50) for SIRT with systemic therapy compared to 25 months (95% CI 15 to 35) for systemic therapy alone ($p = 0.17$). The study included 21 patients treated with SIRT.

Other studies did not include a control arm but compared factors that may influence outcomes from SIRT such as clinical or genomic tumour characteristics, SIRT dose, or previous treatments received. The usefulness of these studies for decision making is unclear; they are reported in the Brief Literature Results section for completeness.

We did not identify any ongoing trials directly comparing SIRT to other interventions in the population of interest.

Areas of uncertainty

The effectiveness of SIRT in people with metastatic colorectal cancer has been assessed as part of recent, UK-relevant evidence reviews and economic evaluations. These differed in the exact indications for which SIRT was considered, and the conclusions and recommendations made. For example, the only randomised controlled trial identified used SIRT alongside fluorouracil monotherapy and compared this to fluorouracil alone. This highlights that the population/indication considered needs to be carefully and clearly defined, and will influence the evidence that is available. Similarly, the current care options available for patients in Wales needs

to be explored, but to do so in full is beyond the scope of this Topic Exploration Report and would require full appraisal.

SIRT has been assessed as a treatment for metastatic colorectal cancer as part of randomised controlled trials, but only one was identified that studied its use beyond first line treatment (Hendsliz 2010), and delivered SIRT alongside chemotherapy: it is not clear whether this is representative of how it would be used in Wales.

Based on the evidence found, it is likely that any appraisal could utilise some evidence from randomised trials but would also need to draw on other sources of evidence, such as UK registry data, for aspects of the appraisal where no or limited evidence from randomised trials is available, such as the use of SIRT as a monotherapy in the population of interest and in comparison to palliative/best supportive care.

At least three types of SIRT exist with UK regulatory approval; these vary in the radioactive substance they use and the type of bead this is delivered in. The evidence of the effectiveness for different types of SIRT varies, and fuller appraisal would be needed to consider this in detail.

Literature search results

Health Technology Assessments and Guidance

NHS England. Clinical Commissioning Policy: Selective internal radiation therapy (SIRT) for chemotherapy refractory / intolerant metastatic colorectal cancer (adults). December 2018.
<https://www.england.nhs.uk/publication/selective-internal-radiation-therapy-for-chemotherapy-refractory-intolerant-metastatic-colorectal-cancer/>

This policy was informed by the following evidence reviews:

- Evidence review: selective internal radiation therapy (SIRT) with holmium-166 microspheres for unresectable, liver-only or liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy intolerant. <https://www.england.nhs.uk/wp-content/uploads/2018/12/Evidence-Review-Holmium-166-mCRC.pdf>
- Evidence review: selective internal radiation therapy (SIRT) with yttrium-90 microspheres for unresectable, liver-only or liver-dominant metastatic colorectal carcinoma who are chemotherapy refractory or chemotherapy-intolerant. <https://www.england.nhs.uk/wp-content/uploads/2018/12/Evidence-Review-Yttrium-90-mCRC.pdf>

NICE. Colorectal cancer. NICE guideline [NG151]. Published: 29 January 2020.
<https://www.nice.org.uk/guidance/ng151>

- Includes the following relevant recommendation:
- 1.5.6. Do not offer selective internal radiation therapy (SIRT) as first-line treatment for people with colorectal liver metastases that are unsuitable for local treatment. For advice on SIRT in line with the NICE interventional procedures guidance on selective internal radiation therapy for unresectable colorectal metastases in the liver, see managing liver metastases in the NICE Pathway on colorectal cancer. This recommends that SIRT should only be offered:
 - with special arrangements for clinical governance, consent, and audit or research to people who are chemotherapy intolerant or who have liver metastases that are refractory to chemotherapy
 - in the context of research to people who can have chemotherapy.
- Two evidence reviews conducted as part of this guideline assessed SIRT:
 - Evidence review D2a: treatment for metastatic colorectal cancer in the liver amenable to treatment with curative intent: <https://www.nice.org.uk/guidance/ng151/evidence/d2a-treatment-for-metastatic-colorectal-cancer-in-the-liver-amenable-to-treatment-with-curative-intent-pdf-253058083672>
 - Evidence review D2b: optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent: <https://www.nice.org.uk/guidance/ng151/evidence/d2b-optimal-combination-and-sequence-of-treatments-in-patients-presenting-with-metastatic-colorectal-cancer-in-the-liver-not-amenable-to-treatment-with-curative-intent-pdf-253058083673>

NICE. Selective internal radiation therapy for unresectable colorectal metastases in the liver. Interventional procedures guidance [IPG672]. Published: 04 March 2020. <https://www.nice.org.uk/guidance/ipg672>

Karanicolas P, Beecroft JR, Cosby R, David E, Kalyvas M, Kennedy E, Sapisochin G, Wong R, Zbuk K; Gastrointestinal Disease Site Group. Regional Therapies for Colorectal Liver Metastases: Systematic Review and Clinical Practice Guideline. Clin Colorectal Cancer. 2021 Mar;20(1):20-28.
<https://doi.org/10.1016/j.clcc.2020.09.008>

NICE Guidance on SIRT in other indications:

Selective internal radiation therapies for treating hepatocellular carcinoma. Technology appraisal guidance [TA688]. Published: 31 March 2021. <https://www.nice.org.uk/guidance/ta688>

Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma. Interventional procedures guidance [IPG630]. Published: 31 October 2018. <https://www.nice.org.uk/guidance/ipg630>

Economic evaluations

Pennington B, Akehurst R, Wasan H, Sangro B, Kennedy AS, Sennfält K, Bester L. Cost-effectiveness of selective internal radiation therapy using yttrium-90 resin microspheres in treating patients with inoperable colorectal liver metastases in the UK. *J Med Econ.* 2015;18(10):797-804. <https://doi.org/10.3111/13696998.2015.1047779>

Individual studies

Sources included in existing secondary evidence:

- Hendlisz A, Van den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, De Keukeleire K, Verslype C, Defreyne L, Van Cutsem E, Delatte P, Delaunoy T, Personeni N, Paesmans M, Van Laethem JL, Flamen P. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol.* 2010 Aug 10;28(23):3687-94. <https://doi.org/10.1200/jco.2010.28.5643>
- Bester L, Meteling B, Pocock N, Pavlakis N, Chua TC, Saxena A, Morris DL. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. *J Vasc Interv Radiol.* 2012 Jan;23(1):96-105. <https://doi.org/10.1016/j.jvir.2011.09.028>
- Seidensticker R, Denecke T, Kraus P, Seidensticker M, Mohnike K, Fahlke J, Kettner E, Hildebrandt B, Dudeck O, Pech M, Amthauer H, Ricke J. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol.* 2012 Oct;35(5):1066-73. <https://doi.org/10.1007/s00270-011-0234-7>

Other sources identified by searches for more recent evidence:

- Haber Z, Lee EW, Price M, Wainberg Z, Hecht JR, Sayre J, Padia SA. Survival Advantage of Yttrium-90 Radioembolization to Systemic Therapy in Patients with Hepatic Metastases from Colorectal Cancer in the Salvage Setting: Results of a Matched Pair Study. *Acad Radiol.* 2021 Jun 4:S1076-6332(21)00203-8. <https://doi.org/10.1016/j.acra.2021.03.033>
- Triviño-Ibáñez EM, Pardo Moreno P, Ciampi Dopazo JJ, Ramos-Font C, Ruiz Villaverde G, González-Flores E, Navarro Vergara PF, Rashki M, Gómez-Río M, Rodríguez-Fernández A. Biomarkers associated with survival and favourable outcome of radioembolization with yttrium-90 glass microspheres for colon cancer liver metastases: Single centre experience. *Rev Esp Med Nucl Imagen Mol (Engl Ed).* 2021 Aug 25:S2253-8089(21)00128-2. <https://doi.org/10.1016/j.remnie.2021.08.001>
- Dabrowiecki A, Sankhla T, Shinn K, Bercu ZL, Ermentrout M, Shaib W, Cardona K, Newsome J, Kokabi N. Impact of Genomic Mutation and Timing of Y90 Radioembolization in Colorectal Liver Metastases. *Cardiovasc Intervent Radiol.* 2020 Jul;43(7):1006-1014. <https://doi.org/10.1007/s00270-020-02463-z>
- Cortesi E, Caponnetto S, Masi G, Urbano F, Mezi S, Gelibter A, Pelle G, Filippi L, Cianni R. Efficacy and Tolerability of Selective Internal Radiotherapy With Yttrium-90 as Consolidation Treatment After Chemotherapy in Metastatic Colorectal Cancer. *Clin Colorectal Cancer.* 2020 Dec;19(4):e272-e276. <https://doi.org/10.1016/j.clcc.2020.06.008>
- Wu V, Li MD, Goodwin JS, Wehrenberg-Klee EP, Zurkiya O, Kalva SP, Ganguli S. Yttrium-90 Hepatic Radioembolization for Advanced Chemorefractory Metastatic Colorectal Cancer: Survival Outcomes Based on Right-Versus Left-Sided Primary Tumor Location. *AJR Am J Roentgenol.* 2021 Feb 17. <https://doi.org/10.2214/ajr.20.25315>
- Alsultan AA, van Roekel C, Barentsz MW, Smits MLJ, Kunnen B, Koopman M, Bruijnen RCG, de Keizer B, Lam MGEH. Dose-response and dose-toxicity relationships for yttrium-90 glass radioembolization in patients

with colorectal cancer liver metastases. J Nucl Med. 2021 Mar 19;jnumed.120.255745.
<https://doi.org/10.2967/jnumed.120.255745>

Ongoing research

We searched for, but did not identify, any ongoing studies that compared SIRT to other care options to treat metastatic colorectal cancer.

Date of search: September 2021

Concepts used: Selective internal radiation therapy; radioembolisation; Yttrium-90; holmium-166