National Institute for Health and Care Excellence

IP228/3 Selective internal radiation therapy for unresectable colorectal metastases in the liver

IPAC date: 12 December 2019

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company SIRTEX	**1.1**	Dear NICE, Many thanks for the opportunity to comment on the draft Interventional procedures guidance for selective internal radiation therapy (SIRT) for unresectable colorectal metastases in the liver. Please find our response below. **In patients who cannot tolerate chemotherapy (chemotherapy intolerant) or have liver metastases that are refractory to chemotherapy (chemotherapy refractory)** Draft Recommendation: In patients who are chemotherapy refractory / chemotherapy intolerant the draft recommendations state that there are “well-recognised and potentially serious safety concerns”, and so the procedure should only be used with special arrangements for clinical governance, consent and audit or research. We are pleased that the decision allows patients to receive SIRT in the chemotherapy-refractory/intolerant setting, however we would like to question the conclusion that there are “well-recognised and potentially serious safety concerns”.	Thank you for your comment. Section 1.1 has been changed to state that there can be serious complications, but these are well recognised and infrequent.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
2	Consultee 1 Company SIRTEX	**1.1**	Safety: The comparative evidence base for SIRT using Y-90 resin microspheres (SIR-Spheres®) did not identify potential safety concerns and demonstrates that SIR-Spheres can limit the burden of disease progression for patients. Hendlisz et al (2010) report Grade 3 or 4 toxicities in six patients after intravenous fluorouracil (FU) monotherapy and in one patient after radioembolization plus FU treatment. Therefore, there were less Grade 3 and 4 adverse events in the patients receiving SIRT + FU than those receiving FU alone. The authors also state that the overall incidence of adverse events after radioembolization remained low and easily manageable and that the reduction in adverse events compared to the FU monotherapy group is likely to reflect the positive impact of SIRT on disease progression. Bester et al (2012) report adverse events, however also highlight that the number and severity of adverse events experienced in patients who had already undergone several failed lines of chemotherapy indicated that SIRT is a safe treatment option with an acceptably low toxicity profile. They also report that within their institution all adverse events were able to be medically managed, with no deaths caused by SIRT occurring within the 3-month follow-up period. Seidensticker et al (2012) also support these findings. They report predominantly grade 1-2 adverse events, all of which were managed medically and were not considered to be life threatening. The 3 cases of radioembolization induced liver disease were also treated medically and were considered to be non-life threatening.	Thank you for your comment. Hendlisz et al. (2010), Bester et al. (2012) and Seidensticker et al. (2012) are all included in table 2 of the overview.

3	Consultee 1 Company SIRTEX	**1.1**	The non-comparative evidence base on SIR-Spheres confirms the low toxicity of SIR-Spheres in this setting. Kennedy et al (2015, 2016) report on the largest non-comparative study of SIRT in patients with chemotherapy-refractory/intolerant mCRC (606 consecutive patients in 11 centres in the US). Authors report that adverse events were usually mild, and were mainly transient and managed with medication, as necessary. Age or the number of prior lines of systemic chemotherapy were not statistically significant predictors of the incidence of adverse events. Authors consider that because elderly patients (defined as >70 years) have an increased risk of significant toxicity associated with systemic chemotherapy and frequently require dose reductions, SIRT "appears to be a particularly attractive alternative for the management of elderly patients with liver-dominant mCRC". We accept, as stated in the IPG that there are some "well-recognised" adverse events associated with the use of SIRT. However, as SIRT is now used in routine clinical care for patients with chemotherapy-refractory/intolerant mCRC these potential adverse events are known and strategies for their prevention are in place (Sangro 2017). For example, the risk of non-implantation of SIRT in target organ (specifically mentioned on p10 of the IPG overview) is mitigated through the work-up procedure during which collateral arteries that could lead in extra-hepatic deposition of the SIRT microspheres can receive prophylactic embolisation. Furthermore, we encourage the Committee to recognise that patients who cannot tolerate chemotherapy or have liver metastases that are refractory to chemotherapy have no other treatment options than best supportive care, associated with a median OS of 4 to 6 months (Foubert et al. 2014) and a significant physical and psychological burden of disease. Based on the results from the comparative and observational studies reported above, and current knowledge of the use of SIRT and the strategies in place to minimise such adverse events we believe the safety profile should not be a limiting factor in the IPG recommendations.	Thank you for your comment. Section 1.1 has been changed to state that there can be serious complications, but these are well recognised and infrequent. Kennedy et al. (2015) and Kennedy et al. (2016) are included in the appendix of the overview. The Sangro (2017) review provides recommendations to MDTs on the optimal medical processes in order to ensure the safe delivery of SIRT. Based on the best available published evidence and expert opinion, it recommends the most appropriate strategies for the prevention, early diagnosis and management of potential radiation injury to the liver and to other organs. It has been added to the appendix in the overview. Foubert et al. (2014) was not included in the overview because it is a general review article describing the treatment options for metastatic colorectal cancer beyond the second line of treatment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
4	Consultee 1 Company SIRTEX	**1.1**	Efficacy: Within this population the 3 comparative studies report an overall survival (OS) benefit: • Bester (2012) showed that median OS was 11.9 months for patients receiving SIRT compared to 6.6 months for patients receiving standard care (95%CI 10.1 to 14.9; p=0.001). • Seidensticker (2012) report median OS of 8.3 months for patients receiving SIRT compared to 3.5 months for patients receiving standard care (HR 0.26, 95%CI 0.15 to 0.48, p<0.001). • Hendlisz et al (2010) compare SIRT plus FU to FU alone, median OS was 10.0 months and 7.3 months respectively (p=0.80). This study was not designed or powered to demonstrate a statistically significant OS benefit as patients were allowed to cross-over to the SIRT arm after progression on FU alone. There are also progression free survival (PFS) and tumour response benefits in these patients. As included in the IPG overview, a partial response or stable disease was reported in 86% of patients who received SIRT plus FU compared with 35% of patients who had FU alone in an RCT of 44 patients (Hendlisz et al 2010). Median time to tumour progression was also longer in the SIRT arm compared to chemotherapy alone (5.5 months vs 2.1 months, P=0.003). (Hendlisz et al 2010). Studies have also reported quality of life data. A phase II clinical trial into the use of Yttrium-90 resin microspheres in patients who had failed previous chemotherapy regimens, collected quality of life data prior to SIRT and at 6 weeks after treatment, using the EORTC QLQC30, and EORTC QLQ CR38. They found that at 6 weeks, patients were not adversely affected by SIRT (only Grade 1 and 2 adverse events were reported), and at 6 weeks follow-up there was a statistically significant improvement in anxiety scores reported by patients (p<0.01) (Cosimelli et al 2010).	Thank you for your comment. Hendlisz et al. (2010), Bester et al. (2012) and Seidensticker et al. (2012) are all included in table 2 of the overview. Cosimelli et al. (2010) is a case series of 50 patients and is included in the appendix of the overview. The committee considered this comment but decided not to change the guidance.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
5	Consultee 1 Company SIRTEX	**1.1**	<u>Existing recommendations:</u> The draft recommendation of the IPG contradicts the decision by NHS England to commission SIRT for patients who have chemotherapy refractory/intolerant metastatic colorectal cancer from April 1st 2019. This decision was reached after considering the place of SIRT in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients and whether its use represents the best use of NHS resources (NHS England 2018). Specialist advisers consulted by the Committee have confirmed that SIRT is performed in routine clinical practice in the UK within this indication. SIR-Spheres® Y-90 resin microspheres are also recommended in this patient population (and the first line setting) within additional guidelines: • The ESMO guidelines for the management of patients with metastatic colorectal cancer (Van Cutsem et al, 2016) also state that "for patients with liver-limited disease failing the available chemotherapeutic options radioembolization with yttrium-90 microspheres should be considered."	Thank you for your comment. The draft recommendation does not contradict the NHS England Clinical Commissioning Policy. The draft guidance recommends that the procedure should only be used with special arrangements for clinical governance, consent and audit. A 'special arrangements' recommendation is made when the committee concludes that there are uncertainties about whether the procedure is safe and effective and does not preclude the procedure being commissioned.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
6	Consultee 1 Company SIRTEX		• The French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (2019) recommend the following settings for SIR-Spheres: - "Progression and/or intolerance during cytotoxic chemotherapy (5FU, irinotecan and oxaliplatin), EGFRi antibodies (if RAS WT) therapy and VEGFi antibodies therapies (…) in case of exclusive or predominant liver metastases with maintained liver function" (grade B) - As "Intra-arterial therapies for patients with liver exclusive or predominant disease": "when hepatic function is maintained (bilirubin <1.5 N) and metastases are liver-limited/liver-predominant and chemo refractory to systemic treatment" (Phelip et al 2019) • The National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology (2018) state that arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation is an option in highly selected patients with chemotherapy resistant/refractory disease and with predominantly hepatic metastases.	Thank you for your comment. The committee considered this comment but decided not to change the guidance.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
7	Consultee 1 Company SIRTEX	**1.1**	Our recommendation: Based on the available evidence base, and existing clinical guidelines for chemotherapy-intolerant / refractory patients, we therefore question the conclusion that there are well-recognised and potentially serious safety concerns, and reiterate the positive impact SIRT has on survival and tumor response outcomes. We believe that changing the recommendation to exclude the requirement for special arrangements would allow these patients, who already have limited treatment options, to have greater access to this effective treatment.	Thank you for your comment. The committee considered this comment but decided not to change the guidance.

8	Consultee 1 Company SIRTEX	**1.1**	In a first-line setting Draft Recommendation: In patients who receive chemotherapy, the IPG states that the evidence on efficacy does not show a benefit on OS or quality of life and so the procedure should only be used in the context of research. Safety: The overview discusses adverse events. Although these were higher in patients receiving SIRT, as discussed by the clinical expert ([redacted]) at the IPG NICE meeting, the patients included in the RCTs are more severely ill than those who would receive treatment in current clinical practice, especially as the trials included patients with extrahepatic spread of their metastatic disease. Therefore, it can be assumed that the adverse event profiles are also non reflective of true outcomes in the UK population. We also believe there is a lack of clarity in the reporting of adverse events in the IPG overview which leads to bias. For example, where the incidence of "death" is reported (p7), it states that "treatment related deaths were reported in 8 patients who had SIRT (…) and 3 patients who had chemotherapy alone". Rather, we would recommend for the overview to reflect that treatment related deaths were reported in patients who had received SIRT plus chemotherapy, and therefore may be attributable to SIRT, chemotherapy or the combination of these treatments. This lack of clear adverse event reporting is consistent throughout the guidance (including in the reporting of pulmonary embolism, peripheral neuropathy, abdominal pain, hepatic failure) and provides an unbalanced view of the findings as it is unclear that those findings are attributable to SIRT. For similar reasons, the safety results for first-line treatment cannot be generalised to other settings, and especially to patients with chemotherapy-refractory/intolerant disease. Within first-line treatment SIRT is used in combination with first-line systemic treatment. Patients therefore also experience adverse events associated with the systemic treatment or interactions between SIRT and systemic treatment, whereas patients in the chemotherapy-refractory/intolerant receive only best supportive care As for the first-line setting. The adverse events associated with SIRT in the chemotherapy intolerant/refractory patients are well known and can be prevented with adequate measures (Sangro et al 2017).	Thank you for your comment. A committee comment has been added, stating that adverse events may be attributable to SIRT, chemotherapy or the combination of the two. The overview has been changed, to include a statement at the beginning of the safety summary to clarify that adverse events may be attributable to SIRT, chemotherapy or the combination of the two.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
9	Consultee 1 Company SIRTEX	**3.6**	Quality of life: The draft recommendations suggest there is limited evidence on patient's quality of life, however, the RCTs did collect quality of life data. Where reported these showed that there was no statistically significant difference between treatments in patients' quality of life, therefore indicating that the adverse events experienced did not have a major impact on patients' quality of life and that the addition of SIRT to standard chemotherapy did not adversely affect quality of life (Wasan 2017).	Thank you for your comment. Wasan et al. (2017) is included in table 2 of the overview.
10	Consultee 1 Company SIRTEX	**1.1**	Our recommendation: Considering the clinical benefit reported above, despite the lack of selectivity within the patient sample which was discussed with the clinical expert [redacted], at the NICE IPG meeting on Thursday 13th June 2019, we believe that this recommendation should be changed to allow the procedure to be undertaken with special arrangements for clinical governance, consent and audit or research. This would allow further evaluation of the use of SIRT within current clinical practice, with a focus on outcomes for patients with right sided primary tumours, whilst also allowing patients access to this effective treatment.	Thank you for your comment. The committee considered this comment but decided not to change the guidance.

11	Consultee 1 Company SIRTEX	**General**	**Differentiation between SIRT technologies and procedures** We would recommend for the Committee to consider SIRT using different types of microspheres as different procedures, when interpreting the available evidence on safety and effectiveness and when issuing recommendations regarding the arrangements for the procedures to be used in the UK. This is based on the following differences: <u>Differences in the radionuclides used</u> Although all procedures rely on the same mode of action which consists in irradiating tumours through the local application of radionuclide-labelled microspheres, it should be noted by the Committee that only yttrium-90 is a pure beta radiation emitter; holmium-166 is also a gamma radiation emitter as it can be imaged with gamma scintigraphy. Furthermore, key radiological characteristics are differing between the radionuclides under consideration: the half-life of holmium-166 is considerably shorter than that of yttrium-90 (26.9 vs 64.1 hours); the beta emission of holmium-166 is also characterised by a lower energy (49.9% at 1.773 MeV and 48.8% at 1.854 MeV) compared to yttrium-90 (100% at 2.279 MeV). This may result in a higher activity (dosage) being required to reach an effective dose of radiation to the tumour. While the impact of these differences in terms of efficacy and safety is unknown due to the lack of evidence on holmium-166 microspheres, we would recommend for the Committee to consider that they warrant individual evaluation of SIRT procedures without assuming equal efficacy and safety. <u>Differences in the administration procedures affecting the clinical effectiveness or safety of SIRT</u> SIR-Spheres are infused with intermittent injection of contrast medium to confirm forward flow throughout the procedure and to allow the clinician to track the distribution of the microspheres. This results in the ability to interrupt the infusion of SIR-Spheres should the contrast medium show that too much of the dose is being delivered to non-target healthy gastrointestinal tissues, for example due to retrograde blood flow.	Thank you for your comment. The following committee comments have been added, which are consistent with IPG630 Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma: ‘There are different types of microspheres used. There are also different types of radionuclides used, but all the evidence considered included studies using yttrium. The committee was told that dosimetry in this procedure is complex and needs significant expertise.‘

			TheraSphere or QuiremSpheres are not infused with contrast medium (TheraSphere instructions for use, QuiremSpheres FAQ). This is particularly important because non-target deposition of SIRT microspheres can be associated with severe complications, and the interventional radiologist is unlikely to be able to detect that the shunting of TheraSphere is occurring in adequate time to stop the infusion (SIR-Spheres and TheraSphere instructions for use, QuiremSpheres FAQ), which may result in an increased incidence of complications due to the non-target implantation of microspheres <u>Differences in dosage affecting the clinical effectiveness or safety of SIRT</u> Despite carrying the same radionuclide yttrium-90, SIR-Spheres and TheraSphere cannot be considered equivalent due to differences in both dosage and administration methods. The average radioactivity per microsphere at the time of calibration varies by a factor of 50 between the two devices: 50 Bq per microsphere for SIR-Spheres versus 2,500 Bq for TheraSphere (Kennedy 2007). Due to the lower activity per microsphere, a typical treatment using SIR-Spheres is performed with approximately 10-15 times more microspheres than a treatment with TheraSphere (Kennedy 2007). This can affect patient outcomes, because the aim of SIRT is to provide sufficiently uniform, tumouricidal doses of radiation to target tumours, while minimising exposure of non-tumoral tissue. Distribution of SIRT microspheres in tumour and liver tissue is guided by blood flow and therefore presents a degree of heterogeneity (Kennedy 2007, Pasciak 2016). A higher number of injected microspheres will increase the homogeneity of the radiation dose delivered to the tumour: conversely, a lower microsphere density in the treated tissue may cause a greater fraction of tumour to receive a lower absorbed dose (Pasciak 2016). Because of this risk, higher amounts of injected radioactivity (Kennedy 2007) and of tumour-absorbed dose (Pasciak 2016, Walrand 2014) are recommended for the administration of TheraSphere compared to SIR-Spheres, such that a tumoricidal dose can be attained in tumour regions receiving less of the injected TheraSphere microspheres. This is reflected in specific dose calculation methods being used for each	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			device, per their licensed instructions for use: both QuiremSpheres and TheraSphere are using the Medical Internal Radiation Dose (MIRD) model, which has not been validated in Phase III trials to date. These differences between SIR-Spheres and TheraSphere may result in different outcomes of SIRT using either device, both in terms of effectiveness and safety, because increased injected radioactivity and radiation dose to the non-tumoural liver parenchyma are associated with increased risks of liver complications of SIRT (Sangro 2017, Walrand 2014). Due to this and to the considerable differences in the quantity and quality of evidence supporting SIRT devices for patients with liver metastases of colorectal cancer, equal efficacy cannot be assumed between these devices. <u>Differences in number of procedures, healthcare resources utilisation and patient burden</u> Differences in the administration procedures for both devices can also affect the patient experience and impact the use of healthcare resources. SIR-Spheres can be administered to both lobes of the liver in one session, as seen in studies referenced in the IPG overview (Bester 2012, Seidensticker 2012, Kennedy 2015). This is because the source vial for SIR-Spheres can be prepared into multiple v-vials for administration in different hepatic arteries of a single patient, each feeding different tumoural regions. In contrast, TheraSphere vials cannot be split, and one vial is required for each injection. This will result in additional resource use, with an increased number of vials being required. For patients with bi-lobar disease, this implies that TheraSphere can only be administered in one lobe per session and that whole-liver treatment requires two sequential hospital admissions.	

12	Consultee 1 Company SIRTEX	Overview	Other recommended changes to the IPG consultation documents In addition to this we have the following comments regarding the IPG overview: • Page 1: In the initial statement outlining the procedure it describes radioactive “beads”. Please amend to microspheres. The term beads is not relevant to this procedure, and of note it was not included within the search terms. • Page 4 onwards: The type of SIRT microspheres are not reported. Its inclusion would provide the reader with a clearer overview of the evidence for each of the SIRT products: all comparative studies include only SIR-Spheres Y-90 resin microspheres, there was no studies using holmium-166 microspheres. • Page 7 onwards: As discussed previously, the reporting of adverse events lacks precision as the true comparators (chemotherapy plus SIRT versus chemotherapy alone; SIRT versus best supportive care). • Page 25: White et al (2019) report that patients with no date of death recorded were censored at their last recorded follow-up date. This resulted in 35% of patients being excluded. Based on this, where “other issues” with this study are reported (p26), we believe it should not only consider the generalisability of the results based on levels of missing data for health-related quality of life, but also for the survival outcomes.	Thank you for your comment. This is a lay description of the procedure, which does not appear in the guidance itself. It has been changed to ‘microspheres (tiny beads)’. Page 33 of the overview states that ‘Most of the evidence is based on the use of resin microspheres for SIRT, but 2 studies used glass microspheres for some or all of the patients.’ The following committee comment has been added ‘There are different types of microspheres used. There are also different types of radionuclides used, but all the evidence considered included studies using yttrium.’ The overview has been changed, to include a statement at the beginning of the safety summary to clarify that adverse events may be attributable to SIRT, chemotherapy or the combination of the two. The following statement will be added to the follow-up issues on page 25: ‘139 (35%) patients

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
				were censored at their last recorded follow-up date.'
13	Consultee 1 Company SIRTEX	**General**	Further papers have been published since the searches were undertaken: • Wang et al (2019) discuss the use of Yttrium-90 as a promising liver directed therapy for patients with unresectable colorectal cancer. They emphasise the large body of evidence which exists supporting the use of SIRT in the salvage setting based on the survival benefit and low toxicities and reflected by the NCCN and ESMO guidelines. • Tchelebi and Sharma (2019) discuss the use of SIRT in the multidisciplinary management of liver metastases in colorectal cancer. Their review is based primarily on the Phase III randomised data. They reinforce the survival and tumor response benefits of SIRT, and also discuss the recent data demonstrating that tumor location (right-sided colon cancer versus left-sided) is of prognostic significance in colorectal cancer. This includes a study by Loupakis et al (2015) which evaluated the association between tumour location and survival in patients from 3 prospective trials and found that patients with right-sided tumours had worse OS compared to patients with left sided tumours. It also includes the study by Gibbs et al (2018) which found that median OS for patients with right-sided primaries was significantly higher for patients in the SIRT arm compared to the control group (22 vs 17 months, P=0.008).	Thank you for your comment. Wang et al (2019) is a review and has been added to the appendix of the overview. Tchelebi et al (2019) is a review and is in the appendix of the overview. Loupakis et al. (2015) is not included in the overview because it focuses on the prognostic impact of primary tumor location in metastatic colorectal cancer in patients who have had first-line chemotherapy with or without bevacizumab. Gibbs et al. (2018) is in table 2 of the overview.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
14	Consultee 1 Company SIRTEX	**1.1**	**Conclusion** In conclusion, we believe that the following changes to the recommendations would allow patients to have access to this effective and safe treatment: • For patients who are chemotherapy intolerant or refractory: changing the recommendation from “to be used with special arrangements” to “standard arrangements”; • For patients who can have chemotherapy from being recommended “only within the context of research” to a recommendation for use “with special arrangements”; • For recommendations to be issued considering the differences between SIRT procedures and the available evidence on effectiveness and safety applicable to SIRT procedures using each available type of SIRT microspheres.	Thank you for your comment. The committee considered this comment but decided not to change the guidance.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
15	Consultee 2 Specialist society BASL	**General**	Selective internal radiation therapy for unresectable colorectal metastases in the liver BASL is grateful for the opportunity to review the information on SIRT and the NICE provisional recommendations. Two clinical scenarios have been investigated and assessed separately: 1. Patients unable to tolerate systemic chemo or are refractory. Conclusion limited efficacy. Use with special arrangement for governance, consent and audit registration. 2. Those able to tolerate chemotherapy. Conclusion : No benefit to survival or QoL. Used within clinical research.	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
16	Consultee 2 Specialist society BASL and BSG	**General**	General comments â€¢ Local registration is unlikely to return useful data on outcomes. A national registry for users should be mandated (and provided). â€¢ Agree may be considered as a neoadjuvant therapy prior to resection but with similar success rates as chemotherapy alone. â€¢ Should remove as neoadjuvant prior to liver transplant as limited evidence to support, not available in UK and would require a prospective RCT to validate. â€¢ Reduction in tumour volume suggested as useful study end point for future evaluation but relevance unclear without evidence of survival benefit or improved QoL. â€¢ Review of evidence would suggest that all important studies have been included and main end points evaluated. This is a joint response from BASL and the BSG.	Thank you for your comment. Section 1.2 of the guidance has been changed to remove the recommendation to review clinical outcomes locally. Section 2.2 of the guidance has been changed to remove reference to neoadjuvant treatment. Section 1.5 of the guidance also includes survival and quality of life as outcomes to be included in further research.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
17	Consultee 3 Company Terumo Europe	**1.5**	We would like to add another topic to the list of further reserch: relation between the delivered radiation absorbed dose and effect Our rationale: There is increasing evidence to suggest the relation between absorbed radiation dose in tissue (both healthy and tumorous) and the resultant effect, both on tumor and patient outcome, are highly correlated. For example, a sub analysis of a large study has shown significant relationships between tumor dose, tumor response and clinical outcome (Allimant, C. et al. J. Vasc. Interv. Radiol. 2018). Although most data has been obtained in primary liver cancer, there is no reason to assume this rationale will not apply to other cancer types such as liver metastases from colorectal cancer. We therefore believe the relation between delivered radiation dose and effect should not only be investigated, but may be revealed to be key factor in the success of SIRT.	Thank you for your comment. Section 1.5 of the guidance has been changed to include details of the intervention in the list of further research.
18	Consultee 3 Company Terumo Europe	**Overview** **Appendix**	We would like to kindly ask that HEPAR 2 is added to the list of potentially relevant publication to the overview Prince JF, van den Bosch MAAJ, Nijsen JFW, et al. Efficacy of Radioembolization with 166 Ho-Microspheres in Salvage Patients with Liver Metastases: A Phase 2 Study. J Nucl Med. 2018;59:582-588.	Thank you for your comment. The cited paper describes a case series of 38 treated patients. This does not meet the remit for inclusion into the appendix because case series with fewer than 50 patients were excluded.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
19	Consultee 4 Company BTG (A Boston Scientific Company)	**1.1**	We are concerned that the data from the Commissioning Through Evaluation (CtE) registry of 399 adults with unresectable, chemotherapy-refractory, CRC liver metastases has not been fully evaluated1 in this draft recommendation. The CtE was carried out over five years at ten UK hospital sites. The study concluded that “SIRT is safe and well tolerated in patients who had previously received multiple lines of chemotherapy and it has shown that SIRT in this population results in overall survival (OS), Progression Free Survival (PFS) and Liver PFS (LPFS) that are consistent with previously published smaller studies”. The NHS England decision to subsequently commission SIRT for chemotherapy refractory / intolerant metastatic colorectal cancer limited to the liver in adults (according to specified criteria;(NHS England Reference 170102P) highlights that there is a recognised role and clinical need for SIRT in salvage/chemorefractory patients. 1 White J, Carolan-Rees G, Dale M, Patrick HE, See TC, Bell JK, Manas DM, Crellin A, Slevin NJ, Sharma RA. Yttrium-90 Transarterial Radioembolization for Chemotherapy-Refractory Intrahepatic Cholangiocarcinoma: A Prospective, Observational Study. Journal of Vascular and Interventional Radiology. 2019 Jun 27.	Thank you for your comments. A publication from the registry is included in table 2 of the overview and was considered by the committee (study 6). The draft recommendation does not contradict the NHS England Clinical Commissioning Policy. The draft guidance recommends that the procedure should only be used with special arrangements for clinical governance, consent and audit. A ‘special arrangements’ recommendation is made when the committee concludes that there are uncertainties about whether the procedure is safe and effective and they feel that is should be used under enhanced clinical governance within the NHS. It does not preclude the procedure being commissioned. The cited study refers to patients with cholangiocarcinoma, which has separate IP guidance (**IPG630**).

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
20	Consultee 4 Company BTG (A Boston Scientific Company)	**1.1**	We would like to highlight that the RCT evidence where SIRT was used as a first line treatment, was based on a study which had suboptimal patient selection and treatment (i.e. Extrahepatic disease and no personalised dosimetry), we would therefore recommend that SIRT requires further research in this area, particularly as benefit was show in right sided tumours which needs further investigation. In terms of the use of glass SIRT in second line, we are awaiting the BTG sponsored EPOCH study which will inform the decision, however in the meantime we would recommend further research and investigation.	Thank you for your comment. The current recommendations state that the procedure should be only be used in the context of research for patients who can have chemotherapy and it should be used with special arrangements for clinical governance, consent, and audit or research in people who cannot tolerate chemotherapy or have liver metastases that are refractory to chemotherapy. Section 1.5 of the draft guidance states that further research should report details of patient selection, whether the primary colorectal tumour arose in the left or right side of the colon, extrahepatic disease, and tumour to liver volume. Outcomes should include survival and quality of life.

21	Consultee 4 Company BTG (A Boston Scientific Company)	**Overview**	We would like to highlight the following publications which support the Commissioning Through Evaluation findings: Benson III, Al B., et al. "Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study." European Journal of Cancer 49.15 (2013): 3122-3130. This study investigated the safety, response rate, progression-free and overall survival of patients with liver metastases treated with 90Y (glass) radioembolisation in a prospective, multicenter phase II study. 151 patients were included (61 with mCRC), the authors concluded that the therapy was safe and efficacious with a median PFS and OS for mCRC of 2.9 months and 8.8 months respectively and a DCR for mCRC of 59%. Lewandowski, Robert J., et al. "Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy." European journal of nuclear medicine and molecular imaging 41.10 (2014): 1861-1869. The study prospectively collected data of 214 patients treated with Y90 at a single center over 12 years. The median overall survival was 10.6 months from date of first Y90 treatment. Predictors of increased survival were - received <2 cytotoxic agents, received no biologic agents, had no extra hepatic disease, tumour burden <25%, ECOG of 0 and albumin >3g/dL. Abbott, A. M., et al. “Outcomes of Therasphere Radioembolization for Colorectal Metastases”. Clin Colorectal Cancer. 14.13 (2015): 146-153. This retrospective review of mCRC patients undergoing Y90 from 2009-2013 included 68 patients. Median and 2 year OS were 11.6 months and 34% respectively. For patients with ≤25% tumour burden and 1 chemotherapy regimen 2 year OS was 63%. Prognostic factors for increased mortality included age, >25% tumour burden, ≥3 lines of chemotherapy and higher CEA. Mulcahy, M. F., et al. “Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres”. Cancer. 115 (2009): 1849-1858.	Thank you for your comment. Benson III AB et al. (2013) is included in the appendix of the overview. Lewandowski R et al. (2014) has been added to the appendix of the overview. Abbott AM et al. (2015) is included in the appendix of the overview. Mulcahy MF et al. (2009) has been added to the appendix of the overview. The ESMO guidelines are described in the ‘Existing assessments of this procedure’ section of the overview.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			72 patients were included in the analysis to determine the safety and efficacy of Y90 therapy for patients with liver dominant mCRC. Toxicities were acceptable. The tumour response rate was 40.3%. The median time to hepatic progression was 15.4 months, and the median response duration was 15 months. The PET response rate was 77%. Overall survival from the first Y90 treatment was 14.5 months. Tumour replacement (≤25% vs >25%) was associated with significantly greater median survival (18.7 months vs 5.2 months). The presence of extrahepatic disease was associated negatively with overall survival (7.9 months vs 21 months). Overall survival from the date of initial hepatic metastases was 34.6 months. The median dose delivered was 118Gy. Equally, the European Society Medical Oncology (ESMO) published consensus guidelines1 for the management of patients with metastatic colorectal cancer which includes a “toolbox” of ablative treatments. Radioembolisation SIRT is included as an option within this toolbox. The ESMO guidelines highlight that for “patients with liver-limited disease failing the available chemotherapeutic options, radioembolization with yttrium-90 microsphere should be considered 1. Van Cutsem, E., “ESMO consensus guidelines for the management of patients with metastatic colorectal cancer”. Annals of Oncology. 27.8 (2016): 1386-1422	

"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."