NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma is a rare type of liver cancer. It is usually not diagnosed until it is too late to use surgery to remove it (unresectable). Selective internal radiation therapy (known as SIRT) involves injecting tiny radioactive 'beads' into blood vessels that supply blood to the liver, where they become trapped. The beads then release radiation directly into the cancer cells. The aim is to kill the cancer cells while causing as little damage to surrounding healthy tissue as possible.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in January 2018 and updated in April 2018

Procedure name

- Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma

Specialist societies

- British Society of Interventional Radiology
- British Nuclear Medicine Society
- British Association of Surgical Oncology
- Association of Upper Gastrointestinal Surgeons of Great Britain & Ireland
- Faculty of Clinical Oncology
- Royal College of Radiology.

Description of the procedure

Indications and current treatment

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).

Intrahepatic cholangiocarcinoma is not usually diagnosed before the symptoms of biliary obstruction occur, by which time the cancer may be too advanced for curative surgical resection. However, surgical removal with curative intent may occasionally be possible by downstaging the tumour using other types of

treatment first. The standard options for palliative treatment include chemotherapy, surgical bypass of the bile duct or inserting a stent using surgical, endoscopic or percutaneous techniques.

Selective internal radiation therapy (SIRT; also known as radioembolisation) can be used as palliative treatment for unresectable primary liver cancer. It may also be used as a neoadjuvant treatment before surgery in patients being considered for curative treatments such as resection or liver transplantation. It aims to deliver radiation directly into the tumour, minimising the risk of radiation damage to surrounding healthy tissue.

What the procedure involves

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.

Outcome measures

The **World Health Organization (WHO)** criteria for tumour response assessment are:

- complete response (CR): disappearance of target tumour
- partial response (PR): more than 50% reduction in tumour size
- no response (NR) or stable disease (SD): less than 50% reduction in tumour size and less than 25% increase in tumour size
- progressive disease (PD): more than 25% increase in tumour size.

Objective response (OR) is the aggregation of CR and PR results.

The **Response Evaluation Criteria in Solid Tumours (RECIST)** criteria for tumour response assessment are:

- CR: disappearance of all target lesions
- PR: at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
- SD: insufficient shrinkage to qualify for PR or insufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
- PD: at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

- Grade 1: mild adverse event
- Grade 2: moderate adverse event
- Grade 3: severe adverse event
- Grade 4: life-threatening or disabling adverse event
- Grade 5: death related to adverse event.

Efficacy summary

Overall survival

In a systematic review and meta-analysis of 224 patients who had treatment for cholangiocarcinoma in 9 observational studies, the median survival was 14.9 months. The survival rate estimates were 56% at 1 year (95% confidence interval [CI] 48% to 63%, I^2=17%; n=224 patients from 9 studies), 33% at 2 years (95% CI 24% to 42%, I^2=49%; n=207 patients from 8 studies) and 20% at 3 years (95% CI 14% to 26%, I^2=0%; n=148 patients from 5 studies). The meta-regression analysis showed that the determinants of best survival were the presence of

mass-forming intrahepatic cholangiocarcinoma type, SIRT as first-line therapy and the adoption of concomitant chemotherapy.[1]

In a systematic review and pooled analysis of 298 patients from 12 non-comparative studies, the weighted median survival was 15.5 months (range 7.0 months to 22.2 months; based on 11 studies).[2]

In a systematic review and meta-analysis of 657 patients comparing Y-90 SIRT (n=127) with hepatic arterial infusion (HAI, n=62), transcatheter arterial chemoembolisation (TACE, n=431) or drug-eluting bead TACE (DEB-TACE, n=37), the cumulative median overall survival was 13.9 months (95% CI 9.5 months to 18.3 months) for Y-90 SIRT, 22.8 months (95% CI 9.8 months to 35.8 months) for HAI, 12.4 months (95% CI 10.9 months to 13.9 months) for TACE and 12.3 months (95% CI 11.0 months to 13.5 months) for DEB-TACE.[3]

In a case series of 45 patients, the median overall survival was 19 months (95% CI 9 months to 29 months). The survival rate estimates were 54% at 1 year and 41% at 2 years.[4]

In a case series of 389 patients including 35 patients with cholangiocarcinoma, the median survival time after radioembolisation was 429 days (95% CI 272 days to 586 days).[5]

In a case series of 29 patients, the median overall survival was 9.1 months (95% CI 1.7 months to 16.4 months). The median overall survival was longer in patients with intrahepatic-only disease at baseline (13.9 months) compared with patients with extrahepatic disease (6.8 months, p=0.04).[6]

In a case series of 24 patients, the median overall survival was 9 months (95% CI 6 months to 12 months). The survival rate estimates were 70% at 6 months, 33% at 1 year and 20% at 2 years and at 30 months. Univariate analysis identified 4 statistically significant factors associated with survival: Child–Pugh class (p=0.001), Eastern Cooperative Oncology Group (ECOG) performance status (p<0.001), lymph node metastases (p=0.002) and tumour response (p<0.001). Multivariate analysis found that ECOG performance status (p=0.002) and lymph node metastases (p=0.019) had a statistically significant influence on survival.[7]

In a UK registry of 61 patients with intrahepatic cholangiocarcinoma, the median overall survival from first SIRT procedure to death was 9 months (95% CI 5 months to 12 months; 33 events). The survival rate estimates were 89% at 3 months, 85% at 6 months, 37% at 1 year and 7% at 2 years. No patients survived to 36 months (although some were censored).[8]

In a retrospective case series of 17 patients, the median overall survival from first SIRT procedure to death or date of last follow-up was 34 months (95% CI 4

months to 65 months; n=14) with a 5-year overall survival of 27% (95% CI 0% to 57%; n=14).[11]

Time to progression

In the case series of 29 patients, the median time to progression was 5.6 months (95% CI 0 to 12.0 months).[6]

In the UK registry of 61 patients, the median progression-free survival from first SIRT procedure to earliest date of hepatic or extrahepatic disease progression (or death) was 2.8 months (95% CI 2.6 months to 3.1 months). In all, 66% (40/61) of patients progressed and 11% (7/61) died. In the same study, the median liver-specific progression-free survival from first SIRT procedure to earliest date of hepatic disease progression (or death) was 3.1 months (95% CI 1.3 months to 4.8 months). In all, 54% (33/61) of patients progressed and 21% (13/61) died.[8]

In the retrospective case series of 17 patients, the median liver progression-free survival from first SIRT procedure to date of imaging showing disease progression or evidence of new lesions using RECIST or Positron Emission Tomography Response Criteria in Solid Tumours (PERCIST) criteria was 4 months (95% CI 0 months to 12 months); 1-year liver progression-free survival was 37.5% (95% CI 9.5% to 66%; n=16).[11]

Tumour response

In the systematic review and meta-analysis of 224 patients, the tumour overall response rate (CR+PR according to the RECIST criteria) was 24% (95% CI 16% to 34%, I^2=28%).[1]

In the systematic review and pooled analysis of 298 patients, the weighted mean tumour response rates (RECIST criteria or mRECIST/PERCIST) at 3 months were 28% for partial response and 54% for stable disease (based on 6 studies).[2]

In the systematic review and meta-analysis of 657 patients, the tumour response rates (RECIST criteria) were 27% for Y-90 SIRT, 57% for HAI and 17% for TACE for complete or partial response. For stable disease, the response rates were 55% for Y-90 SIRT, 42% for HAI, 47% for TACE and 62% for DEB-TACE.[3]

In the case series of 45 patients, the best tumour response (RECIST criteria) was 13% (6/45) for partial response, 71% (32/45) for stable disease and 16% (7/45) for progressed disease (time interval not specified).[4]

In the case series of 29 patients, the tumour response rates at 3 months (RECIST 1.1 criteria; n=26 patients) were 12% (3/26) for partial response, 62% (16/26) for stable disease and 27% (7/26) for progressed disease.[6]

In the case series of 24 patients, the tumour response rates at 3 months (RECIST criteria) were 36% (8/22) for partial response, 46% (10/22) for stable disease and 18% (4/22) for progressed disease.[7]

Downstaging

In the systematic review and pooled analysis of 298 patients, downstage to surgical resection was reported in 10% (7/73) of patients from 3 studies.[2]

In the case series of 45 patients, downstage to surgical resection was reported in 20% (9/45) of patients.[4]

In the case series of 29 patients, downstage to surgical resection was reported in 1 patient.[6]

In the retrospective case series of 17 patients, downstage to surgical resection was reported in 1 patient.[11]

Quality of life

In the UK registry of 61 patients, there was no statistically significant change in EQ-5D-5L score (0.84 to 0.86; n=15 patients) or EQ-VAS score (72 to 77; n=16 patients) from baseline to 3 months after the procedure.[8]

Change in tumour biomarker (CA19.9) level

In the case series of 29 patients, there was a tumour biomarker response (defined as a decline in carbohydrate antigen (CA) 19-9 level from the pre-SIRT baseline) in 86% (12/14) of patients (these values were only available for 48% [14/29] of patients).[6]

In the case series of 24 patients, the tumour biomarker (CA19.9) was positive in 11 patients. The tumour biomarker response 1 month after the procedure was complete in 18% (2/11) of patients and partial in 18% (2/11); there was no response in 45% (5/11) and there was disease progression in 18% (2/11).[7]

Safety summary

Total rate of adverse events

In the systematic review and meta-analysis of 224 patients from 9 observational studies, the clinical adverse events rate (which did not included biochemical toxicities) was 68% (95% CI 53% to 80%, I^2=70%).[1]

In the systematic review and meta-analysis of 657 patients comparing Y-90 SIRT (n=127) with HAI (n=62), transcatheter arterial chemoembolisation (TACE, n=431) or drug-eluting bead TACE (DEB-TACE, n=37), the rate of hepatic toxicity events per patient was highest for HAI (0.75; 95% CI 0.65 to 0.86) compared with Y-90 SIRT (0.64; 95% CI 0.55 to 0.72), TACE (0.09; 95% CI 0.06 to 0.12) or DEB-TACE (0.08; 95% CI 0.0 to 0.17).[3]

In the case series of 24 patients, 21% (5/24) of patient had grade 3 side effects. The rest of the reported side effects were either grade 1 or 2.[7]

In the UK registry of 61 patients with intrahepatic cholangiocarcinoma, 49 all causality adverse events were reported in 49% (30/61) of patients (4 of these events were grade 3 or more).[8]

Death

One patient died in the systematic review and pooled analysis of 298 patients from 12 non-comparative studies.[2]

Two patients died in the UK registry of 61 patients. The first patient died 15 days after the procedure from tumour lysis syndrome, and the other patient died 45 days after the procedure from portal vein thrombosis and liver decompensation.[8]

One patient died within 30 days of the procedure in a case series of 25 patients.[9]

Post-radioembolisation syndrome

Fatigue

Fatigue was reported in none to 64% of patients in the systematic review and pooled analysis of 298 patients (based on 7 studies).[2]

Fatigue was reported in 7% (2/30) of procedures within 30 days of treatment in the case series of 29 patients.[6]

Fatigue was reported in 88% (21/24) of patients within 3 months of the procedure in the case series of 24 patients.[7]

Fatigue was reported in 33% (16/49) of all adverse events across all follow-ups in the UK registry of 61 patients (2 of these events were grade 3 or more).[8]

Pain

Abdominal pain was reported in none to 85% of patients in the systematic review and pooled analysis of 298 patients (based on 8 studies).[2]

Abdominal pain was reported in 58% (10/24) of patients within 3 months of the procedure in the case series of 24 patients (it was a grade 3 side effect in 4 of the patients).[7]

Severe abdominal pain was reported in 1 patient on the day of the procedure in the UK registry of 61 patients. In the same registry, 22% (11/49) of all adverse events across all follow-ups was reported as abdominal pain.[8]

Moderate pain was reported in 2 patients during the procedure in a case series of 20 patients.[10]

Fever

Fever was reported in none to 3% of patients in the systematic review and pooled analysis of 298 patients (based on 3 studies).[2]

Fever was reported in 13% (3/24) of patients within 3 months of the procedure in the case series of 24 patients.[7]

Fever accounted for 4% (2/49) of all adverse events across all follow-ups in the UK registry of 61 patients (1 of these events was grade 3 or more).[8]

Nausea

Nausea was reported in none to 61% of patients in the systematic review and pooled analysis of 298 patients (based on 5 studies).[2]

Nausea was reported in 63% (15/24) of patients within 3 months of the procedure in the case series of 24 patients.[7]

Nausea accounted for 4% (2/49) of all adverse events across all follow-ups in the UK registry of 61 patients (none of these events were grade 3 or more).[8]

Vomiting

Vomiting was reported in 17% (4/24) of patients within 3 months of the procedure in the case series of 24 patients (it was a grade 3 side effect in 1 of the patients).[7]

Anorexia

Anorexia was reported in 79% (19/24) of patients within 3 months of the procedure in the case series of 24 patients.[7]

Radiation-induced disease and liver toxicity

Radiation-induced liver disease accounted for 2% (1/49) of all adverse events across all follow-ups in the UK registry of 61 patients.[8]

Acute radiation hepatitis was reported in 2 patients and chronic radiation hepatitis was reported in 1 patient in the systematic review and pooled analysis of 298 patients (based on 1 study of 40 patients).[2]

Radiation cholecystitis accounted for 2% (1/49) of all adverse events across all follow-ups in the UK registry of 61 patients.[8]

Jaundice was reported in none to 5% of patients in the systematic review and pooled analysis of 298 patients (based on 3 studies).[2]

Hepatic abscess was reported in 1 patient 5 months after the procedure in the case series of 20 patients.[10]

Hepatic encephalopathy was reported in 1 patient in the case series of 45 patients. The patient died 5 months after the procedure.[4]

Ascites was reported in 15% (11/71) of patients in the systematic review and pooled analysis of 298 patients (based on 2 studies).[2]

Gastroduodenal or duodenal ulcer

A gastroduodenal ulcer and 2 duodenal ulcers were reported in the systematic review and pooled analysis of 298 patients (based on 3 studies).[2]

An oesophagogastric junction ulcer was reported in 1 patient 18 days after the procedure in the case series of 24 patients; it was treated and healed after 6 months.[7]

Diarrhoea

Diarrhoea and abdominal cramping (grade 3 or more) were reported once across all follow-ups in the UK registry of 61 patients.[8]

Pleural effusion

Pleural effusion was reported in 6% (4/71) of patients in the systematic review and pooled analysis of 298 patients (based on 2 studies).[2]

Pulmonary embolism

Pulmonary embolism was reported in 1 patient in the systematic review and pooled analysis of 298 patients.[2]

Sepsis

Sepsis was reported in 2 patients within 30 days of the procedure in the case series of 25 patients.[9]

Blood vessel injury

Hepatic artery laceration was reported in 1 patient in the retrospective case series of 17 patients. It was treated with stenting. In the same study, gastric artery branch dissection was reported in 1 patient. It was treated conservatively.[11]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: non-target embolisation causing non-radiation-induced pain and cachexia. They considered that the following was a theoretical adverse event: exposure to ionising radiation increasing the risk of cancer.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to SIRT for unresectable primary intrahepatic cholangiocarcinoma. The following databases were searched, covering the period from their start to 8 January 2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see Literature search strategy for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with unresectable primary intrahepatic cholangiocarcinoma.
Intervention/test	Selective internal radiation therapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 1,233 patients from 3 systematic reviews and meta-analyses[1-3], 7 case series[4-7,9,10,11] (including 2 conference abstracts[9,10]) and 1 UK registry[8].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in the appendix.

Table 2 Summary of key efficacy and safety findings on SIRT for unresectable primary intrahepatic cholangiocarcinoma

Study 1 Cuchetti A (2017)

Details

Study type	**Systematic review and meta-analysis**
Country	Italy
Recruitment period	Literature search done on 1/09/2016 (PubMed and Scopus databases)
Study population and number	n=**224** patients from 9 observational (6 prospective and 3 retrospective) studies with intrahepatic cholangiocarcinoma
Age and sex	Mean 61 years; 53% (118/224) male
Patient selection criteria	Inclusion criteria: Study population formed by patients who had treatment for cholangiocarcinoma or extractable from studies in which SIRT was done also for other clinical malignancies; studies with a sufficient description of the study population; a description of patient survival rates for at least 1 year after SIRT. Exclusion criteria: studies which were reviews, letters, case reports, editorials, or comments, or were in languages other than English. If a study was followed by a more complete study or studies that included the original data set, the most recent and complete report was chosen.
Technique	SIRT with yttrium-90. Glass microspheres were used in 2 studies (Edeline and Mouli; n=70) and resin-based microspheres were used in the other 7 studies (n=154).
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Study design issues:

- The primary outcome measure was patient survival.
- A meta-analysis was done using a random-effects model. Meta-regression was applied to investigate relationships between clinical and tumour features and the primary outcome.
- If additional data or results were needed, the corresponding author of each report was contacted.

Study population issues:

- The proportion of naive patients was 20%.
- The proportions of infiltrative tumours and of bilobar tumours, and the mean delivered activity with 90-Yttrrium, accounted for a degree of heterogeneity (I^2)>75%. The proportions of naive patients, of extrahepatic metastases, of tumour burden>25% and of patients having SIRT in combination with chemotherapy accounted for a degree of heterogeneity between 50 and 75%.

Other issues:

- 12 studies were originally identified; of these, 2 (Haug 2011 and Ibrahim 2008) were excluded because they were subsequently updated and 1 (Rayar 2015) because it duplicated another more complete report.
- The Mouli (2013), Camacho (2014), Saxena (2010) and Hoffmann (2012) studies were also included in the Al-Adra (2015) systematic review and pooled analysis.
- The Saxena (2010), Hoffmann (2012) and Rafi (2013) studies were also included in the Boehm (2015) systematic review and meta-analysis.

Key efficacy and safety findings

Efficacy and Safety

Number of patients analysed: **224** from 9 studies

Characteristics of the 9 studies included in the meta-analysis

Author (year)	Number of patients	Extrahepatic lesions	Concomitant CHT	Naive	Objective response RECIST*	Clinical adverse events	1-, 2-, 3-year survival (%)
Mosconi (2016)	23	9% (2)	52% (12)	17% (4)	15% (3/20)	43% (10/23)	68; 21; 12
Soydal (2016)	16	31% (5)	56% (9)	25% (4)	31% (5/16)	NA	34; 10; NA
Edeline (2015)	24	21% (5)	100% (24)	100% (24)	25% (6/24)	83% (20/24)	68; 53; NA
Filippi (2015)	17	24% (4)	88% (15)	12% (2)	NA	53% (9/17)	59; NA; NA
Camacho (2014)	21	NA	100% (21)	0	0%	NA	62; 33; 20
Mouli (2013)	46	35% (16)	NA	39% (18)	NA	54% (25/46)	43; 36; 16
Rafi (2013)	19	58% (8)	NA	0	11% (2/19)	89% (17/19)	56; 10; NA
Hoffmann (2012)	33	24% (8)	NA	0	36% (12/33)	85% (28/33)	57; 43; 25
Saxena (2010)	25	48% (12)	NA	24% (6)	26% (6/23)	64% (16/25)	56; 40; 27

*Defined as complete response+partial response according to the RECIST criteria.

Meta-analysis results for patient survival after SIRT

	1-year survival	2-year survival	3-year survival
Number of patients	224	207	148
Number of studies	9	8	5
Survival (95% CI)	55.7% (48.2% to 63.2%)	33.1% (24.1% to 42.1%)	20.2% (14.4% to 26.0%)
Heterogeneity (I^2)	17%	48.9%	0%

Survival (median): 14.9 months

Tumour overall response rate (complete response+partial response according to the RECIST criteria): 24.1% (95% CI 16.4% to 34.0%, I^2=27.7%)

Clinical adverse events rate (not including biochemical toxicities): 68.1% (95% CI 53.4% to 80.0%, I^2=70.3%)

Meta-regression analysis showed that determinants of best survival were:

- The presence of mass-forming intrahepatic cholangiocarcinoma type (median survival: 19.9 months compared with 8.1 months for the infiltrative type, p=0.002) that also accounted for most of the heterogeneity between included studies (residual I^2=0)
- SIRT as first-line therapy (median survival: 24 months compared with 11.5 months for non-naive patients, p=0.048)
- The adoption of concomitant chemotherapy (median survival 19.5 months compared with 5.5 months in patients not having chemotherapy, p=0.042)

Abbreviations used: CHT, chemotherapy; CI, confidence interval; NA, not available; SIRT, selective internal radiation therapy.

Study 2 Al-Adra D P (2015)

Details

Study type	**Systematic review and pooled analysis**
Country	Systematic review: Canada/ UK Studies included: Australia (2), USA (7), Germany (1), Turkey (1), NA (1)
Recruitment period	Search covering years 2000-13
Study population and number	n=**298** patients from 12 non-comparative studies (including 7 conference abstracts and 3 studies with less than 10 patients) with unresectable intrahepatic cholangiocarcinoma There were 7 prospective case series and 5 retrospective cohort studies.
Age and sex	Mean 62 years; gender not available for all the included studies
Patient selection criteria	Study selection: Human case series with more than 1 patient, randomised controlled trials, non-randomised controlled trials and prospective cohort series were included. The target population consisted of adult (>18 years old) male or female patients with unresectable ICC. Manuscripts published in abstract form were included.
Technique	Radioembolisation therapy with yttrium-90 microspheres (glass or resin). The yttrium-90 microsphere treatment may be done before, synchronously, or after systemic chemotherapy.
Follow-up	**Median 11 months**
Conflict of interest/source of funding	None

Analysis
Study design issues:

- The primary outcomes are overall survival and radiological response to radioembolisation therapy with yttrium-90 microspheres.
- Pooled analysis was done on the data from included studies. Due to the high heterogeneity among the studies and lack of randomised controlled trials, a meta-analysis was not deemed appropriate.
- A PRISMA flow diagram showing the selection of the studies for the review was included in the paper.
- The quality of the studies included was not assessed.

Study population issues: Most patients had had previous treatment for their ICC; 54% had had chemotherapy or surgical resection (33%).
Other issues:

- Of the studies that were reported in full-text, Hyder et al. (2013) did not provide patient details for each intra-arterial therapy (IAT; 46/198 patients were SIRT) that was investigated, and Mouli et al. (2013) did not present overall survival for the whole group only by tumour morphology. Not all the studies reported the type of SIRT that was used.
- The Mouli (2013), Camacho (2014), Saxena (2010) and Hoffman (2012) studies were also included in the Cuchetti (2017) systematic review and meta-analysis.
  The Saxena (2010) and the Hoffman (2012) were also included in the Boehm (2015) systematic review and meta-analysis.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **298** from 12 studies

Radiological responses and survival of the 12 studies included in the systematic review

Reference	Number of patients	Follow-up (median, months)	Radiology criteria	Response at 3 months (%)				Survival (median, months)
				C	Pa	S	Pr	7
Bower (2013)	23	NA	NA	NA	35	22	NA	7
Camacho (2013)	21	NA	mRECIST	NA	NA	NA	NA	16 (7–25)
Camacho (2013)	9	NA	PERCIST	22	33	33	11	22
Chaiteerakij (2011)	20	NA	mRECIST	0	100[b]		0	15 ± 4 (SE)
Hoffmann (2012)	33	10	RECIST	0	36	52	15	22
Hyder (2013)	46	NA	mRECIST	3[a]	22[a]	62[a]	13[a]	11
Martinez (2013)	2	NA	RECIST	NA[a]	NA[a]	NA[a]	NA[a]	NA
Mouli (2013)	46	29	WHO	0	25	73	2	5 (n=10), 14 (n=36)
Prajapati (2012)	24	NA	RECIST	NA	NA	NA	NA	12
Saxena (2010)	25	8	RECIST	NA	24	48	20	9
Shridhar (2012)	40	6	NA	NA	NA	NA	NA	7
Turkmen (2013)	9	NA	NA	NA[a]	NA[a]	NA[a]	NA[a]	mean±SE 18± 3

[a]Radiological response grouped with other intra-arterial treatment modalities.

[b]Partial and stable responses were pooled.

Weighted median overall survival: 15.5 months (range 7-22.2, based on 11 studies).

Tumour response at 3 months (RECIST criteria or mRECIST/PERCIST) based on 6 studies

- Weighted mean partial response rate: 28%
- Weighted mean stable disease rate: 54%

Downstage to surgical resection: 10% (7/73) of patients from 3 studies.

Safety

Complications

Complication	Study reference	% of patients or number of events
Mortality	Saxena (2010)	1 death
	Hoffmann (2012); Bower (2013)	0%
Fatigue	Saxena (2010)	64%
	Mouli (2013)	54%
	Chaiteerakij (2011)	39%
	Hyder* (2013); Prajapati (2012)	17%
	Shridhar (2012)	15%
	Bower (2013)	0%
Abdominal pain	Hoffmann (2012)	85%
	Saxena (2010)	40%
	Mouli (2013)	28%
	Prajapati (2012)	17%
	Chaiteerakij (2011)	13%
	Hyder* (2013)	12%
	Shridhar (2012)	8%
	Bower (2013)	0%
Fever	Hyder* (2013)	3%
	Bower (2013); Chaiteerakij (2011)	0%
Nausea	Hoffmann (2012)	61%
	Mouli (2013)	22%
	Saxena (2010)	16%
	Hyder* (2013)	6%
	Bower (2013)	0%
Jaundice	Shridhar (2012)	5%

	Hyder* (2013)	2%
	Bower (2013)	0%
Gastroduodenal or duodenal ulcer	Mouli (2013)	1 GD ulcer
	Prajapati (2012)	1 duodenal ulcer
	Saxena (2010)	1 duodenal ulcer
Pleural effusion	Mouli (2013)	4% (2/46)
	Saxena (2010)	8% (2/25)
Ascites	Mouli (2013)	15% (7/46)
	Saxena (2010)	16% (4/25)
Pulmonary embolism	Saxena (2010)	1
Radiation hepatitis	Shridhar (2012)	Acute (2), chronic (1)
Bilirubin increase	Hoffmann (2012)	70%
	Chaiteerakij (2011)	35%
	Prajapati (2012); Saxena (2010)	8%
	Mouli (2013)	7%
AST increase	Hoffmann (2012)	55%
	Saxena (2010)	0%
Alk Phos increase	Chaiteerakij (2011)	93%
	Saxena (2010)	4%

*Complications grouped with other modes of intra-arterial therapies.

Abbreviations used: Alk Phos, alkaline phosphatase; AST, aspartate transaminase; C, complete; GD, gastroduodenal; ICC, intrahepatic cholangiocarcinoma; (m)RECIST, (modified) response evaluation criteria in solid tumours; NA, not available; Pa, partial; PERCIST, PET response evaluation criteria in solid tumours; Pr, progress; SIRT, selective internal radiation therapy; S, stable; SE, standard error; WHO, World Health Organization.

Study 3 Boehm L M (2015)

Details

Study type	**Systematic review and meta-analysis**
Country	USA
Recruitment period	Search covering years 1990-2013 (from the PubMed database only)
Study population and number	n=**657** patients with ICC (**127 Y-90 [from 5 non-comparative studies] versus 62 HAI [from 4 studies] versus 431 TACE [from 10 studies] versus 37 DEB-TACE [from 2 studies]**) 60% of the studies were prospective and 40% were retrospective. In the 5 studies using Y-90 included in the meta-analysis, 4 were prospective and 1 was retrospective.
Age and sex	Mean 63 years; gender not reported
Patient selection criteria	Criteria for study inclusion: clinical trials, prospective cohort studies and retrospective studies of human subjects, published in English. Studies reporting the primary outcome of interest on patients with unresectable ICC having hepatic artery based therapies. Criteria for study exclusion: case reports or case series of less than 10 patients, studies including patients having concomitant systemic chemotherapy, and patients having concomitant radiotherapy; studies on patients with resectable tumour and studies reporting outcomes of patients with mixed histology such as ICC with hepatocellular carcinoma.
Technique	Y-90 (4 studies involving SIR-spheres and 1 study involving TheraSpheres), HAI, TACE or DEB-TACE
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Study design issues:

- This review examined the comparative effectiveness of hepatic artery based therapies, including 5 studies using Y-90 microspheres, for unresectable ICCs.
- The primary outcome of interest was overall survival.
- A PRISMA flow diagram showing the selection of the studies for the review was included in the paper.
- The quality of the studies included for data analysis was assessed with the Centre for evidence-based medicine guidelines. 70% of the studies were assigned as level 2b and 30% were level 4. The confounding factors were described adequately only in 24% of the papers and therefore could not be used for analysis.
- There was heterogeneity in the studies in the reporting of outcomes.

Study population issues:

- Details of previous treatment regimens were not provided.
- Extrahepatic disease was present in 44% of all patients. Rates of extrahepatic disease were highest in the TACE arm (48%) versus DEB-TACE (42%) versus Y-90 (37%) versus HAI (36%).
- There was heterogeneity in the patient populations and selection criteria for hepatic artery based therapies.

Other issues:

- It is possible that 2 of the studies (Haug et al. 2011; Hoffman et al. 2012) included overlapping patient populations.
- The Saxena (2010), Hoffmann (2012) and Rafi (2013) studies were also included in the Cuchetti (2017) systematic review and meta-analysis.
- The Saxena (2010) and the Hoffman (2012) were also included in the Al-Adra (2015) systematic review and pooled analysis.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **657 patients (127 Y-90 [from 5 non-comparative studies] versus 62 HAI [from 4 studies] versus 431 TACE [from 10 studies] versus 37 DEB-TACE [from 2 studies])**

Summary of the 5 Y-90 studies selected for the meta-analysis

Reference	Sample	RECIST response (complete+partial response; number of patients)	Median survival (months)	Toxicities[a]
Ibrahim (2008)	24	6[b]	15	5
Saxena (2010)	25	6	9	5
Haug (2011)	26	5	12	NR
Hoffman (2012)	33	12	22	NR
Rafi (2013)	19	2	12	2

[a] NCI/WHO Grade III/IV toxicities.

[b] Survival calculated from the date of diagnosis in the Ibrahim 2008 study.

Results of the meta-analysis of median overall survival and tumour response (using a random effect model)

	Y-90 (95% CI)	HAI (95% CI)	TACE (95% CI)	DEB-TACE (95% CI)
Cumulative median OS (months)	13.9 (9.5 to 18.3)	22.8 (9.8 to 35.8)	12.4 (10.9-13.9)	12.3 (11.0 to 13.5)
RECIST tumour response				
Complete/ partial response (%)	27.4 (17.4 to 37.5)	56.9 (41.0 to 72.8)	17.3 (6.8 to 27.8)	-
Stable disease (%)	54.8 (45.2 to 56.7)	42.2 (17.1 to 67.2)	46.9 (35.5 to 58.4)	61.5 (42.8 to 80.2)

The forest plot of the meta-analysis indicated that there was heterogeneity between the studies.

Safety

Toxicity (events per patient having treatment)

	Y-90 (95% CI)	HAI (95% CI)	TACE (95% CI)	DEB-TACE (95% CI)
Hepatic complications	0.64 (0.55 to 0.72)	0.75 (0.65 to 0.86)	0.09 (0.06 to 0.12)	0.08 (0.0 to 0.17)

None of the studies using Y-90 reported complications according to NCI/WHO criteria and could not be used for quantitative synthesis of complications for comparison.

Abbreviations used: CI, confidence interval; DEB-TACE, drug-eluting bead TACE; HAI, hepatic arterial infusion; ICC, intrahepatic cholangiocarcinoma; NCI, national cancer institute; NR, not reported; OS, overall survival; TACE, transcatheter arterial chemoembolisation; WHO, World Health Organization; Y-90, Yttrium^{90} radioembolisation.

Study 4 Beuzit L (2016)

Details

Study type	**Retrospective case series**
Country	France
Recruitment period	2010-14
Study population and number	n=**45** patients with unresectable ICC (ECOG 0-2)
Age and sex	Median 64 years; 53% (24/45) male
Patient selection criteria	Inclusion criteria: histologically-proven ICC, at least 6 months follow-up after the treatment by Y-90 SIRT and available baseline contrast-enhanced computed tomography scan obtained within 2 months before the first Y-90 SIRT injection and at least 1 CT done up to 3 months after the treatment. Exclusion criteria: Child–Pugh class B cirrhosis, total bilirubin>35 micromol/L, involvement by the tumour of more than 70% of the liver (50% in case of cirrhosis) and performance status>2; extra hepatic spread and a concomitant active neoplasia.
Technique	TheraSphere
Follow-up	**Not reported**
Conflict of interest/source of funding	The authors of this manuscript declared relationships with the following companies: Etienne GARIN and Yan ROLLAND—Consultant, BTG International Ltd.

Analysis

Follow-up issues: The median time between the baseline pre-treatment scan and Y-90 SIRT was 17 days (range 1–44 days); it was 49 days (range 27–77 days) between Y-90 SIRT and the first post-treatment scan. Thirty-five patients (78%) had 2 or more post-treatment scans. The median time between Y-90 SIRT and the second post-treatment scan was 133 days (range 83–343 days).

Study design issues: The objective of this study was to compare Choi criteria with RECIST for the prediction of overall survival, in patients having treatment with Y-90 SIRT for ICC.

Study population issues:

- Y-90 SIRT was done for recurrent cholangiocarcinoma in 18 patients (40%). A total of 8 (18%) patients had cirrhosis, always classified Child–Pugh A.
- Forty-one patients (91%) had prior chemotherapy, and 13 (29%) had concomitant chemotherapy (i.e. started at a maximum of 3 months before Y-90 SIRT, and continued after Y-90 SIRT).
- Other previous treatments were chemoembolisation (1 patient) and percutaneous radiofrequency ablation (2 patients), but in all patients other lesions were used for response evaluation in this study.
- 22% of patients had 2 sessions of SIRT and 4% had 3 sessions.
- Extra –hepatic metastases were present in none of the patients.

Other issues: None.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **45** **Median overall survival**: 19 months (95% CI 9 months to 29 months) **1-year overall survival**: 54% **2-year overall survival**: 41% **Downstage to surgical resection**: 20% (9/45) **Tumour response (RECIST criteria):** • Complete response: 0% (best response) • Partial response: 13% (6/45) (best response) • Stable disease: 71% (32/45) (best response) • Progressed disease: 16% (7/45) (best response) **Progression of the disease at the time of analysis**: 56% (25/45)	**Hepatic encephalopathy**: 2% (1/45) The patient died 5 months after treatment.
Abbreviations used: ECOG, Eastern Cooperative Oncology Group; ICC, intrahepatic cholangiocarcinoma; Y-90, Yttrium^{90}.	

Study 5 Paprottka K J (2017)

Details

Study type	**Retrospective case series**
Country	Germany (single centre)
Recruitment period	2013
Study population and number	n=**389 consecutive patients who had radioembolisation including 35** patients with cholangiocarcinoma
Age and sex	Median 64 years; 60% (232/389) male
Patient selection criteria	Inclusion criteria: absence of significant progressive extrahepatic disease, remaining liver function considered to be sufficient, and hepatic arterial anatomy allowing safe delivery of the Y-90 resin microspheres to the liver only. Exclusion criteria: limited hepatic reserve, ascites or other clinical signs of liver failure, compromised bone marrow or renal function, or other severe comorbidities.
Technique	Y-90 resin microspheres
Follow-up	**Minimum 3 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: The mean length of follow-up was not reported.

Study design issues:

- The aim of this study was to determine pre-therapeutic predictive factors for overall survival after Y-90 radioembolisation.
- Some of the patients initially recruited were excluded after the baseline evaluation.

Study population issues:

- Extrahepatic disease was present in 69% (267/389) of the patients.
- 10% (40/389) of patients had multiple SIRT treatments.

Other issues: None.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **35 patients with cholangiocarcinoma** **Median survival time after radioembolisation** (days): 429 (95% CI 272 to 586)	No safety events reported.
Abbreviations used: CI, confidence interval; Y-90, Yttrium^{90}.	

Study 6 Swinburne N C (2017)

Details

Study type	**Retrospective case series**
Country	USA (single centre)
Recruitment period	2008-15
Study population and number	n=**29** consecutive patients with unresectable ICC (ECOG 0-2)
Age and sex	Mean 66 years; 48% (14/29) male
Patient selection criteria	Consecutive patients with unresectable ICC treated with SIRT using Y-90.
Technique	SIRT using Y-90. 17 patients had treatment with SIR-Spheres and 12 patients with TheraSpheres.
Follow-up	**Mean 8 months**
Conflict of interest/source of funding	3 of the authors disclosed the following potential conflicts of interest: consulting work for Sirtex or BTG International or sponsored lectures by BTG International.

Analysis

Follow-up issues:

- All patients had an initial outpatient office visit which included laboratory value assessment and imaging review. Treatment efficacy was determined by single observer blinded review of baseline and 90-day post-SIRT follow-up computed tomography and MRI using RECIST criteria version 1.1.
- Post-procedural adverse effects were assessed through 30 days from the date of Y-90 administration by review of outpatient and inpatient medical records.
- Overall survival was determined from medical records and calculated using Kaplan-Meier methodology.
- Survival data were censored for patient loss to follow-up or liver resection after SIRT.
- Median survival between subgroups was determined using the log-rank test.
- Baseline and post-SIRT follow-up imaging were available in 90% (26/29) of patients. The patients lacking available baseline and follow-up imaging could not be assessed with respect to RECIST 1.1 tumour response to Y-90 treatment but were included for the evaluation of safety and median overall survival.

Study design issues:

- 34 patients with unresectable ICC that was treated with SIRT during the study period. Of these, 5 patients without histopathological confirmation of ICC were excluded.

Study population issues:

- 28% (8/29) of patients were treatment naive before the procedure. The remaining 21 patients had collectively had 25 prior treatment modalities before SIRT: 52% (15/29) of patients had chemotherapy treatment before having SIRT. 24% (7/29) had prior surgery, 7% (2/29) had external radiation and 3% (1/29) had transarterial chemoembolisation.
- Extrahepatic metastasis was present in 38% (11/29) of patients (baseline imaging was unavailable in 1 patient).
- A total of 30 SIRT treatments were done, with 1 patient having 2 separate SIRT procedures.

Other issues: The authors wrote that ''the toxicity rates might be underestimated due to incomplete documentation in patient medical records, although it is less likely that severe (CTCAE grade 3 or 4) toxicities would have gone unrecorded.''

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 29

Tumour response at 3 months (RESIST 1.1 criteria, n=26 patients):
Complete response: 0%
Partial response: 12% (3/26)
Stable disease: 62% (16/26)
Progressed disease: 27% (7/26)
Tumour biomarker (CA19.9) response (defined as a decline in CA 19-9 level from the pre-SIRT baseline; these values were available for 48% (14/29) of patients).
Yes: 86% (12/14)
No: 14% (2/14)
Median time to progression (months): 5.6 (95% CI 0 to 12.0)

Median overall survival (months)
From SIRT: 9.1 (95% CI 1.7 to 16.4)
From diagnosis: 26.1 (95% CI 12.8 to 39.4)
Median overall survival was longer in patients with intrahepatic-only disease at baseline (13.9 months) compared with patients with extrahepatic disease (6.8 months, p=0.04).
Downstage to surgical resection: 3% (1/29)</td><td>Toxicity within 30 days of SIRT<table><tr><th>Variable</th><th>% of treatments (n=30)</th></tr><tr><td>Bilirubin[a]</td><td>13% (4/30)</td></tr><tr><td>AST[a]</td><td>3% (1/30)</td></tr><tr><td>Alkaline phosphatase[a]</td><td>3% (1/30)</td></tr><tr><td>Fatigue[a]</td><td>7% (2/30)</td></tr></table>[a] Grade1 by National Cancer Institute CTCAE Criteria.</td></tr>
<tr><td colspan="2">Abbreviations used: CA, carbohydrate antigen; CI, confidence interval; CTCAE, common terminology criteria for adverse events; ECOG, Eastern Cooperative Oncology Group; ICC, intrahepatic cholangiocarcinoma; Y-90, Yttrium^{90}</td></tr>
</table>

Study 7 Jia Z (2017)

Details

Study type	**Retrospective case series**
Country	USA (single centre)
Recruitment period	2006-15
Study population and number	n=**24** patients with unresectable, chemorefractory ICC. ECOG 0-1.
Age and sex	Mean 62 years; 33% (8/24) male
Patient selection criteria	All patients with unresectable, chemorefractory ICC who had resin-based Y-90 microspheres were included in this study.
Technique	SIRT using Y-90 SIR-spheres.
Follow-up	**Mean 11 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Follow-up was conducted systematically with a pre-established protocol using telephone surveys, outpatient visits, and bedside visits if the patient was hospitalised. All patients had a minimum of 2 calls, on the first day after the treatment and 1 week later. Subsequent calls were made as needed until resolution of symptoms.
- The first outpatient clinical follow-up visit was scheduled 1 month after the treatment with subsequent visits at 3-month intervals, or sooner if clinically necessary. Visits included laboratory testing, contrast-enhanced MRI, and the evaluation of bone, chest, etc., as necessary.

Study design issues:

- Tumour response was measured according to mRECIST criteria on follow-up MRI. Contrast-enhanced MR scans were obtained before Y-90 treatment to serve as a baseline. After treatment follow-up, imaging was obtained at 1 and 3 months.
- Carbohydrate antigen199 (CA199, normal <37 UI/ml) levels were analysed at baseline and after therapy. The type of response was defined as complete if the levels normalised, partial if the decrease was>20% from baseline, no response if the decrease was <20% or increase was <20%, or progression if the elevation was >20%.
- The severity of side effects was assessed using Common Terminology Criteria for Adverse Events version 4.03.

Study population issues:

- All patients had had first-line cisplatin and gemcitabine.
- Extrahepatic metastasis was present in 13% (3/24) of patients.
- Previous liver-directed therapy was not reported.
- A total of 27 Y-90 treatments were administered in 24 patients with 3 patients having a second treatment.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **24**

Median overall survival from the time of first Y-90 procedure: 9 months (95% CI 6 months to 12 months)

6-month survival: 70%

1-year overall survival: 33%

2-year overall survival: 20%

30-month overall survival: 20%

Tumour response at 3 months (RECIST criteria):

- Complete response: 0%
- Partial response: 36% (8/22)
- Stable disease: 46% (10/22)
- Progressed disease: 18% (4/22)

22 patients were available to evaluate the tumour response.

Tumour biomarker (CA19.9) changes between pre- and 1-month post Y-90 treatment:

- Complete: 18% (2/11)
- Partial: 18% (2/11)
- None: 45% (5/11)
- Progression: 18% (2/11)

CA19.9 was positive in 11 patients.

- Of the 10 factors analysed by Cox regression model, univariate analysis identified 4 significant factors associated with survival: Child–Pugh class (p=0.001), ECOG performance status (p<0.001), lymph node metastases (p=0.002) and tumour response (p<0.001).
- Multivariate analysis found that ECOG performance status (p=0.002) and lymph node metastases (p=0.019) had a statistically significant influence on survival.

Safety

Side effects and complications within 3 months of 90-Y treatment

	% Patients
Post-radioembolisation syndrome	
Fatigue	88% (21/24)
Anorexia	79% (19/24)
Nausea	63% (15/24)
Abdominal pain	58% (10/24)
Vomiting	17% (4/24)
Fever	13% (3/24)
*White blood cell ($X10^3$/microlitre)**	
Pre-treatment	6.8 ± 1.7
1 month post-treatment	6.2 ± 1.8
3 months post-treatment	6.2 ± 1.4
*Total bilirubin (mg/dL)**	
Pre-treatment	0.6 ± 0.2
1 month post-treatment	0.7 ± 0.3
3 months post-treatment	0.8 ± 0.5
*Alanine aminotransferase (U/L)**	
Pre-treatment	39.2 ± 16.8
1 month post-treatment	41.8 ± 19.2
3 months post-treatment	40.2 ± 16.6
*Aspartate aminotransferase (U/L)**	
Pre-treatment	51.9 ± 23.0
1 month post-treatment	64.1 ± 40.5
3 months post-treatment	66.1 ± 42.5
*Alkaline phosphatase (U/L)**	
Pre-treatment	212.1 ± 200.9
1 month post-treatment	249.8 ± 172.8
3 months post-treatment	231.3 ± 156.7
Oesophagogastric junction ulcer The ulcer was diagnosed at day 18 and it took 6 months to heal with medical treatment.	4% (1/24)

* *p* value not statistically significant

There were 21% (5/24) of patients who had Grade 3 side effects, including abdominal pain (n=4) and vomiting (n=1). The rest of the reported side effects were either Grade 1 or 2.

Abbreviations used: CA, carbohydrate antigen; ECOG, Eastern Cooperative Oncology Group; ICC, intrahepatic cholangiocarcinoma; Y-90, $Yttrium^{90}$

Study 8 SIRT Commissioning through evaluation (CtE) registry (2017)

Details

Study type	**Registry (SIRT CtE registry)**
Country	England (10 NHS centres)
Recruitment period	2013-17
Study population and number	n=**61 patients with ICC** (ECOG 0-2) and 399 patients with CRC
Age and sex	Mean 62 years; 53% (32/61) male
Patient selection criteria	Adults with unresectable, chemotherapy-refractory primary ICC.
Technique	SIRT using Y-90 microspheres (SIR-spheres [74% of ICC patients] or TheraSpheres).
Follow-up	**Median 14 months**
Conflict of interest/source of funding	The SIRT procedure (including related care) and data submission activities were funded by NHS England through the CtE scheme.

Analysis

Follow-up issues:

- Patients who had treatment shortly before the data were extracted for analysis had very short follow-up periods.
- Sites were expected to follow patients up every 2 to 3 months after their SIRT procedure until progression was detected (and later for survival data). Follow-up appointments would usually consist of an abdominal CT scan and in some cases an MRI or PET scan was also carried out. In addition, sites invited patients to complete the generic HRQoL questionnaire, EQ-5D-5L (Herdman et al. 2011), before SIRT and every 3 months until progression. Follow-up assessments after progression were occasionally recorded in the registry.

Study design issues:

- Pseudonymised data relating to patient characteristics, treatment planning, the SIRT procedure, safety and adverse events, imaging results, survival, and HRQoL were prospectively collected by the clinical teams and submitted to a pre-existing online SIRT registry (hosted by the British Society of Interventional Radiology [BSIR]).
- The criteria used for grading the adverse events was not prescribed although it was assumed that most centres would use the Common Terminology Criteria for Adverse Events (CTCAE) system.
- Patients who did not have a date of death were censored at the latest point they were known to be alive, and patients missing this information were excluded from the analysis.
- A total of 514 patients had treatment under the scheme until close of data entry at the end of February 2017. A total of 474 patients were added to the SIRT registry, of which 460 were valid data entries.
- Across the 10 SIRT centres in England, the numbers of patients who had treatment ranged from 15 to 120.

Study population issues:

- Most ICC patients (81%) had had 1 or 2 lines of chemotherapy before SIRT.
- Most patients had a single SIRT procedure of palliative intent.
- A minority of patients had concomitant chemotherapy (12% in ICC cohort) with SIRT. Some patients also had chemotherapy after SIRT.
- Extrahepatic metastasis was present in 41% of patients with ICC.
- Most patients had not had prior hepatic procedures (84% ICC).
- The median duration from primary diagnosis to the first SIRT procedure was 1.1 years in the in the ICC cohort.

Other issues:

- Relatedness of complications or adverse events to the SIRT intervention was not recorded in the registry.
- External validation of each patient against the CtE eligibility criteria was not possible, and from the information gathered in the SIRT registry it was not possible to confirm that patients who had only 1 previous line of chemotherapy were in fact intolerant to standard chemotherapy.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **61**

Survival

Outcome (median in months)	ICC cohort (95% CIs)
OS from first SIRT procedure to death	8.7 (5.3 to 12.1) (33 events)
PFS from first SIRT procedure to earliest date of hepatic or extrahepatic disease progression (or death)	2.8 (2.6 to 3.1) 40 (66%) progressed 7 (11%) died
LPFS survival from first SIRT procedure to earliest date of hepatic disease progression (or death)	3.1 (1.3-4.8) 33 (54%) progressed 13 (21%) died

3-month overall survival: 89%

6-month overall survival: 85%

1-year overall survival: 37%

2-year overall survival: 7%

No patients survived to 36 months (although some were censored).

Quality of life

- EQ-5D-5L at baseline: 0.84
- EQ-5D-5L at 3 months: 0.86
- p=NS, n=15 patients

- EQ-VAS at baseline: 72
- EQ-VAS at 3 months: 77
- p=NS, n=16 patients

Safety

Deaths related to complications

One patient had "**tumour lysis syndrome**" recorded and died 15 days after SIRT.

One patient had "**portal vein thrombosis and liver decompensation**" recorded and died 45 days after SIRT.

Number of patients with severe day-of-treatment complications, product incidents recorded at time of procedure, and all causality adverse events

Event type	Number of patients
Severe day-of-treatment complications	
Yes	2% (1/61) **Severe abdominal pain**
No	95% (58/61)
Missing	3% (2/61)
Product incident	
Yes	0
No	64% (39/61)
Missing	36% (22/61)
All causality adverse events (at least 1 event)	
Yes	49% (30/61)
No	51% (31/61)

Total number of all-cause adverse events and grade ≥3 events recorded across all follow-ups (does not include day-of-treatment complications recorded in procedural data)

Category of event	All adverse events (% of all AEs)	Grade ≥3 adverse events
Fatigue	33% (16/49)	2
Abdominal pain	22% (11/49)	0
Nausea	4% (2/49)	0
Fever	4% (2/49)	1
Radiation-induced liver disease	2% (1/49)	0
Radiation cholecystitis	2% (1/49)	0
Other	33% (16/49)*	1 (diarrhoea and abdominal cramping)
Total	100% (49/49)	4

*In most cases these events were gastrointestinal-related such as diarrhoea, constipation, anorexia, and indigestion/reflux.

Total number of abnormal laboratory value events

Category of abnormal laboratory result event	All events	Grade ≥3
AST increased	22% (17//77)	1
ALT increased	18 % (14/77)	0
Hypoalbuminemia	16% (12/77)	0
Hyperbilirubinemia	13% (10/77)	2

	Neutrophil count decreased	1% (1/77)	0
	Platelet count decreased	16% (12/77)	0
	Other	14% (11/77)	0
	TOTAL	100% (77/77)	3

Abbreviations used: ALT, alanine aminotransferase; AST, aspartate transaminase; CI, confidence interval; CtE, commissioning through evaluation; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQoL 5-dimension 5-level; HRQoL, Health-related quality of life; ICC, intrahepatic cholangiocarcinoma; LPFS: liver-specific progression-free survival; NS, not statistically significant; OS, overall survival; PFS, progression-free survival.

Study 9 Shridhar R (2017) – *Conference abstract only*

Details

Study type	**Case series**
Country	Not reported
Recruitment period	2010-13
Study population and number	n=**25** patients with intrahepatic cholangiocarcinoma
Age and sex	Median 76 years; gender not reported
Patient selection criteria	No evidence of extrahepatic metastases, Childs-Pugh A, without main portal vein thrombus, bilirubin <2mg/dL, ECOG 0-2, and no prior chemotherapy, liver embolisation or radiation therapy for ICC.
Technique	SIRT using Y-90 glass microspheres
Follow-up	**Median 13 months**
Conflict of interest/source of funding	Not reported.

Analysis

Follow-up issues: 20 patients came off study because they died or because the disease progressed.

Study design issues:

- Phase 2 study.
- The primary endpoint was progression-free survival.

Key efficacy and safety findings

Efficacy	Safety
Efficacy findings from conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview.	No grade 3 gastrointestinal or general disorder toxicities. • **Grade 3 ALT increase**: 4% (1/25) • **Grade 3 AST increase**: 4% (1/25) • **Grade 3 alkaline phosphatase increase**: 8% (2/25) • **Grade 4 hyperbilirubinemia**: 4% (1/25) • **Grade 4 thrombocytopenia**: 4% (1/25) • **Sepsis within 30 days of treatment**: 8% (2/25) • **Death within 30 days of treatment**: 4% (1/25)
Abbreviations used: AST, aspartate transaminase; ALT, alanine aminotransferase; ICC, intrahepatic cholangiocarcinoma	

Study 10 Muli Jogi R K (2015) – *Conference abstract only*

Details

Study type	**Case series**
Country	Australia (single centre)
Recruitment period	2009-14
Study population and number	n=**20** patients (21 treatments) with unresectable intrahepatic cholangiocarcinoma
Age and sex	Not reported
Patient selection criteria	Patient with unresectable intrahepatic cholangiocarcinoma.
Technique	Radioembolisation with yttrium-90
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: The primary end points were overall survival, tumour response and safety.

Key efficacy and safety findings

Efficacy	Safety
Efficacy findings from conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview.	• **Moderate pain during treatment**: 10% (2/20) • **Hepatic abscess** at 5 months: 5% (1/20)

Study 11 Shaker T M (2018)

Details

Study type	**Retrospective case series**
Country	USA (1 centre)
Recruitment period	2006-16
Study population and number	n=**17** patients with unresectable and metastatic ICC
Age and sex	Median 69 years; 41% (7/17) male
Patient selection criteria	Inclusion criteria: at least 18 years of age with a tissue diagnosis of ICC. Patients had radiographic evidence of unresectable disease. Patient selection for Y-90 was based on the recommendations from a multidisciplinary GI tumour board (MTB). All patients with stage IV disease were recommended for treatment with systemic chemotherapy, per MTB. Patients who had had previous surgical resection, or who had evidence of extrahepatic disease were also included. Exclusion criteria: patients for whom there was incomplete data.
Technique	Radioembolisation with Y-90 glass or resin microsphere. TheraSpheres were used for procedures done up until September 2014, and SIR-Spheres were used for procedures done after that date based on institutional availability.
Follow-up	**Median 21 months (range 9-70 months)**
Conflict of interest/source of funding	None

Analysis
Follow-up issues: All patients had pre-procedure CT or MRI, and CT or MRI within 3 months after the procedure.
Study design issues: Primary outcome measures included overall median survival and progression-free survival. Overall survival was defined by the date of first Y-90 procedure and date of death, or date of last follow-up. Progression-free survival was defined by date of first Y-90 procedure and date of imaging showing disease progression, or evidence of new lesions, using RECIST or PERCIST criteria.
Study population issues:

- Fourteen patients had 1 treatment, 2 patients had 2 treatments and 1 patient had 3 treatments.
- The average largest dimension of the primary tumour was 7.4±3.3 cm.
- Five patients had Stage I cancer at diagnosis (29.4%), 5 patients had Stage II disease (29.4%), 2 patients had Stage IVa disease (11.8%), and 5 patients had Stage IVb disease (29.4%).
- Four patients had liver surgery before treatment with Y90 (23.5%) and 7 patients had extrahepatic disease (41.2%) at the time of treatment.
- Nine patients did not have any treatment with systemic chemotherapy (52.9%), 5 patients had pre-Y90 chemotherapy (29.4%), and 3 patients had post-Y90 chemotherapy (17.6%).
- Nine patients (52.9%) had treatment with SIR-Spheres and 8 patients (47.1%) had treatment with TheraSphere.
- There was a statistically significant difference in the total radiation dose received by the TheraSphere and SIR-Sphere groups, 158.2 ± 128.1 Gy and 34.5 ± 16.3 Gy respectively, ($p<0.001$).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 17

Oncologic outcomes
<table>
<tr><td>5-year overall survival</td><td>27%</td><td>95% CI 0% to 57%, n=14</td></tr>
<tr><td>Median overall survival</td><td>33.6 months</td><td>95% CI 4 to 65 months, n=14</td></tr>
<tr><td>Median liver progression-free survival</td><td>4 months</td><td>95% CI 0 to 12 months</td></tr>
<tr><td>1-year liver progression-free survival</td><td>37.5%</td><td>95% CI 9.5% to 66%, n=16</td></tr>
<tr><td>Liver Progression</td><td>10/16 (62.5%)</td><td></td></tr>
<tr><td>Extrahepatic Progression</td><td>11/16 (68.8%)</td><td></td></tr>
<tr><td colspan="3">Progression-Free Survival</td></tr>
<tr><td>TheraSphere patients</td><td>2.4 months</td><td rowspan="2">p=0.469</td></tr>
<tr><td>SIR-Sphere patients</td><td>15.6 months</td></tr>
</table>
One patient had margin negative liver resection after a single treatment.</td><td>Post-procedure 90-day mortality: 0%
The earliest patient mortality occurred 137 days after treatment with Y-90, and was secondary to unrelated causes.

Complications related to technical issues
-a right hepatic artery laceration that was immediately treated with stenting.
-a gastric artery branch dissection that was treated conservatively</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval; CT, computed tomography; GI, gastrointestinal; ICC, intrahepatic cholangiocarcinoma.</td></tr>
</table>

Validity and generalisability of the studies

- In the studies included in Table 2, 2 brands of CE-marked microspheres were used for the SIRT procedure: SIR-spheres (Sirtex Medical Ltd) and TheraSpheres (Biocompatibles UK Ltd). Both are Y-90 microspheres. A third medical device, QuiremSpheres (Quirem Medical) which uses poly-L-lactic acid microspheres containing holmium-166 has recently been CE marked for use in SIRT and is available in the UK but none of the studies included in Table 2 report the use of this device for the procedure.
- The longest follow-up for the studies included in Table 2 was a median of 21 months[11].
- 3 systematic reviews and meta-analyses were included in Table 2: Cuchetti (2017)[1] was the most recent one, Al-Adra (2015)[2] included data from conference abstracts and reported data on safety and the Boehm (2015)[3] study compared SIRT with other hepatic artery based therapies.
- 2 conference abstracts[9,10] were included for safety data.
- Data from the SIRT UK registry[8] was also included in table 2.
- There were no randomised controlled trials identified.
- Studies included a mixed group of patients with regard to chemotherapy history. Patients who were chemotherapy-naive and patients with chemotherapy-refractory disease were included.
- Quality of life outcomes were only reported in the UK registry[8].
- Only the studies that reported on outcomes specifically for patients with primary intrahepatic cholangiocarcinoma were included.
- Studies included a very heterogeneous group of patients with a wide range of tumour sizes.

Existing assessments of this procedure

- The National Comprehensive Cancer Network (NCCN) Clinical practice guidelines in oncology, for Hepatobiliary cancers[12] published in February 2018 stated:

  ‘’*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.‘’

- The European Society of Medical Oncology (ESMO) published guidelines for the diagnosis, treatment and follow-up of biliary cancer in 2016 [13]. They stated:

  ‘’ *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, randomised 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 European Association for the Study of the Liver (EASL) published guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma in 2014[14]. They stated:

  ''*Transarterial chemoembolization and transarterial radioembolization have shown anti-tumor effects with acceptable toxicities in patients with iCCA but require further examination in appropriately designed clinical trials and therefore cannot be recommended as standard therapy for patients with unresectable iCCA*.''

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cholangiocarcinoma or pancreatic adenocarcinoma. NICE Interventional Procedures Guidance 464 (2013). Available from http://www.nice.org.uk/guidance/ipg464
- Selective internal radiation therapy for primary hepatocellular carcinoma. NICE Interventional Procedures Guidance 460 (2013). Available from http://www.nice.org.uk/guidance/ipg460
- Selective internal radiation therapy for non-resectable colorectal metastases in the liver. NICE Interventional Procedures Guidance 401 (2011). Available from http://www.nice.org.uk/guidance/ipg401
- Photodynamic therapy for bile duct cancer. NICE Interventional Procedures Guidance 134 (2005). Available from http://www.nice.org.uk/guidance/ipg134

Medtech innovation briefings

- SIR-Spheres for treating inoperable hepatocellular carcinoma. NICE Medtech Innovation Briefing 63 (2016). Available from https://www.nice.org.uk/advice/mib63

- TheraSphere for treating operable and inoperable hepatocellular carcinoma. NICE Medtech Innovation Briefing 62 (2016). Available from https://www.nice.org.uk/advice/mib62

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Five Specialist Adviser Questionnaires for selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 3 companies who manufacture a potentially relevant device for use in this procedure. NICE received 3 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Ongoing studies:
    - NCT01798147: Selective Internal Radiotherapy (SIRT) Versus Transarterial Chemoembolisation (TACE) for the Treatment of Cholangiocellular Carcinoma (CCC); Single centre pilot RCT (doxorubicin drug-eluting bead trans arterial chemo-embolization to SIRT in

chemotherapy naïve; location: Germany; estimated enrolment: 24; estimated primary completion date: June 2018

- NCT02807181: SIRT Followed by CIS-GEM Chemotherapy Versus CIS-GEM Chemotherapy Alone as 1st Line Treatment of Patients With Unresectable Intrahepatic Cholangiocarcinoma; multicentre open label RCT (SIRT prior to chemotherapy (cisplatin-gemcitabine) or chemotherapy alone); location: international; estimated enrolment: 180; estimated completion date: 2019

- NCT02512692: 90Y Transarterial Radioembolization (TARE) Plus Gemcitabine and Cisplatin in Unresectable Intrahepatic Cholangiocarcinoma; location: USA; estimated enrolment: 24; estimated Primary Completion Date: August 2018
- NCT02167711: Treatment for Bile Duct Cancer in the Liver; location: Hong Kong; estimated enrolment: 30; estimated Primary Completion Date: October 2018

- NCT01912053: Efficacy Study of Intra-hepatic Administration of TheraSphere in Association With Intravenous Chemotherapy to Treat Cholangiocarcinoma; location: France; estimated enrolment: 41; estimated completion date: April 2018

- NCT00858429: Yttrium Y 90 Glass Microspheres and Capecitabine in Treating Patients With Liver Cholangiocarcinoma or Liver Metastases;

location: USA; estimated enrolment: 30; estimated completion date: December 2018

- Registries:
  - NCT02305459: CIRSE registry for SIR-Spheres Therapy (CIRT); location: Europe (Austria); estimated enrolment; 1200; estimated completion date: November 2020
  - NCT02685631: Yttrium Y 90 Resin Microspheres Data Collection in Unresectable Liver Cancer: the RESIN Registry; location: USA; estimated enrolment: 1000; estimated completion date: August 2021

References

1. Cucchetti Alessandro, Cappelli Alberta, Mosconi Cristina et al. (2017) Improving patient selection for selective internal radiation therapy of intra-hepatic cholangiocarcinoma: A meta-regression study. Liver International 37, 1056-1064
2. Al-Adra D P, Gill R S, Axford S J et al. (2014) Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: A systematic review and pooled analysis. European Journal of Surgical Oncology
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7. Jia Z, Paz-Fumagalli R, Frey G et al. (2017) Resin-based Yttrium-90 microspheres for unresectable and failed first-line chemotherapy intrahepatic cholangiocarcinoma: preliminary results. Journal of Cancer Research & Clinical Oncology 143, 481-489
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9. Shridhar R, Frakes J M, Yue B et al. (2017) Phase II study of first-line radioembolization with yttrium-90 glass microspheres for intrahepatic cholangiocarcinoma. Journal of Clinical Oncology 35(4 Supplement 1) http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.482
10. Muli Jogi RK, Tibballs J, Samuelson S. (2015) Selective internal radiation therapy (SIRT) with yttrium-90 for unresectable intrahepatic

cholangiocarcinoma: Survival, efficacy and safety. Cardiovascular and Interventional Radiology in Europe (CIRSE); Abs. 2206.4.

11. Shaker T M, Chung C, Varma M K et al. (2018) Is there a role for Ytrrium-90 in the treatment of unresectable and metastatic intrahepatic cholangiocarcinoma?. American Journal of Surgery 215(3), 467-470
12. The National Comprehensive Cancer Network (NCCN) Clinical practice guidelines in oncology, for Hepatobiliary cancers. Version 2.2018-June 7, 2018. https://www.nccn.org/professionals/physician_gls/default.aspx
13. Valle J M, Borbath I, Khan S A et al. (2016) Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. Volume 27, Issue suppl_5, 1 September 2016, Pages v28–v37, https://doi.org/10.1093/annonc/mdw324
14. Bridgewater J, Galle P R, Khan S A et al. (2014) Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. Journal of Hepatology 60(6):1268-89. doi: 10.1016/j.jhep.2014.01.021.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	30/04/2018	Issue 4 of 12, April 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	30/04/2018	Issue 3 of 12, March 2018
HTA database (Cochrane Library)	30/04/2018	Issue 4 of 4, October 2016
MEDLINE (Ovid)	30/04/2018	1946 to present with Daily Update
MEDLINE In-Process (Ovid)	30/04/2018	April 27, 2018
MEDLINE Epubs ahead of print (Ovid)	30/04/2018	April 27, 2018
EMBASE (Ovid)	30/04/2018	1974 to 2018 Week 18

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 SIRT.tw.
2 (selective* adj4 internal* adj4 radiotherap*).tw.
3 (selective* adj4 internal* adj4 radiation* adj4 therap*).tw.
4 (internal* adj4 radiation* adj4 therap*).tw.
5 (internal* adj4 irradiat*).tw.
6 Brachytherapy/
7 brachytherap*.tw.
8 (radioemboli?ation or radio-emboli?ation).tw.
9 (intravascular adj4 radiation).tw.
10 (local adj4 radioablation).tw.
11 (radionuclide adj4 therap*).tw.
12 (targeted adj4 hepatic adj4 therap*).tw.
13 (transarterial adj4 radiotherap*).tw.
14 or/1-13
15 Yttrium/
16 exp Yttrium Radioisotopes/
17 yttrium*.tw.
18 (90Y or Y-90).tw.
19 or/15-18
20 microsphere*.tw.

21 Microspheres/
22 or/20-21
23 SIR-Sphere*.tw.
24 TheraSphere*.tw.
25 (sirtex or nordion).tw.
26 19 and 22
27 or/23-26
28 Cholangiocarcinoma/
29 Cholangiocarcinoma$.tw.
30 Bile Duct Neoplasms/
31 (bile adj4 duct* adj4 (cancer* or neoplasm* or carcinom*)).tw.
32 or/28-31
33 14 and 32
34 27 and 32
35 or/33-34
36 animals/ not humans/
37 35 not 36
38 limit 37 to ed=20170712-20181231

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Abeysinghe V, Sundararajan S, Delriviere L, et al. (2018) Selective internal radiation therapy (SIRT) with yttrium-90 microspheres for unresectable intrahepatic cholangiocarcinoma. BMJ Case Reports 2018, bcr-2017-223539	Single case report FU=6 years post-diagnosis	Follow-up MRI and PET FDG scan showed marked response (using Response Evaluation Criteria for Solid Tumours criteria) to SIRT, but there was still some residual activity in the periphery. She then had further 6 cycles of gemcitabine and paclitaxel and a second SIRT treatment with 1 GBq at 10 months post-diagnosis. Further PET FDG scans showed a complete metabolic response and reduction in size of the lesion on MRI and PET. The patient has remained well and is now 6 years post-diagnosis.	A single case report. Larger studies are already included in Table 2. No new safety events were reported.
Camacho J C, Kokabi N, Xing M et al. (2014) Modified response evaluation criteria in solid tumors and European Association for The Study of the Liver criteria using delayed-phase imaging at an early time point predict survival in patients with unresectable intrahepatic cholangiocarcinoma following yttrium-90 radioembolization. Journal of Vascular & Interventional Radiology 25, 256-65	Case series n=9 FU=3 months	Median overall survival (OS) from Y-90 therapy was 21.7 months. At 3 months, PERCIST objective response rate of target lesions was 77.7%, and target objective response on PERCIST correlated significantly to prolonged OS (p=0.022). Overall objective PERCIST response at 3 months had significant correlation with OS (p=0.011). Probability of death was significantly higher in overall non-responders by PERCIST (hazard ratio, 12.3). No objective response was seen with RECIST.	This study was included in 1 of the systematic reviews and meta-analyses included in table 2.
Camacho J C, Kokabi N, Xing M, Schuster D M et al.	Prospective case series	Median overall survival from the time of (90)Y	This study was included in 2 of the

(2014) PET response criteria for solid tumors predict survival at three months after intra-arterial resin-based 90Yttrium radioembolization therapy for unresectable intrahepatic cholangiocarcinoma. Clinical Nuclear Medicine 39, 944-50	n=21 FU=3 months	therapy was 16.3 months. Significant differences between mRECIST and European Association for the Study of the Liver (EASL) versus RECIST were found when categorising patients into responders and non-responders (p<0.001). Significantly prolonged OS was observed for patients with targeted objective response based on modified mRECIST and EASL criteria (p=.005 and p=.001, respectively) at 3 months. RECIST was not found to correlate with survival at 1- or 3-month follow-up.	systematic reviews and meta-analyses included in table 2.
Edeline J, Du F L, Rayar M, Rolland Y et al. (2015) Glass Microspheres 90Y Selective Internal Radiation Therapy and Chemotherapy as First-Line Treatment of Intrahepatic Cholangiocarcinoma. Clinical Nuclear Medicine 40, 851-5	Retrospective case series n=24 FU=not reported	Selective internal radiation therapy combined with concomitant chemotherapy seems a promising strategy as first-line treatment for unresectable intrahepatic cholangiocarcinoma.	This study was included in the Cuchetti (2017) systematic review and meta-analysis included in Table 2.
Filippi L, Pelle G, Cianni R et al. (2015) Change in total lesion glycolysis and clinical outcome after (90)Y radioembolization in intrahepatic cholangiocarcinoma. Nuclear Medicine & Biology 42, 59-64	Prospective case series n=17 FU=6 weeks	According to PET Response Criteria in Solid Tumors, partial response was found in 14 patients (82%), stable disease in 3 (18%). No patient showed complete metabolic response. The mean OS for all patients was 64.5+/-5.0 weeks. Time to progression resulted of 28.9+/-3.8 weeks for the whole cohort.	This study was included in the Cuchetti (2017) systematic review and meta-analysis included in Table 2.
Gaba R C, Lewandowski R J, Kulik L M et al. (2009) Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. Annals of Surgical Oncology 16, 1587-96	Case series n=20 (cholangiocarcinoma, n=3) Follow-up=median 19 months (whole cohort)		Larger studies or studies with longer follow-up are already included in table 2.
Gaba R C, Riaz A, Lewandowski R J et al. (2010) Safety of yttrium-90 microsphere	Retrospective case series n=12 (1 cholangiocarcinoma)	With 90-Y glass microspheres, there was a good safety profile in the setting of tumour-related	Larger studies or studies with longer follow-up are

radioembolization in patients with biliary obstruction. Journal of Vascular and Interventional Radiology 21, 1213-1218	FU=median 23 months (whole cohort)	biliary obstruction in patients with normal or near-normal bilirubin levels in this series, without evidence of therapy-related progressive leucocytosis, bilirubin increase, or infectious or biliary complications after treatment.	already included in table 2.
Haug A R, Heinemann V, Bruns C J et al. (2011) 18F-FDG PET independently predicts survival in patients with cholangiocellular carcinoma treated with 90Y microspheres. European Journal of Nuclear Medicine & Molecular Imaging 38, 1037-45	Case series n=26 Follow-up=unclear	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. FDG PET/CT was able to predict patient outcome after radioembolisation treatment, with the change in metabolically active tumour volume at 3 months being the best independent predictor.	This study was included in the Boehm (2015) systematic review and meta-analysis included in Table 2.
Hoffmann R T, Paprottka P M, Schon A et al. (2012) Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. Cardiovascular & Interventional Radiology 35, 105-16	Retrospective case series n=33 FU=median 10 months	Radioembolisation is an effective and safe option for patients with unresectable ICC. Predictors for prolonged survival are performance status, tumour burden, and RECIST response.	This study was included in the 3 systematic reviews and meta-analyses included in table 2 and in the Table 2 of the previous overview.
Hyder O, Marsh J W, Salem R et al. (2013) Intra-arterial therapy for advanced intrahepatic cholangiocarcinoma: a multi-institutional analysis. Annals of Surgical Oncology 20, 3779-86	Retrospective case series n=198 (46 SIRT) FU=not reported	Median overall survival was 13.2 months and did not differ on the basis of the type of intra-arterial therapy (cTACE, 13.4 months vs. DEB 10.5 months vs. TAE, 14.3 months vs. yttrium-90, 11.3 months; p=0.46).	This study was included in the Al-Adra (2015) systematic review and meta-analysis included in Table 2.
Ibrahim S M, Mulcahy M F, Lewandowski R J et al. (2008) Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. Cancer 113, 2119-28	Prospective case series n=24 FU: median 18 months	Radioembolisation with (90)Y may be a therapeutic option for the treatment of unresectable ICC.	This study was included in the Boehm (2015) systematic review and meta-analysis included in table 2 and in the Table 2 of the previous overview.

Kuei A, Saab S, Cho S K et al. (2015) Effects of Yttrium-90 selective internal radiation therapy on non-conventional liver tumors. World Journal of Gastroenterology 21, 8271-83	Systematic review n=8 studies	Although the indications for yttrium-90 SIRT in non-conventional liver metastases are less well-defined, initial results of small studies are largely favourable.	No new study included in this systematic review.
Lam M G. E. H, Louie J D, Iagaru A H et al. (2013) Safety of repeated yttrium-90 radioembolization. CardioVascular and Interventional Radiology 36, 1320-1328	Case series n=8 (2 cholangiocarcinoma) FU=median 752 days after second treatment (whole cohort)	The risk of radioembolisation - induced liver disease appears to be elevated for repeated radioembolisation. Objective tumour responses were seen, but establishment of safety limits will need improvement in dosimetric measurement and prediction.	Larger studies or studies with longer follow-up are already included in table 2.
Mosconi C, Gramenzi A, Ascanio S et al. (2016) Yttrium-90 radioembolization for unresectable/recurrent intrahepatic cholangiocarcinoma: a survival, efficacy and safety study. British Journal of Cancer 115, 297-302	Case series n=23 FU=16 months	In unresectable ICC, (90)Y-TARE is safe and offers a survival benefit in naive patients, as well as in responders.	This study was included in the Cuchetti (2017) systematic review and meta-analysis included in Table 2.
Mouli S, Memon K, Baker T et al. (2013) Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: safety, response, and survival analysis. Journal of Vascular & Interventional Radiology 24, 1227-34	Prospective case series n=46 FU=29 months	Radioembolisation with (90)Y is safe and shows antitumoural response and survival benefit in select patients with ICC. Results are most pronounced in patients with solitary tumours, for whom conversion to curative resection is possible.	This study was included in the Cuchetti (2017) and in the Al-Adra (2015) systematic reviews and meta-analyses included in Table 2.
Nezami N, Kokabi N, Camacho JC, et al. (2018) 90Y radioembolization dosimetry using a simple semi-quantitative method in intrahepatic cholangiocarcinoma: Glass versus resin microspheres.	Retrospective comparative case series n=10 (5 glass versus 5 resin) FU=none	Both 90Y glass and resin-based microsphere 90Y-RE are feasible and safe in patients with ICC, while 90Y glass microsphere delivers higher dose of 90Y to the targeted tumours.	Larger studies or studies with longer follow-up are already included in table 2. No new safety events were reported
Pieper CC, Willinek WA, Thomas D et al. (2016) Incidence and risk factors of early arterial blood flow stasis during first radioembolization of primary and secondary liver	Retrospective case series n=362 (26 chloangiocarcinoma) FU=unclear	Early stasis was observed in 24.8 % of resin-based REs. In the presence of the identified risk factors, extra care should be taken during microsphere administration.	Study objective was to determine the incidence of early arterial blood flow stasis and its influencing factors during resin-based

malignancy using resin microspheres: an initial single-center analysis. European Radiology 26, 2779-2789			radioembolisation (RE) of liver tumours.
Rafi S, Piduru SM, El-Rayes B et al. (2012) Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: Survival, efficacy, and safety study. Cardiovascular Interventional Radiology ePub doi: 10.1007/s00270-012-0463-4	Case series n=19 FU=median 15 months	Y-90 radioembolisation is effective for unresectable standard-chemorefractory ICC.	This study was included in the Cuchetti (2017) and in the Boehm (2015) systematic reviews and meta-analyses included in Table 2. It was also included in the previous overview.
Reimer P, Virarkar M K, Binnenhei M et al. (2018) Prognostic factors in overall survival of patients with unresectable intrahepatic cholangiocarcinoma treated by means of yttrium-90 radioembolization: results in therapy-naive patients. CardioVascular and Interventional Radiology 41(5), 744-752	Retrospective case series n=21 therapy-naive patients	The overall median survival was 15 months. Survival was statistically significantly (p=0.009) prolonged in patients with tumour burden of 25% or less (n=8, OS 37.5 months) compared with those with a tumour burden of 25-50% (n=13, OS 15 months). The other variables: tumour morphology (infiltrative vs. peripheral), tumour distribution (solitary vs. multifocal), lobes involved (unilobar vs. bilobar), FDG PET status (FDG avid vs. non-avid), RE treatment sessions (1 session vs. 2 sessions), metastases (metastasis vs. no metastasis) and RECIST criteria, had no significant impact on survival.	Larger studies or studies with longer follow-up are already included in table 2. No new safety events were reported.
Sangro B, Martinez-Urbistondo D, Bester L, Bilabo JI et al. (2017) Prevention and Treatment of Complications of Selective Internal Radiation Therapy: Expert Guidance and Systematic Review. HEPATOLOGY, Vol 00, No 00 2017	Review	Local practices used to prevent and treat SIRT complications vary between centres. This article analysed the literature to identify the incidence, natural course and risk factors for the main 4 complications and the relevance of subclinical damage to the corresponding tissues. Based on the available evidence, recommendations have been made and new	General review on the prevention and treatment of complications of selective internal radiation therapy

		medical approaches proposed. Specific recommendations have been made for the diagnostic work-up and treatment of complications induced by SIRT.	
Saxena A, Bester L, Chua T C et al. (2010) Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. Annals of Surgical Oncology 17, 484-91	Prospective case series n=25 FU=8 months	(90)Y radioembolisation may be a relatively safe and efficacious treatment for unresectable ICC. In the absence of other effective therapeutic options, this treatment warrants further investigation.	This study was included in the 3 systematic reviews and meta-analyses included in table 2 and in the Table 2 of the previous overview.
Servajean C, Gilabert M, Piana G et al. (2014) One case of intrahepatic cholangiocarcinoma amenable to resection after radioembolization. World Journal of Gastroenterology 20, 5131-4	Case report n=1 FU=1 year	Radioembolisation can be useful in the treatment of cholangiocarcinoma, allowing in some cases a secondary resection.	Larger studies or studies with longer follow-up are already included in table 2.
Soydal C, Kucuk O N, Bilgic S et al. (2016) Radioembolization with (90)Y resin microspheres for intrahepatic cholangiocellular carcinoma: prognostic factors. Annals of Nuclear Medicine 30, 29-34	Case series n=16 FU=243 days	Fluorodeoxyglucose (FDG) avidity and the dimension of the largest liver lesion, tumour load, and radiological response are prognostic factors in patients having radioembolisation for cholangiocellular carcinoma. Patients with lower tumour load, FDG-negative tumours, and smaller tumours seem to survive longer after radioembolisation.	This study was included in the Cuchetti (2017) systematic review and meta-analysis included in Table 2.
Sperling J, Justinger C, Schuld J et al. (2014) Intrahepatic cholangiocarcinoma in a transplant liver - Selective internal radiation therapy followed by right hemihepatectomy: Report of a case. World Journal of Surgical Oncology 12, 198	Case report n=1 FU=4 years	Because of a recurrent intrahepatic cholangiocarcinoma after liver transplantation, a selective internal radiation therapy with yttrium-90 microspheres was done followed by right hemihepatectomy. Four years later, the patient is tumour-free and in a healthy condition.	Larger studies or studies with longer follow-up are already included in table 2.
Sun B, Lapetino S R, Diffalha S A. L et al. (2016) Microvascular injury in persistent gastric ulcers after yttrium-90 microsphere radioembolization for liver	Case series n=3 (2 cholangiocarcinoma)	These findings suggest that the persistent gastric ulceration is a result of localised ischemic injury in response to Y-90 MRE-induced vascular damage.	Larger studies or studies with longer follow-up are already included in table 2.

malignancies. Human Pathology 50, 11-14	FU=13 months		
Vouche M, Lewandowski R J, Atassi R et al. (2013) Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. Journal of Hepatology 59, 1029-36	Case series n=83 (8 cholangiocarcinoma) FU=9 months	Radiation lobectomy by Y-90 is a safe and effective technique to hypertrophy the future liver remnant. Volumetric changes are comparable to portal vein embolisation while the right lobe tumour is treated synchronously. This novel technique is of particular interest in the bridge-to-resection setting.	Larger studies or studies with longer follow-up are already included in table 2.
Wijlemans J W, van Erpecum, K J, Lam M G. E. H et al. (2011) Trans-arterial 90yttrium radioembolization for patients with unresectable tumors originating from the biliary tree. Annals of Hepatology 10, 349-354	Case reports n=2 FU=9 months and 2 years	The presented cases show the potential of yttrium-90 radioembolisation as a palliative treatment option for malignant tumours of the biliary tree.	Larger studies or studies with longer follow-up are already included in table 2.
Yang L, Shan J, Shan L, et al. (2015) Transarterial embolisation therapies for unresectable intrahepatic cholangiocarcinoma: a systematic review. J Gastrointest Oncol. 2015 Oct;6(5):570-588. doi: 10.3978/j.issn.2078-6891.2015.055.	Systematic review n=20 studies (7 SIRT)	Transarterial therapies are safe and effective treatment options which should be considered routinely for unresectable ICC. Consistent and standardised methodology and data collection is needed for a meta-analysis. Randomised controlled trials will be valuable in the future.	All the studies were already included in at least 1 systematic review and meta-analysis included in table 2.