National Institute for Health and Clinical Excellence

IP 1038 Selective internal radiation therapy for primary hepatocellular carcinoma

Consultation Comments table

IPAC date: 14 March 2013

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 British Society of Interventional Radiology	**1.1**	Please find attached a response from the British Society of Interventional Radiology (supported by The Royal College of Radiologists) to the consultation on 'Selective internal radiation therapy for primary hepatocellular carcinoma'. The BSIR notes that the provisional recommendations are broadly similar to the guidance produced for SIRT for unresectable colorectal liver metastasis. As such they are favourable and the BSIR feels they should lead to the wider availability of this therapy for primary liver tumours, where there is little effective treatment possible. However, overall the BSIR feels the draft guidance is accurate and supportive	Thank you for your comment. The consultee agrees with the recommendations.
2	Consultee 2 NHS Professional	**1.1**	I fully support the recommendation that the current evidence on the efficacy and safety of selective internal radiation therapy (SIRT) for primary hepatocellular carcinoma is adequate for use.	Thank you for your comment. The consultee agrees with the recommendations.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
3	Consultee 3 NHS Professional	**1.1**	We agree with these comments	Thank you for your comment. The consultee agrees with the recommendations.
4	Consultee 4 NHS Professional	**1.1**	support the recommendation that the current evidence on the efficacy and safety of selective internal radiation therapy (SIRT) for primary hepatocellular carcinoma is adequate for use.	Thank you for your comment. The consultee agrees with the recommendation.
5	Consultee 5 Manufacturer	**1.1**	We welcome the provisional recommendations in 1.1.	Thank you for your comment. The consultee agrees with the recommendation.
6	Consultee 6 NHS Professional	**1.1**	Agreed but there is evidence of efficacy in cases not suitable for other endovascular treatments (eg portal vein thrombosis)	Thank you for your comment – this was not highlighted by the Specialist Advisers or in the evidence reviewed but a relevant case series (Memon 2012) has been identified in the post-consultation literature search and added to Appendix A of the Overview.
7	Consultee 7 Specialist Adviser	**1.1**	In view of a lack of level 1A/B or II evidence on efficacy, clinicians should only use this treatment within the remit of a clinical trial.	Thank you for your comment. Sections 1.1 and 1.2 of the Guidance refers to entry into trials. The Committee considered it unrealistic to specify RCTs. Section 1.4 of the Guidance reports the outcomes that should be audited.
8	Consultee 2 NHS Professional	**1.2**	I think that the appropriate selection criteria for HCC patients receiving SIRT could be better defined e.g. unresectable liver-only or liver-dominant HCC, life expectancy >12 weeks, ECOG performance status 0?2, total bilirubin level <34 μmol/L, well-compensated liver disease (Child-Pugh class A?B ≤7 points)."	Thank you for your comment. It is outside the remit of the IP Programme to make specific recommendations about the selection of patients for procedures. Section 1.2 of the Guidance recommends that this should be done by a multidisciplinary team.

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9	Consultee 8 NHS Professional	**1.2**	There needs to be additional guidance regarding patient selection - these patients often have underlying liver dysfunction (classified by Child-Pugh score). In order to be eligible for SIRT, patients with well-compensated liver disease should be selected (Child-Pugh A and possibly B with no more than 7 points). In addition, patients should be of good performance status (PS0-1, possibly 2) and have disease not amenable to curative intervention.	Thank you for your comment. Please see response to comment 8.
10	Consultee 5 Manufacturer	**1.2**	In 1.2, IPAC may wish to consider making reference to some general criteria for choosing patients which is suggested by the literature: SIRT is suitable for unresectable liver-only or liver-dominant HCC, life expectancy > 12 weeks, ECOG performance status ≤ 2, total bilirubin < 34 µmol/L (< 2.0 mg/dL), and well-compensated liver disease (Child-Pugh class A or B, ≤ 7 points).	Thank you for your comment. Please see response to comment 8.
11	Consultee 4 NHS Professional	**1.2**	I think that the appropriate selection criteria for HCC patients receiving SIRT could be better defined e.g. unresectable liver-only or liver-dominant HCC, life expectancy >12 weeks, ECOG performance status 0?2, total bilirubin level <34 μmol/L, well-compensated liver disease (Child-Pugh class A?B ≤7 points)."	Thank you for your comment. Please see response to comment 8.
12	Consultee 6 NHS Professional	**2.1**	Agreed but same comments as in section 1 Also some comment regarding performance status should be mentioned.	Thank you for your comment. The performance status of patients was not highlighted as an issue for consideration either in the evidence reviewed or by the Specialist Advisers. Please see response to comment 8.

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13	Consultee 3 NHS Professional	**2.1**	We should also look at the question of down staging to allow for either resection or transplant	Thank you for your comment. Evidence on down staging was specifically sought and section 2.3.4 of the Guidance presents relevant data.
14	Consultee 6 NHS Professional	**2.2**	agreed	Thank you for your comment. The consultee agrees with section 2.2 of the Guidance.
15	Consultee 3 NHS Professional	**2.2**	We agree with these comments	Thank you for your comment. The consultee agrees with section 2.2 of the Guidance.
16	Consultee 9 NHS Professional	**2.2.2**	The comments are on generic points relating to the SIRT method, so could also be considered for the consultation on SIRT for cholangiocarcinoma. With regards to the Nuclear Medicine scan in 2.2.2 : consideration should also be given to tomographic (SPECT-CT) imaging where available. This allow areas of extrahepatic leakage to be picked up in workup stage, allowing time to address cause before treatment & reducing risk of radiation induced morbidity."	Thank you for your comment. The Committee considered the comment but did not change the Guidance.
17	Consultee 5 Manufacturer	**2.2.3**	In 2.2.3, we suggest replacing the word ‘embolise’ with the word ‘lodge’ to avoid confusion with the mechanism of action of TA(C)E, which—unlike SIRT—works by inducing ischaemia.	Thank you for your comment. Section 2.2.3 of the Guidance has been changed accordingly.
18	Consultee 8 NHS Professional	**2.3**	it would be worth stating that there is no prospective phase III study evaluating SIRT with TACE as the first bullet-point. This is consistent with the first recommendation 1.1.	Thank you for your comment. The IP Programme does not comment on the absence of evidence in this section or on the evidence for alternative treatments.

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19	Consultee 5 Manufacturer	**2.3**	2.3 does not refer to Sangro 2011 (Sangro B, Carpanese L, Cianni R et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona Clinic Liver Cancer stages: a European evaluation. Hepatology 2011;54(3):868-878.). This paper, a retrospective evaluation of 325 patients in eight European centres, is important not only because of the size of the study population but also because it is in a European (rather than an Asian) population. As a multi-centrestudy, it is more robust than the single-centre data presented. This paper is not includedin Table 2a of the overview (main extraction table) and despite being the largest study of SIRT in HCC appears only in the Appendix A list of relevant papers from which data were not extracted.	Thank you for your comment. The Sangro (2011) paper has been added to table 2a of the Overview.
20	Consultee 2 NHS Professional	**2.3**	Unfortunately the largest study of SIRT in HCC (Sangro B et al. Hepatology 2011; 54: 868?78) which was conducted in 8 European centres and is most relevant to the UK clinical setting has been omitted from review in Table 2a of the overview document and therefore is not presented in the draft guidance.	Thank you for your comment Please see response to comment 19.
21	Consultee 6 NHS Professional	**2.3**	No mention of the series as outlined by Sangro B et al	Thank you for your comment Please see response to comment 19.

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22	Consultee 4 NHS Professional	**2.3**	The largest study of SIRT in HCC (Sangro B et al. Hepatology 2011; 54: 868?78) which was conducted in 8 European centres and is most relevant to the UK clinical setting has been omitted from review in Table 2a of the overview document and therefore is not presented in the draft guidance.	Thank you for your comment Please see response to comment 19.
23	Consultee 1 British Society of Interventional Radiology	**2.3**	The BSIR is content that an extensive and complete review of the available literature has been performed. However, the BSIR suggests there is one significant omission as follows: Hepatology, 2011 Sep 2; 54(3): 868-78. doi: 10.1002/hep.24451. Epub 2011 Jun 30. *Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation.* Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, Paprottka PM, Fiore F, Van Buskirk M, Bilbao JI, Ettorre GM, Salvatori R, Giampalma E, Geatti O, Wilhelm K, Hoffmann RT, Izzo F, Iñarrairaegui M, Maini CL, Urigo C, Cappelli A, Vit A, Ahmadzadehfar H, Jakobs TF, Lastoria S; European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY).	Thank you for your comment. Please see response to comment 19.

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24	Consultee 5 Manufacturer	**2.3**	2.3 refers to downstaging. Reference might also be usefully be made to SIRT's ability to induce hypertrophy in untreated areas of the liver, which may permit resection in patients with an insufficient functional liver reserve, while at the same time providing tumour control and downsizing. This aspect of the treatment is also not referred to in the overview.	Thank you for your comment. The Specialist Advisers did not identify induction of hypertrophy as an efficacy outcome to assess.
25	Consultee 9 NHS Professional	**2.3**	"The use of trials (or central databases) should be encouraged to look at/collect info on Â patient-specific radiation dosimetry. If correlation between dose and response or side effects can be shown, this would allow better selection of patients. The aim would be to exclude those most at risk, permit modification of treatment to reduce risk & predict the best responders. The use of patient-specific dosimetry is vastly underutilised in unsealed source radioactive treatments, but as with external beam radiotherapy or brachytherapy there should be more done to optimise treatments to reduce morbidity & mortality."	Thank you for your comment. Relevant professional societies, led by the BSIR have worked with the manufacturer to develop a national register which is live on the BSIR website. Your comment was passed to Dr Munneke who is leading the development of the register. Dr Munneke has confirmed that the national register will include data providing extra evidence in the areas requested by the consultee
26	Consultee 3 NHS Professional	**2.3**	There are two large multi-centre RCTs in progress one from South East Asia and one in Euopre results are expected in 12-24 months. This should provide more robust data. Unfortunatley the NCRN declined to be part of the European trial.	Thank you for your comment. A list of ongoing trials has been included in the Overview. We are unable to identify the 2 RCTs referred to by the consultee based on the information provided.
27	Consultee 6 NHS Professional	**2.4**	agreed	Thank you for your comment

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28	Consultee 10 British Liver Trust	**2.4**	Written information for both patient and carer of all of these side effects should be given prior to treatment starting and clearly explained so both can monitor and report any side effects and request treatment for them if required	Thank you for your comment. NICE produces an *Information for public* version of the Guidance which outlines the safety and efficacy outcomes. This document is written to help people who have been offered this procedure to decide whether to consent to it or not. The document also includes some questions patients may want to ask to help reach a decision. Where available, sources of further information and support are also provided.
29	Consultee 10 British Liver Trust	**2.4**	as highlighted in 2.4.7 fatigue is a significant issue for the majority of patients treated with SIRT - both patients and carers should be prepared for this and information provided to alleviate this side effect eg: http://www.macmillan.org.uk/Cancerinformation/Livingwithandaftercancer/Symptomssideeffects/Fatigue/Fatigue.aspx	Thank you for your comment. Please see response to comment 28.
30	Consultee 3 NHS Professional	**2.4**	Extra care must always be taken in those patients with small liver, poor heaptic reserve and who have received anti-angiogenic chemotherapy in the 6 months prior to treatment. Special care may be needed for those who have travelled from overseas for SIRT to ensure all medical data is correct	Thank you for your comment. It is outside the remit of the IP Programme to make specific recommendations about the selection of patients for procedures. Section 1.2 of the Guidance recommends that this should be done by a multidisciplinary team.

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31	Consultee 1 British Society of Interventional Radiology	**2.4**	The consultation document necessarily refers to safety data when it is available. However headline figures of radiation pneumonitis of 4/80 (5%) and Gi ulceration 3/27 (11%) would not be acceptable in today's practice. Pnemonitis in particular is now considered a never event and the paper the figure is quoted from dates back to 1995. However, overall the BSIR feels the draft guidance is accurate and supportive.However, overall the BSIR feels the draft guidance is accurate and supportive.	In sections 2.4.2 and 2.4.3, the Guidance refers to new methods used to prevent radiation damage outside the liver. The Committee has added a comment to section 2.5.2 of the Guidance to note that safety outcomes from older published studies may not reflect current practice in which prophylactic coil embolisation is now used.
32	Consultee 6 NHS Professional	**2.5**	Hence the importance of the registry	Thank you for your comment.
33	Consultee 3 NHS Professional	**2.5**	Agreed which is why we await the RCT data	Thank you for your comment.

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34	Consultee 5 Manufacturer	**Overview**	Comments relating specifically to HCC The largest and only multi-centre study published to date (Sangro 2011) reporting outcomes using SIRT in HCC in 8 European centres has not been included in Table 2a. Two significant comparative studies are also missing (Salem 2011; D'Avola 2009). In contrast, studies conducted before the current generation of SIRT products werecommercialised (Lau 1998; Leung 1995; Mantravadi 1982) or are smaller and provideless relevant clinical data (Geschwind 2004; Kooby 2010) have been included.• Sangro 2011 is an analysis of safety and survival in 325 patients treated with SIRT. It is largest study of SIRT and the only multi-centre study published to date. Since the study was conducted at eight European centres, the results are more relevant to the UK population than some of the other studies included in Table 2a. • Salem 2011 is a comparison of safety and survival between SIRT and TACE in 122 vs 123 patients with HCC. It is the largest comparative study of SIRT and TACE reported to date;• D'Avola 2009 is a comparison of survival between SIRT and best supportive care or active therapy in 35 vs 43 patients with HCC, respectively. It is the comparative study of SIRT and standard therapy (typically systemic or i.v. therapies) or bestsupportive care in patients that are typically not candidates for TACE.	Thank you for your comment. The Sangro (2011), Salem (2011) and D'Avola (2009) studies have been added to table 2a of the Overview.

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35	Consultee 5 Manufacturer	**Overview**	One of the confounding factors in reporting overall survival in patients with HCC is the need to stratify results by the widely used BCLC prognostic stages. Unless patients can be characterised in a specific BCLC stage, comparisons of survival are meaningless (see the Sangro 2011 review paper (Sangro B, Inarrairaegui M. Radioembolization for hepatocellular carcinoma: evidence-based answers to frequently asked questions. Journal of Nuclear Medicine & Radiation Therapy 2011; 2: 110 ePub doi: 10.4172/2155-9519.1000110.).	Thank you for your comment which has been shared with the BSIR in order to check that the national register will collect the necessary data to allow such analyses. It has been confirmed that the national register will include data providing extra evidence in the areas requested by the consultee The Sangro (2011), study has been added to table 2a of the Overview.
36	Consultee 5 Manufacturer	**Overview**	We suggest that the words 'SIRT aka' are inserted before "Radio-embolization through transarterial delivery of microspheres…" (para 4, page 2).	Thank you for your comment. This has been changed in the Overview.

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37	Consultee 5 Manufacturer	**Overview**	In the introduction, IPAC may wish to make reference to patient selection criteria for SIRT. These are not well-defined in either the guidance or the overview. These have been proposed by Coldwell 2011 (Coldwell D, Sangro B, Wasan H et al. General selection criteria of patients for radioembolization of liver tumors: an international working group report. American Journal of Clinical Oncology 2011;34:337–341.) and Kennedy 2007 (Kennedy A, Nag S, Salem R et al. Recommendations for radioembolization of hepaticmalignancies using yttrium-90 microsphere brachytherapy: A consensus panel report from the Radioembolization Brachytherapy Oncology Consortium (REBOC). International Journal of Radiation Oncology, Biology and Physics 2007;68:13–23.).	Thank you for your comment. A reference to the consensus panel report published by REBOC has been added to the Overview.

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38	Consultee 5 Manufacturer	**Overview**	These include: Inclusion criteria: • unresectable liver-only or liver-dominant tumour(s) from primary liver cancer or metastatic disease; • life expectancy >12 weeks; • ECOG performance status 0–2; Absolute exclusion criteria: • ascites or other clinical signs of liver failure on physical examination (i.e. not solely on imaging); • pregnancy; • potential for excess radiation exposure (>30 Gy) to the lung as determined by pre-treatment lung-shunt study; • shunting to the gastrointestinal tract (stomach, bowel, or pancreas) that cannotbe corrected by embolization prior to the procedure (as demonstrated by hepatic angiogram); Relative exclusion criteria (reviewed on a case-by-case basis): • compromised main portal vein as demonstrated on triple-phase CT scan unless selective or super-selective radioembolization can be performed; • previous radiation therapy to the liver; • excessive tumour burden with limited hepatic reserve; • abnormal organ	Thank you for your comment. Please see response to comment 37.
39	Consultee 5 Manufacturer	**Overview**	We suggest that ‘lodge’ should replace ‘embolise’ in the penultimate paragraph on page 2 (see our comments on 2.2.3 of the draft HCC and of the ICC guidance).	Thank you for your comment. Please see response to comment 17.

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40	Consultee 5 Manufacturer	**Overview**	We suggest that Sangro 2011 (Sangro B, Carpanese L, Cianni R et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona Clinic Liver Cancer stages: a European evaluation. Hepatology 2011;54(3):868-878.) be included in Table 2a. This paper, a retrospective evaluation of 325 patients in eight European centres, is important not only because the size of the study population but also because it is in a European population (rather than an Asian population with some differences in the causation and pattern of disease and associated cirrhosis). As a multi-centre study, it is even more robust than the single-centre data presented. This is also the largest study of SIRT in HCC.	Thank you for your comment. The Sangro (2011) study has been added to table 2a of the Overview.
41	Consultee 5 Manufacturer	**Overview**	On page 6, referring to Lewandowski 2009, the statistical significance of time to overall progression is not stated. This was also p=0.005.	Thank you for your comment. The information on statistical significance has been added to table 2a of the Overview.

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42	Consultee 5 Manufacturer	**Overview**	On page 8, referring to Kooby 2010, SIRT was associated with a significantly shorter mean hospital length of stay vs TACE (1.7 vs 6.0 days, respectively; p=0.05), which may be relevant for healthcare payers and providers. The number of patients with any complication was significantly lower for patients receiving SIRT compared to TACE (44% vs 70%; p=0.05)	Thank you for your comment. Following consultation, this study has been included in table 2a of the Overview in relation only to a safety outcome . Information on patients with complications has been added. Information on efficacy outcomes including hospital length of stay has been added to Appendix A of the Overview.
43	Consultee 5 Manufacturer	**Overview**	On page 9, referring to Steel 2004, although the quality of life results at 6 months follow-up are stated (when n = 14 patients), the results at 3 months follow-up (when the results on the full cohort of 28 patients were available) have been omitted. These data revealed that patients treated with SIRT reported significantly higher scores on scales measuring functional well-being ($p < 0.001$) and overall health-related quality of life ($p < 0.001$) vs patients treated with cisplatin.	Thank you for your comment. Results for overall health-related quality of life results for 3 months are reported in table 2a of the Overview. The results of the functional well-being have been added to table 2a of the Overview.
44	Consultee 5 Manufacturer	**Overview**	On page 11, referring to Geschwind 2004, the overview notes (under 'Key safety findings') that "Death: 60% (48/80)". This was reported as part of the survival analysis (it is an outcome expected in patients treated palliatively), and not as a safety finding.	Thank you for your comment. This has been changed in table 2a of the Overview.

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45	Consultee 5 Manufacturer	**Overview**	On page 13, referring to Lau 1998, IPAC should note that this study was conducted several years before the current generation of SIRT products were approved. The study was conducted in Hong Kong, in a population that is not as representative of a European population compared with other larger studies that have been, in our view incorrectly,not included in Table 2a (Sangro 2011 on 325 patients in a European multi-centreanalysis). Under 'Key safety findings' the table notes that "Death: 70% (51/71)" and the causes of death are noted in a table. However, the majority of these (intrahepatic residual or recurrent disease; bone metastases; lung metastases; unrelated cause etc) are unrelated to safety and come from the analysis of survival.	Thank you for your comment. The Lau (1998) study has been removed from table 2a of the Overview and added to Appendix A. The Sangro (2011) study has been added to table 2a of the Overview.

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46	Consultee 5 Manufacturer	**Overview**	On page 15, referring to Leung 1995, IPAC should note that this study was conducted at an early stage of clinical development of the current generation of SIRT products. The study reports the identification of radiation pneumonitis as a potential consequence of shunting of excessive radiation dose to the lung. As a consequence of these results, the 99mTc MAA lung-shunt study was indicated as a routine pre-treatment assessment in the Package Insert of the SIRT products, with dose reductions in patients with a 10% to 20% lung-shunt and contra-indication for SIRT in those with >20% lung-shunt or >30 Gy exposure to the lung.	Thank you for your comment. Radiation pneumonitis was reported as a theoretical adverse event by Specialist Advisers. Therefore this study was included in table 2a of the Overview. The Committee has added section 2.5.2 to the Guidance to acknowledge that techniques have been developed which reduce adverse events.
47	Consultee 5 Manufacturer	**Overview**	On page 15, referring to Popperl 2005, the case described used resin microspheres, not glass as stated.	Thank you for your comment. This has been changed in the Overview.
48	Consultee 5 Manufacturer	**Overview**	On page 17, referring to Mantravadi 1982, the study was conducted nearly 20 years before the current generation of SIRT products were developed.	Thank you for your comment. Specialist Advisers had listed pancytopenia due to bone marrow suppression as an adverse event reported in the literature. Therefore the Mantravadi (1992) study has been included in table 2a of the Overview.

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49	Consultee 5 Manufacturer	**Overview**	On pages 6 to 17 (Table 2a), pages 25 to 27, and Appendix A, studies and case series on SIRT in HCC that have not been included in either Table 2a or Appendix A (and therefore the commentary) and should be referenced are: - Moreno-Luna 2012: a matched case-control comparison of SIRT vs TACE in 61 vs 55 patients with HCC (Moreno-Luna LE, Yang JD, Sanchez W et al. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients withhepatocellular carcinoma. Cardiovascular and Interventional Radiology 2012 Oct 24; ePub doi: 10.1007/s00270-012-0481-2.); • Ibrahim 2012: a case study on down-staging to liver transplantation in 8 patients with HCC (Ibrahim SM, Kulik L, Baker T et al. Treating and downstaginghepatocellular carcinoma in the caudate lobe with yttrium-90 radioembolization.Cardiovascular and Interventional Radiology 2012;35(5):1094-1101.);	Thank you for your comment. The references cited by the consultee have been identified in the update search and included in the post consultation literature table: The following studies have been added to Appendix A: Moreno-Luna (2012) Ibrahim (2012)

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50	Consultee 5 Manufacturer	**Overview**	- Mazzaferro 2012: a prospective phase II study in 52 patients with HCC (Mazzaferro V, Sposito C, Bhoori S et al. Yttrium90 radioembolization for intermediate-advanced hepatocarcinoma: A phase II study. Hepatology 2012 Aug 22; ePub doi: 10.1002/hep.26014.); Memon 2012: a case study of SIRT in 63 patients with HCC (Memon K, Kulik L,Lewandowski RJ et al. Radioembolization for hepatocellular carcinoma with portal vein thrombosis: Impact of liver function on systemic treatment options at disease progression. Journal of Hepatology 2012 Sep 18; ePub doi:10.1016/j.jhep.2012.09.003.); Ettorre 2010: a case study on down-staging to liver transplantation in HCC (Ettorre GM, Santoro R, Claudio P et al. Short-term follow-up of radioembolization with yttrium-90 microspheres before liver transplantation: new perspectives in advanced hepatocellular carcinoma. Transplantation 2010;90:930–931.);	Thank you for your comment. The references identified by the consultee have been included in the post consultation literature table. The following studies have been added to Appendix A of the Overview: Ettore (2010) Mazzaferro (2012) Memon (2012)

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51	Consultee 5 Manufacturer	**Overview**	• Iñarrairaegui 2010: a comparison of SIRT in elderly and younger patients showing similar survival in both cohorts, including 99 patients with HCC (Iñarrairaegui M, Bilbao JI, Rodríguez M et al. Liver radioembolization using 90Y resin microspheres in elderly patients: tolerance and outcome. Hospital Practice (Minneapolis) 2010;38:103–109.); • Gaba 2009: a case study of SIRT in 17 patients with HCC and 3 with cholangiocarcinoma (Gaba RC, Lewandowski RJ, Kulik LM et al. Radiation lobectomy:Preliminary findings of hepatic volumetric response to lobar Yttrium-90radioembolization. Annals of Surgical Oncology 2009;16:1587–1596.); • Riaz 2009: a case study of SIRT in 35 patients with HCC (Riaz A, Kulik L,Lewandowski RJ et al. Radiologic–pathologic correlation of hepatocellular carcinomatreated with internal radiation using Yttrium-90 microspheres. Hepatology 2009;49:1185–1193.); • Rhee 2008: a case study on imaging in 20 patients with HCC (Rhee TK, Naik NK, Deng J et al. Tumor response after yttrium-90 radioembolization for hepatocellularcarcinoma: comparison of diffusion-weighted functional MR imaging with anatomicMR imaging. Journal of Vascular and Interventional Radiology 2008;19:1180–1186.);	Thank you for your comment. The references cited by the consultee have been added to Appendix A of the Overview.

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52	Consultee 5 Manufacturer	**Overview**	Barakat 2008: a case study of down-staging to resection using SIRT in a patient with HCC (Barakat O, Skolkin MD, Toombs BD et al. Major liver resection for hepatocellular carcinoma in the morbidly obese: a proposed strategy to improve outcome. World Journal of Surgical Oncology 2008;6:100.); • Rivera 2006: a case study of SIRT in a patient with HCC post-transplantation (Rivera L, Giap H, Miller W et al. Hepatic intra-arterial infusion of yttrium-90 microspheres in the treatment of recurrent hepatocellular carcinoma after liver transplantation: a case report. World Journal of Gastroenterology 2006;12:5729–5732.); • Goin 2005: a risk-stratification analysis following SIRT in 121 patients with HCC (Goin JE, Salem R, Carr BI et al. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: a risk-stratification analysis. J Vasc Interv Radiol 2005;16:195–203.); • Goin 2004: a comparison of the post-embolisation syndrome from SIRT vs TACE in 34 vs 29 patients with HCC (Goin JE, Dancey JE, Roberts CA et al. Comparison ofpost-embolization syndrome in the treatment of patients with unresectablehepatocellular carcinoma: Trans-catheter arterial chemo-embolization versus yttrium-90 glass microspheres. World Journal of Nuclear Medicine 2004;3:49–56.);	Thank you for your comment. The references cited by the consultee have been added to Appendix A of the Overview.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
53	Consultee 5 Manufacturer	**Overview**	Chui 2004: a study reporting bridging to liver transplantation in HCC (Chui A, Rao A, Island E et al. Multimodality tumor control and living donor transplantation for unresectable hepatocellular carcinoma. Transplantation Proceedings 2004;36:2287– 2288.); • Carr 2004: a case study of SIRT in 65 patients with HCC (Carr BI. Hepatic arterial 90Yttrium glass microspheres (Therasphere) for unresectable hepatocellular carcinoma: interim safety and survival data on 65 patients. Liver Transplantation 2004;10:S107–S110.); • Szeto 2001: a case study of SIRT in a patient with HCC post-transplantation (Szeto C, Wong T, Leung C et al. Selective internal radiation therapy by yttrium-90 microspheres for hepatocellular carcinoma after renal transplantation. Clinical Transplantation 2001;15:284–288.).	Thank you for your comment. The Carr (2004) paper cited by the consultee is included in table 2a of the Overview (in relation to a safety event). The Chui (2004) and Szeto (2001) studies have been added to Appendix A of the Overview.

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54	Consultee 5 Manufacturer	**Overview**	On page 25, discussing overall survival, comments would be more accurate and useful if data on the outcomes by BCLC stage from the two largest series to be published (Salem et al 2010, n = 291; Sangro et al 2011, n = 325) patients with HCC treated using SIRT (Salem R, Lewandowski RJ, Mulcahy MF et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 2010;138(1):52-64.; Sangro B, Carpanese L, Cianni R et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology 2011;54(3):868-878.). Some non-randomised comparisons of SIRT vs TACE are included, but the largest comparison against TACE (Salem 2011) (Salem R, Lewandowski RJ, Kulik L et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2011;140(2):497-507 e2.) and the comparison vs best supportive care or standard therapy by D'Avola et al (D'Avola D, Iñarrairaegui M, Bilbao JI et al. Aretrospective comparative analysis of the effect of Y90-radioembolization on the survivalof patients with unresectable hepatocellular carcinoma.	Thank you for your comment The Sangro (2011), Salem (2011) and D'Avola (2009) papers have been added to table 2a of the Overview.

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55	Consultee 5 Manufacturer	**Overview**	Hepatogastroenterology 2009;56(96):1683-1688.) are not included. The n = 71 patient study quoted is in an Asia Pacific population reported several years before any SIRT product was commercialised.	Thank you for your comment.
56	Consultee 5 Manufacturer	**Overview**	Under 'Efficacy – hepatocellular carcinoma', we suggest that it would be helpful to have an additional section on inducing hypertrophy in untreated liver. One of the effects more recently established following SIRT is the degree of hypertrophy that develops in the untreated areas of the liver following SIRT. Some patients considered unresectable because of insufficient future liver remnant (FLR) may develop sufficient functioning liver tissue to enable a resection following SIRT, and at the same time as treating the tumour.	Thank you for your comment. The Specialist Advisers did not identify induction of hypertrophy as an efficacy outcome to assess.

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57	Consultee 5 Manufacturer	**Overview**	This has been reported across a range of different tumour types, including HCC: Gaba 2009 in 17 HCC (all with cirrhosis) and 3 cholangiocarcinoma reported a 40% increase in the median volume of untreated left hepatic lobe (and a 52% decrease in the treated right lobe) (Gaba RC, Lewandowski RJ, Kulik LM et al. Radiation lobectomy: Preliminary findings of hepatic volumetric response to lobar Yttrium-90 radioembolization. Annals of Surgical Oncology 2009;16:1587–1596.); • Ahmadzadehfar 2012 reported a 70% median increase in untreated left hepatic lobe of patients receiving SIRT to the right lobe (and a 16% decrease in the right lobe volume), and a 30% median increase in the left hepatic lobe of patients receiving SIRT to first the right lobe followed at four to six weeks to the left lobe (and a 10% decrease in the volume of the right lobe) (Ahmadzadehfar H, Meyer C, Ezziddin S et al. Hepatic volume changes induced by radioembolization with 90Y resin microspheres. A single-centre study. European Journal of Nuclear Medicine and Molecular Imaging 2012 Oct 13; ePub doi: 10.1007/s00259-012-2253-2.).	Thank you for your comment. The paper by Gaba (2009) has been added to Appendix A of the Overview. The Ahmadzadehfar (2012) study does not include patients with primary liver cancer.

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58	Consultee 5 Manufacturer	**Overview**	On page 27, discussing radiation pneumonitis, the overview should make clear that the treatments reported occurred at an early stage of clinical development, and the data led to the development of pre-treatment protocols (which reduce the prescribed activity in patients with a high lung-shunt [10% to 20%] and contraindicate SIRT in patients with a lung shunt > 20%). These recommendations are incorporated into the Package Insert of the approved SIRT products.	Thank you for your comment. The data reported for radiation pneumonitis was from a study where a scan to determine lung shunting had been done before treatment with SIRT. This has been noted in table 2a of the Overview. The Committee has added section 2.5.2 to the Guidance to acknowledge that techniques have been developed which reduce adverse events.
59	Consultee 5 Manufacturer	**Overview**	In 'existing assessments of this procedure' (page 29), the 2007 CADTH assessment (ref #27) is an older review that has been replaced by a 2011 review (CADTH. Yttrium-90 microspheres for cancer patients with primary or secondary liver tumors: clinical and cost-effectiveness. CADTH 13 June 2011. Available from http://www.cadth.ca/media/pdf/htis/june-2011/RB0369_Yttrium-90_Microspheres_Final.pdf. Themore recent review concluded that "Evidence suggests that Yttrium-90 microsphereradioembolization is a safe and efficient therapy for patients with primary or secondary liver tumors."	Thank you for your comment. The CADTH (2011) assessment has been identified in the updated literature search and the summary has been updated in the Overview.

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60	Consultee 5 Manufacturer	**Overview**	In the same section, IPAC should note that the Swedish HTA (ref #28) was published before the publication of the comparative studies by Hendlisz et al 2010, Seidensticker et al 2012 and Bester et al 2012 (Hendlisz A, Van den Eynde M, Peeters M et al. 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. Journal of Clinical Oncology 2010;28:3687–3694.; Seidensticker R, Denecke T, Kraus P et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovascular and Interventional Radiology 2012;35;1066– 1073.; Bester L, Meteling B, Pocock N et al. Radioembolization versus standard care of hepatic metastases: Comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. Journal of Vascular and Interventional Radiology 2012;23:96–105.). These studies were not therefore included in the analysis but might have changed the conclusions of this review.	Thank you for your comment. The conclusions presented for the Swedish HTA (Rizell 2010) in the Existing Assessments section of the Overview is based on the summary available for the publication.

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61	Consultee 5 Manufacturer	**Overview**	IPAC may wish also to consider including reference to the 2012 ESMO HCC guidelines (Verslype C, Rosmorduc O, Rougier P et al. Hepatocellular carcinoma: ESMO–ESDO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 (Suppl 7):vii41–8), in the overview. This stated that "The role of radioembolization with glass or resin Y-90 spheres may be competitive with sorafenib or TACE in subsets of patients, such as those with prior TACE failure, excellent liver function, macrovascular invasion and the absence of extra-hepatic disease."	Thank you for your comment. The evidence section on radioembolisation in the ESMO-ESDO guidance is based on 1 study -Sangro (2011) and has been added to the Existing Assessments section of the Overview.
62	Consultee 5 Manufacturer	**Overview**	We recognise that the Specialist Advisers' opinions (page 30) are not the opinions of IPAC, but IPAC should note that it is not the case that RFA is a comparator for SIRT, as one opinion states, since SIRT is intended for the treatment of tumours which are not surgically resectable or ablatable.	Thank you for your comment. This is the opinion of a Specialist Adviser and will not be changed.
63	Consultee 5 Manufacturer	**Overview**	On page 31, under issues for consideration, SORAMIC should include the clinicaltrials.gov identifier NCT01126645.	Thank you for your comment. The Overview has been changed to include the NCT identifier.
64	Consultee 5 Manufacturer	**Overview**	On page 36 (Appendix A), discussing Carr (2010), the overview should note that the overall survival was significantly longer for patients receiving SIRT compared to TACE ($p < 0.05$).	Thank you for your comment. The p value has been added to Appendix A of the Overview.

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65	Consultee 5 Manufacturer	**Overview**	On page 37 (Appendix A), discussing D'Avola (2009), although the intention-to-treat data are reported, the overview should state that the primary outcome was a comparison of patients treated with SIRT vs standard therapy, which showed a significant benefit in favour of SIRT (16 vs 8 months; $p < 0.001$). This is the only comparative study vs standard therapy comprising active treatment or best supportive care. No other similar studies have been included in the overview of efficacy. We suggest that this study should be included in Table 2a.	Thank you for your comment. The D'Avola (2009) study has been added to table 2a of the Overview.
66	Consultee 5 Manufacturer	**Overview**	On page 45, the references to Sangro 2006 (n=24) and Sangro 2011 (n=325) have been transposed, with Sangro 2006 referring to the 2011 study and vice versa. Sangro 2011 is the largest study of SIRT and the only multi-centre study published to date. Since the study was conducted at eight European centres, the results are more relevant to the UK population than many studies included in Table 2a and we suggest that this study should be included in Table 2a.	Thank you for your comment. The references have been changed. The Sangro (2011) study has been added to table 2a of the Overview.
67	Consultee 3 NHS Professional	**Notes**	We are a study centre for FOXFIRE	Thank you for your comment.
68	Consultee 4 NHS Professional	**Notes**	I am Principal Investigator in [redacted] for the FOXFIRE trial (evaluating SIRT with chemo in patients with liver mets from CRC)	Thank you for your comment.
69	Consultee 6 NHS Professional	**Notes**	Have acted as Medical Consultant to [redacted] medical	Thank you for your comment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
70	Consultee 8 NHS Professional	**Notes**	The [redacted] is a recruiting site for the phase III FOXFIRE study (evaluating the urility of SIRT in patients with colorectal cancer liver metastases). No conflict with respect to this indication (hepatocellular carcinoma).	Thank you for your comment.
71	Consultee 9 NHS Professional	**Notes**	[redacted] is currently participating in the FOXFIRE SIRT trial	Thank you for your comment.