National Institute for Health and Care Excellence

IP1081/2 Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma

IPAC 12/07/18

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company Terumo Europe	**1.1**	"Research": does it mean only clinical trials or would the SIRT Register be acceptable?	Thank you for your comment. 'Research only' recommendation means that the procedure should only be carried out in the context of formal research studies, as approved by a research ethics committee. Observational studies (such as cohort studies using registry data) are considered as research if undertaken under research governance arrangements. Section 1.2 of the guidance recommends the type of studies and the outcomes that should be addressed in these studies as follows: 1.2 *Further research in the form of prospective studies, including randomised controlled trials, should address patient selection, quality-of-life outcomes and overall survival. Patient selection for the research studies should be done by a multidisciplinary team. The procedure should only be done in specialist centres by clinicians trained and experienced in managing cholangiocarcinoma*.

				Additionally, the committee made the recommendation to enter patient data onto a suitable register that meets NICE standards in section 1.3 as follows: *1.3 Clinicians should enter details about all patients having selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma onto a suitable registry.*
2	Consultee 1 Company Terumo Europe	**1.1**	We note that the 2013 guidance recommended "special arrangements". It is not clear why NICE has heightened the governance requirements from "special arrangements" to "research only"	Thank you for your comment. When the committee considered this procedure for the updated guidance (2018) they made the decision for 'research only' guidance based on the current evidence base which the committee decided was inadequate for efficacy, and showed that rare safety issues can occur. Section 1.1 of the guidance explains the recommendations for research as follows: *1.1 Current evidence on the safety of selective internal radiation therapy (SIRT) for unresectable primary intrahepatic cholangiocarcinoma shows that there are well-recognised, serious but rare safety concerns. Evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.*
3	Consultee 1 Company Terumo Europe	**2.1**	This description of the type of cancer needs to be clarified. There are several types of bile duct	Thank you for your comment. Section 2.1 has been changed as follows:

			cancers including intrahepatic and the title only mentions intrahepatic	*2.1 Intrahepatic cholangiocarcinoma is a rare type of primary liver cancer originating in the bile ducts within the liver parenchyma. It accounts for about 10% of all cholangiocarcinomas (bile duct cancers).*
4	Consultee 1 Company Terumo Europe	**2.4**	Incorrect description of the types of radiation emitted. Could you please use the following wording: SIRT involves delivering microspheres containing radionuclides such as yttrium-90 or holmium-166 that emit beta or gamma radiation directly into the tumour via the hepatic artery. In addition microspheres containing holmium-166 also emit gamma radiation for imaging purposes and dosimetry.	Thank you for your comment. Section 2.4 has been changed as follows: *2.4 SIRT involves delivering microspheres containing radionuclides that emit beta radiation directly into the tumour via the hepatic artery. Under local anaesthesia with fluoroscopic guidance, the radioactive microspheres, which are made of glass, resin or poly(L lactic) acid, are injected into branches of the hepatic artery supplying the tumour. Usually, the percutaneous femoral or radial approach is used. The microspheres are designed to lodge in the small arteries surrounding the tumour and release high doses of localised radiation directly into the tumour. The procedure may be repeated depending on the response*.
5	Consultee 1 Company Terumo Europe	**2.4**	Incorrect description of the procedure. Could you please use the following wording: The microspheres are designed to lodge in the small arteries inside the tumour and release high doses of localised radiation directly into the tumour	Thank you for your comment. Section 2.4 has been changed as follows: *2.4 SIRT involves delivering microspheres containing radionuclides that emit beta radiation directly into the tumour via the hepatic artery. Under local anaesthesia with fluoroscopic guidance, the radioactive microspheres, which*

				are made of glass, resin or poly(L lactic) acid, are injected into branches of the hepatic artery supplying the tumour. Usually, the percutaneous femoral or radial approach is used. The microspheres are designed to lodge in the small arteries surrounding the tumour and release high doses of localised radiation directly into the tumour. The procedure may be repeated depending on the response. is used. The microspheres are designed to lodge in the small arteries surrounding the tumour and release high doses of localised radiation directly into the tumour. The procedure may be repeated depending on the response
6	Consultee 1 Company Terumo Europe	**3.6**	We would suggest to complete the sentence with this information: The committee was told that dosimetry in this procedure is complex and needs significant expertise, although companies are developing software solutions to perform post treatment verification (as required by Euratom), and patient specific dosimetry.	Thank you for your comment. The committee considered your comment but decided not to change the guidance.
7	Consultee 1 Company Terumo Europe	**Overview**	We would recommend adding the British Society of Interventional Radiology (BSIR) to the mist of specialist advisers	Thank you for your comment. The BSIR is already listed as a Specialist society in the overview. We received 1 questionnaire from one of its members.
8	Consultee 2 Patient organisation AMMF - The Cholangiocarcinoma Charity	**1.1**	"Dear NICE Interventional Procedures Guidance Group We are writing from AMMF â€“ The Cholangiocarcinoma Charity, in response to the IPG for the use of SIRT in the treatment of	Thank you for your comment. The committee considered your comment and discussed the issue of this group of patients having few treatment options, but decided not to change the recommendations.

			patients with intrahepatic cholangiocarcinoma (ICC). We have serious concerns on the recommendations made, and find it difficult to understand how the conclusions were reached. We believe this is an injustice to this group of inoperable patients who, following standard chemotherapies, have no further clinically proven treatment options available to them. We believe that SIRT can provide these patients with additional months of life, which are free from debilitating treatment-related adverse events.	The committee added the following comment to the guidance: *3.11 Primary intrahepatic cholangiocarcinoma is a rare condition with a limited life expectancy*.
9	Consultee 2 Patient organisation AMMF - The Cholangiocarcinoma Charity	**1.1**	The recommendations made contradict two current national guidelines: â€¢ The European Society of Medical Oncology (ESMO) Biliary Cancer Guidelines were published in September 2016. They were based on the study by Al-Adra (2014) which was included in the IPG review. This was a pooled analysis of 12 studies (298 patients), which reported median overall survival of 15.5 months, and treatment response rate of 28% in patients treated with SIRT. Furthermore, within this study 10% of patients were converted to resectable disease. https://academic.oup.com/annonc/article-pdf/27/suppl_5/v28/6678340/mdw324.pdf â€¢ The National Comprehensive Cancer Network (NCCN) Clinical practice guidelines in oncology, for Hepatobiliary cancers, also recommend the use of â€œLocoregional therapyâ€ including	Thank you for your comment. The committee considered these guidelines but decided not to change the recommendations. The European Society of Medical Oncology (ESMO) guidelines for the diagnosis, treatment and follow-up of biliary cancer published in 2016 are noted in the overview in the ''Existing assessments of this procedure'' section. They state: • '' *Radioembolisation may be considered in patients with inoperable intrahepatic cholangiocarcinoma, usually after first-line chemotherapy; patients should be encouraged to participate in clinical trials.*'' • ''*Experience is growing in the use of radioembolisation using 90Y-microspheres for patients with iCCA. Prospective, rando-*

			â€œArterially directed therapiesâ€ for the treatment of ICC. These were published very recently, in February of this year. **https://www.nccn.org/professionals/physician_gls/default.aspx** We ask how this recommendation can go against both of these clinical guidelines? Were these guidelines, which are developed with strong clinical support from international experts, also reviewed within the NICE process? This IPG also seems to contradict the recommendations from the previous review completed in 2013, when there has been no change in the safety of the procedure, and contradicts recommendations made for the use of SIRT by NICE IPG in other liver indications, i.e. hepatocellular carcinoma (HCC), and liver dominant metastatic colorectal cancer (mCRC). How is this anomaly justified?	*mised data are lacking; a pooled analysis of 12 studies including 298 patients showed a median OS of 15.5 months and response rate of 28%. Importantly, 7/73 (10%) patients in three selected studies were converted to resectable disease, highlighting the importance of reassessment of patients in the multidisciplinary team in the event of a good response to any treatment*.'' The National Comprehensive Cancer Network (NCCN) Clinical practice guidelines in oncology, for Hepatobiliary cancers published in February 2018 state: • ''*Locoregional therapies such as RFA, TACE, DEB-TACE, or TACE drug-eluting microspheres and TARE with yttrium-90 microspheres have been shown to be safe and effective in a small retrospective series of patients with unresectable intrahepatic cholangiocarcinomas. ''* • *''In a systematic review of 12 studies with 298 patients, the effects of radioembolization with yttrium-90 microspheres in unresectable intrahepatic cholangiocarcinoma were assessed. The overall weighted median survival for this treatment was 15.5 months, partial tumor response was seen for 28% of patients, and SD was seen for 54% of patients. Other small series have also reported favorable response rates and survival benefit for patients with unresectable intrahepatic cholangiocarcinoma treated with TARE with yttrium-90 microspheres. Due to the rarity of the disease, none of these locoregional*

				approaches has been evaluated in randomized clinical trials. ‘’ • *‘’Based on the available evidence as discussed above, the panel has included locoregional therapy as a treatment option that may be considered for patients with unresectable disease or metastatic cancer without extrahepatic disease. ‘’* They have been included in the overview.
10	Consultee 2 Patient organisation AMMF - The Cholangiocarcinoma Charity	**1.1**	We would also like to stress that ICC is a rare disease, and so the evidence should be reviewed appropriately. Although most of the clinical studies are retrospective and non-comparative, they still provide invaluable evidence on the safety and efficacy of SIRT, and include substantial patient numbers. This information should not be discarded as inadequate due to the research methods used. We feel that the current lack of funding for SIRT in England is inexcusable because, as mentioned, this is the only treatment option open to these patients following standard chemotherapies, and because clinical studies have shown it to increase median overall survival. Although we acknowledge that the IPG process only considers efficacy and safety, and not cost-effectiveness, we feel that these recommendations will only serve to further deny NHS patient access to this important procedure.	Thank you for your comment. The committee considered your comment and discussed the issue of this being a rare disease, but decided not to change the recommendations. The committee added the following comment to the guidance: *3.11 Primary intrahepatic cholangiocarcinoma is a rare condition with a limited life expectancy*.

			Based on these points, we strongly ask that you re-consider your draft recommendations. [redacted] [redacted] - AMMF [redacted] [redacted] - AMMF www.ammf.org.uk	
11	Consultee 3 Company BTG	**1.3**	Clinicians are advised to enter details about all patients having SIRT for primary intrahepatic cholangiocarcinoma onto the UK SIRT register. Please note the following statement, from the BSIR website, following the link in the guidance: â€œThis is formally a BSIR registry following agreement with SIRTEX on data collection and subsequent utilization for any potential publication. The registry is available for all proprietary radio-embolization products in addition to SIRTEX products and members are encouraged to submit their data on lineâ€□. If the registry is intended to collect data for all NHS patients treated with SIRT, the promotion of one product over another, unintentional or otherwise, is not appropriate. In addition, since the CtE ceased, it is questionable whether patient data is being collected via this mechanism. Furthermore, the input of data onto this platform is laboursome and	Thank you for your comment. NICE is not responsible for the content of the BSIR website. Section 1.3 of the guidance has been changed as follows: *1.3 Clinicians should enter details about all patients having selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma onto a suitable registry.*

			if this continues as the primary means to collect data relating to SIRT treatment in the NHS, physicians may not use it.	
12	Consultee 3 Company BTG	**3.5**	â€œall the evidence considered by the committee included studies with yttriumâ€□. The definition of SIRT in 2.4 refers to â€œradionucelotides such as yttrium-90 or holmium-166â€□ - yet section 3.5 highlights that the only studies considered are with yttrium. Not all radiation treatments are the same, nor are they loaded/used in the same way - and since there is no clinical data supporting the safety or efficacy of Holmium-166, (nor was it included in the CtE programme), it is therefore not appropriate to include holmium-166 in the guidance.	Thank you for your comment. The committee considered your comment but decided not to change the guidance.
13	Consultee 3 Company BTG	**General**	The draft guidance has been produced for the use of SIRT in unresectable primary intrahepatic cholangiocarcinoma. IPG459 (July 2013) is for the use of SIRT for primary intrahepatic cholangiocarcinoma. It is therefore noted that this is new guidance which does not supersede IPG459.	Thank you for your comment. This guidance is a review of IPG459 and it will replace it. The title of the guidance was modified when it was decided to update IPG 459. The intention was for the title to give a clearer indication for the SIRT treatment. When the guidance is published it will be clear on the NICE website that it does replace IPG459.
14	Consultee 3 Company BTG	**1.1**	The suggestion that SIRT in unresectable ICC be considered for "research only" does still pose an access issue for patients with this disease: the small numbers of patients with this disease makes	Thank you for your comment. The committee considered your comment but decided not to change the guidance.

			clinical studies challenging - and there is no treatments currently available on the NHS for this population. The previous IPG guidance on primary ICC, where the same studies were considered (in fact, less studies were included), recommended SIRT be used with "special arrangements" . There appears to be a disconnect between that guidance and this recommendation.	When the committee considered this procedure for the updated guidance (2018) they made the decision for 'research only' guidance based on the current evidence base which the committee decided was inadequate for efficacy, and showed that rare safety issues can occur.
15	Consultee 4 Company SIRTEX	**Overview**	p. 14 Table of â€œCharacteristics of the 9 studies included in the meta-analysisâ€ Soydal (2016), 1-, 2-, 3-year survival (%) 24;10;NA should read: 34;10;NA From Table 1 of Cuchetti (2017) which reports 33.5 p.17 : Alk Phos increase Chaiteerakij (2011), 35% Should read: 93% From Table 4 p6 of Al-Aldra (2015).	Thank you for your comment. Thank you for pointing out these typos in the overview. They will be corrected.

			p.27 : Table â€œDetailsâ€ Study population and number. 388 patients with CRC Should read: 399 patients with CRC From p82 of White (2017)	
16	Consultee 4 Company SIRTEX	**1.1**	The draft recommendations suggest there are safety concerns, and that evidence on the efficacy of SIRT for the treatment of ICC is inadequate in quality and quantity. We dispute this and outline our reasons below.	Thank you for your comment. The committee considered your comment but decided not to change the guidance.
17	Consultee 4 Company SIRTEX	**1.1**	Firstly, we disagree with the statement that it is a â€œnew and novelâ€ procedure. Since receiving initial marketing authorisation in 2002, the use of SIR-Spheres Y-90 resin microspheres has been steadily increasing with cumulative dose sales of 12,578 units in 2017 (financial year). SIR-Spheres Y-90 resin microspheres are now used across all indications in >1,090 centres globally (>40 countries), (Sirtex, 2017). Cumulative dose sales in the UK from 2004 to 2017 are [redacted] (commercial in confidence) â€“	Thank you for your comment. The committee considered your comment but decided not to change the guidance. The IP programme considers new/novel procedures for new guidance, and it also updates existing guidance. Two specialist advisors stated that, in their opinion, this procedure was ‘’definitely novel and

			this is despite no funding since the Commissioning through Evaluation (CtE) completed in March 2017. We believe that, due to the number of procedures which have been undertaken the evidence accumulated (although primarily non-RCT, and across indications) is adequate to make an informed decision on the safety of undertaking the procedure as routine care within England.	of uncertain safety and efficacy'' in their questionnaires. The recommendations made by the committee are based on the peer-reviewed evidence available for the procedure evaluated, not on the cumulative dose sales or on the number of procedures undertaken. The committed added the following comment in section 3.10: *3.10 The committee noted that this procedure has been available since 2002.*
18	Consultee 4 Company SIRTEX	**1.1**	SIRT, for the treatment of ICC, has in fact now been included within 2 clinical guidelines: â€¢ The European Society of Medical Oncology (ESMO) Biliary Cancer Guidelines were published in September 2016. They were based on the study by Al-Adra (2014) which was included in the IPG review. This was a pooled analysis of 12 studies (298 patients), which reported median overall survival of 15.5 months, and treatment response rate of 28% in patients treated with SIRT. Furthermore, within this study 10% of patients were converted to resectable disease. https://academic.oup.com/annonc/article-pdf/27/suppl_5/v28/6678340/mdw324.pdf	Thank you for your comment. Please refer to comment 9.

			â€¢ The National Comprehensive Cancer Network (NCCN) Clinical practice guidelines in oncology, for Hepatobiliary cancers, also recommend the use of â€œLocoregional therapyâ€ including â€œArterially directed therapiesâ€ for the treatment of ICC. These were published very recently, in February of this year. https://www.nccn.org/professionals/physician_gls/default.aspx We would like to understand how the NICE recommendations can go against these clinically validated and accepted guidelines?	
19	Consultee 4 Company SIRTEX	**1.1**	The IPG recommendations appear to accept the evidence on the safety of SIRT in ICC by stating there are â€œwell-recognised serious but rare safety concernsâ€. We agree with this conclusion, and it has been discussed within an expert consensus paper (Sangro et al., 2017) which acknowledges the adverse events associated with the procedure, and there are both treatment options, and prevention options to avoid these problems.	Thank you for your comment. The consultee agrees with the conclusions of the committee regarding the safety of this procedure and notes that there are treatment and preventive options to avoid SIRT complications. 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.
20	Consultee 4 Company SIRTEX	**1.1**	The recommendations also question the adequacy of the evidence in terms of quantity and quality, and suggest that further prospective studies, including RCTs are required. We dispute this recommendation primarily based on the categorisation of ICC as a rare disease. The World Health Organisation (WHO), and European Medicines Agency (EMA) define a rare disease in the European Union (EU) as one when the number of people affected is less than 5/10,000. Based on the incidence of ICC provided within the Specialist Advisors questionnaires of 1.67/100,000 (USA), and in Bridgewater (2014) of 2.1/100,000 (Western Countries) ICC meets this criterion. The WHO also acknowledge that these â€œpresent fundamentally different challenges from those of common diseasesâ€¦.â€ in the clinical development stage. This is particularly in regard to the small numbers of patients, who may be widely dispersed, and clinical expertise only available in specialised centres. The WHO therefore report that â€œassessment methods should be adapted to small and very small patient populations. (WHO, http://www.who.int/medicines/areas/priority_medicines/Ch6_19Rare.pdf Accessed on 4th June 2018).	Thank you for your comment. The committee considered your comment and discussed the 'rare disease' issue, but decided not to change the recommendations. The committee added the following comment to the guidance: *3.11 Primary intrahepatic cholangiocarcinoma is a rare condition with a limited life expectancy*..

			Despite the acknowledged challenges to undertaking clinical research for rare diseases, it appears that the evidence within this IPG evaluation has been reviewed harshly due to its non RCT methodology. However, as far as we are aware, there are no RCT data available on any product/procedure specifically in ICC. The SIRCCA trial which compares SIRT followed by CIS-GEM chemotherapy to CIS-GEM chemotherapy alone as first line treatment of patients with unresectable ICC is in fact the first to be undertaken, and is due for completion in June 2021. (https://clinicaltrials.gov/ct2/show/NCT02807181) This we believe is due to the rare nature of the disease and heterogeneity in terms of disease presentation. Based on this the evidence of efficacy of any product used to treat ICC would be considered inadequate, and most of the treatments for ICC patients with failed 1-st line chemotherapy would not be recommended.	
21	Consultee 4 Company SIRTEX	**3.1**	Since the NICE IPG review, three further papers have been published, all showing the benefit of the use of SIRT in this patient population: â€¢ Reimer et al., (2018) investigated the potential role of Y-90 SIRT in therapy-naive patients with inoperable ICC, and potential	Thank you for your comment and for sending us references of new publications. The Reimer (2018) paper was retrieved by our update literature search and it has been added to the Appendix in the overview. It is a retrospective case series of 21 therapy-naïve patients.

			prognostic indicators. The study reported a median overall survival for all patients of 15months. This was significantly prolonged in patients with a tumor burden of â‰¥ 25% when compared to those with a tumor burden of 25-50%, with OS of 37.5months and 15months respectively. â€¢ Nezami et al., (2018) undertook a study to evaluate intratumoural radiation does and targeted liver bio-distribution of Y-90 delivered through SIR-Spheres microspheres or TheraSphere Yttrium-90 Glass Microspheres in patients with ICC. The study concluded that that both SIR-Spheres microspheres and TheraSpheres are feasible and safe therapeutic options in patients with ICC. â€¢ Shaker et al., (2018) reported the results of a retrospective study of 17 patients with unresectable or metastatic ICC who were treated with SIRT using either SIR-Spheres microspheres (n=9) or TheraSphere (n=8) at a single institution. The median follow-up of patients was 21.3 months. Median OS for both treatment groups was 33.6 months, and the 5-year survival rate was 26.8%. Liver PFS rate at 1 year was 37.5% and median liver PFS was 4 months. One patient became eligible for resection after a single treatment. Ninety days after treatment, the post-procedure mortality rate was 0%. The earliest reported post-procedure mortality occurred after 137 days and was attributed to causes unrelated	The Nezami (2018) paper was retrieved by our update literature search and it has been added to the Appendix in the overview. It is a retrospective comparative case series of 10 patients. The Shaker (2018) paper was retrieved by our update literature search and it has been added to Table 2 in the overview as it reports 2 new complications related to technical issues. It is a retrospective case series of 17 patients. The committee considered your comment and the findings of these papers but decided not to change the recommendations.

			to treatment. Reported complications included one patient with hepatic artery laceration requiring immediate stenting and one with a gastric artery branch dissection that was treated conservatively. No other adverse events were reported. The authors concluded that treatment with SIR-Spheres microspheres or TheraSpheres for unresectable or metastatic ICC is safe and promising, although further research is needed. We believe that these studies add to the clinical evidence in favour of SIRT for the treatment of ICC. It should also be noted that the previous IPG guidance for SIRT in ICC (IPG 459) produced in July 2013 has a more favourable recommendation and is less restrictive despite at the time there was less clinical data to evaluate. IPG 459 recommended, that due to the rare condition with a variable history, the â€œaccumulation of useful evidence is difficultâ€□ and encouraged further research. When reviewing the studies included in the review it is clear that many of the studies were post 2013, and therefore in line with these recommendations. (https://www.nice.org.uk/guidance/ipg459) The WHO recommendations on rare diseases also discuss the use of â€œdrug repurposingâ€□ for interventions for rare diseases. This allows the development for the use of an intervention to treat an indication, where it has already demonstrated potential for other indications:	

			â€¢ IPG 401 into the use of SIRT for metastatic colorectal cancer (mCRC) states that â€œCurrent evidence on the safety of selective internal radiation therapy (SIRT) for non-resectable colorectal metastases in the liver is adequate.â€™ (https://www.nice.org.uk/guidance/ipg401) â€¢ IPG 460 into the use of SIRT for hepatocellular carcinoma (HCC) undertook a review of the evidence, and stated that â€œcurrent evidence on the efficacy and safety of selective internal radiation therapy (SIRT) for primary hepatocellular carcinoma is adequate for use with normal arrangements for clinical governance, consent and auditâ€ https://www.nice.org.uk/guidance/ipg460/chapter/1-Guidance . We would like to understand why the use of SIRT for ICC is not viewed the same as for HCC and mCRC? The HCC evidence reviewed included RCTâ€™s, and we question whether the SIRT evidence of safety in ICC should be considered so different to that of HCC or mCRC where the safety profile has not changed.	
22	Consultee 4 Company SIRTEX	**1.1**	The WHO recommendations on rare diseases also discuss the use of â€œdrug repurposingâ€ for interventions for rare diseases. This allows the development for the use of an intervention to treat	Thank you for your comment. The committee considered your comment but decided not to change the recommendations.

			an indication, where it has already demonstrated potential for other indications: â€¢ IPG 401 into the use of SIRT for metastatic colorectal cancer (mCRC) states that â€œCurrent evidence on the safety of selective internal radiation therapy (SIRT) for non-resectable colorectal metastases in the liver is adequate.â€™ (https://www.nice.org.uk/guidance/ipg401) â€¢ IPG 460 into the use of SIRT for hepatocellular carcinoma (HCC) undertook a review of the evidence, and stated that â€œcurrent evidence on the efficacy and safety of selective internal radiation therapy (SIRT) for primary hepatocellular carcinoma is adequate for use with normal arrangements for clinical governance, consent and auditâ€ https://www.nice.org.uk/guidance/ipg460/chapter/1-Guidance . We would like to understand why the use of SIRT for ICC is not viewed the same as for HCC and mCRC? The HCC evidence reviewed included	The committee reflected that it may be fine to draw conclusions about the safety of a procedure for a specific indication from the use of this procedure for other indications. However, they also reflected that the efficacy of a specific procedure will usually differ according to its specific indication.

			RCTâ€™s, and we question whether the SIRT evidence of safety in ICC should be considered so different to that of HCC or mCRC where the safety profile has not changed.	
23	Consultee 4 Company SIRTEX	**1.1**	To summarise, we question the recommendations made in the draft consultation: â€¢ SIRT is not a new and innovative treatment option, it is in fact an established and innovative intervention, with a sound evidence base in terms of safety and efficacy. â€¢ There are 2 international clinical guidelines which contradict the recommendations in the draft consultation. â€¢ As ICC is categorised as a rare disease, the requirement for RCTs should not apply, and the adequacy of the quality and quantity of the efficacy data should be reviewed within this context. â€¢ The concept of drug repurposing should be applied, where RCT data for SIRT are available for patients with HCC, and where a previous IPG review has deemed this to be â€œadequate for use with normal arrangements for clinical governance, consent and audit.â€	Thank you for your comment. The committee considered your comment but decided not to change the recommendations..

			In a rare disease, where there are no RCT data available for this or alternative treatments, the application of these recommendations would limit significantly patient access to treatment options within small and very sick group of patients.	
24	Consultee 4 Company SIRTEX	**References**	References: â€¢ Bridgewater J, Galle PR, Khan SA, Llovet JM, Park J-W, Patel T, et al. (2014) Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. Journal of Hepatology Vol 60: 1268-1289. â€¢ Clinical trials.gov. Accessed on 7th June 2018 https://clinicaltrials.gov/ct2/show/NCT02807181 â€¢ ESMO Biliary Cancer Guidelines (2016). Accessed on 18th June 2018: https://academic.oup.com/annonc/article-pdf/27/suppl_5/v28/6678340/mdw324.pdf â€¢ European Medicines Agency, Orphan Diseases, Accessed on 7th June 2018 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac05800240ce â€¢ NCCN Clinical practice guidelines in Oncology, Hepatobiliary cancers (2018).	Thank you for your comment. The Bridgewater (2014) paper on the guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma and the ESMO guidelines are already listed in the overview. The Nezami (2018), Reimer (2018) and Shaker (2018) papers have been added to the overview. The NCCN Clinical practice guidelines in Oncology, Hepatobiliary cancers (2018) has also been added to the overview. The Sangro (2017) paper is a general review on the prevention and treatment of complications of selective internal radiation therapy. It has been added to the Appendix in the overview.

			Accessed 18th June 2018. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf â€¢ Nezami N, Kokabi N, Camacho JC, Schuster DM, Xing M, Kim HS. (90)Y radioembolization dosimetry using a simple semi-quantitative method in intrahepatic cholangiocarcinoma: glass versus resin microspheres. Nucl Med Biol. 2018;59:22-28. â€¢ NICE IPG 461 Selective internal radiation therapy for non-resectable colorectal metastases in the liver. Accessed 18th June, 2018 https://www.nice.org.uk/guidance/ipg401 â€¢ NICE IPG459 Selective internal radiation therapy for primary intrahepatic cholangiocarcinoma. Accessed on 7th June 2018 https://www.nice.org.uk/guidance/ipg459 â€¢ NICE IPG460 Selective internal radiation therapy for primary hepatocellular carcinoma. Accessed 7th June 2018 https://www.nice.org.uk/guidance/ipg460 â€¢ Reimer P, Virarkar MK, Binnenhei M, Justinger M, Schon MR, Tatsch K (2017) Prognostic factors in Overall Survival of Patients with Unresectable Intrahepatic Cholangiocarcinoma Treated by Means of Yttrium-90 Redioembolisation: Results in Therapy-NaÃ¯ve patients. Chardiovasc Intervent Radiol. Published 18th January 2018. â€¢ Sangro B, Martinez-Urbistondo D, Bester L, Bilabo JI, Coldwell DM, Flamen P et al (2017)	

			Prevention and Treatment of Complications of Selective Internal Radiation Therapy: Expert Guidance and Systematic Review. HEPATOLOGY, Vol 00, No 00 2017. â€¢ Shaker TM, Chung C, Varma MK, Doherty MG, Wolf AM, Chung MH, Assifi MM. Is there a role for Ytrrium-90 in the treatment of unresectable and metastatic intrahepatic cholangiocarcinoma? Am J Surg. Published Online: November 8, 2016 (doi: 10.1007/s00432-016-2291-4). â€¢ Sirtex Annual Report (2017) Accessed on 20th June 2018. https://www.sirtex.com/media/168332/sirtex_annual_report_2017.pdf â€¢ World Health Organisation, Priority diseases and reasons for inclusion. Chapter 6.19 Rare diseases. Accessed on 5th June 2018 http://www.who.int/medicines/areas/priority_medicines/Ch6_19Rare.pdf	
25	Consultee 5 Patient organisation British Liver Trust	**General**	Cholangiocarcinoma (sometimes called bile duct cancer) is a relatively rare form of cancer, with around 1,000 new cases each year in the UK. It is more common in women than men. Evidence suggests that rates of cholangiocarcinoma have been rising. The British Liver Trust has also received increasing numbers of calls and enquiries from patients affected by bile duct cancer to its Helpline and on its online community forum (with 12,000 active members) which is moderated by our nurse led service.	Thank you for your comment. The committee very much welcomes hearing about patients who have undergone this procedure and considered their experience and views in their deliberations. In particular the committee discussed the rarity of the disease, the often late presentation, and the very poor survival rate. The committee also noted the description of the disease as ‘brutal’ and the hopelessness expressed in the quotes.

			A diagnosis of cholangiocarcinoma is devastating to both the patient and their families. Compared with other cancers, there is a very poor survival rate - only 14% of those diagnosed will live for five years. There are often no symptoms in the early stages. Patients report feeling extremely unwell, very tired and weak. Relatives have described the condition as "brutal - the worst possible way to go". They live with uncertainty, hopelessness and often stigma and isolation due to the image of liver disease. When patients are diagnosed, they often experience depression from the poor prognosis and a range of symptoms including severe pain that cannot be treated without worsening their condition. Some comments from patients on receiving a diagnosis of bile duct cancer: "The roof fell in when I heard the news." "I was utterly destroyed." "It is absolutely hopeless â€¦ hopeless." One male patient, aged 47, after he received his diagnosis called our Helpline and described his feelings: "Utter despair and deep sadness at the feeling my life will be cut short. How can I provide for my wife and how do I tell my daughter who is due to have our first grandchild?"	The committee considered your comment but decided not to change the recommendations.

			Although most cases occur in people over 60 years of age, the numbers of younger patients with bile duct cancer is increasing. Extra time is of particular importance to people who may have young families and working lives to put in order before death. Surgery, to completely remove the cancer is currently the only potentially curative treatment for cholangiocarcinoma. This involves a major operation and, often, because the disease is too far advanced, or the patient is already too poorly, surgery is not possible. Patients are often diagnosed late when it is too late for surgery. Itâ€™s a really difficult cancer to treat and there are often no other treatment options. Patients find this fact particularly difficult to comprehend. The Trust has had contact from patients who have had access to selective internal radiation therapy. The stories from some of these patients who have received treatment have been inspiring and offered real hope. Some patients have shared their story on our online forum and discussions have taken place with other sufferers and their carers. The feedback has been that for some people it has been successful and prolonged life. One caller for example, had lived for an additional 18 months and been able to see their daughter get married. More recently the Trust has had contact from patients concerned that as Commissioning through Evaluation (CtE) programme has now closed; patients are not currently eligible to receive SIRT funded by the NHS. We have explained that the data is currently being looked at but patients are very concerned that this treatment may no longer been an option. The draft	

			recommendations suggest there are safety concerns, and that evidence on the efficacy of SIRT for the treatment of ICC is inadequate in quality and quantity. However, patients are aware that the SIRT treatment is currently globally available (including across much of Europe and the USA) and they do not understand why it is not available in the UK. The Trust has reviewed some of the other studies (including some not mentioned in the documentation) and believes that there is more research now available. We need to understand why the new proposed recommendation is more limiting than the previous IPG from 2013 despite there being more supportive data available.	
26	Consultee 5 Patient organisation British Liver Trust	**3.1**	For example, one study by Nezami et al., (2018) concluded that that “both SIR-Spheres microspheres and TheraSpheres are feasible and safe therapeutic options in patients with ICC”. Reimer et al., (2018) investigated the potential role of Y-90 SIRT in therapy-naieve patients with inoperable ICC, and potential prognostic indicators. The study reported an average overall survival for all patients of 15 months. This was significantly prolonged in patients with certain types of tumor.	Thank you for your comment and for sending us references of new publications. The Nezami (2018) paper was retrieved by our update literature search and has been added to the Appendix in the overview. It is a retrospective comparative case series of 10 patients. The Reimer (2018) paper was retrieved by our update literature search and it has been added to the Appendix in the overview. It is a retrospective case series of 21 therapy-naïve patients.
27	Consultee 5 Patient organisation	**1.1**	We believe that intrahepatic cholangiocarcinoma should be viewed and evaluated as a “rare	Thank you for your comment.

	British Liver Trust		disease" and so the evidence should be evaluated from this perspective. Because of the small patient samples random control trials can be impractical. These patients currently often have no other treatment options.	The committee considered your comment but decided not to change the recommendations. The committee added the following comment to the guidance: *3.11 Primary intrahepatic cholangiocarcinoma is a rare condition with a limited life expectancy.*.
28	Consultee 5 Patient organisation British Liver Trust	**General**	The Trust understands that other NICE IPGs for the use of SIRT have reported that the evidence is "adequate for use with normal arrangements" in the NHS and we would like clarification as to why these risks have now changed. Why should it be different for patients this type of cancer where the risks associated with SIRT remain the same?	Thank you for your comment. The committee considered your comment but decided not to change the recommendations. IPAC makes recommendations for the use of a procedure for a specific indication and has issued separate guidance for the use of SIRT for other indications. Section 1.1 of the guidance reads: *1.1 Current evidence on the safety of selective internal radiation therapy (SIRT) for unresectable primary intrahepatic cholangiocarcinoma shows that there are well-recognised, serious but rare safety concerns. Evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research*.

29	Consultee 6 Clinician on behalf of BSIR	**1.1**	Intrahepatic cholangiocarcinoma is a rare disease with a poor outlook, limited treatment options and limited responses seen with chemotherapy. SIRT has been recommended as a treatment option in the ESMO guidelines of September 2016 (and NCCN guidelines). The ESMO guidelines reference a median survival of 15.5 months and a treatment response rate of 28% (Al-Adra et al, European Journal of Surgical Oncology 2015 plus a pooled analysis of three studies found a 10% conversion rate to resectable disease. Median survival with standard of care chemotherapy are no better.	Thank you for your comment. Please refer to comment 9. The committee considered these issues in its deliberations ("a rare disease with a poor outlook, limited treatment options and limited responses seen with chemotherapy"), and took account of the ESMO guidelines. The committee decided not to change their recommendations. The committee added the following comment to the guidance: *3.11 Primary intrahepatic cholangiocarcinoma is a rare condition with a limited life expectancy.*
30	Consultee 6 Clinician on behalf of BSIR	**General**	It is my belief that the group of patients with Mass forming cholangiocarcinoma limited to the liver do well with SIRT, achieving stabilisation of their disease that has lasted 1-2 years, with re-treatments with SIRT possible.This is based on treating apx 10 patients with intrahepatic cholangiocarcinoma in my institution. The SIRCCA RCT is randomising between chemo and SIRT + chemo and is ongoing.	Thank you for your comment and for sharing your experience of the procedure. The SIRCCA RCT is mentioned in the overview and (if available) the results are likely to be included in any future update of the guidance.

"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."