NHS England

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

First published: Month Year

Updated: Not applicable

Prepared by: Cedar on behalf of NHS England Specialised Commissioning

Abbreviations:

^{166}Ho	holmium-166
CI	confidence interval
CRC	colorectal cancer
CRCLM	colorectal cancer liver metastases
SIRT	selective internal radiation therapy

Contents

1. Introduction

Colorectal cancer (CRC) is a cancer that develops in the colon or rectum. It is the fourth most common cancer in the UK with 41,265 new cases diagnosed in 2014. It is more common in men than women; 1 in 14 compared to 1 in 19 for women, and over 40% of cases are diagnosed in those aged 75 years and over.

It is estimated that 50% of all patients with a primary colorectal cancer will develop secondary liver metastases at some point during the illness. The liver is a common site for metastatic disease which can originate from a wide range of primary tumors throughout the body. There may be no symptoms in the early stage of metastases but in the later stages, the cancer can cause the liver to swell or obstruct the normal flow of blood and bile. When this happens, the following symptoms can include, but are not limited to, loss of appetite, weight loss, dark urine, abdominal swelling or bloating and jaundice.

Once diagnosed with secondary liver metastases, the prognosis of the patient deteriorates significantly. Current treatment options at this stage of illness can include subtotal hepatectomy, or in some cases radiofrequency ablation. However, only 20-30% of patients are eligible for these procedures due to the number and advanced stage of the tumours at the time of symptom presentation. Therefore, most patients are left with only palliative treatment options. Even though there have been many developments on targeted cytostatic (chemotherapy) and biological agents for tumours, there are still certain types of tumours that do not respond to such targeted treatments and the long-term survival for these remains very low. Therefore the most common palliative treatment option for unresectable metastatic liver disease is systemic chemotherapy. Chemotherapy drugs are distributed throughout the entire body and destroy any cell that divides rapidly, including tumour and healthy cells. This causes severe side effects which can make the treatment intolerable, with some patients also becoming insensitive/resistant to the chemotherapy treatment. For this reason a new treatment option is needed.

A newly developed therapy for primary and secondary liver cancer is selective internal radiation therapy (SIRT). SIRT is a minimally invasive therapy where radioactive microspheres are inserted into the hepatic artery in the groin via a catheter. These travel to the liver and become lodged in the small blood vessels around the tumour, delivering radiation directly to the cancer cells destroying them. The radiation travels a short distance causing very little damage to healthy tissue. The most common variation of SIRT is with yytrium 90, however a different variation, holmium-166, has recently been developed for the same purpose.

The purpose of this evidence review is to examine the clinical and cost effectiveness and safety of using SIRT with holmium-166 (^{166}Ho) microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant. The questions this review will aim to answer are:

1. ***What is the evidence on clinical effectiveness of using selective internal radiation therapy (SIRT) with holmium-166 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?***
2. ***What is the evidence relating on the safety of selective internal radiation therapy (SIRT) with holmium-166 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?***
3. ***What is the evidence on the cost effectiveness of selective internal radiation therapy (SIRT) with holmium-166 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?***
4. ***Does the evidence of clinical and cost-effectiveness identify any subgroups of patients with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from using selective***

internal radiation therapy (SIRT) with holmium-166 compared with best supportive care?

2. Summary of results

One study was identified and included in this review. This study was a prospective single-arm study carried out in The Netherlands. The study included 23 participants with a primary diagnosis of colorectal cancer (CRC), although other patients with other types of primary cancer were also included. All patients had liver metastases refractory to systemic therapy and ineligible for surgical resection.

The main outcome of the study was disease control (percentage of patients who achieve complete response, partial response or stable disease) of two target lesions in the liver after treatment with SIRT with holmium-166 microspheres. Sixteen out of 22 patients (73%) with CRC showed disease control of the target lesions at 3 months. Ten of 22 patients with colorectal cancer showed whole liver disease control at 3 months. Overall survival of patients with CRC was 13.4 months.

The main limitation of this review is the shortage of evidence. Furthermore, the one included study does not compare SIRT with holmium-166 with best supportive care. The results of this study are limited as the majority of outcome measures were not stratified by primary cancer diagnosis, including adverse events and quality of life.

3. Methodology

Literature search

A strategy was developed in Ovid Medline (see Section 10) and was adapted to the following databases: Medline In-Process; Embase; Cochrane Library (components: CDSR, DARE, CENTRAL, HTA, NHS EED); Pubmed (epub ahead of press only). The searches were limited to the English language. The manufacturer's website was searched for additional studies as well as NHS Evidence. Results of all searches were combined in a Reference Manager 12 database.

Study selection

After de-duplication, one reviewer (HM) selected publications that were considered relevant based on titles and/or abstracts using the inclusion and exclusion criteria presented in section 9. In a second selection round, two reviewers (HM or JW) independently assessed the full text articles for eligibility and selected studies to be included in the review; any uncertainties were discussed and a decision was agreed. Decisions at each stage were recorded in the Reference Manager 12 database.

The review search yielded 29 potentially relevant studies, 3 were retained for assessment of eligibility at full-text. Following this assessment 1 was retained for inclusion in the review.

Data extraction

Data extraction was carried out by LK into the evidence table in Section 7. This was checked by HM.

Quality assessment of evidence

The quality of the evidence was assessed in accordance with the NHS England guidance for conducting evidence reviews and critically appraised using the SURE critical appraisal checklists.

4. Results

The literature search identified 29 records. On screening the title and abstracts three were deemed to be relevant and the full text articles of these records were assessed for eligibility using the inclusion and exclusion criteria presented in section 9. One prospective single-arm study (Prince et al 2017) was chosen for inclusion in this review.

Thirty-eight participants were included in the Prince et al (2017) study, 23 of which had a primary diagnosis of CRC. All patients included had liver metastases refractory to systemic treatment and ineligible for surgical resection. The primary outcome measure was disease control rate of two target lesions within the liver at 3 months according to Response Evaluation Criteria in Solid Tumours (v1.1) after treatment with SIRT with holmium-166 microspheres. Sixteen out of 22 (73%) patients with CRC showed disease control of target lesions at 3 months post treatment. Survival analysis showed the median overall survival of these patients with disease control of their target lesions at 3 months was 14.1 months (95% CI, 8.2 - ∞ months). Those with progression of their target lesions had a median survival of 7.1 months (95% CI, 3.3 - ∞ months, p=0.44). It should be noted that this is not an appropriate methodology for this sample given the small sample sizes. Median overall survival for all patients with CRC was 13.4 months (95% CI, 8.2-15.7 months).

Ten out of 22 (45%) patients with CRC showed whole liver disease control as shown on CT imaging after 3 months (one patient was not included in this analysis because they did not receive IV contrast agent). One patient with CRC died within 3 months of treatment. This patient developed hepatic failure, for which expedited diagnostic studies were performed that showed intrahepatic and extrahepatic disease progression.

Adverse events and quality of life data were collected. However, the results were not stratified by primary cancer diagnosis so they cannot be reported in relation to patients with CRC only.

1. ***What is the evidence on clinical effectiveness of using selective internal radiation therapy (SIRT) with holmium-166 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?***

A single non-comparative study was identified. No evidence was identified that met the inclusion criteria comparing holmium-166 microspheres with best supportive care

2. ***What is the evidence relating on the safety of selective internal radiation therapy (SIRT) with holmium-166 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?***

No evidence was identified that met the inclusion criteria comparing holmium-166 microspheres with best supportive care. The one included study did not report safety outcomes stratified on primary diagnosis.

3. ***What is the evidence on the cost effectiveness of selective internal radiation therapy (SIRT) with holmium-166 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are***

chemotherapy-refractory or chemotherapy-intolerant?

No cost-effectiveness evidence was identified in relation to SIRT with holmium-166.

4. ***Does the evidence of clinical and cost-effectiveness identify any subgroups of patients with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from using selective internal radiation therapy (SIRT) with holmium-166 compared with best supportive care?***

No evidence was identified that met the inclusion criteria comparing holmium-166 microspheres with best supportive care. The one included study did not report any subgroup analyses.

5. Discussion

One study which investigated the efficacy of SIRT with holium-166 was included in this review (Prince et al, 2017). The paucity of published evidence on this technology to treat patients with unresectable, chemotherapy-refractory CRC means that the results from this study cannot be compared and validated in relation to other studies.

The reported median survival of 13.4 months after treatment with SIRT holmium-166 is within the previously reported range of 8.3-15.2 months after SIRT with yttrium-90 treatment (Rosenbaum et al, 2013). The primary outcome reported in this study was disease control of target lesions. Seventy-three percent of patients with CRC treated with holium-166 SIRT had disease control of target lesions within 3 months of treatment. This is significantly higher than disease control rates for CRC patients when applying best supportive care which is estimated to be 10% (Van Cutsem et al, 2007). However, it should be noted that follow-up times on these studies were longer than that of Prince et al and so therefore are not directly comparable.

The non-comparative study design and small sample size of Prince et al. (2017) mean that the study provides limited evidence on the efficacy of SIRT with holmium-166. Methods and results in the study are poorly reported. Outcome measure definitions are unclear and the choice of primary outcome measure is unusual (overall survival is more relevant in this population). Several outcomes (i.e. quality of life and adverse events) are not stratified on primary diagnosis which limits their usefulness to this review. The subgroup analyses reported should be interpreted cautiously due to the very small sample size, and choice of an inappropriate subgroup (a post-randomisation event). Therefore there is a need for comparative research using best supportive care or other treatments with results stratified into different primary cancer diagnoses.

6. Conclusion

This review provides limited evidence on the clinical- and cost-effectiveness of SIRT with holmium-166 for the treatment of unresectable, chemotherapy-refractory CRC liver metastases due to a paucity of high quality studies. Furthermore, the available evidence did not provide any relevant evidence on the safety of this technology in this population. Future studies must include a control group using best supportive care or another comparator treatment.

7. Evidence Summary Table

Use of Holmium-166 microspheres to treat unresectable, chemotherapy refractory liver dominant metastatic colorectal carcinoma								
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results –those reported are for the colorectal subgroup only**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Prince 2017	P1 – Prospective, Single-arm study Single centre, The Netherlands, May 2012 – March 2015	23/38 with metastatic colorectal cancer (CRC). Eligibility criteria for all participants: • Disease outside of the liver limited to the following; sum of lesion diameters <50% the sum of lesions inside the liver. • Estimated life expectancy of >3 months. • Adequate liver, renal and bone marrow function • WHO performance	Intervention was holmium-166 SIRT microspheres.	Median overall survival (months; 95% CI)	Median overall survival for CRC patients was 13.4 months (95% CI, 8.2 – 15.7 months)	5	Direct	Limitations (author): A limitation of this study was that the confidence intervals for the primary outcome were not adjusted for the interim analysis because no valid methodology is known; the reported intervals are probably narrower than they should be Limitations (review team): Unclear if consecutive enrolment of patients Some methods used such as QL-LMC20 are not described
				Median follow-up (months; range)	Median 13.3 months (range 2.5 – 39.3 months) This is for the whole sample of 38 participants.			
				Median progression free survival (months; 95%)	Not reported			
				Median liver-specific progression free survival (months; 95%)	Not reported			
				% survival	Results These were not stratified between primary cancer diagnoses. Therefore cannot be reported.			
				Tumour response (RECIST criteria; CR – complete	These were not stratified between primary cancer diagnoses. Therefore cannot be reported.			

		score of ≤ 2 Median age (yrs): Not reported for patients with CRC Female: Not reported for patients with CRC Male: Not reported for patients with CRC Prior chemotherapy lines: Not reported Chemo naive patients: 0 Prior resection: state number: Not reported EHM:: Not stratified by diagnosis. Exclusions: Not reported		response, PR – partial response, SD – stable disease, PD – progressive disease)				anywhere and the reporting of these results is very poor with no n's in the results table. Inconsistent reporting of results. Not all results stratified by primary cancer diagnosis and some results are mentioned in the appendix but not in the main results section. Funding sources and conflicts of interest: • MGEHL is a consultant for BTG and Mirada. He received honoraria from Sirtex. • JFWN and BAZ are inventors on the patents related to the ^{166}Ho
				Overall response rate	These were not stratified between primary cancer diagnoses. Therefore cannot be reported.			
				Disease control rate	16/22 of CRC patients had disease control of target lesions at 3 months. Median overall survival of these patients was 14.1 months (95% CI, 8.2 - ∞ months). Median overall survival of CRC patients without disease control was 7.1 months (95% CI, 3.3 - ∞months, p=0.44). 10/22 CRC patients showed whole liver disease control after 3 months.			

				Quality of life	*N was not reported for the QLQ-LMC21, which is specific to CRC patients. Therefore no QoL results were reported.*			microspheres which are assigned to University Medical Center Utrecht Holding BV (patent numbers US 6373068 B1 and US 2005/0201940A1). • JFWN is co-founder and chief scientific officer (0.5FTE) of Quirem Medical BV. He has a minority share in the company Quirem Medical BV. He is inventor on the following patent families: USA Patent No.6373068 B1, 8632751, EP07112807.8, 10190254.2, and P112614NL00. • MLJS had accommodation expenses reimbursed
				Adverse events	*Not stratified by primary cancer diagnosis so cannot report.*			

							by Quirem Medical BV. • BAZ received honoraria from GSK Netherlands, he also received honoria, consulted for, received research funding from and had expenses reimbursed by Novartis Pharm Inc. • SN reports personal fees from Mapi Group consultancy, outside the submitted work. • The department of Radiology and Nuclear Medicine of the UMC Utrecht receives royalties from Quirem Medical BV. • The study was sponsored by a grant from the Dutch Cancer Society (KWF Kankerbestrijding). It had no role in the

							writing of the manuscript or the decision to submit it for publication.

8. Grade of evidence table

Use of Holmium-166 microspheres to treat patients with primary colorectal cancer with secondary liver metastases. Non-comparative study					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Median overall survival	Prince et al (2017)	5	Direct	C	Median overall survival for patients with CRC was 13.4 months. As there was no comparator group using best supportive care, the benefit of the treatment cannot be determined.
Disease control rate	Prince et al (2017)	5	Direct	C	This is defined as disease control of target lesion. Those CRC patients with disease control of their target lesions after treatment with SIRT with holmium 166 survived approximately twice as long as those without disease control of their target lesion. However, this

					methodology was inappropriate given the small sample sizes.

9. Literature Search Terms

Search strategy *(terms in **bold** in the right-hand column were used to construct the search)*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Individuals with **unresectable**, **liver**-only or **liver**-dominant **metastatic colorectal carcinoma** who are chemotherapy-refractory (progression following at least two lines of standard chemotherapy e.g. irinotecan and oxaliplatin based chemotherapy) or chemotherapy-intolerant.
I – Intervention Which intervention, treatment or approach should be used?	**Selective internal radiation therapy** (SIRT) with resin **holmium-166** microspheres.
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Best supportive care
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	<u>Critical to decision-making:</u> • Overall survival • Progression free survival • Liver specific progression free survival • Overall response rate • Disease control rate • Adverse events • Quality of life (HRQoL) • Cost effectiveness Any other relevant outcome from included studies.
Assumptions / limits applied to search	
Inclusion Criteria	Patients with liver-only or liver dominant metastatic colorectal carcinoma English language Published studies from 2007 onwards
Exclusion Criteria	Conference abstracts Sample sizes <30 Studies in which CRCLM patients are not analysed separately

10. Search Strategy

Ovid MEDLINE(R) <1946 to November Week 4 2017>

1 Holmium/

2 holmium.tw.

3 166 Ho.tw.

4 Ho microsphere*.tw.

5 QuiremSphere*.tw.

6 Terumo.tw.

7 "Reactor Institute".tw.

8 or/1-7

9 (selective* adj3 internal* adj3 radiotherap*).tw.

10 (selective* adj3 internal* adj3 radiation* adj3 therap*).tw.

11 (internal* adj3 radiation* adj3 therap*).tw.

12 radioemboli*.tw.

13 or/1-9

14 8 and 13

15 8 or 14

16 (liver adj2 metasta*).tw.

17 mCRC.tw.

18 ((unresectable or non-resectable) adj (liver or hepatic) adj (tumo?r* or malignanc*)).tw.

19 (inoperable adj (hepatic or liver) adj tumo?r*).tw.

20 Liver Neoplasms/sc

21 or/16-20

22 15 and 21

23 limit 22 to (yr="2007-Current" and english language)

11. Evidence selection

- Total number of publications reviewed: 29

- Total number of publications considered relevant: 3
- Total number of publications selected for inclusion in this briefing: 1

12. References

Prince, J.F., van den Bosch, M.A., Nijsen, J.F.W., Smits, M.L., van den Hoven, A.F., Nikolakopoulos, S., Wessels, F.J., Bruijnen, R.C., Braat, M., Zonnenberg, B.A. and Lam, M., 2017. Efficacy of radioembolization with holmium-166 microspheres in salvage patients with liver metastases: a phase 2 study. *Journal of Nuclear Medicine*, 2017, 101-117.

Rosenbaum, C.E., van den Bosch, M.A., Veldhuis, W.B., Huijbregts, J.E., Koopman, M. and Lam, M.G., 2013. Added value of FDG-PET imaging in the diagnostic workup for yttrium-90 radioembolisation in patients with colorectal cancer liver metastases. *European radiology*, *23*(4), pp.931-937.

Van Cutsem, E., Peeters, M., Siena, S., Humblet, Y., Hendlisz, A., Neyns, B., Canon, J.L., Van Laethem, J.L., Maurel, J., Richardson, G. and Wolf, M., 2007. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *Journal of clinical oncology*, *25*(13), pp.1658-1664.