Selective Internal Radiation Therapy (SIRT)

A rapid review of the submitted evidence

This commentary is based upon the literature review appended to the draft policy statement prepared by the radiotherapy, hepatobiliary and interventional radiology CRGs. 5 data summaries were submitted along with the SIRT clinical commissioning policy. One each on Hepatocellular Carcinoma (HCC), Intrahepatic Cholangiocarcinoma (ICC), Colorectal Cancer Liver Metastases (mCRC) Neuroendocrine Tumour Liver Metastases (mNET) and liver metastases from 'various' tumour types.

The evidence submitted was reviewed using data sheets provided and abstracts of literature. The overall conclusions are that the evidence supporting the clinical efficacy and safety of SIRT is weak and of low quality. Furthermore, no cost effectiveness studies of the treatment were available. More studies with robust study designs are warranted.

1. Hepatocellular Carcinoma

Most studies had weak study designs i.e. retrospective with small sample sizes and generally under powered. No cost-effectiveness studies were reported. One systematic review (Xie et al (2012) which included retrospective small sampled studies was available and reported a longer overall survival in patients treated with SIRT. Two other reviews (Vente et al 2009 & Lau et al 2011) did not provide statistical analysis on outcomes.

- Systematic reviews/meta analysis (n=3)
  - Xie et al (2012) reported significantly longer overall survival and time to progression following treatment with SIRT compared with chemoembolization in a meta analysis. It must be noted that most studies included in the analysis were small observational studies and/or SIRT was combined with other non-TACE therapies.
  - Vente et al (2009) and Lau et al (2011) included small studies with historical controls and did not provide statistical analysis on outcomes.
  - Lau et al (2011) reported microspheres to be safe and well tolerated but further statistical analysis was not provided on outcomes.

- Comparative studies (n=10, see Table 1):
  - SIRT (radioembolization) was compared with chemoembolization in studies, results of most of which did not differ in survival between the two treatments and/or were not statistically significant (Moreno-Luna et al 2012, Salem et al 2011, Lance et al. 2011, Kooby et al. 2010).

  - Iñarrairaegui et al 2012 did not evaluate and report clinical efficacy of actual treatment but survival of downgraded patients receiving further surgical treatment in patients post radioembolization.

  - 4 studies reported statistically significant difference in survival demonstrated between comparison groups (Carr et al 2010, D'Avola et al. 2009, Woodall et al. 2009, Lewandowski et al 2009). Of these:
    - Carr et al (2010) compared TARE (SIRT/radioembolisation) with TACE (chemoembolisation) with a good sample size (TARE= 99, TACE= 691) showing slightly better survival (11.5 months Vs 8.5 months) however, the selection criteria indicated a small but significant bias toward milder disease in the TARE group.

- Results from D'Avola et al. 2009 showed radioembolization significantly improved survival however the study compared TARE with conventional care (13 vs. 10 months; $p < 0.05$).
- Woodall et al. 2009 aimed to establish efficacy of SIRT in patients with or without venous or caval thrombosis. Results showed patients treated patients thrombosis had a median overall survival of 13.9 months versus 2.7 months for those treated with thrombosis and 5.2 months for the untreated group given best supportive care only ($p = 0.01$). However, the sample size was small (n=52).
- Lewandowski et al 2009, only uncensored data was significant.

- Non- comparative studies (n=7)
  - Without a comparison group it is not difficult to draw any valid conclusions concerning the clinical benefits attributable to treatment with SIRT.

- Down staging studies (n=13)
  - One comparative study and 12 non-comparative studies were included which reported down-staging of tumour to enable surgical resection, ablation, or liver transplantation. Most of these studies were very small, but they suggest that SIRT may be effective in down-staging inoperable tumours in a small but proportion of patients. It is unclear how this translates to overall clinical outcomes.

2. Intrahepatic Cholangiocarcinoma

All studies had weak study designs i.e. retrospective with small sample sizes and no comparator group. Without a comparison group it is difficult to draw any valid conclusions concerning the clinical benefits attributable to treatment with SIRT. No cost-effectiveness studies were reported.

- Comparative/n >20 studies (n=5, see Table 2):
  - Sulpice et al 2012 was a small retrospective study claimed a survival advantage in patients with liver-only recurrence following surgical resection who were treated with SIRT.
  - Saxena et al 2010, Ibrahim et al 2008, Hoffmann et al 2012, Haug et al 2011 all had small sample sizes (n<33).

3. Colorectal Cancer Liver Metastases

Based on the current evidence available, it is felt that there is a need for well designed, adequately powered phase III trials assessing the effect of SIRT when used with modern combination chemotherapy regimens. This would be beneficial to inform the use of SIRT in colorectal cancer liver metastases. Further studies are also needed for patients with refractory disease with a particular focus on the impact on quality of life.

- Meta analysis/systematic review (n=2, see Table3)
  - One meta analysis (Vente et al. 2009) comparing SIRT with TACE was identified which did not report a difference in response to treatment in a salvage setting. The study did not report survival.

  - A Cochrane review found no significant difference in outcomes in studies comparing SIRT and chemotherapy with chemotherapy alone.

- RCT

- An RCT (Hendlisz et al 2009) reported significant improvements in time to liver progression, time to progression and disease control rate. No difference in overall survival was found due to the cross over design. The study had a small sample size of 44 patients with chemorefractory liver only unresectable m CRC.

Two studies (van Hazel et al. 2004 & Gray et al 2001) of first line use of SIRT compared with chemotherapy were included, both showing a survival advantage for SIRT. Two comparative studies (Bester et al. 2012 & Seidensticker et al 2011) of salvage therapy using SIRT also showed a survival advantage for SIRT. The comparator group in Bester et al. (2012) comprised of patients unsuitable for SIRT due to potential for non-target delivery to the GI tract or lungs, or reasons relating to patient consent who received conventional therapy / best supportive care. Seidensticker et al (2011) included a small sample size of 29 patients in each group.

The eight remaining studies had no comparator group. There were 7 miscellaneous studies and case reports of relatively low quality which reported down-staging of tumour to enable surgical resection, or ablation in a proportion of patients.

Furthermore, there is a NICE guidance interventional procedure guidance on the topic (2011) which states:

- There is inadequate evidence on clinical efficacy for the use of SIRT in chemotherapy-naïve patients with mCRC .
- Highlights the need for more evidence on clinical efficacy for the use of SIRT in patients with mCRC who chemotherapy-naïve patients and the procedure if used should be undertaken under special arrangements for clinical governance and audit.
- Safety of selective internal radiation therapy (SIRT) for non-resectable colorectal metastases in the liver is adequate.

4. Neuroendocrine Tumour Liver Metastases

All studies had weak study designs with small sample sizes and no comparator interventions (except one study)- see Table 4.

- The only study with a comparator group compared radioembolization with drug-eluting beads with doxorubicin treatment and showed radioembolization to be a more expensive option and inferior (Whitney et al. 2011).
- Seven non-comparative studies were reported (Memom et al 2011 Shaheen et al 2012, Saxena et al 2010, Cao et al 2010, Kennedy et al 2008, King et al 2008, Rhee et al 2008) and one comparative study of SIRT using glass versus resin spheres. Without a comparison group it is not difficult to draw any valid conclusions concerning the clinical benefits attributable to treatment with SIRT.

5. Liver metastases from various tumour types

All studies had weak study designs with small sample sizes, no comparator interventions (except one study- Bester 2012) nor statistical significance reported (except 2 studies- Bester 2012 & Bangash 2007).

In 7 studies survival outcomes were not reported (Nosher 2011, Piana 2011, Lewandowski 2009, Sato 2006, Lim 2005, Cao 2010, Gulec 2009). There are no comparative studies of the use of SIRT in metastatic

breast cancer, uveal melanoma, pancreatic cancer, or renal cell carcinoma. Furthermore, it is very difficult to interpret the studies which different primary cancers in the same study.

Table 1: Published literature on the clinical efficacy and safety of SIRT in patients with Hepatocellular Carcinoma (HCC)

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
Clinical effectiveness	Study type Observational study Patients 115 patients with intermediate-stage unresectable hepatocellular carcinoma (HCC) Intervention Patients with unresectable HCC without portal vein thrombosis treated with Transarterial radioembolization using β-emitting yttrium-90 integral to the glass matrix of the microspheres (TARE) (n = 61) were retrospectively frequency-matched by age, sex, and liver dysfunction with Transarterial chemoembolization (TACE) treated patients (n = 55). Imaging studies were reviewed, and clinical and safety outcomes were abstracted from the medical records.	Survival rates and adverse events	Clinical efficacy • Complete tumour response was more common after TARE (12 %) than after TACE (4 %) (p = 0.17) • When complete response was combined with partial response and stable disease, there was no difference between TARE and TACE • Median survival did not differ between the two groups (15.0 months for TARE and 14.4 months for TACE; p = 0.47) • Two-year survival rates were 30 % for TARE and 24 % for TACE Adverse events • Compared with TACE, TARE was more likely to induce fatigue (p = 0.003) but less likely to cause fever (p = 0.02). Other • Treatment with TARE required less hospitalization than treatment with TACE	Moreno-Luna et al 2012	• Only abstract reviewed • Observational study • Results showed median survival did not differ between the two groups and results were not significant • There was only a small difference in at two years • No significant difference in survival was found between chemo and radioembolization

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 21 patients with UNOS T3 stage who had received radioembolization with yttrium-90 ((90)Y) resinmicrospheres were retrospectively identified and included in this analysis Intervention Patients who had received radioembolization with yttrium-90 resin microspheres were retrospectively identified and included in this study to describe and analyze the overall survival (OS) in these patients compared with patients of the same baseline stage (UNOS T3), who were not eligible for radical treatment after radioembolization.	Overall survival following surgery postradioembolization	• 6 of 21 patients were downstaged and treated radically between 2 and 35 months post-radioembolization. • Three patients were resected, 2 received liver transplantation and 1 was ablated and then resected. • Patients treated radically were significantly younger (62 vs. 73 years, p = 0.006) and had higher tumour volume (583 mL vs. 137 mL, p = 0.001) than patients who did not achieve radical treatment. • There were no differences between the groups in number of lesions, BCLC stage, previous cirrhosis, activity administered per tumour volume, or median levels of alpha-fetoprotein or total bilirubin. • Across the whole series, the median OS was 27.0 months (95% CI 5.0-48.9), varying significantly between those treated radically (OS not reached after a median follow-up of 41.5 months since radical therapy) and those who received palliative treatment only (22.0 months; 95% CI 15.0-30.9).	Iñarrairaegui et al 2012	• Only abstract reviewed • Observational study • This study does not evaluate and report clinical efficacy of actual treatment but survival of downgraded patients receiving further surgical treatment in patients post radioembolization

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 245 patients with hepatocellular carcinoma (HCC) Intervention Data from 245 patients (122 who received chemoembolization and 123 who received radioembolization with Yttrium-90 glass microspheres) who were treated with transarterial locoregional therapies over a 9-year period was collected for comparison and analysed retrospectively.	Overall survival, safety, response rate, time-to-progression (TTP) and signs of toxicity	Clinical efficacy • Patients treated with radioembolization had a higher response rate than with chemoembolization (49% vs 36%, respectively, P = .104) • Time-to-progression was longer following radioembolization than chemoembolization (13.3 months vs 8.4 months, respectively, P = .046) • Median survival times were not statistically different (20.5 months vs 17.4 months, respectively, P = .232) • Among patients with intermediate-stage disease, survival was similar between groups that received chemoembolization (17.5 months) and radioembolization (17.2 months, P = .42) Adverse events • Abdominal pain and increased transaminase activity were more frequent following chemoembolization (P < .05)	Salem et al 2011	• Only abstract reviewed • Observational study • No significant difference in survival was found between chemo and radioembolization • Time to progression was the only measure which was statistically significant • Reduced toxicity following radioembolization compared to chemoembolization

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 73 patients with unresectable hepatocellular carcinoma (HCC) Intervention Data from patients with HCC who underwent index embolization with radioembolization (n = 38; 52.1%) orchemoembolization (n = 35; 47.9%) was collected and analysed retrospectively.	Overall survival	Clinical efficacy • There was no significant difference in survival between the radioembolization (median 8.0 months) and chemoembolization (median 10.3 months) cohorts (P = .33) Adverse events • Postembolization syndrome was significantly more severe in patients who underwent chemoembolization, which led to increased total hospitalization rates in these patients • The rates of other complications and rehospitalisation were similar between groups.	Lance et al. 2011	• Only abstract reviewed • Observational study • No significant difference in survival was found between chemo and radioembolization

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 71 patients with unresectable hepatocellular carcinoma (HCC) Intervention Data for patients treated with either chemoembolization (n = 44, 62%) or radioembolization (n = 27, 38%) was collected and analysed retrospectively.	Disease progression, overall survival and adverse events	Clinical efficacy • Progressive disease at 3 months was observed in 16 (36%) of the 44 patients treated with chemoembolization and nine (33%) of the 27 patients treated with radioembolization (P = not statistically significant). • Median overall survival was similar for both groups (6 months with chemoembolization vs 6 months with radioembolization, P= .7) Adverse events • Grade 3 or higher toxicity was observed in 24 of the 71 patients (34%). Tumour multifocality, vascular invasion, and hepatitis C seropositivity were independently associated with worse survival, whereas method of treatment was not.	Kooby et al. 2010	• Only abstract reviewed • Observational study • No difference in survival between the two groups. Furthermore, the results were not statistically significant • No difference in toxicity between the two groups was found

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Cohort study Patients 790 patients with unresectable hepatocellular carcinoma (HCC) Intervention In a 2 cohort study, one cohort of 691 patients received repetitive, cisplatin-based chemoembolization (TACE); and a separate cohort of 99 patients who had similar treatment criteria received a planned, single dose of Intrahepatic arterial yttrium 90 ((90)Y) microspheres (TARE).		Clinical efficacy • Overall survival was slightly better in the (90)Y group compared with the TACE group (median survival, 11.5 months vs 8.5 months). • Using stratification into a 3-tier model with patients dichotomized according to bilirubin levels <1.5 mg/dL, the absence of portal vein thrombosis (PVT), and low alpha-fetoprotein plasma levels (<25 U/dL), an analysis of survival in clinical subgroups indicated that the 2 treatments resulted in similar survival. In addition, patients who had PVT or high alpha-fetoprotein levels also had similar survival in both treatment groups.	Carr et al 2010	• Only abstract reviewed • Cohort study • No statistical significance report. • Overall survival was slightly better however, the selection criteria indicated a small but significant bias toward milder disease in the (90)Y group.

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 78 patients with unresectable HCC Intervention Data was gathered and analysed for 35 patients with unresectable HCC who received 90Y-labeled resin microspheres as first-line treatment and their overall survival compared from the time of diagnosis with that of a cohort of 43 patients with unresectable HCC that were potential candidates for Y90-Radioembolization but had received conventional care due to unavailability or technical contraindications.	Overall survival	Clinical efficacy • Median survival from diagnosis was significantly higher in the radioembolization group compared with controls (16 vs. 8 months; $p < 0.05$) • In an intention-to-treat analysis, patients evaluated for radioembolization (finally treated or not) survived longer than controls (13 vs. 10 months; $p < 0.05$)	D'Avola et al. 2009	• Only abstract reviewed • Observational study • Results showed radioembolization significantly improved survival compared with conventional care

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 86 patients with HCC Intervention Patients were treated with either TACE (n = 43) or transarterial radioembolization with Yttrium-90 microspheres (TARE-Y90; n = 43. Data was used to compare the downstaging efficacy of transarterial chemoembolization (TACE) versus transarterial radioembolization	Partial response rate, down staging, time to progression, Event-free survival and overall survival	Clinical efficacy • Partial response rates favoured TARE-Y90 versus TACE (61% vs. 37%) • Downstaging from UNOS T3 to UNOS T2 was achieved in 31% of TACE and 58% of TARE-Y90 patients. • Time to progression according to UNOS criteria was similar for both groups (18.2 months for TACE vs. 33.3 months for TARE-Y90, p = 0.098). • Event-free survival was significantly greater for TARE-Y90 than TACE (17.7 vs. 7.1 months, p = 0.0017). • Overall survival favoured TARE-Y90 compared to TACE (censored 35.7/18.7 months; p = 0.18; uncensored 41.6/19.2 months; p = 0.008).	Lewandowski et al 2009	• Only abstract reviewed • Observational study • TARE appears to be superior than TACE. Downstaging was achieved in 58% of TARE patients, greater event free survival and increased overall survival

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Quasi experimental study Patients Fifty-two patients with HCC Intervention Of the 52 patients- 20 patients without VT who received SIRT, 15 patients with VT who were treated, and 17 patients (10 with VT) who were not treated because of preprocedure screening failure.	Overall survival and treatment related mortality	Clinical efficacy Treated patients without thrombosis had a median overall survival of 13.9 months versus 2.7 months for those treated with thrombosis and 5.2 months for the untreated group given best supportive care only (p = 0.01). Adverse events No treatment-related deaths	Woodall et al. 2009	• Only abstract reviewed • Child's score was different between groups • There might be no benefit of SIRT for patients with VT • NO comparator group
	N/A	N/A	N/A	Goin et al 2004	• Study was not retrieved following search in google, pubmed or the journal

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Meta analysis Patients n = 13 HCC studies; 597 *vs.* 1,233 patients treated with embolization/SIRT and TACE, respectively Intervention Meta-analysis of studies comparing microsphere embolization, including SIRT *vs.* TACE in unresectable HCC	Overall survival, time to progression	Clinical efficacy • overall survival was significantly longer following embolization/SIRT compared to TACE (HR 0.73; 95% CI 0.60–0.88; p=0.0009) • TTP was significantly longer following embolization/SIRT compared to TACE (HR 0.61; 95% CI 0.41–0.89; p=0.01)	Xie et al. 2012	• Studies on SIRT are combined with other non-TACE therapies • Included studies were small observational studies with historical controls
	Study type Meta analysis Patients n = 14 HCC studies; 425 patients (29% treated with SIR-Spheres; 71% using TheraSphere) Intervention Meta-analysis of studies comparing microsphere embolization, including SIRT *vs.* TACE in unresectable HCC	Median survival	Clinical efficacy . • For hepatocellular carcinoma (HCC), response was 89% for resin microspheres and 78% for glass microspheres	Vente et al. 2009	• Included studies were small observational studies with historical controls • No statistical method was available to assess median survival based on data presented in the literature.

Hepatocellular Carcinoma					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Systematic review Intervention Studies were identified by searching Medline and PubMed databases for articles from 1990 to 2009 using the keywords "selective internal irradiation," "hepatocellular carcinoma," "therapeutic embolization," and "yttrium-90."	Median survival	Clinical efficacy • Microspheres are a safe and well-tolerated therapy for unresectable HCC (median survival range, 7 -21.6 months)	Lau et al 2011	• Included studies were small observational studies with historical controls • No statistical analysis provided

Table 2: Published literature on the clinical efficacy and safety of SIRT in patients with Intrahepatic Cholangiocarcinoma (ICC)

Intrahepatic Cholangiocarcinoma (ICC)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**

Intrahepatic Cholangiocarcinoma (ICC)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 87 patients with ICC who underwent liver resection Intervention The aim of the study was to evaluate risk factors for recurrence following hepatectomy with curative intent for intrahepatic cholangiocarcinoma (ICC), and predictors of survival after intrahepatic recurrence. linicopathological factors likely to influence recurrence and postrecurrence survival were assessed by univariable and multivariable analysis. Total of 87 patients were analysed. R0 resection was achieved in 65 patients (75 per cent).		Clinical efficacy Repeat hepatectomy (P = 0·003) and intra-arterial yttrium-90radiotherapy (P = 0·048) were associated with longer survival after intrahepatic recurrence.	Sulpice et al 2012	• Only abstract reviewed • Observational study • Study's primary aims were not to evaluate the clinical efficacy of TARE with standard treatment but to evaluate risk factors for recurrence following hepatectomy and predictors of survival after intrahepatic recurrence. • No comparator group

Intrahepatic Cholangiocarcinoma (ICC)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 25 patients with unresectable ICC Intervention Twenty-five patients underwent resin-based (90)Y radioembolization for unresectable ICC. Patients were assessed at 1 month and then at 3-month intervals after treatment. Radiologic response was evaluated with the Response Criteria in Solid Tumours (RECIST) criteria. Clinical and biochemical toxicities were prospectively recorded. Survival was calculated by the Kaplan-Meier method and potential prognostic variables were identified.	Imaging response	Clinical efficacy • The median follow-up was 8.1 (range, 0.4-56) months and the median survival after (90)Y radioembolization was 9.3 months. • Two patients died within 1 month of treatment; the median follow-up for the remaining 23 was 8.9 (range, 1.5-56) months. • Two factors were associated with an improved survival: peripheral tumour type (vs. infiltrative, P = .004) and Eastern Cooperative Oncology Group performance status of 0 (vs. 1 and 2, P < .001). • On imaging follow-up of 23 patients, a partial response to treatment was observed in 6 patients(24%), stable disease in 11 patients (48%), and progressive disease in 5 patients (20%). Adverse events • Most common clinical toxicities were fatigue (64%) and self-limiting abdominal pain (40%). Two patients (8%) each developed grade III bilirubin and albumin toxicity. One patient (4%) developed grade III alkaline phosphatase toxicity.	Saxena et al 2010	• Only abstract reviewed • Observational study • Small sample size • No comparator

Intrahepatic Cholangiocarcinoma (ICC)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	<u>Study type</u> Cohort study <u>Patients</u> 24 patients with histologically proven ICC <u>Intervention</u> 24 patients with intrahepaticcholangiocarcinoma (ICC) underwent radioembolization with yttrium-90 ((90)Y) microspheres.	Biochemical and clinical toxicity, imaging response according to World Health Organization and European Association for the Study of Liver Disease (EASL) criteria, and 3) median survival after the first treatment	<u>Clinical efficacy</u> • On imaging follow-up of 22 patients, tumours demonstrated a partial response in 6 patients (27%), stable disease in 15 patients (68%), and progressive disease in 1 patient (5%). By using EASL guidelines, 17 patients (77%) showed >50% tumour necrosis on imaging follow-up. Two patients (9%) demonstrated 100% tumour necrosis. • The median overall survival for the entire cohort (n = 24) was 14.9 months. The median survival for patients with an ECOG performance status of 0, 1, and 2 was 31.8 months, 6.1 months, and 1 month, respectively (P < .0001); the median survival for patients without and with PVT was 31.8 months and 5.7 months, respectively (P = .0003); and the median survival for patients with peripheral versus periductal-infiltrative tumours was 31.8 months and 5.7 months, respectively (P = .0005) <u>Adverse events</u> • Fatigue and transient abdominal pain were reported in 18 patients (75%) and 10 patients (42%), respectively. • One patient (4%) developed grade 3 bilirubin toxicity. One patient (4%) developed a treatment-related gastroduodenal ulcer	Ibrahim et al 2008	• Only abstract reviewed • Cohort study • Small sample size • No comparator

Intrahepatic Cholangiocarcinoma (ICC)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 33 patients with unresectable ICC Intervention Patients with unresectable ICC were treated with (90)Y resin-microspheres and assessed at 3-monthly intervals. Radiologic response was evaluated by using Response Criteria in Solid Tumours (RECIST). Baseline characteristics, biochemical/clinical toxicities, and response were examined for impact on TTP and OS.	Radiological response and overall survival (OS)	Clinical efficacy • 2 patients had a partial response, 17 had stable disease, and 5 had progressive disease after 3 months. • The median OS was 22 months posttreatment and 43.7 months postdiagnosis. • Median TTP was 9.8 months. • Survival and TTP were significantly prolonged in patients with ECOG 0 (vs. ECOG 1 or 2; median OS: 29.4, 10, and 5.1 months; TTP: 17.5, 6.9, and 2.4 months), tumour burden ≤25% (OS: 26.7 vs. 6 months; TTP: 17.5 vs. 2.3 months), or tumour response (PR or SD vs. PD; OS: 35.5, 17.7 vs. 5.7 months; TTP: 31.9, 9.8 vs. 2.5 months), respectively ($P < 0.001$)	Hoffmann et al 2012	• Only abstract reviewed • Observational study • Small sample size • No comparator

Intrahepatic Cholangiocarcinoma (ICC)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 26 consecutive patients suffering from nonresectable ICC	Percentage changes in peak (ΔSUV(max)) and mean (ΔSUV(mean)) FDG uptake and in metabolic tumour volume (ΔVol(2SD)) relative to baseline	Clinical efficacy • Of 23 patients in whom follow-up MRI was available, 5 (22%) showed a partial response, 15 (65%) stable disease and 3 (13%) progressive disease. • ΔVol(2SD) responders had a median survival of 97 weeks versus 30 weeks in nonresponders (P = 0.02), whereas ΔSUV(max) and ΔSUV(mean) responders had a median survivalof 114 weeks (responder) versus 19 weeks (nonresponder) and 69 weeks in patients with stable disease (P < 0.05)	Haug et al 2011	• Only abstract reviewed • Observational study • Small sample size • Study aimed to evaluate the prognostic power of FDG PET/CT and that of pretherapeutic scintigraphy with (99m)Tc-labelled macroagglutinated albumin (MAA), an index of tumour vascularization.

Table 3: Published literature on the clinical efficacy and safety of SIRT in patients with Colorectal Cancer Liver Metastases (mCRC)

Colorectal Cancer Liver Metastases (mCRC)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	NICE Interventional Procedure Guidance 93 Selective internal radiation therapy for non-resectable colorectal metastases in the liver	N/A	Clinical efficacy The evidence on its efficacy in chemotherapy-naïve patients is inadequate in quantity. Clinicians should offer eligible patients who have not been previously treated by chemotherapy entry into well-designed research studies such as the FOXFIRE trial (www.octo-oxford.org.uk/alltrials/trials/FOXFIRE). For patients who are not eligible or who prefer not to enter a research trial, the procedure should be used with special arrangements for clinical governance, consent and audit. For patients who have previously been treated with chemotherapy, there is evidence that SIRT can prolong time to progression of hepatic metastases, but more evidence is required on survival and quality of life. Therefore for patients who have been previously treated with chemotherapy this procedure should be used with special arrangements for clinical governance, consent and audit. Adverse events Current evidence on the safety of selective internal radiation therapy (SIRT) for non-resectable colorectal metastases in the liver is adequate		• Evidence submitted was not looked as a NICE guidance published in 2011 was available and the latest publication submitted by CRG was from 2011

Colorectal Cancer Liver Metastases (mCRC)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Meta analysis Patients n = 14 HCC studies; 425 patients (29% treated with SIR-Spheres; 71% using TheraSphere) Intervention Meta-analysis of studies comparing microsphere embolization, including SIRT *vs.* TACE	Response and Median survival	Clinical efficacy . • In a salvage setting, response was 79% for (90)Y-RE combined with 5-fluorouracil/leucovorin (5-FU/LV), and 79% when combined with 5-FU/LV/oxaliplatin or 5-FU/LV/irinotecan, and in a first-line setting 91% and 91%, respectively.	Vente et al. 2009	• Included studies were small observational studies with historical controls • No statistical method was available to assess median survival based on data presented in the literature.

Colorectal Cancer Liver Metastases (mCRC)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	<u>Study type</u> Review <u>Intervention</u> Selection criteria included randomised controlled trials comparing SIRT and chemotherapy (systemic and/or regional) with chemotherapy alone, or comparing SIRT alone with best supportive care in patients with metastatic colorectal cancer	Progression free survival and median survival	<u>Clinical efficacy</u> • Two studies were included. One study of 21 patients compared SIRT and systemic chemotherapy (fluorouracil and leucovorin) with chemotherapy alone was included and a second study of 63 eligible patients compared SIRT and regional chemotherapy (floxuridine) with regional chemotherapy alone. • There was no significant difference in progression free survival and median survival seen with SIRT, in either the total patient group or in the 22 patients with disease limited to the liver. There was no significant increase in toxicity with the addition of SIRT to regional chemotherapy. • Lack of evidence that SIRT improves survival or QoL in patients with mCRC	Townsend et al 2009	• No significant difference was found in outcomes • Only 2 studies met eligibility criteria. There is a need for well designed studies.

Colorectal Cancer Liver Metastases (mCRC)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type RCT Patients 44 patients with chemotherapy refractory liver-only unresectable mCRC Intervention Phase III RCT of SIRT (SIR-Spheres) + prolonged 5FU infusion *vs.* 5FU alone	Time to liver progression, time to progression, disease control rate	Clinical efficacy • SIRT significantly improved TTLP (5.5 vs. 2.1 months; HR 0.38; p=0.003) • SIRT significantly improved TTP (4.5 vs. 2.1 months; HR 0.51; p=0.03) • SIRT significantly increased DCR (86% vs. 35%; p=0.001) • SIRT patients had fewer grade 3+ AEs (1 vs. 6; p=0.10) • No overall survival difference due to cross-over to SIRT (10 vs. 7.3 months; p=0.80)	Hendlisz et al 2009	• Small sample size • No overall survival

Table 4: Published literature on the clinical efficacy, cost-effectiveness and safety of SIRT in patients with Neuroendocrine Tumour Liver Metastases (mNET)

Neuroendocrine Tumour Liver Metastases (mNET)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational Study Patients 43 patients with metastaticneuroendocrine tumours Intervention 15 patients received yttrium-90 treatments and 28 patients received drug-eluting beads with doxorubicin (DEBDOX) treatments.		Clinical efficacy • After a median follow-up of 12 months, response rates were similar with the two treatments, but then there was a significantly lower response rate in the yttrium-90 group at 12 months than in the DEBDOX group. Cost-effectiveness • Median cost for yttrium-90 was $25,243 and the median cost for DEBDOX was $13,400	Whitney et al. 2011	• Only abstract reviewed • Observational study • Small sample size • Results show SIRT inferior to DEBDOX after 12 months post treatment • SIRT more expensive than DEBDOX

Neuroendocrine Tumour Liver Metastases (mNET)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 40 patients with hepatic neuroendocrine metastases Intervention Patients with hepatic neuroendocrine metastases were treated with (90)Y radioembolization	Response to therapy, time to response and overall survival and toxicities	Clinical efficacy • Different responses were noted by WHO (complete response, 1.2%; partial response, 62.7%) and EASL (complete response, 20.5%; partial response, 43.4%). • Median time to response was 4 and 4.9 months by lesion and patient, respectively. The 1-, 2-, and 3-year overall survival rates were 72.5%, 62.5%, and 45%, respectively. Adverse events • Clinical toxicities included fatigue (63%), nausea/vomiting (40%), abdominal pain (18%), fever (8%), diarrhoea and weight loss (5%); Grade 3 and 4 bilirubin toxicities were experienced by 2 patients and 1 patient, respectively	Memom et al 2011	• Only abstract reviewed • Observational study • Small sample size • No comparator • Satisfactory tumour response and patient survival with low toxicity
	Study type Observational study Patients 25 patients with hepatic neuroendocrine metastases Intervention patients with hepatic neuroendocrine metastases were treated with (90)Y radioembolization	N/A	Clinical efficacy N/A	Shaheen et al 2012	• Only abstract reviewed • Observational study • Small sample size • The aims of the present study were to define factors that predict the response to radio-embolization in patients with NET liver metastases.

Neuroendocrine Tumour Liver Metastases (mNET)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 48 patients with hepatic neuroendocrine metastases Intervention Patients with hepatic neuroendocrine metastases were treated with (90)Y radioembolization	Median survival, imaging response, prognostic factors	Clinical efficacy • Median survival was 35 months (range: 5-63). On imaging follow-up, 7 patients (15%) had a complete response and 19 patients (40%) had a partial response to treatment. Eleven patients (23%) had stable disease and 11 patients (23%) had progressive disease. • Five prognostic factors were associated with an improved survival: complete/partial response (P=0.003), low hepatic tumour burden (P=0.022), female gender (P=0.022), well-differentiated tumour (P=0.001), and absence of extra-hepatic metastasis (P<0.001). Three factors were associated with a complete/partial response: female gender (P=0.040), well-differentiated tumour (P<0.001) and low hepatic tumour burden (P=0.041). There was a significant increase in the level of alkaline phosphatase over the 6-month period (P<0.001).	Saxena et al 2010	• Only abstract reviewed • Observational study • Small sample size • This study is the first to evaluate the prognostic variables that influenced radiologic response and survival in patients with unresectable NETLM who were treated with 90Y radioembolization

Neuroendocrine Tumour Liver Metastases (mNET)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 58 with neuroendocrine tumour liver metastases. Intervention Patients with neuroendocrine tumour liver metastases were treated with (90) Y microspheres	Radiographic response and overall survival	Clinical efficacy • Six patients achieved a complete response, 14 a partial response, 14 had stable disease and 17 had disease progression. • Overall survival rates at 1, 2 and 3 years were 86, 58 and 47 per cent respectively; median survival was 36 (range 1-61) months.	Cao et al 2010	• Only abstract reviewed • Observational study • Small sample size • No comparator
	Study type Observational study Patients 148 patients Intervention Patients with neuroendocrine tumour liver metastases were treated with (90) Y microspheres. all patients were followed with laboratory and imaging studies at regular intervals until death, or censured whether other therapy was given after brachytherapy. Toxicities (acute and late) were recorded, and survival of the group determined.	Radiographic response and mean survival	Clinical efficacy • Imaging response was stable in 22.7%, partial response in 60.5%, complete in 2.7% and progressive disease in 4.9%. No radiation liver failure occurred. • The median survival is 70 months Adverse events • No acute or delayed toxicity of grade 3 in 67% of patients, with fatigue (6.5%) the most common side effect	Kennedy et al 2008	• Only abstract reviewed • Observational study • No comparator

Neuroendocrine Tumour Liver Metastases (mNET)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 34 patients with neuroendocrine liver metastases Intervention Patients with neuroendocrine tumour liver metastases were treated with (90) Y microspheres	Radiographic response and overall survival	Clinical efficacy • Radiologic liver responses were observed in 50% of patients and included 6 (18%) complete responses and 11 (32%) partial responses • Mean overall survival was 29.4 +/- 3.4 months) Adverse events • Complications after (90)Y radioembolization included abdominal pain, which was mild to severe; nausea and fever; and lethargy that lasted from 1 week to 1 month. • Two patients developed biopsy-proven radiation gastritis, 1 patient developed a duodenal ulcer, and there was 1 early death from liver dysfunction and pneumonia	King et al 2008	• Only abstract reviewed • Observational study • Small sample size • No comparator

Neuroendocrine Tumour Liver Metastases (mNET)					
Indicator	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	Study type Observational study Patients 42 patients with neuroendocrine liver metastases Intervention Patients with neuroendocrine tumour liver metastases were treated with (90) Y microspheres	Median survival and toxicity	Clinical efficacy Median survival was 22 months (glass) and 28 months (resin) (P = 0.82). Adverse events Six patients experienced grade 3/4 toxicities during the follow-up period.	Rhee et al 2008	• Only abstract reviewed • Observational study • Small sample size • No comparator

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