Interventional procedure overview of selective internal radiation therapy for neuroendocrine tumours that have metastasised the liver

Contents

Table 1 Abbreviations

Abbreviation	Definition
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group score
^{166}HoI	Holmium-166 radioisotope
IQR	Inter-quartile range
mNET	Metastatic neuroendocrine tumour
NET	Neuroendocrine tumour
OR	Odds ratio
PRRT	Peptide receptor radionuclide therapy
RECIST	Response Evaluation Criteria in Solid Tumours
mRECIST	Modified Response Evaluation Criteria in Solid Tumours
SF-36	Short form-36 questionnaire
SIRT	Selective internal radiation therapy
SMD	Standardised mean difference
TACE	Transarterial chemoembolisation
TAE	Transarterial embolisation
^{90}Y	Yttrium-90 radioisotope

Indications and current treatment

NETs grow in many organs of the body. The tumours start in cells that release hormones into the bloodstream (neuroendocrine cells). The tumours commonly spread (mNETs) from other organs to the liver, where it may not be possible to remove them with surgery. Some mNETs produce hormones which can cause carcinoid syndrome. The main symptoms of carcinoid syndrome are flushing of the skin, diarrhoea, fast heart rate and breathlessness.

Current treatment options depend on the history, clinical and histological presentation of mNETs. They include:

- surgical resection
- percutaneous ablation
- systemic chemotherapy
- systemic somatostatin analogues
- PRRT
- other intra-arterial therapies such as:
  - TAE
  - TACE
  - drug-eluting-bead-TACE.

What the procedure involves

In SIRT, microspheres containing sources of beta radiation (either the radioactive isotope ^{90}Y, or ^{166}HoI) are infused through the hepatic artery and carried by blood flow to the vessels that supply the tumour. Infusion through this route minimises damage to healthy liver tissues because they are mainly supplied by the portal vein, whereas the tumours are mainly supplied by hepatic arteries.

The procedure is done in 2 stages. First, the work-up is done to assess blood supply to the tumour, assess lung shunt, exclude extrahepatic uptake and plan personalised dosimetry. Then during SIRT, the microspheres containing the radionuclide are infused through a catheter placed in the hepatic artery. Catheterisation is done under local anaesthetic.

The procedure is done in specialist centres. Suitability of SIRT is discussed by a multidisciplinary team experienced in interventional and vascular radiology and nuclear medicine. It takes 1 to 2 hours to complete.

It may be possible to cure the cancer with SIRT, but expert feedback indicated that the main purposes of SIRT are to enable further treatment if SIRT successfully reduces tumour size, slows tumour growth or controls the symptoms of carcinoid syndrome.

Unmet need

Around 4,000 people are diagnosed with NETs in the UK every year. People with NETs metastatic to the liver have worse outcomes than NETs that have not spread to the liver. This is because tumours are more difficult to treat and carcinoid syndrome is more common in this group. Treatment options depend on the clinical presentation of disease and multiple therapies are often used in sequence; for example, emerging evidence is exploring using SIRT after PRRT. Innovation to improve outcomes for people with mNETs with novel non-surgical approaches is needed because a small proportion of mNETs can be surgically resected.

SIRT is less invasive than alternative techniques and can be done when surgery is contraindicated. It does not need hospital admission. SIRT delivers localised radiation to the tumour with the aim of limiting damage to nearby healthy tissues. These characteristics of SIRT may mean it has fewer side effects, needs fewer hospital resources and has better quality of life outcomes than alternative therapies.

Outcome measures

PEQs indicated that disease control and symptom control were the key aims of SIRT for this indication. Efficacy outcomes reported in the included studies were tumour response, symptom response, overall survival, progression-free survival and quality of life. Safety outcomes were mostly reported in terms of clinical toxicity. The standardised measures used across most studies are detailed in the following paragraphs.

RECIST

The RECIST criteria standardise the measurement of tumour response to treatment. Response is in terms of change in tumour size, measured on the length of selected lesions. Change in size is summarised into categorical outcomes: complete response, partial response, stable disease and disease progression. Further categorisation into objective response (the combined rates of complete and partial response) and disease control (the combined rates of complete and partial response and stable disease) can be used. There are several versions of this outcome measure (RECIST, mRECIST, RECIST v1.1). RECIST and RECIST v1.1 are most commonly used in studies measuring tumour response because they were developed earlier and are widely used across a range of tumour types. mRECIST was developed specifically to measure hypervascular liver metastases treated with locoregional therapy because it can account for tumour necrosis and the remaining proportion of 'viable tumour' rather than overall tumour size. Professional expert questionnaires indicated that mRECIST may better reflect mNET response to intravascular interventions.

SF-36

SF-36 is a 36-item, validated, patient-reported questionnaire that measures health-related quality of life. It has 8 domains: general health, physical functioning, bodily pain, role limitations attributable to physical health, mental health, vitality, social functioning, role limitations attributable to emotional health. Each domain score and the overall score can range from 0 to 100.

CTCAE

CTCAE is a standardised classification system and severity grading scale for adverse events in cancer therapy. Severity of clinical and laboratory toxicities are graded from 1 to 5. Grade 1 is low (mild) and grade 5 is high (death). Some studies did not distinguish clinical and laboratory toxicities; toxicity only summarised by grade. This has been reported in table 3.

Clavien Dindo Scale

The Clavien Dindo Scale is a classification system used for grading adverse events in surgical procedures. It is graded from 1 to 5. Grade 1 is mild and grade 5 is death.

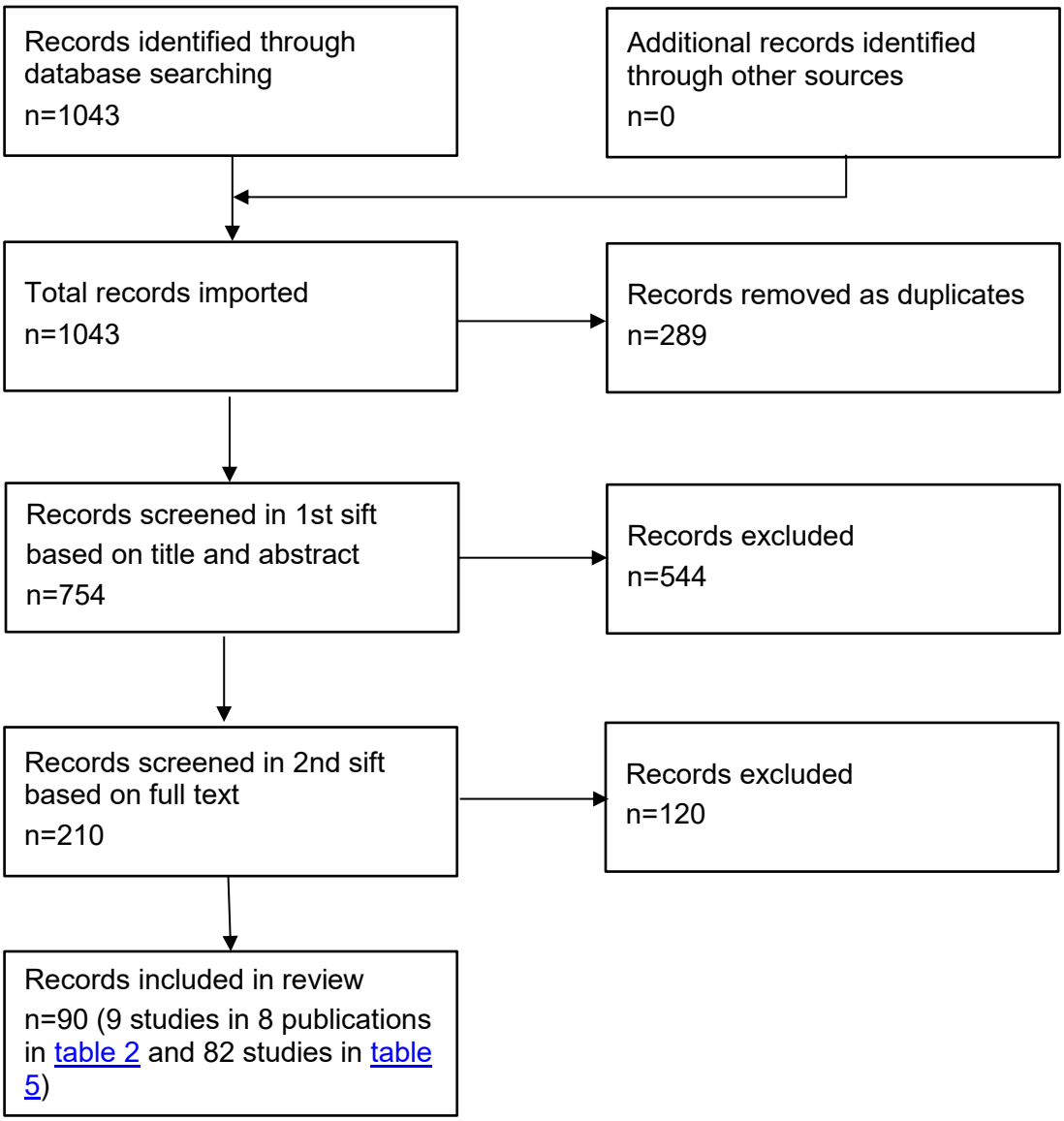
Evidence summary

Population and studies description

This interventional procedures overview is based on about 1,965 patients from 9 studies reported in 8 publications. The evidence is comprised of 2 systematic review and meta-analyses (Frilling, 2019a; Ngo, 2021), a US-based multicentre retrospective comparative study of 248 people (Egger, 2020), a retrospective analysis of 170 people in an international prospective registry (RESiN Registry; Wong, 2022), an international retrospective case series of 244 people (Braat, 2019), a single-arm, single-centre trial of 30 people based in the Netherlands (Braat, 2020), a retrospective analysis of UK single-centre prospective data from 24 people (Frilling, 2019b), a retrospective case series of 93 people in the US (Tomozawa, 2018) and a prospective case series of 30 people from a single centre in the US (Cramer, 2017).

This is a rapid review of the literature, and a flow chart of the complete selection process is shown in Figure 1 in the appendix. This overview presents 9 studies reported in 8 publications as the key evidence in table 2 and table 3, and lists 74 other relevant studies in table 5.

Figure 1 Flow chart of study selection



Evidence evaluating SIRT against a comparator intervention was reported in a meta-analysis (Ngo, 2021) and in the retrospective comparative study of 248 people (Egger, 2020). The retrospective study of 248 people was included in the meta-analysis but includes additional outcome data. Of the total sample of 1,965 people in this overview, 1,316 had SIRT and 619 people had a comparative intra-arterial treatment (TACE). One study compared toxicity outcomes of SIRT when done as a unilobar treatment with bilobar treatment (Tomozawa, 2018). In this study, 48 people had unilobar and 45 had bilobar treatment.

The meta-analysis comparing SIRT with TACE included 6 retrospective case series published between 2013 and 2020 (Ngo, 2021), including the retrospective comparative study of 248 people that was also included in the main evidence (Egger, 2020). The second meta-analysis reported findings from 27 studies published between 2006 and 2018 (Frilling, 2019a). Both prospective and retrospective data from studies with between 6 and 148 people who had SIRT were included in this study.

Demographics

People's age was reported in 6 studies (Braat, 2020; Cramer, 2017; Egger, 2020; Frilling, 2019b; Tomozawa, 2018; Wong, 2022). Average age in these studies ranged from 58 to 66, and mostly had little variation around this within their samples, except for the prospective case series of 30 people in which the age range was 25 to 76 (Cramer, 2017). The average age of NET diagnosis in the UK is between 50 and 60 years. Between 27% and 57% of samples were women, among the studies that reported this information. The Surveillance, Epidemiology and End Results Programme (US) suggests slightly more women than men are diagnosed with NETs. UK hospital episode statistics (2021 to 2022) show that more women than men were diagnosed with secondary malignant neoplasm of liver and intrahepatic bile duct (C78.7). The meta-analyses (Frilling, 2019a; Ngo,

2021) and the retrospective case series of 244 people (Braat, 2019) did not report the age or gender distribution of the sample.

Follow up

When average follow up was reported, it ranged between 6 months (Braat, 2020) and 34 months (Egger, 2020). The 4 largest primary research studies reported data collected in registries or databases over several years; the RESiN registry analysis used data between 2015 and 2021 (Wong, 2022); the comparative retrospective case control study reported data between 2000 and 2018 (median=34 months; Egger, 2020); the retrospective study of 244 people used data collected between 2004 and 2016, with up to 12 years of follow up (Braat, 2019); and the retrospective case series of 93 people reported all patient data (until death or last known follow-up) between 2007 and 2015.

Previous therapies

Six of 9 studies reported whether patients had previous treatment. Most patients had at least 1 type of intervention before SIRT. Treatment history before SIRT was heterogeneous within and between studies.

The systematic review and meta-analysis comparing SIRT with TACE reported that history of resection or ablation was similar between groups but the SIRT group were more likely to have had previous systemic chemotherapy and octreocide therapy (both p=0.009; Ngo, 2021).

In the RESiN registry study (Wong, 2022), 14% of people had previous hepatic resection, 37% had previous liver-directed therapy, 85% had previous cytostatic or systemic therapy. This was non-exclusive meaning some people had multiple previous treatments.

In the retrospective case series of 244 people (Braat, 2019), 95% of the sample had multiple treatments before SIRT, 3% had surgical resection and 2% had no previous intervention.

In the single-arm trial of 30 people (Braat, 2020), everyone had 4 cycles of PRRT within 20 weeks before they had SIRT. Also, 8% of people had previous liver-directed therapy, 38% had surgical resection of the primary tumour, 71% had somatostatin analogues, 9% had sunitinib, 6% had everolimus and 6% had external-beam radiotherapy to the primary tumour.

In the retrospective analysis of prospectively collected UK data from 24 people (Frilling, 2019b), everyone had at least 1 previous treatment. Most commonly these were surgery, TACE, systemic chemotherapy, somatostatin analogues and PRRT.

In the retrospective case series of 93 people (Tomozawa, 2018), 62% of people had previous therapies. Most commonly, people had TACE or TAE (26%) and resection (23%). Other therapies included systemic chemotherapy (16%), and ablation (38%).

In the prospective case series of 30 people (Cramer, 2017) previous treatments included surgical research of the primary NET (n=13), surgical hepatic resection (n=8), chemotherapy (n=24) and locoregional therapy (n=6). These were not presented as percentages of the sample, so it is unclear what proportion of the sample had one, multiple or no previous treatment.

Details of previous therapies were not reported in the systematic review and meta-analysis of 27 studies (Frilling, 2019a), or in the retrospective comparative study of 248 people comparing SIRT with TACE (Egger, 2020).

Post-SIRT treatment

It was unclear whether people went on to have other therapies during their follow-up period in most studies. In the RESiN registry study (Wong, 2022), the authors reported that a median of 22 months (range 12 to 37) after SIRT, 5% (9/170) had PRRT. In the retrospective study of 244 people (Braat, 2019), 66% of people had additional therapy after SIRT. Time elapsed between SIRT and following treatments was not reported. In the retrospective analysis of prospectively collected UK data from 24 people (Frilling, 2019b), everyone had corticosteroids, ursodeoxycholic acid and omeprazole for 4 weeks after SIRT to minimize the incidence of post-radioembolisation syndrome. No other information was provided on other treatments during follow up in this study. In the retrospective case series of 93 people, 17% (9/52) of people who reached 1-year follow up had systemic chemotherapy and 1 person had TAE (Tomozawa, 2018).

Other studies did not comment on treatment following SIRT.

Disease profile

In the systematic review meta-analysis comparing SIRT with TACE, the location of primary tumour sites was similar; there was no statistically significant difference between groups in the proportion of people with pancreatic, lung and gastrointestinal primary tumours. The proportion of people with hepatic tumour burden greater than 50% was reported in 3 studies. This was not statistically different between groups (p=0.07) and there was no statistically significant difference in the proportion of people with grade 2 or 3 tumours (p=0.66, p=0.82, respectively). Proportion of people with functional status according to ECOG greater than or equal to 1 was not statically significant between groups (p=0.31).

In the retrospective study of 248 people comparing SIRT with TACE (Egger, 2020), the most common primary tumour sites were the small bowel (36%) and pancreas (25%). People who had TACE were more likely to have synchronous

disease ($p<0.05$) and carcinoid syndrome ($p<0.001$). Tumour grade was higher in people with who had SIRT.

In the RESiN registry study, the most common primary tumour site was midgut (36%), followed by foregut (26%), pancreatic (24%) and hindgut (7%; Wong, 2022). Most tumours were graded as well differentiated (70%) and median tumour burden was 26%. 47% had bilobar tumours and 48% had extrahepatic metastases. According to ECOG assessment, baseline functioning was 0 in 48%, 1 in 37% and 2 or more in 15% of people.

In the retrospective case series of 244 people (Braat, 2019), 91% had progressive disease at baseline. The most common primary tumour sites were the pancreas (31%) and small bowel (35%). Most tumours were grade 1 (39%) or grade 2 (36%) and 66% had extrahepatic metastases. Tumour differentiation was not known for 71% of people. According to ECOG assessment, baseline functioning was 0 in 47%, 1 in 43%, and 2 or higher in 8%.

In the single-arm trial of 30 people (Braat, 2020), the most common primary tumour sites were the pancreas (32%) and small bowel (29%). Most tumours were grade 2 (65%; 35% were grade 1). Extrahepatic disease was present in 76% of people and 75% of people had less than 25% fractional liver involvement. According to ECOG assessment, baseline functioning was 0 in 59% of people, 1 in 38% of people, and 2 in 1 person (3%).

In the retrospective analysis of prospectively collected UK data from 24 people (Frilling, 2019b), the most common primary tumour sites were the small bowel (52%) and pancreas (25%). These were categorised as grade 1 in 46% and grade 2 in 42% of the sample. Everyone had progressive disease before treatment and 38% had extrahepatic metastases. At baseline, functioning score for everyone was less than 2 according to ECOG.

In the retrospective case series of 93 people (Tomozawa, 2017), 60% of tumours were classed as well differentiated and 16% were moderate to poorly differentiated. Most were carcinoid tumours (71%). Hepatic tumour burden was heterogeneous in this sample: 38% of people had less than 25% hepatic tumour burden, 33% of people had 25% to 50%, and 28% had more than 50%. Extrahepatic metastases were present in 34% of people. At baseline, functioning score according to ECOG was 0 in 51% of people, 1 in 44% and 2 in 5%.

In the prospective case series of 30 people (Cramer, 2017), the primary tumour location was most commonly unknown (37%) but 30% of primary tumours were in the pancreas. According to ECOG, everyone had a functioning score of 0 (47%) or 1 (50%).

Baseline data was not reported in the systematic review and meta-analysis of 27 studies (Frilling, 2019b).

Table 2 presents study details.

Table 2 Study details

Study no.	First author, date country	Patients (men: women; M:W)	Age	Study design	Inclusion criteria	Intervention	Follow up
1	Ngo, 2021 Included studies from Turkey, US, and one international study conducted in China, Germany and the US	n=643 (221 had SIRT and 422 had TACE; data gathered from 6 retrospective cohort studies) M:W pooled analysis showed OR=0.99 [95% CI 0.69 to 1.42] between SIRT and TACE	SMD between SIRT and TACE groups was -0.14 years [95%CI -0.32, 0.03]	Systematic review and meta-analysis of studies that compared SIRT with TACE between 2013 and 15 February 2020	Published, primary research studies reporting survival outcomes in people who had SIRT and TACE for mNETs. Studies had to have at least one distinct subgroup of people with mNETs treated with SIRT and one with TACE, and report mean or median overall survival. Systematic reviews, case reports and abstracts were excluded.	SIRT with ^{90}Y compared with TACE	Not reported
2	Frilling, 2019a	n=27 studies (n=842 patients/procedures) M:W not reported	Not reported	Systematic review and meta-analysis Search date: 30 April 2018	Publications in English, German, Dutch, French or Danish; at least 5 human subjects; response data; entire or subpopulation with mNETs who had SIRT.	SIRT with ^{90}Y microspheres (glass or resin)	Not reported
3	Egger, 2020	N=248 (n=51 had SIRT; n=197 had TACE)	Median=60 years	Retrospective comparative study of people	All adult patients with mNETs that had SIRT or TACE between	SIRT with ^{90}Y glass microspheres	Median=34 months

Study no.	First author, date country	Patients (men: women; M:W)	Age	Study design	Inclusion criteria	Intervention	Follow up
	US	45% men; 55% women	45% men	at 2 US academic medical centres	2000 and 2018. People received treatment if they had unresectable disease, minimal or no extrahepatic disease, adequate liver function.	(Therasphere, BTG)	
4	Wong, 2022 International registry data from 36 institutions.	n=170 56% men, 44% women	Median age=66 (IQR= 56 to 73)	Retrospective analysis of prospective international registry data (RESiN-Radiation Emitting SIR-Spheres in Non-resectable liver tumour registry) between 2015 and 2021	People aged 18 or over who could provide informed consent and were considered appropriate for arterial therapy.	SIRT with ^{90}Y resin microspheres (SIR-Spheres, Sirtex Medical).	Average follow-up was not reported. Registry data between 2015 and August 2021 were used.
5	Braat, 2019 8 centres across US, Germany, Belgium, UK, Netherlands	n=244 M:W not reported	Not reported	International, multicentre retrospective case series with data between July 2004 and May 2016	Histologically proven mNET of any origin treated with ^{90}Y resin microspheres, at least baseline and 3 (+ or - 1.5) months follow-up cross-sectional imaging.	SIRT with ^{90}Y resin microspheres (SIR-Spheres, Sirtex Medical)	Range= 51 days to 12 years
6	Braat, Bruijnen, 2020	n=30 (n=34 in the original sample but 3	Mean=62 years (SD=8)	Single centre, single-arm trial	18 years or older, histologically	^{166}Holmium SIRT within 20	6 months

Study no.	First author, date country	Patients (men: women; M:W)	Age	Study design	Inclusion criteria	Intervention	Follow up
	Netherlands	were excluded after consent because they did not meet inclusion criteria and 1 person died from overproducing insulinoma so did not complete follow up) 73% (22/30) men, 27% (8/30) women.		(HEPAR PLuS) between October 2014 and September 2018	confirmed grade 1 or 2 mNET, at least 3 unresectable measurable liver metastases, ECOG less than or equal to 2, life expectancy greater than 12 weeks, previous treatment with 4 cycles of PRRT. People with a previous cardiac event within 3 months or increased risk of liver toxicity were excluded.	weeks of finishing 4 cycles of PRRT	
7	Frilling, 2019b UK	n=24 people 63% men, 37% women	Median=62 years (range 45 to 75)	Retrospective analysis of a prospective registry of all consecutive people with mNETs that had SIRT at an NHS Trust between January 2007 and December 2017.	People with non-resectable mNETs, grade 1/2 mNETs, disease progression following previous treatments, adequate haematological renal and hepatic function including clotting profile, and good performance status (ECOG less than 2). Decision to deliver SIRT was by MDT and low volume	SIRT with ^{90}Y labelled resin microspheres (SIR-Spheres, Sirtex Medical, Sydney, Australia)	Median=18 months (range= 2 to 90)

Study no.	First author, date country	Patients (men: women; M:W)	Age	Study design	Inclusion criteria	Intervention	Follow up
					extrahepatic metastases and or primary tumour in situ were not exclusion criteria.		
8	Tomozawa, 2018 US	n=93 (n=48 people had unilobar treatment; n=45 had whole liver treatment) 50% men, 50% women	Mean=59 years (SD=14)	Retrospective case series from a single centre between 2007 and 2015	People with mNETs that: i) had CT or MR imaging available and were not surgical candidates; ii) had available details or treatment planning and delivery; iii) were aged 18 to 99. People who were considered unsafe to treat because of extra-arterial flow to the gastrointestinal tract, had hepatopulmonary shunt fraction greater than 20% or had previous external beam radiation therapy to the liver were excluded.	SIRT with ^{90}Y resin microspheres (SIR-Spheres; Sirtex Medical Ltd, North Sydney, Australia)	Average follow up was not reported. All patient data (until death or last known follow-up) between 2007 and 2015; 56% of people had greater than 1 year follow-up.
9	Cramer, 2017 US	n=30 43% men, 57% women	Median=60.5 years (range 25 to 76)	Prospective case series from a single centre between August 2009 to July 2013.	People with mNETs that were not surgical candidates, 18 or over, ECOG less than or equal to 2, life expectancy greater	SIRT with ^{90}Y labelled microspheres (SIR-Spheres, Sirtex, Australia)	24 months

Study no.	First author, date country	Patients (men: women; M:W)	Age	Study design	Inclusion criteria	Intervention	Follow up
					than 3 months. Lung shunt fraction greater than 20% were excluded.		

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Ngo, 2021	**Tumour response** There was no statistically significant difference in tumour response within 3 months between the SIRT and TACE groups (OR=2.9, 95% CI= 0.8 to 10.2; p=0.1; n=2 studies). There was no statistically significant difference in tumour response at follow ups after 3 months between the SIRT and TACE groups (OR=1.0, 95%CI= 0.1 to 7.9; p=0.99; n=3 studies). **Symptom response** No statistically significant difference in symptom improvement after treatment (OR=0.3, 95% CI= 0.1 to 1.5; p=0.13, n=2 studies): • 75% of people who had SIRT reported symptom improvement • 52.6% of people who had TACE reported symptom improvement. **Overall survival** Median OS was statistically significantly better in the TACE group compared to SIRT (OR=1.92; 95%CI= 1.1 to 3.2, p=0.01; n=6 studies): • median OS in the SIRT subgroup ranged from 14.5 to 66.8 months	**Mortality** Not reported. **Major adverse events (clinical and biochemical)** There was no statistically significant difference in major adverse event rates between groups (OR=1.16, 95% CI= 0.5 to 2.5, p=0.71, n=2 studies): • 6.9% of people who had TACE reported major adverse events • 8.5% of people who had SIRT. **Minor adverse events (clinical and biochemical)** There were no statistically significant differences in minor adverse event rates between groups (OR=1.08, 95%CI= 0.39–2.99; p= 0.88): • 44.6% of people who had TACE reported minor adverse events • 58.8% of people who had SIRT. **Clinical toxicity events** Common minor clinical adverse events included abdominal pain, nausea, vomiting, anorexia, fatigue, fever and flushing. **Biochemical toxicity** Common minor biochemical adverse events included

First author, date	Efficacy outcomes	Safety outcomes
	• median OS in the TACE group ranged from 16.8 to 81.9 months. **Hepatic progression free survival** There was no statically significant difference in hepatic progression free survival between SIRT and TACE groups (OR= 1.0, 95%CI=0.8 to 1.4, p=0.96; n=5 studies).	elevations in aspartate aminotransferase or alanine aminotransferase.
Frilling, 2019a (systematic review & meta-analysis)	**Tumour response** The weighted mean objective response rate was 51% (95%CI= 47% to 54%; n=27 studies) The weighted mean disease control rate was 88% (95%CI= 85% to 90%; n=27 studies). **Overall survival** Median overall survival was 32 months (range 18 to 57). • 1-year overall survival ranged from 71 to 95% (n= 9 studies). • 2-year overall survival ranged from 18.5% to 87.4%. (n=8 studies; excluding the outlying study which reported 18.5%, the 2-year overall survival rate ranged from 45% to 87.4%). • 3-year overall survival ranged from 45% to 77.6% (n=5 studies). • 5-year overall survival rate ranged from 18.5% to 60% (n=3 studies).	Safety data was not reported in this meta-analysis.

First author, date	Efficacy outcomes	Safety outcomes
Egger, 2020	**Tumour response at 6 months (RECISTv1.1)** Disease control rate was statistically significantly higher for people who had TACE compared with people who had SIRT (p=.004) • 83% (34/42) of people who had SIRT showed disease control (complete response=4%, partial response=20%, stable disease=59%, progressive disease=17%) • 96% (134/139) of people who had TACE showed disease control (complete response=4%, partial response=27%, stable disease=66%, progressive disease=4%). **Median percent change in largest liver metastasis size** Median percent decrease in size of largest liver metastasis was significantly greater in people who had TACE compared with people who had SIRT (p=0.05) • Median decrease in largest liver metastasis was 9% in people who had SIRT (IQR=0, 27%) • Median decrease in largest liver metastasis size was 19% (IQR=6 to 34%) **Overall survival** There was no statistically significant difference in overall survival between people who had SIRT and people who had TACE (p=0.3): • Median overall survival was 35.9 months in people who had SIRT	**Mortality** There was no statistically significant difference in 30-day mortality between groups (p=1.0). The authors did not report whether these were treatment related deaths: • 2% (1/51) of people who had SIRT died within 30 days • 3.1% (6/198) of people who had TACE died within 30 days. There was no statistically significant difference in 90-day mortality between groups (p=0.2). The authors did not report whether these were treatment related deaths: • 9.8% (5/51) of people who had SIRT died within 90 days • 5.2% (10/197) of people who had TACE died within 90 days. **Major adverse events** This study reported 'major complication rates' as any grade 3 or 4 complication within 30 days of SIRT (Clavien-Dindo scale). The wording implies these are clinical events related to treatment, but it is not clear. There was no statistically significant difference in major complication rates between groups (p=0.58): • 5.9% (3/51) of people who had SIRT had a grade 3 or 4 complication • 9.2% (18/198) of people who had TACE had a grade 3 or 4 complication.

First author, date	Efficacy outcomes	Safety outcomes
	• Median overall survival was 50.1 months in people who had TACE. • This remained non-significant in a sensitivity analysis of only people with well-differentiated grade 1 or 2 tumours. There was no statistically significant difference in 5-year overall survival rates between people who had SIRT and people who had TACE (p=0.27). **Progression free survival** There was no significant difference in progression free survival (p=0.37) • Median progression free survival was 15.9 months for people who had SIRT. • Median progression free survival was 19.9 months for people who had TACE. • This remained non-significant in a sensitivity analysis of only people with well-differentiated grade 1 or 2 tumours. **Length of stay** Length of stay was statistically significantly longer for people who had TACE than people who had SIRT (p<.001). • median length of stay after SIRT was 0 days • median length of stay after TACE was 1 day.	**Overall adverse events** This study reported overall complication within 30 days of SIRT (Clavien-Dindo scale). The wording implies these are clinical events related to treatment, but it is not clear. There was no statistically significant difference in overall complication rates between people who had SIRT and people who had TACE (p=0.17): • 13.7% (7/51) of people who had SIRT had a complication • 22.6% (44/197) of people who had TACE had a complication. **Clinical adverse events** The wording of 'complication rates' (reported above) implies these were clinical events, but it is not clear. **Biochemical toxicity** People who had TACE had: • significantly greater increase in post-procedure bilirubin (favours SIRT; +55% vs 0%, p < 0.001) • significantly greater increase in post-procedure creatinine (favours SIRT; +12% vs -13%, p < 0.001)

First author, date	Efficacy outcomes	Safety outcomes
	92% of people who had SIRT had treatment in outpatient appointments, compared with 99% of people who had TACE who spent at least 1 night in hospital.	
Wong, 2022	**Tumour response at 6 months (RECISTv1.1)** Data was available for n=99/121 people with imaging data at 6 months. Percentages are as reported in the publication which used 121 as the denominator. • 4% (n=5) had complete response • 32% (n=39) had partial response • 32% (n=39) had stable disease • 13% (n=16) had progressive disease. **Overall survival** Median overall survival was 33 months (95%CI=25 to n/a): • 1-year survival was 75% • 2-year survival was 62% • 3-year survival was 46%. There was no statistically significant difference in overall survival by primary tumour location (p=0.1) or by degree of tumour differentiation (well, moderate, poor; p=0.67). Hazard ratios indicated that overall survival was lower for people with ECOG greater than or equal to 2 (p=0.01) and if the person had ascites at baseline (p=0.049) **Progression free survival**	**Mortality** 39% (67/170) died within the follow-up period. Cause of death was available in 44 of these people. • The most common cause was tumour progression (33/44 records). • 1 person died of liver failure 11 months after treatment. This person had multiple prior chemotherapy treatments including cisplatin and irinotecan. • Other grade 5 toxicities are listed in Table 4 of the publication. **Major adverse events** 139 adverse events that were rated grade 3, 4 or 5 (CTCAE v5) across 59 categories were listed in the publication. • These were in 34% (58/170) of people • 19% of toxicities (20/107 evaluated events) were attributed as definitely or probably related to treatment. **Minor adverse events** Minor adverse events (rated grade 1 or 2 according to CTCAE v5) were not reported in this study.

First author, date	Efficacy outcomes	Safety outcomes
	Median progression free survival was 25 months (95%CI=22 to 35 months). • 1-year progression free survival was 70% • 2-year progression free survival was 54% • 3-year progression free survival was 35%. There was no statistically significant difference in progression free survival by primary tumour location (p=0.3) or by degree of tumour differentiation (well, moderate, poor; p=0.96) Intrahepatic progression was seen in 42% (71/170) of people. This was in a previously treated region in 37% (26/71) of people with progressive disease. Extrahepatic progression was seen in 36% of (61/170) people. Hazard ratios indicated that ECOG greater than or equal to 2 (p=0.01) and baseline ascites (p=0.0001) was associated with shorter progression free survival. People who had unilobar treatment (p=0.03) and with 25% or greater tumour burden (p=0.049) were associated with longer progression free survival.	**Clinical adverse events** Of the 20 grade 3 to 5 events that were classed as definitely or probably related to treatment, clinical events included: death, abdominal pain (grade 3 and 4), hepatic abscess (grade 3) and lymphopenia (grade 3). • The most common grade 3 to 5 adverse events were abdominal pain (7/139) and anorexia (5/139) • Of 15 patients with colonized bile ducts, one patient (7%) developed a hepatic abscess. **Biochemical toxicity** Of the 20 grade 3 to 5 events that were classed as definitely or probably related to treatment, liver function toxicities in the absence of progressive hepatic disease included: • bilirubin (n= 5, 3%) • new ascites (n= 8, 5%) • alanine aminotransferase (n= 1, 0.6%) • alkaline phosphatase (n= 1, 0.6%). • of the 5 patients with Grade 3 hyperbilirubinemia, 2 normalized within 3 months, leaving 13 (7.6%) with durable hepatic function toxicities.
Braat, Kappadath, 2019	Disease control rate was 91% at all time points on all outcome measures not correlated with tumour grade. **Tumour response at 3 months (RECIST v1.1)**	**Mortality** Treatment related mortality was not reported in this study.

First author, date	Efficacy outcomes	Safety outcomes
	244 people were assessed according to RECIST v1.1 criteria at a mean of 68 days (SD=34) after SIRT: • 2% (4/244) had complete response • 14% (34/244) had partial response • 76% (185/244) had stable disease • 9%(21/244) had progressive disease. **Tumour response at 3 months (mRECIST)** 126 people were assessed according to mRECIST at a mean of 89 days (SD=78) after SIRT: • 8% (10/126) had complete response • 35% (44/126) had partial response • 48% (61/126) had stable disease • 9% (11/126) had progressive disease **Tumour response at 6 months (RECIST v1.1)** 116 people were assessed according to RECIST v1.1 at a mean of 187 days (SD=48) after SIRT: • 1% (1/116) had complete response • 28% (32/116) had partial response • 63% (73/116) had stable disease • 9% (10/116) had progressive disease **Tumour response at 6 months (mRECIST)** 70 people were assessed according to mRECIST at a mean of 189 days (SD=38) after SIRT: • 9% (6/70) had complete response • 54% (38/70) had partial response	**Major adverse events** Only biochemical toxicity was described in terms of severity of event (CTCAE v4.03). The authors reported grade 3 to 4 biochemical and haematological toxicities were limited; most common was lymphocytopenia in 6.7% of people. **Minor adverse events** Only biochemical toxicity was described in terms of severity of event (CTCAE v4.03). These occurred in up to 52% of people. Details are described under biochemical toxicity. **Clinical adverse events** Note that the authors reported that clinical toxicities were not recorded for 12% and 39% of people at 3 and 6 months, respectively (missing data). • At 3 months, 56% of people experienced known radioembolisation-related adverse events (fatigue, abdominal pain, nausea). • At 6 months, 6% of people had persistent adverse events (mainly abdominal pain) • There were no clinical toxicities in 32% of people at 3 months, and no clinical toxicities in 55% of people at 6 months. • 3% (7/244) people had radiation-induced gastric ulcer • 0.8% (2/244) of people had radiation-induced liver disease

First author, date	Efficacy outcomes	Safety outcomes
	• 29% (38/70) had stable disease • 9% (6/70) had progressive disease **Symptom response** Clinical symptom response was observed in 79% of people who reported symptoms at baseline (60% of 244 people): • 44% reported improvement in symptoms • 35% reported complete symptom resolution. **Overall survival** Median overall survival was 2.6 years (95%CI=2.2 to 3 years).	• 1 person (of 244, 0.4%) had radiation pneumonitis • 1 person (of 244, 0.4%) had liver abscess with bilioenteric anastomosis (without antibiotic prophylaxis) • 1 person (of 244, 0.4%) had cholangitis with bilioenteric anastomosis (without antibiotic prophylaxis) **Biochemical toxicity** • Grade 1 to 2 bilirubin elevation and/or decreased albumin levels occurred in 6%. • Grade 1 to 2 lymphocytopenia in 52%, • Thrombocytopenia occurred in 17%, • Grade 1 to 2 anaemia or leukopenia occurred in 8%, • Coagulation was unaffected as measured by the international normalized ratio. **Other adverse events** • 0.8% (2/244) people had arterial dissection from the angiography procedure • Treatment was stopped for 3 people because of complaints.
Braat, Bruijnen, 2020	Note that before SIRT in this study, all participants had PRRT. After the last of 4 cycles of PRRT, 17% (5/30) patients had progressive intrahepatic disease, 56%	Note that before SIRT in this study, all participants had PRRT. **Mortality** 1 person died from radioembolisation induced liver

First author, date	Efficacy outcomes	Safety outcomes
	(17/30) had stable disease, and 27% (8/30) had partial response, according to RECIST v1.1. **Tumour response at 3 months (RECIST v1.1)** • 0% (0/30) had complete response • 43% (13/30) partial response • 50% (15/30) stable disease • 7% (2/30) progressive disease **Tumour response at 3 months (mRECIST)** • 10% (3/30) had complete response • 50% (15/30) partial response • 27% (8/30) stable disease • 0% (0/30) progressive disease • 13% (4/30) could not be evaluated because they had hypovascular disease that precluded mRECIST evaluation. **Tumour response at 6 months (RECIST v1.1)** • 0% (0/30) had complete response • 47% (14/30) partial response • 37% (11/30) stable disease • 13% (4/30) progressive disease • 3% (1/30) could not be evaluated because they died before follow-up.	disease. Symptoms started 6 weeks after SIRT and the person died after 4 months. 1 person died because of hypoglycaemia caused by an overproducing insulinoma, considered unrelated to treatment. **Major adverse events** Treatment related clinical toxicity was assessed within 6 months and biochemical toxicity at 3 and 6 months (CTCAE v4.03) • Major clinical toxicity considered related to SIRT was observed in up to 10% (3/31 had grade 3 abdominal pain; see clinical toxicity); 1 grade 5 related event was observed (see mortality). • Major biochemical toxicity was observed in up to 47% at 3 months, and up to 50% at 6 months (grade 3 γ-glutamyltransferase increase); 3 grade 4 events happened at 3 months and 1 grade 4 event happened at 6 months. **Minor adverse events** Treatment related clinical toxicity was assessed within 6 months and biochemical toxicity at 3 and 6 months (CTCAE v4.03) • Minor clinical toxicity considered related to SIRT was observed in up to 68% (21/31 had grade 1 to 2 abdominal pain; see clinical toxicity). • Minor biochemical toxicity was observed in up to 80% at 3 months (grade 1 to 2 alkaline

First author, date	Efficacy outcomes	Safety outcomes
	Tumour response at 6 months (mRECIST) • 7% (2/30) complete response • 50% (15/30) partial response • 23% (7/30) had stable disease • 3% (1/30) had progressive disease • 17% (5/30) could not be evaluated because 1 person died before follow-up and the rest had hypovascular disease which precluded mRECIST measurement. **Tumour-related hormonal symptom resolution** • 22% (2/9) people with symptoms after PRRT reported complete resolution of their symptoms • 56% (5/9) reported an improvement • 22% (2/9) reported stable symptoms.	phosphatase increase), and up to 83% at 6 months (grade 1 to 2 aspartate aminotransferase increase). **Clinical toxicity** There were no grade 4 clinical toxicities related to treatment. Grade 1 to 2 treatment-related clinical toxicity events included: • abdominal pain (68%, 21/31) • fatigue (58%, 18/31) • nausea (61%, 19/31) • vomiting (42%, 13/31) • malaise (25%, 8/31) • subfebrile (13%, 4/31) • shivering (10%, 3/31) • oedema (6%, 2/31). Grade 3 treatment-related clinical toxicities included: • abdominal pain (10%, 3/31) • fatigue (3%, 1/31) • nausea (3%, 1/31). **Biochemical toxicity** Biochemical toxicities included: • Increases in: bilirubin, alkaline phosphatase, γ-glutamyltransferase, aspartate

First author, date	Efficacy outcomes	Safety outcomes
		aminotransferase, alanine aminotransferase, lactate dehydrogenase, ammonia • Decreases in albumin • Anaemia, leucopoenia, neutropoenia, lymphocytopenia, thrombocytopaenia **Other adverse events** 1 person had a bleeding gastric ulcer and perforated cholecystitis. This was considered unrelated to treatment because of no evidence of microspheres on the histopathology.
Frilling, 2019b (retrospective case series of prospectively collected data)	**Tumour response at 3 months (RECIST v1.1)** • 4% (1/24) had complete response • 54% (13/24) had partial response • 29% (7/24) had stable disease • 8% (2/24) had mixed response • 4% (1/24) had progressive disease. **Tumour response at 6 months (mRECIST)** • 4% (1/24) had complete response • 54% (13/24) had partial response • 29% (8/24) had stable disease • 8% (2/24) had mixed response • 0% (0/24) had progressive disease. **Symptom response at 6 months**	**Mortality** There were no treatment related deaths. **Major adverse events** There were no grade 3 or 4 biochemical toxicities. Clinical adverse events were not graded. **Minor adverse events** 54% (13/24 people) had grade 1 to 2 biochemical toxicities. Clinical adverse events were not graded. **Clinical adverse events** • 25% (6/24) of people had radioembolisation-related clinical side-effects (4/6 were abdominal pain; 2/6 were fatigue). • No other radioembolisation-specific side-effects such as gastric ulcer, liver abscess,

First author, date	Efficacy outcomes	Safety outcomes
	90% (9/10) people who were symptomatic at baseline and completed a quality of life questionnaire reported being "not at all" symptomatic at 6 months. 10% (1/10) reported being "a little symptomatic" at 6 months. **Overall survival** Median overall survival was 57 months (95%CI=41 months to n/a). Overall survival rates were: • 95% at 12 months • 87% at 24 months • 78% at 36 months. **Progression free survival** Median progression free survival was 41 months (95%CI=31 months to n/a). At a median of 18 months, 1 person had intrahepatic progression and 7 people had extrahepatic disease progression, 1 person had both intra- and extra-hepatic progression. Progression free survival rates were: • 66% after 12 months • 50% after 24 months • 50% after 36 months.	radioembolisation-induced liver disease or radiation pneumonitis were recorded during follow-up. • One person was re-hospitalised for 24 hours for pain management. They had previous extensive abdominal surgery including right hemicolectomy and left hepatectomy. • No peri-interventional carcinoid crisis or any intervention-related complications. **Biochemical toxicity** • There were no grade 3 or 4 biochemical toxicities. • 54% (13/24 people) had grade 1 to 2 haematological toxicity, including 12 cases of lymphocytopenia and 1 case of thrombocytopenia. • No toxicity (affecting alkaline phosphatase, gamma-glutamyl transferase, aspartate/alanine transaminase or lactate dehydrogenase levels) were seen in 14 people. • No changes in bilirubin levels or coagulation profile assessed by the international normalisation ratio occurred.
Tomozawa, 2018	**Tumour response at 1 year (RECIST)** At 1 year after SIRT: • 25% (13/52) had partial response	**Mortality**

First author, date	Efficacy outcomes	Safety outcomes
	• 67% (35/52) had stable disease • 8% (4/52) had progressive disease During this time 17% (9/52) of people had systemic chemotherapy and 1/52 had TAE. **Overall survival** Median overall survival was 28 months (95%CI=16.2 to 40).	During the study period, 45% (42/93 people) died. The authors did not report whether deaths were considered treatment-related. **Major adverse events** At 6 months, 1 grade 3 event was seen (ascites). At 1 year, 10 grade 3 adverse events were seen (6/10 events were ascites). No grade 4 events were reported. **Minor adverse events** At 6 months and 1 year, the most common grade 2 event was elevated alkaline phosphatase (5 and 13 events reported at each follow-up, respectively). No grade 1 events were reported. **Clinical toxicity** At 1 year, 29% (15/52 people) developed imaging signs of cirrhosis-like morphology or portal hypertension after • 12% (6/52) of people had ascites • 13% (7/52) had cirrhosis-like morphology (defined as hepatic surface nodularity and enlargement of caudate lobe) • 17% (9/52) had splenomegaly • 4% (2/52) had varices. Of these 24 events, 19 were in people who had bilobar treatment.

First author, date	Efficacy outcomes	Safety outcomes
		During this time 17% (9/52) of people had systemic chemotherapy and 1/52 had TAE. **Biochemical toxicity** People who had unilobar therapy only showed increased alkaline phosphatase levels. People with bilobar therapy had the following biochemical toxicities: • Grade 2 biochemical toxicities included increases in: albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, haemoglobin, leukocytes, ascites. These were also seen at 1 year, as well as decrease in platelet count. • Grade 3 events at 6 months included 1 case of ascites. At 1 year, changes to ascites, bilirubin, albumin and alkaline phosphatase were seen.
Cramer, 2017	**Overall survival** Mean overall survival was 32.9 months. At study completion, 37% (11/30) had died. **Quality of Life (SF-36 v1)** There was no statistically significant difference in any of the 8 health related quality of life domains at 1 and 3 months, compared to baseline.	Adverse events were not reported in this study.

First author, date	Efficacy outcomes	Safety outcomes
	At 6 months, mean mental health domain score was significantly better than baseline (baseline score=74 compared with 6-month score=81, p=.007, scale=0 to 100). No other domains had a statistically significant difference at 6 months. At 12 months, the mean social functioning domain score was significantly better than baseline (baseline score=64 compared with 12-month score=89, p=.019, scale=0 to 100). There were no other statistically significant differences at 12 months. At 24 months, there were no statistically significant differences in any domain.	

Procedure technique

Type of radioactivity and microsphere

Of 9 studies, 5 reported evidence from ^{90}Y labelled resin microspheres (Braat, 2019; Cramer, 2017; Frilling, 2019b; Tomozawa, 2018; Wong, 2022). The retrospective study of 248 people comparing SIRT with TACE (Egger, 2020) used ^{90}Y labelled glass microspheres. Both meta-analyses considered evidence from both glass and resin ^{90}Y microspheres and made no distinction between these in the results (Frilling, 2019a; Ngo, 2021). The HEPAR PLuS single-arm trial of 30 people was the only study that included people who had SIRT with ^{166}Ho labelled microspheres (Braat, 2020).

Treatment work-up and parameters

Methods of work-up, dosing and the administered activity were not uniformly reported across studies. When described, work-up was done mostly using ^{99m}Tc-labelled macroaggregated albumin to assess arterial anatomy and determine hepatopulmonary shunting. The body surface area method was most commonly used to calculate dose. Some studies reported using a dose reduction method when lung shunt fraction was high. When bilobar treatment was needed, there was a mixture of approaches within and between studies as to whether SIRT was delivered sequentially or in the same session. When the number of SIRT cycles was reported, this also varied within and between studies. The retrospective case series of 244 people (Braat, 2019) was the only study to explicitly extract outcomes after the first cycle of SIRT. The available details of work-up and procedure from each study are reported below.

The systematic review and meta-analysis comparing SIRT with TACE (Ngo, 2021) and the systematic review and meta-analysis of 27 studies (Frilling, 2019a) did not describe details of the procedure other than the type of microspheres used.

The retrospective study of 248 people comparing SIRT with TACE (Egger, 2020) reported that if lung shunt fraction was found to be less than 15% during the work-up, SIRT was done. In total, 58% of the SIRT group had bilobar treatment in which SIRT was delivered to the first lobe then to the second lobe, 4 weeks later. Methods used to calculate dose, treatment schedule or actual activity administered were not reported.

Work-up method was not described in the RESiN registry study (Wong, 2022). In this study, 48% (82/170) had bilobar treatment. Median activity delivered was 1.3 GBq (IQR= 0.9 to 1.5 GBq) and 1.9 GBq (IQR= 1.7 to 2.2 GBq) for unilobar and bilobar treatments, respectively. Dose was calculated according to body surface area method in 91% of the sample. Most people had a single cycle of SIRT; 98% had a single cycle and 4 people had 3 or 4 cycles.

In the retrospective case series of 244 people (Braat, 2019), body surface area method was used to calculate dose in 84% of the sample. Prophylactic intravenous octreotide infusion or prophylactic antibiotic treatment was given at the discretion of the treating physician and according to the institutes' guideline. Lung shunt fraction was calculated during work-up and dose was adjusted accordingly. Median lung shunt fraction was 5.6% (range 0.7% to 33%) and median administered activity was 1.8GBq. Activity reduction was applied in 7.4% of the sample and coil embolisation was reported in 50% of the sample. Whole liver treatment was administered in a single session in 56% of the sample, while 14% had whole liver sequentially; 26% had a single right lobar treatment and 3% had single left lobar. In this study, all results were extracted after the first cycle of SIRT.

In the single-arm trial of 30 people (Braat, 2020), they used a 'scout dose' of ^{166}Ho instead of Tc-labelled macroaggregated albumin to do the work-up. SIRT was either delivered in 1 session or split into 2 based on this. In total, 57% had

whole liver single session and 23% had whole-liver sequential sessions. The remaining had single lobe treatment. Activity prescribed was calculated in relation to liver weight. Mean ^{166}Ho delivered was 6769MBq (SD=2419). Number of SIRT cycles was not reported.

In the retrospective analysis of prospectively collected UK data from 24 people (Frilling, 2019b), dose was modified according to pulmonary shunting detected in the work-up. People with shunt fraction of greater than 20% did not have treatment. Coil embolisation was used to seal non-target vessels in 11 people. Dose was calculated from body surface area, tumour volume and dose reduction was implemented based on lung shunt fraction. Peri-procedural octreotide infusion was given to minimise risk of carcinoid crisis. After SIRT, treatment with corticosteroids, ursodeoxycholic acid and omeprazole was done for 4 weeks to reduce risk of post-radioembolisation syndrome. Median net activity delivered was 1.4 GBq (range 0.5–2.4). Dose reduction of the activity prescribed was needed in 6 patients and number of sessions varies: whole liver single session (n=4), whole liver sequential (n=10), right lobe single session (n=10), and segmental (n=2). The number of cycles was not reported.

In the retrospective case series of 93 people (Tomozawa, 2018), body surface area was used to calculate dose. 52% of people had unilobar treatment and the rest had sequential bilobar treatment. Most people had 2 treatments (46%), followed by 40% who had 1 treatment and the remainder had 3 or 4. Total administered activity was 1.92GBq (SD=0.91).

In the prospective case series of 30 people (Cramer, 2017), they referenced general details of SIRT but these were not specific to the sample in their study. People with bilobar disease had sequential treatment with 1 month in between sessions. If, at 4 weeks, residual or recurrent tumour was observed, or if there

were residual symptoms related to tumour burden. No other details were reported.

Efficacy

Tumour response

Eight of 9 studies reported tumour response outcomes. Most commonly, studies evaluated response according to RECIST v1.1 but 3 studies reported outcomes on both RECIST v1.1 and mRECIST. One study reported median change in largest liver metastasis size in addition to RECIST data.

Disease control rates (the sum of complete and partial response and stable disease rates) were reported in 7 of the 8 studies. This was consistently high across studies and response criteria. Disease control rates ranged from 83% at 6 months according to RECIST v1.1 in the retrospective comparative study (Egger, 2020) to 100% at 6 months according to mRECIST at 6 months in the UK-based study of 24 people (Frilling, 2019b; sum of all response categories except progressive disease). The retrospective case series of 93 people reported 92% disease control rate at 1 year (Tomozawa, 2018; sum of all response categories except progressive disease).

Complete response rates were low in all studies that reported this independently. The lowest rate was 0% at 3 months according to RECISTv1.1, reported in the HEPAR PLuS single-arm trial (Braat, 2020). The highest complete response rate was 10%, reported in the same study on the mRECIST criteria at 3 months (Braat, 2020).

Comparative evidence between TACE and SIRT was reported in 2 studies and showed mixed findings (Egger, 2020; Ngo, 2021). The disease control rate at 6 months was statistically significantly higher for people who had TACE than people who had SIRT in the retrospective comparative study of 248 people

(Egger, 2020). This study also reported that decrease in largest liver metastasis was significantly greater in people who had TACE compared to SIRT, but this only just reached significance (p=0.05). But, when combined with the findings of 2 smaller studies with data beyond 3 months in the meta-analysis (Ngo, 2021), there was no statistically significant difference (n=3 studies). In this meta-analysis, there was also no statistically significant difference in disease control rate between SIRT and TACE within 3 months of treatment, but this trended toward favouring TACE (n=2 studies).

Symptom response

Symptom response was reported in 4 of 9 studies (Braat 2019; Braat 2020; Frilling, 2019b; Ngo 2021). Primary research studies reporting this data summarised rates in a subgroup of the sample that had symptoms at baseline. Symptom response was measured in different ways across studies but between 79% and 100% of people reported a response or stabilisation of symptoms; 22% (2/9) of people reported stable symptoms in the HEPAR PLuS single-arm trial (Braat, 2020) and 1/10 people in the UK-based study of 24 people reported being a little symptomatic (Frilling, 2019b).

Overall survival

Overall survival was reported in all 9 studies. The range of overall survival was broad within studies but average overall survival was quite consistent between studies. Median overall survival in people who had SIRT ranged from 14.5 months to 66.8 months in the meta-analysis comparing SIRT with TACE (Ngo, 2021). A similarly large range was reported in the meta-analysis of 27 studies, in which median overall survival ranged from 18 to 57 months (Frilling, 2019a). However, aggregated median overall survival among the 27 included studies was 32 months and this was similar to average estimates reported in most other studies included in the main evidence. Notably longer

median overall survival of 57 months was reported in the single arm trial of 30 people (Braat, 2020).

Comparative evidence from the meta-analysis suggested that people who have TACE have statistically significant longer overall survival than people who have SIRT (Ngo, 2021). But the largest study in this meta-analysis was also included in the main evidence and this showed no statistically significant difference when SIRT was compared with TACE (Egger, 2020).

Progression-free survival

Four studies reported progression-free survival (Egger, 2020; Frilling, 2019b; Ngo, 2021; Wong, 2022). The meta-analysis comparing SIRT with TACE found no significant difference in hepatic progression-free survival (Ngo, 2021) and this was consistent with the findings of the retrospective study of 248 people comparing SIRT with TACE (Egger, 2020). The RESiN registry study found that median progression-free survival was 25 months and ranged from 22 to 35 months (Wong, 2022). This contrasted with the UK-based analysis of 24 people that found that median progression-free survival was 41 months (Frilling, 2019b). However, 1- and 2-year progression-free survival rates were similar between studies (66% and 70% at 1 year and 50% and 54% at 2 years in Frilling, 2019b and Wong, 2022, respectively).

Quality of life

The most complete report of quality of life data was reported in the prospective case series of 30 people (Cramer, 2017). Of the 8 domains measured at 1, 3, 6, 12 and 24 months, the only domains and timepoints to show a significant, positive difference to baseline were mental health at 6 months, social functioning domain at 12 months.

A NET-specific health-related quality of life measure (EORTC QLQ-GINET 21 questionnaire) was used in the UK-based analysis of 24 people (Frilling, 2019b) but this data was not presented in full. Only symptom response was reported and this has been reported in the summary above.

Quality of life was also measured in the single arm-trial of 30 people (Braat, 2020) but this was only presented in a figure. Quantitative data was not reported in a way that could be extracted.

Length of stay

Length of stay was reported in the retrospective study of 248 people comparing SIRT with TACE (Egger, 2020). Length of stay was statistically significantly longer for people who had TACE than people who had SIRT; 92% of people who had SIRT had treatment in outpatient appointments, compared with 99% of people who had TACE, who spent at least 1 night in hospital.

Safety

Seven of 9 studies reported safety data. There were many types of adverse event, as exemplified by the list of 59 categories of CTCAE grade 3 or higher adverse events in the RESiN registry study (Wong, 2022). These are summarised here but refer to table 3 for more detail.

Mortality

Four studies reported mortality data with cause of death. The UK-based analysis of 24 people (Frilling, 2019b) reported no treatment-related deaths. The single-arm trial of 30 people reported 1 death caused by radiation-induced liver disease (Braat, 2020). The RESiN registry study reported that 1 person died of liver failure 11 months after treatment but said that the person had multiple previous chemotherapy treatments and did not state whether death was considered caused by SIRT (Wong, 2022). Other grade 5 events are reported in this

publication. There was no statistically significant difference between SIRT and TACE on 30- and 90-day mortality in the study of Egger (2020), but the authors did not report whether these were treatment related deaths.

Major adverse event rates

Major adverse events are here classified as those which were reported as 'major' or which were classified as grade 3 or higher using a grading system. Event rates varied between studies and is likely a reflection of whether biochemical and clinical toxicities were aggregated or not. Major adverse events were most commonly grade 3 across all studies. The highest major adverse event rates were presented in the single arm trial of 30 people (Braat, 2020) in which major biochemical toxicities were seen in up to 50% of people at 6 months. Clinical toxicity rates were lower with up to 10% of people having grade 3 abdominal pain. Contrastingly, major biochemical adverse event rates were much lower in the retrospective case series of 244 people (Braat, 2019), with 77% of people having grade 3 to 4 events. Combined toxicity rates were also lower than the single-arm trial in the RESiN registry study (Wong, 2022), 19% of all toxicities were attributed as definitely or probably associated with SIRT. Major adverse event rates were lower still across the rest of the studies that reported this information: in the retrospective comparative study of SIRT and TACE (Egger, 2020), major adverse events were reported in 66% of people. This study is not clear but implies these were clinical events only. In the UK study of 24 people, there were no grade 3 or 4 biochemical toxicities (Frilling, 2019b). Clinical events were not graded in this study.

Minor adverse event rates

Minor adverse event rates were higher than major adverse event rates across all studies. Between 52% (Braat, 2019) and 83% (Braat, 2020) of people

experienced a grade 1 or 2 minor adverse events. When clinical and biochemical events were graded separately, clinical toxicity was lower.

Clinical adverse events

Most studies that reported rates of individual clinical events showed that abdominal pain was the most common. Other commonly reported clinical adverse events were fatigue, nausea, vomiting, anorexia, fever and flushing. The retrospective case series of 244 people (Braat, 2019) measured these at 3 and 6 months; by 6 months, only 6% of people had persistent adverse events (mainly abdominal pain) and 55% had no clinical toxicities. Less common adverse events included: hepatic abscess in a person with colonised bile duct, persistent abdominal pain at 6 months, radiation-induced gastric ulcer, radiation-induced liver disease, radiation pneumonitis, cholangitis with bilioenteric anastomosis, malaise, subfebrile, shivering and oedema. Longer-term (1 year) adverse events are described below.

Biochemical toxicity

The following biochemical toxicities were reported: bilirubin, creatine, alanine aminotransferase, alkaline phosphatase, neutropoenia, lymphocytopenia, thrombocytopaenia, anaemia, leucopoenia, γ-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, ammonia, albumin. Comparative evidence of unilobar compared with bilobar treatment biochemical adverse event rates showed that people who people who had unilobar therapy only showed increased alkaline phosphatase levels (Tomozawa, 2018). Multiple grade 2 and 3 biochemical toxicities were seen in people who had bilobar treatment.

Clinical toxicity at 1 year

One study explicitly measured clinical toxicity at 1 year (Tomozawa, 2018). Of 52 people, 29% (n=15) had cirrhosis-like morphology or portal hypertension at 1 year. This was more common in people who had bilobar treatment.

Comparison of other adverse event rates between SIRT and TACE

The meta-analysis comparing SIRT with TACE (Ngo, 2021) found that there were no statistically significant differences in the rates of major or minor adverse events between groups. In the retrospective comparative study of 248 people (Egger, 2020), the authors noted that while post-procedure biochemical toxicity favoured SIRT over TACE, there were no differences in 30-day overall or major complication rates between groups.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal adverse events:

- carcinoid crisis caused by SIRT
- gastritis
- perforation of the bowl
- ischaemic effects.

Nine professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- Studies included in this overview reported consistently high rates of disease and symptom control. Complete response rates were low. Different RECIST criteria were used within and between studies to measure tumour response. These had different findings on granular outcome classifications such as complete and partial response and stable disease, but they tended to find the same proportions of people who were classed in the disease control and progressive disease groups.
- Average overall survival was relatively consistent across studies, but overall survival varied with wide confidence intervals within studies.
- There is some inconsistency in the evidence that compares tumour response outcomes between people who had SIRT and TACE.
- There were many types of adverse event that ranged in severity from mild to death. Event rates varied between studies but biochemical toxicities were generally more common than clinical adverse event rates. There were reports of cirrhosis-like morphology and portal hypertension in the longer-term (evidence at 1 year; Tomozawa, 2018). Comparative evidence between people who had SIRT and TACE suggests that minor and major event rates are comparable between these 2 procedures.
- The evidence includes some large, international studies with a range of study designs, including some comparative evidence. One study was done exclusively in the UK (Frilling, 2019b). A few studies had reasonable follow up but the extent to which long-term data contributed to safety data was unclear in some studies. Most studies reported tumour and symptom response at 3 and 6 months. One study (Tomozawa, 2018) explicitly examined 1-year

safety data. The only randomised evidence found in this search was a pilot study. This was small (n=11) and had high risk of bias, so was not included in the main evidence.

- Dose and planning methods varied between studies. Some studies used dose reduction methods if there was evidence of lung shunting over a threshold. Other studies split treatment sessions if bilobar treatment was needed. Professional expert questionnaires reflected this finding with advice that dose and planning methods are evolving. Professional expert questionnaires advise that because SIRT is embolic and a form of brachytherapy, precise dose planning and vascular radiology and nuclear medicine expertise is needed. They reported that toxicity may be related to experience of the team.
- The type of microsphere (glass or resin) and radioisotope (^{90}Y or ^{166}Ho) varied between studies. Most frequently, studies used microspheres labelled with ^{90}Y. Only 1 study used ^{166}Ho.
- Treatment histories and disease profiles were often complex and heterogeneous within and between studies. Studies generally had similar inclusion criteria and samples of a similar age. Professional expert questionnaires advised that patient selection is complex, and people with mNETs are a relatively rare and heterogeneous disease group. Treatment history is likely to be heterogeneous in practice. Some studies reported prognostic factors (not reported in this overview) that associate with better response to SIRT but there were many and authors commented that they are not yet well-recognised.
- It was unclear whether people had further treatment after SIRT in most studies. Three studies explicitly reported that people who had SIRT went on to have other interventions after SIRT (Braat, 2019; Frilling, 2019b; Wong, 2022). No study explained whether or how this was accounted for in follow-up data and findings.

- The systematic review and meta-analysis by Ngo (2021) was reasonable in quality and examined an important comparison between SIRT and another intra-arterial procedure (TACE). The meta-analysis only included 6 retrospective studies, and fewer studies contributed to the pooled analysis of tumour and symptom response data. The meta-analysis showed that other than overall survival, the procedures were comparable in tumour and symptom response and safety outcomes. The authors did not report whether differences in the length of follow up between studies included in pooled outcomes may have affected the findings. The more recent and larger studies included in the meta-analysis (which included the retrospective comparative analysis of 248 people by Egger, 2020 that was also included in the main evidence) showed similar efficacy between groups and a trend toward fewer minor adverse events in SIRT. The authors acknowledge that laboratory and clinical adverse events were not analysed separately. The authors concluded that comparative and better-quality evidence was needed to confirm the findings that TACE was better than SIRT for overall survival. There were differences in some baseline characteristics. The authors note that overall survival did not relate to disease control rate. They acknowledge that subsequent treatment could have affected survival outcomes in this analysis. They ask for research to clarify whether subgroups may benefit from most from SIRT and TACE. No conflicts of interest were reported for this study.
- The meta-analysis of 27 studies (Frilling, 2019a) was of poor quality but included a lot of evidence and findings seem to be consistent with earlier meta-analyses that included fewer and less recent studies (for example, Devcic, 2014, in table 5). Outcomes were summarised together regardless of follow-up point. The authors did not report how this might have affected the findings. They report that the findings support the clinical effectiveness and safety of SIRT. The authors acknowledge that the optimal timepoint to measure response to SIRT is unclear. Overall, the authors reported that SIRT

has good potential for people with carcinoid syndrome and acknowledge that this will probably be used in combination and sequence with other therapies. They state more research is needed to identify which patients are most likely to benefit from this treatment. Some conflicts of interest with one of the companies that manufacture SIRT device were declared. This was the same publication that reported the retrospective case series of 24 people in the UK.

- In the retrospective study of 248 people that compared SIRT with TACE (Egger, 2020), there were some differences in baseline characteristics between groups. The authors state that both SIRT and TACE showed safe and effective control of unresectable mNETs. They highlight that the hospital stay is longer for TACE but that the short-term radiographic response was not as good. They report that the lower disease control rate in the SIRT group compared with the TACE and with outcomes reported in other studies of SIRT might be because more than 10% of the group had poorly differentiated tumours. The authors highlight the heterogeneity of the disease group and state that further, prospective and comparative research is needed to understand the patients most likely to benefit. This study was the largest study included in the Ngo (2021) meta-analysis. No conflicts of interest were declared.
- In the RESiN registry study (Wong, 2022), the authors report that, given their findings reflect previous research, SIRT is effective for mNETs and has an acceptable toxicity profile. They acknowledge that dosimetry methods that became outdated in 2021 were mostly used. The authors acknowledge that there is no randomised evidence comparing SIRT with other intra-arterial therapies. Multiple authors reported conflicts of interest with one of the companies that manufacture a SIRT device.
- In the retrospective study of 244 people (Braat, 2019), the authors reported that SIRT was shown to be safe and effective for the treatment of mNETs, although they also note high rates of missing data for clinical toxicity at

6 months (39%). The authors highlight the utility of SIRT in relieving symptoms of carcinoid syndrome and that positive outcomes for tumour response might be seen after 3 months. The authors state that randomised evidence is needed and more understanding about which people with mNETs might benefit most, and where SIRT sits in the sequencing of other treatment options, is needed. Several authors had received funding or consulted for one of the companies that manufacture a SIRT device. Travel and accommodation expenses were partially covered by this company.

- In the single-arm trial of 30 people (Braat, 2020), the centre that did the trial owns royalties for the ^{166}Ho microspheres. This was the only study that reported data on this radionuclide. This study reported notably higher average overall survival than other studies. Everyone in the trial also previously had systemic therapy (PRRT). The authors report that the combination of SIRT with PRRT was safe and effective in their study, but that randomised evidence is needed. No quantitative quality of life data could be extracted from this study for the overview but the authors report that mostly small, temporary decreases in quality of life were observed following treatment.
- In the retrospective case series of 93 people (Tomozawa, 2018), the authors acknowledge that therapies had before or after SIRT may have affected the long-term safety findings that they report. They also note that cause of death was not available for some people. They report that SIRT is a safe and promising treatment option for unresectable mNETs, although bilobar treatment did result in more frequent evidence of toxicity. The authors acknowledge that prospective evidence is challenging to collect but is needed. Some conflicts of interest including grants from companies that manufacture SIRT devices were reported.
- In the prospective case series of 30 people (Cramer, 2017), no conflicts of interest were declared. In contrast with studies that presented patient-reported symptom response, this study reported quality of life data using standardised

measure of health-related quality of life. However, there was a high drop-out rate (50% of the sample did not complete a survey 1 month-post treatment and 17% completed the last follow-up at 24 months).

Ongoing trials:

- ArTisaN trial protocol: a single centre, open-label, phase II trial of the safety and efficacy of TheraSphere selective internal radiation therapy (SIRT) in the treatment of inoperable metastatic (liver) neuroendocrine neoplasia (NENs). DOI: 10.1186/s12885-022-09859-9. NCT04362436; Single arm trial; n=24. Due to complete September 2024.

Existing assessments of this procedure

European Neuroendocrine Tumour Society (ENETS) 2022 Consensus Guidelines on carcinoid syndrome and carcinoid heart disease recommended:

- Loco-regional therapies may be considered for patients with predominant liver inoperable metastases, requiring carcinoid symptom control. TAE, TACE or SIRT controls carcinoid syndrome symptoms in up to 75% cases and can be repeated if there is preserved liver function. For patients with carcinoid syndrome and grade 1 intestinal NET, where chemotherapy offers little benefit, bland hepatic embolisation is preferred.
- TACE or SIRT may be reserved for grade 2 intestinal or non-intestinal NET. In the absence of conclusive data on which trans-arterial treatment is most efficient, the selection should be made based on individual factors such as tumour load, topography of metastases, and arterial anatomy.

European Neuroendocrine Tumor Society (ENETS) 2016 Consensus Guidelines Update for the management of distant metastatic disease of intestinal,

pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary origin recommended:

- Locoregional therapies, including TAE, TACE, SIRT and ablative techniques, should be considered for the control of symptoms and tumour growth in unresectable disease.
- Choice of locoregional therapy is based on individual patient features and physician expertise.
- There is consensus that SIRT is investigational and comparative trial evidence of SIRT compared to TAE is required as well as more long-term safety data to establish the procedure in the treatment of NETs.

Recommendations from the NET-Liver-Metastases Consensus Conference (2012) were endorsed by European–African Hepato-Pancreato-Biliary Association (E-AHPBA), the European Neuroendocrine Tumor Society (ENETS), the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), the European Society of Surgical Oncology (ESSO), the Great Britain and Ireland Hepato-Pancreato-Biliary Association (GBIHPBA), the International Hepato-Pancreato-Biliary Association (IHPBA) and the UK and Ireland Neuroendocrine Tumour Society (UKINETS). The recommendations, published in Kennedy, et al., (2015), were:

- TAE, TACE and SIRT were all recommended for use in mNETs.
- The quality and strength of reports available at the time did not allow any modality to be determined as superior in terms of imaging or symptomatic response, or in terms of overall survival.
- SIRT may be more beneficial than TAE and TACE because it may have less side effects and requires less treatment sessions.
- Based on European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines at the time, the recommendations stated that SIRT can be

substituted for TAE or TACE in patients with either liver-only disease or those with limited extrahepatic metastases.

Related NICE guidance

Interventional procedures

NICE interventional procedures guidance on melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver. Recommendation: special for metastases in the liver from ocular melanoma; otherwise research only.

NICE interventional procedures guidance on selective internal radiation therapy for unresectable colorectal metastases in the liver. Recommendation: special arrangements for people who cannot tolerate chemotherapy or have liver metastases refractory to chemotherapy; research only for people who can have chemotherapy.

NICE interventional procedures guidance on selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma. Recommendation: research only.

NICE interventional procedures guidance on microwave ablation for treating liver metastases. Recommendation: standard arrangements.

NICE interventional procedures guidance on selective internal radiation therapy for primary hepatocellular carcinoma. Recommendation: standard arrangements.

NICE interventional procedures guidance on irreversible electroporation for treating liver metastases. Recommendation: research only.

NICE interventional procedures guidance on cryotherapy for the treatment of liver metastases. Recommendation: special arrangements.

NICE interventional procedures guidance on radiofrequency ablation for colorectal liver metastases. Recommendation: standard arrangements.

Technology appraisals

NICE technology appraisal guidance on selective internal radiation therapies for treating hepatocellular carcinoma. Recommendation: SIR-Spheres and Therasphere recommended as an option in a subgroup and with provision under commercial arrangements; QuiremSpheres is not recommended for use.

NICE technology appraisal guidance on lutetium (177Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours.

NICE technology appraisal guidance on everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease.

Professional societies

- British Association for the Study of the Liver (BASL)
- European Neuroendocrine Tumour Society (ENETS)
- UK and Ireland Neuroendocrine Tumour Society (UKI NETS)
- Association of Cancer Physicians
- British Association of Surgical Oncology (BASO)
- British Institute of Radiology
- British Nuclear Medicine Society
- British Society of Gastrointestinal and Abdominal Radiology

- British Society of Interventional Radiology
- British Society for Neuroendocrinology
- Royal College of Radiologists
- Society of Radiographers
- Royal College of Physicians
- Royal College of Physicians and Surgeons of Glasgow
- Royal College of Physicians of Edinburgh
- Royal College of Surgeons

Evidence from patients and patient organisations

NICE received 1 questionnaire from a patient who had the procedure.

Patients' views on the procedure were consistent with the published evidence and the opinions of the professional experts. See the patient commentary summary for more information.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. 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.

References

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2. Frilling A, Clift AK, Braat AJAT, et al, (2019). Radioembolisation with ^{90}Y microspheres for neuroendocrine liver metastases: an institutional case series, systematic review and meta-analysis, HPB, 21, 773-783.

3. Egger ME, Armstrong E, Martin RCG, et al, (2020). Transarterial chemoembolization vs radioembolization for neuroendocrine liver metastases: A multi-institutional analysis, Journal of the American College of Surgeons, 230(4), 363-371

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6. Braat AJAT, Bruijnen RCG, van Rooij R, et al, (2020). Additional holmium-166 radioembolisation after lutetium-177-dotatate in patients with neuroendocrine tumour liver metastases (HEPAR PLuS): a single-centre, single-arm, open-label, phase 2 study, The Lancet, 21, 561-570.

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8. Cramer B, Xing M, Kim HS (2017). Prospective Longitudinal Quality of Life Assessment in Patients With Neuroendocrine Tumor Liver Metastases Treated With ^{90}Y Radioembolization, Clinical Nuclear Medicine, 41(12), 493-497.

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10. Kennedy A, Bester L, Salem R, et al, (2015). Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver-Metastases Consensus Conference, HPB, 17, 29–37.

11. Pavel M, O'Toole D, Costa F, et al, (2016). ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site, Neuroendocrinology, 103, 172-185.

Methods

NICE identified studies and reviews relevant to selective internal radiation therapy from the medical literature. The following databases were searched between the date they started to 31st May 2023: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology.
- Patients with neuroendocrine tumours metastatic to the liver.
- Intervention or test: selective internal radiation therapy.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE ALL (Ovid)	17/01/2024	1946 to Jan 16, 2024
EMBASE (Ovid)	17/01/2024	1974 to 2024 Jan 16
EMBASE Conference (Ovid)	17/01/2024	1974 to 2024 Jan 16
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	17/01/2025	Issue 1 of 12, January 2024
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	17/01/2024	Issue 1 of 12, January 2024
International HTA database (INAHTA)	19/01/2024	-

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

MEDLINE search strategy

Ovid MEDLINE(R) <1946 to May 31, 2023>

neuroendocrine tumors/ and exp liver/
(neuroendocrine adj4 (tumo* or neoplas* or carcinoma* or cancer* or metast*) adj4 (liver or hepat*)).tw.
((net or mnet) adj4 (liver or hepat* or metast*)).tw.
nelm.tw.
exp Carcinoid Tumor/ and exp liver/
(carcinoid adj4 (tumo* or syndrome*) adj4 (liver or hepat*)).tw.
or/1-6
("selective internal radiotherap*" or "selective internal radiation therap*" or "select internal radiotherap*" or sirt).tw.
Embolization, Therapeutic/
(radioembolization or radioembolisation or radioembolotherap* or tare).tw.
(intraarterial brachytherapy or intra arterial brachytherapy).tw.

exp yttrium/
(yttrium 90 or y90 or 90y).tw.
Holmium/
(holmium 166 or 166Ho).tw.
Microspheres/
(bead* or microbead* or sphere* or microsphere* or particle*).tw.
or/8-17
7 and 18
(sir sphere or therasphere or quiremsphere*).tw.
19 or 20
animal/ not human/
21 not 22
limit 23 to english language/
limit 23 to ed=20230501-20240131

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Table 5 additional studies identified

Article	Study design, number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Addeo P, Mathelin P, Marini P et al (2023). Sequential Y90 liver radioembolization and portal vein embolization: an additional strategy to downstage liver tumors and to enhance liver hypertrophy before major hepatectomies. Langenbeck's Archives of Surgery, 408: 339.	Retrospective comparative study n=30 (n=5 people had SIRT) Mean follow-up was not reported but data was from between January 2019 and September 2022. Resection happened a mean of 189 days after SIRT.	All people who had SIRT in this study also had portal vein embolization followed by resection. They were selected for SIRT on a case-by-case basis. When compared with portal vein embolization alone and liver venous deprivation, SIRT before portal vein embolization had statistically significantly higher hypertrophy ratio and hypertrophy degree and shorter time to normalize bilirubin and prothrombin time. It took longer to complete the therapy. The authors conclude it is a safe alternative to downstage liver tumors and to enhance liver hypertrophy before major hepatectomies.	Larger, prospective studies were included in the main evidence.

Alsultan, A.A., Smits, M.L.J., Barentsz, M.W. et al (2019). The value of yttrium-90 PET/CT after hepatic radioembolization: a pictorial essay, *Clinical and Translational Imaging, 7,* 303–312.	Retrospective case reports n=1 mNET (n=5 total) Patients were followed until the article was submitted.	Patient alive at submission of article. Severe pain in liver, fever, abscess in necrotic tissue requiring surgical drainage and antibiotics following treatment. Authors recommend that PET/CT used to improve dose planning and that treatment went as planned.	Studies with prospective designs, larger samples and more clinical outcomes measures were included.
Andrews, J.C., Walker, S.C., Ackermann, R.J. et al., (1994). Hepatic Radioembolization with Yttrium-90 Containing Glass Microspheres: Preliminary Results and Clinical Follow-Up, *J Nucl Med, 35*,1637-1644.	Prospective dose escalation study n=6 mNET (n=24 total) Follow-up until disease progression	16 weeks after therapy, 3 people had minimal response and 3 people showed stable disease. Four of 6 people (66%) survived with stable disease for 16 months after SIRT.	Studies with larger samples and more clinical outcome measures in the sample of interest were included.
Arslan, N., Emi, M., Alagoz, E., et al (2011). Selective intraarterial radionuclide therapy with Yttrium-90 (Y-90) microspheres for hepatic neuroendocrine metastases: initial experience at a single center, *Vojnosanit Pregl, 68*(4), 341–348.	Retrospective case series n=10 Mean follow-up= 6 months	Overall response rate was 90% (9/10). Complete response in 30%, partial response in 50%, stable disease in 1 person and disease progression in 1 person. Tolerance was satisfactory for most. Almost all people reported some degree of mild-to-moderate abdominal pain, nausea, lethargy, anorexia, and fever from 1 week to 1 month after the treatment. No cases	This study was included in the meta-analysis by Frilling (2019). Studies with prospective designs, larger samples and longer follow up periods were included in Table 2.

		of radiation pneumonitis or radiation induced liver disease.	
Barbier, C.E., Garske-Roman, U., Sandstrom, M., et al., (2016). Selective internal radiation therapy in patients with progressive neuroendocrine liver metastases. *Eur J Nucl Med Mol Imaging , 43*, 1425–1431.	Retrospective case series n=40 Mean follow-up=20 months	At a mean of 3 months, disease control was seen in 94% of people. At a mean of 20 months, disease control was seen in 57%. Mean overall survival from the first SIRT was 34.8 months and survival rates at 1, 2, 3 and 5 years were 76%, 59%, 52% and 35% respectively. Adverse effects were generally mild and easily manageable except in one patient who died from radiation-induced liver failure.	This study was included in the Frilling (2019) meta-analysis. Studies with larger samples, prospective designs, longer follow-up periods were included.
Benson, A.B., Geschwind, J.F., Mulcahy, M.F., et al., (2013). Radioembolisation for liver metastases: Results from a prospective 151 patient multi-institutional phase II study, *European Journal of Cancer, 49,* 3122-130.	Prospective multicentre case series n=43 people with mNETs (n=151 total) People were followed up every 6 months until deceased.	No patients had complete response; 21% had partial response; 72% had stable disease and 7% had progressive disease. Hepatic progression free survival was 17.9 months (95%CI=13.6 to n/a). Overall survival at 2 years was 79%.	This study was included in the Frilling (2019) meta-analysis. More recent studies and studies with larger samples were included. A long list of adverse events was reported but not specific to mNETs.

Braat, A.J.A.T, Ahmadzadehfar, H., Kappadath, S.C., et al (2020). Radioembolization with 90Y Resin Microspheres of Neuroendocrine Liver Metastases After Initial Peptide Receptor Radionuclide Therapy. *Cardiovasc Intervent Radiol, 43,* 246–253	Retrospective case series n=44 All data that was collected between December 2006 and May 2016.	All procedures followed PRRT. Median overall survival was 3.5 years (95%CI 1.8 to 5.1). Disease control rate was 91% at 3 months. Clinical response was 65% (15/23 symptomatic patients). Clinical toxicity was observed in 26% of people, lymphocytopenia in 42% but other grade 3 or 4 toxicities in less than or equal to 10%.	Studies with larger samples, prospective designs and longer follow-up periods were included.
Braat, MNGJA, Ebbers SC, Ahmed AA et al (2023). Prophylactic Medication during Radioembolization in Metastatic Liver Disease: Is It Really Necessary? A Retrospective Cohort Study and Systematic Review of the Literature. Diagnostics 13: 3652.	Retrospective case series and systematic review n=70 (n=30 mNETs) in the case series. N=8 studies (n=5 included mNETs or a mixture of mNET and colorectal metastases) Case series follow-up=at least 3 months	This study explored the role of periprocedural prophylactic medication for SIRT. The retrospective analysis of 70 people found no association between use of prophylactic medication and clinical toxicity. The systematic review found clinical adverse events grade 3 or higher happened in 12% of people. Each study used different medication types, for different lengths of time and for different indications. The authors conclude that people who have SIRT for either mNETs or colorectal metastases, the use of periprocedural prophylactic medication is not	Larger prospective studies and larger reviews that each included data on more clinical outcomes were included in the key evidence.

		supported by conclusive evidence and there are no standardised protocols.	
Cao, C.Q., Yan, T.D., Bester, L., et al. (2010). Radioembolization with yttrium microspheres for neuroendocrine tumour liver metastases, *British Journal of Surgery Society Ltd, 97*, 537-543.	Prospective database from 2 centres analysed retrospectively n=58 Follow-up included all data collected between 2003 and 2008	10% had complete response, 24% partial response, 24% had stable disease and 29% had disease progression. Overall survival rates at 1, 2 and 3 years were 86%, 58% and 47% respectively; median survival was 36 (range 1–61) months.	This study was included in the Frilling (2019) meta-analysis. More recent studies have been included in Table 2.
Celeen, F., Theisen, D., Garcia de Albeniz, X., et al., (2015). Towards New Response Criteria in Neuroendocrine Tumors: Which Changes in MRI Parameters Are Associated With Longer Progression-Free Survival After Radioembolization of Liver Metastases? *JOURNAL OF MAGNETIC RESONANCE IMAGING, 41,* 361–368.	Retrospective case series n=45 Follow-up= 3 months	At 3 months, no patients were in complete remission, 13% showed partial response, 82% showed stable disease and 5% showed progressive disease. Decreases in tumour arterial enhancement, increase in necrosis and decrease in tumour diameter were statistically significantly associated with increased progression free survival.	Studies with larger samples prospective designs, longer follow-up periods and more clinical outcomes were included.
Chasanti, O., Jahangiri, Y., Matsui, Y. et al (2017). Tumor Dose Response in Yttrium-90 Resin Microsphere Embolization for Neuroendocrine Liver	Retrospective case series from a single centre	In this sample of people for whom surgery was not suitable, 67% (8/12) showed complete or partial response at	This study was included in the meta-analysis by Frilling

Metastases: A Tumor-Specific Analysis with Dose Estimation Using SPECT-CT. *J Vasc Interv Radiol, 28,* 1528–1535.	n=15 Median follow-up= 7.6 months.	follow-up. The mean absorbed dose of radiation was higher in responders than non-responders (p=.007). mNET cell differentiation, tumour grade, and overall tumour burden, were not associated with response.	(2019). Studies with larger samples prospective designs, longer follow-up periods and more clinical outcomes were included.
Chen, J.X., Rose, S., White, S.B., et al., (2017). Embolotherapy for Neuroendocrine Tumor Liver Metastases: Prognostic Factors for Hepatic Progression-Free Survival and Overall Survival, Cardiovasc Intervent Radiol, 40, 69-80.	Retrospective case series from multiple institutions. N=155 Data between 2004 and 2015 were analysed.	Radioembolisation tended toward worse overall survival than TACE and TAE. There were no significant differences in hepatic progression free survival between types of embolotherapy.	This study was included in the meta-analyses by Frilling (2019) and Ngo (2021). Larger studies reporting similar outcomes were also included.
Currie, B.M., Hoteit, M.A., Ben-Josef, E., et al., (2019). Radioembolization-Induced Chronic Hepatotoxicity: A Single-Center Cohort Analysis. *J Vasc Interv Radiol, 30,* 1915–1923	Retrospective case series from a single centre n=53 mNET (n=98 total) Follow-up data collected between 2005 and 2014.	SIRT-induced chronic hepatotoxicity (occurring at least 6 months after therapy and persisting) was observed in 7/53 people with mNETs.	Studies with larger samples, prospective designs and more clinical outcomes were included. Another study included in the main evidence explicitly reported the effects of SIRT on

			long term clinical toxicity (Su, 2017).
Currie, B.M., Nadolski, G., Mondschein, J. et al., (2020). Chronic Hepatotoxicity in Patients with Metastatic Neuroendocrine Tumor: Transarterial Chemoembolization versus Transarterial Radioembolization, *J Vasc Interv Radiol, 31*, 1627–1635	Retrospective cohort n=91 total (n=28 had SIRT; n=63 had TACE) Follow-up was until death, loss to follow up or initiation of alternative treatment	A statistically significant difference in the number of people who had intrahepatic disease progression favoured SIRT over TACE (43% and 75%, respectively, p=.005). There was no statistically significant difference but a trend for more embolotherapy induced chronic hepatic toxicity in the SIRT than TACE cohort (14% and 3%, respectively, p=0.07). There was no statistically significant difference but a trend for more grade 4 and 5 injuries in the SIRT than TACE cohort (27% and 5% of people, p=.06). Delayed hepatotoxicity was observed at a median of 2 (range 1 to 6 years) and 2.3 (range 6 months to 5 years) in the TACE and SIRT groups, respectively.	Studies with larger samples prospective designs were included. Another study included in the main evidence explicitly reported the effects of SIRT on long term clinical toxicity (Su, 2017).
Devcic, Z., Rosenberg, J., Braat, A.J.A., et al., (2014). The Efficacy of Hepatic ^{90}Y Resin Radioembolization for Metastatic Neuroendocrine Tumors: A Meta-Analysis, *The*	Systematic review and meta-analysis n=12 studies (n=435 procedures)	Pooled objective response rate was 50% (95%CI= 38 to 62%) and disease control rate was 86% (95%CI= 78 to 92%). Median overall	The Frilling (2019) meta-analysis in Table 2 is more recent and has

Journal of Nuclear Medicine, 55(9), 1404-1410.	Follow-up information was not reported.	survival was 28.5 months (range 14 to 70 months).	more studies. The findings were similar in both studies.
Do Minh, D., Chapiro, J., Gorodetski, B., et al., (2017). Intra-arterial Therapy of Neuroendocrine Tumor Liver Metastases: Comparing conventional TACE, Drug-Eluting Beads TACE and ^{90}Yttrium Radioembolization as Treatment Options using a Propensity Score Analysis Model, *Eur Radiol, 27*(12), 4995–5005	Retrospective cohort n=192 (n=44 SIRT, n=122 TACE, n=26 DEB-TACE) Median follow-up=75.6 months	Median overall survival for TACE, DEB-TACE and SIRT was 33.8 months, 21.7months and 23.6 months, respectively. TACE demonstrated significantly longer median overall survival compared with DEB-TACE(p=.04) and SIRT (p=.03). The five-year survival rate after initial TACE, DEB-TACE and SIRT was 28.2%, 10.3% and 18.5%, respectively. Adverse events were considered similar across groups.	This study was included in Ngo et al., (2021) and the Frilling (2019) meta-analyses. Larger studies with prospective data were included.
Doyle PW, Workman CS, Grice JV (2024). Partition Dosimetry and Outcomes of Metastatic Neuroendocrine Tumors after Yttrium-90 Resin Microsphere Radioembolization. Journal of Vascular and Interventional Radiology.	Retrospective case series n=36 people Median follow-up=582 days	This study explored the relationship between mean tumour absorbed dose and outcomes after SIRT. Overall response according to mRECIST was 85%. The tumours that were classed as responders had higher tumour absorbed dose. The authors conclude that doses of 120 Gy or more led to higher likelihood of overall response.	Larger, prospective studies and studies with longer follow-up were included in the key evidence.

Ebbers, S.C., Roekel, C, Braat ,M.N.G.J.A., et al., (2022). Dose–response relationship after yttrium-90-radioembolization with glass microspheres in patients with neuroendocrine tumor liver metastases, *European Journal of Nuclear Medicine and Molecular Imaging, 49*, 1700-1710.	Retrospective case series for dose response analysis n=26 Follow-up=3 months	There is a clear dose-response relationship such that higher doses of 90Y was related to better response outcomes on RECIST v1.1. The authors recommend a minimum planned tumour absorbed dose of 150Gy.	Larger, prospective studies with longer follow-up and more outcomes were included.
Ebbers, Brabander, T., Tesselaar, M.E.T., et al., (2022). Inflammatory markers and long term hematotoxicity of holmium-166-radioembolizatio n in liver-dominant metastatic neuroendocrine tumors after initial peptide receptor radionuclide therapy, *EJNMMI Research, 12*(7).	Secondary analysis of prospective single arm trial (HEPAR PLuS trial) data for a toxicity analysis n=31 Follow-up=12 months	Toxicity after sequential treatment with PRRT and ^{166}Ho-radioembolization is limited and temporary. No significant relationship with survival was found. Thombocyte-to-lymphocyte ratio 3 weeks after treatment may be a predictor of tumour response.	All participants were from the HEPAR plus study which is included. This study reported laboratory toxicity, there was no focus on clinical toxicity.
Ekmekcioglu O, Erdem U, Arican P, et al (2023). The value of radioembolisation therapy on metastatic liver tumours - A single centre experience. Nuclear Medicine 62: 214-219.	Retrospective case series n=34 (n=10 had mNETs) Mean follow-up was not reported but data were collected between 2016 and 2022	Mean survival rate was 14.59 ± 12.59 months after treatment but this included people with multiple types of tumour not just mNETs. People with neuroendocrine tumour type had a longer life expectancy after treatment than those with colon carcinoma. Response rates after SIRT were the highest in the mNET group (70 %) and overall survival was 26 months.	Studies that reported more clinical outcomes in a larger group of people with mNETs were included.

Elf, A.K., Andersson, M., Henrikson, O., et al., (2018). Radioembolization Versus Bland Embolization for Hepatic Metastases from Small Intestinal Neuroendocrine Tumors: Short- Term Results of a Randomized Clinical Trial, *World Journal of Surgery, 42,* 506-513.	Pilot RCT comparing SIRT with TAE. n=11 (n=6 had SIRT; n=5 had TAE) Median follow-up=195 days	There were no responders in the SIRT group at 3 months (0/6). All people who had TAE showed partial response (5/5, p=.002). At 6 months, there was no significant difference in the proportion of people who showed tumour response (p=0.24). Median hospital stay was significantly longer for people who had TAE compared with SIRT (p=0.02).	Studies with larger samples and longer follow-up were included.
Engelman, E.S., Leon-Ferre, R., Naraev, B.G. et al., (2014). Comparison of Transarterial Liver-Directed Therapies for Low-Grade Metastatic Neuroendocrine Tumors in a Single Institution. *Pancreas, 43*(2), 219–225.	Retrospective case series from a single centre comparing TACE, HAE and SIRT outcomes. n=42 (n=12 had SIRT). The study included data from medical records between 2001 and 2011.	Time to progression in patients treated with SIRT was 33.4 months, compared with HAE (12.1 months) or TACE (15.1 months; comparisons were not significant). SIRT did not have increased toxicity compared to HAE or TACE and the toxicity profile overall was acceptable for all modalities.	This study was included in the meta-analysis by Ngo (2021). More recent studies with larger samples prospective designs and more clinical outcomes were included.
Ezziddin, S., Meyer, C., Kahancova, S., et al (2012). ^{90}Y Radioembolization After Radiation Exposure from Peptide Receptor Radionuclide Therapy. *The*	Retrospective case series from a single centre n=23	All procedures followed PRRT. Median overall survival was 29 months (95%CI= 4 to 54) months after SIRT. Tumour	This study was included in the Frilling (2019) meta-analysis.

Journal of Nuclear Medicine, 53(11), 1663–1669.	Median follow-up=38 months	response indicated disease control in 91% at 3 months. Symptomatic response at 3 months was 80%. No grade 4 toxicity. One grade 2 gastroduodenal ulcer.	Studies with larger samples prospective designs, longer follow-up periods and more clinical outcomes were included.
Fan, K.Y., Wild, A.T., Halappa, V.G., (2016). Neuroendocrine tumor liver metastases treated with yttrium-90 radioembolization. *Contemporary Clinical Trials, 50*, 143–149.	Retrospective case series n=38 Median follow-up= 17 months	Median survival was 29.2 months. Disease control in 86% and 5 people (14%) developed progressive disease. Grade 3 non-serologic toxicities included abdominal pain (11%), fatigue (11%), nausea/vomiting (5%), ascites (5%), dyspnoea (3%), diarrhoea (3%), and peripheral oedema (3%). No grade 4 or 5 toxicity was reported.	This study was included in the Frilling (2019) meta-analysis. Studies with larger samples, prospective designs and longer follow-ups were included.
Fidelman, N., Kerlan, R.K., Hawkins, R.A., et al., (2014). ^{90}Y Glass Microspheres for the Treatment of Unresectable Metastatic Liver Disease from Chemotherapy-Refractory Gastrointestinal Cancers: A Pilot Study, *Journal of Gastrointestinal Cancer, 45,* 168-180.	Prospective cohort study n=9 people with mNETs (n=30 total sample) Follow-up= 6 months	No people with mNETs reached complete response. Partial response was observed in 78% (7/9) and stable disease in 22% (2/9). Two of 3 SAEs were reported in mNET patients (1 person had carcinoid crisis at the time of SIRT which required hospitalisation for 6 days. After stabilised they received a second dose of SIRT.	This publication was included in the meta-analysis by Frilling (2019). A more recent publication of this sample is also in the appendix.

		The other patient had grade 4 gastric ulcer).	
Fidelman, N., Kerlan, R.K., Hawkins, R.A., et al., (2016). Radioembolization with ^{90}Y glass microspheres for the treatment of unresectable metastatic liver disease from chemotherapy-refractory gastrointestinal cancers: final report of a prospective pilot study. *Journal of gastrointestinal Oncology, 7*(6), 860-874.	Prospective cohort study n=11 people with mNETs (n=30 total sample) Median follow-up=48.2 months	100% (6/6) patients that had carcinoid syndrome reported near or complete remission of symptoms within 1 month of SIRT. Median time to maximum response was 11 months (range= 5 to 29.6 months). After median follow-up of 48.2 months, 73% had disease progression in the treated lobe. Median response duration was 23.4 months (range=9.3 to 48 months).	This study was included in the meta-analysis by Frilling (2019). Prospective studies with larger samples were included. This study does not report adverse events by indication.
Filippi, L., Ciorra, A., Sardella, B., et al., (2014). Sequential Use of ^{90}Y Microspheres Radioembolization and ^{177}Lu-Dotatate in Pluri-Metastatic Neuroendocrine Tumors: A Case Report. *Nuclear Medicine and Molecular Imaging*, *48*, 321-325.	Case study n=1 Follow-up= 3 months	SIRT was applied before PRRT to downstage the gross hepatic lesion and also after PRRT as consolidation therapy for the liver residual disease. They suggest SIRT can be safely used in combination with PRRT, especially in case of liver-dominant tumour.	Studies with more participants and more outcomes were included.
Filippi, L., Scorpinaro, F., Pelle, G., et al., (2016). Molecular response assessed by 68Ga-DOTANOC and survival after ^{90}Y microsphere therapy in patients with liver metastases from neuroendocrine tumours. *Eur J Nucl Med Mol Imaging, 43*, 432–440.	Case series n=15 Minimum follow-up= 36 months or until death	In this sample of people with unresectable mNETs, mean overall survival was 31 months (95%CI= 27 to 35); 9/15 were classed as responders. 7/15 people had nausea and mild abdominal	This study is included in the Frilling (2019) meta-analysis. Studies with more people were included.

		pain within 10 hours of treatment. Late complications included grade 2 gastritis (2/15) and grade 2 cholecystitis (1/15).	
Gozstonyi, B., Pestalozzi, B., Kenkel, D., et al., (2022). A descriptive analysis of the characteristics, treatment response and prognosis of hepatic dominant solid tumors undergoing selective internal radiation therapy (SIRT). *J Gastrointest Oncol, 13*(6), 3240-3253.	Retrospective case series n=182 (n=18 mNETs) This study analysed medical records of people who had SIRT between Jan 2015 and May 2019.	Neuroendocrine tumours showed the third longest median post-SIRT survival (12.4 months) and the second longest median progression-free survival (5.2 months), compared to other indications treated with SIRT.	Studies with prospective designs, more clinical outcomes and larger samples in the group of interest were included.
Gulec, S.A., Mesoloras, G., Dezarn, W.A., et al (2007). Safety and efficacy of Y-90 microsphere treatment in patients with primary and metastatic liver cancer: The tumor selectivity of the treatment as a function of tumor to liver flow ratio. *Journal of Translational Medicine 5*(15).	Retrospective case series n=10 mNET (n=40 total) Mean follow-up= 19 weeks	mNET tumour response was 100%. None of the patients had clinical venoocclusive disease or therapy-induced liver failure.	Studies with prospective designs, more clinical outcomes in the group of interest and larger samples were included.
Habibollahi, P., Bai, H.X., Sanampudi, S., et al (2020). Effectiveness of Liver-Directed Therapy for the Management of Intractable Hypoglycemia in Metastatic Insulinoma. *Pancreas, 49*, 763–767.	Retrospective case studies n=2 people who had SIRT (n=7 total) Follow-up = up to 75 months	Both people had chemoembolization before SIRT for intractable hypoglycemia resultant from insulinoma. There was a 100% symptomatic response rate. At 75 months, 1 person was alive and 1 person	Studies with prospective designs, more clinical outcomes in the group of interest and larger samples were included.

		died at 22 months from liver failure.	
Ingenerf M, Grawe F, Winkelmann M et al (2024). Neuroendocrine liver metastases treated using transarterial radioembolization: Identification of prognostic parameters at 68Ga-DOTATATE PET/CT. Diagnostic and interventional imaging 105: 15-25.	Retrospective case series n=47 Follow-up was not reported.	This was a Kaplan-Meier study of prognostic factors. Median overall survival, progression free survival and hepatic progression free survival were 49.6, 13.1 and 28.3 months, respectively. High pre-interventional tumour to liver ratio, and high maximum standardized uptake value were prognostic of longer survival in this study.	Studies with prospective data collection and more clinical outcomes were included in the key evidence.
Ingenerf, M., Kiesl, S., Karim, S., et al., (2021). 68Ga-DOTATATE PET/CT and MRI with Diffusion-Weighted Imaging (DWI) in Short- and Long-Term Assessment of Tumor Response of Neuroendocrine Liver Metastases (NELM) Following Transarterial Radioembolization (TARE). *Cancers, 13,* 4321.	Retrospective case series from a single centre n=32 Median follow-up=58.7 months	Median overall survival was 68.8 months (95%CI=35 to 102). One year survival was 100% and 2 year survival was 84%. Median overall progression free survival was 12.7 months (95%CI=11 to 15).	Studies with prospective designs and larger samples were included.
Jia, Z., Paz-Fumagalli, R., Frey, G., et al., (2017). Single-institution experience of radioembolization with yttrium-90 microspheres for unresectable metastatic neuroendocrine liver tumors. *Journal of Gastroenterology and Hepatology, 32*, 1617–1623.	Retrospective case series from a single centre n=36 Median follow-up=27 months	Median overall survival 41 months. Overall disease control rate was 88.9% (32/36) at 3 months. Symptomatic improvement in 94% (15/16) patients with carcinoid syndrome. Radiation induced gastrointestinal ulcers in 5.6% (2/36). Other side effects were fatigue (86%),	This study was included in the meta-analysis by Frilling (2019). Studies with prospective designs and larger samples were

		anorexia (72%), nausea (42%), vomiting (39%), abdominal pain (28%), fever (22%).	included in Table 2.
Kalinowski, M., Dressler, M., Konig, A., et al., (2009). Selective Internal Radiotherapy with Yttrium-90 Microspheres for Hepatic Metastatic Neuroendocrine Tumors: A Prospective Single Center Study*, Digestion, 79*, 137-142.	Prospective single arm cohort n=9 Mean follow up=21.7 months	No major complications. Survival rates were 100, 57 and 57% for 1, 2 and 3 years. Partial response in 66%, stable disease in 33% at 6 months meaning overall disease control was 99%. Quality of life at 6 months improved in 6 of 7 evaluable patients ($p < 0.05$). Quality of life later deteriorated but this was not significant and was usually related to recurrence of disease and/or other factors.	More recent studies with larger samples and longer follow up were included.
Kanabar, R., Barriusi, J., McNamara, M.G. et al., (2021). Liver Embolisation for Patients with Neuroendocrine Neoplasms: Systematic Review, *Neuroendocrinology, 111*, 354-369.	Systematic review and meta-analysis of all types of embolization for mNETs n=20 studies with 772 patients (n=101 total studies) Median follow-up=39.6 (95%CI=23.1 to 56.1)	Pooled weighted mean number of people that had symptomatic response was 77.4% (95%CI=47.1 to 100%). This was higher than the pooled mean for all types of liver directed therapy (55%). Pooled weighted mean overall survival was 40.1 months (95%CI=29.2 to 51). Pooled weighted mean progression free survival was 12.6 months (95%CI=0 to	The references for studies reporting SIRT outcomes were not available. Other reviews with more specific focus on SIRT were included.

		30.4 months; n=2 studies).	
Katharina-Ingenerf, M., Karim, H., Fink, N., et al., (2022). Apparent diffusion coefficients (ADC) in response assessment of transarterial radioembolization (TARE) for liver metastases of neuroendocrine tumors (NET): a feasibility study. *Acta Radiologica, 63*(7), 877-888.	Retrospective case series from a single centre n=43 Mean= 74 days	According to RECIST 1.1: 23% (27/120) target lesions showed partial response, 73% (87/120) showed stable disease and 5% (6/120) showed progressive disease. According to mRECIST: 0.8% (1/120) showed complete response, 63% (76/120) showed partial, 23% (28/120) showed stable and 7% (8/120) showed progressive disease.	Studies with prospective designs, longer follow-up, more and clinical outcomes and larger samples were included.
Kennedy, A.S., Dezarn, W.A., McNeillie, P. (2008). Radioembolization for Unresectable Neuroendocrine Hepatic Metastases Using Resin 90Y-Microspheres: Early Results in 148 Patients. *American Journal of Clinical Oncology, 31*(3), 271–279.	Retrospective case series n=148 Median follow-up=42 months	The median survival was 70 months. 33% of patients experienced grade 3 or 4 side effects. Fatigue (6.5%) was the most common side effect. Disease control was observed in 95% and progressive disease in 4.9%. No radiation induced liver failure occurred.	This study was included in the Frilling (2019) meta-analysis. More recent studies with prospective designs have been included.
King, J., Quinn, R., Glenn, D.M., et al., (2008). Radioembolization With Selective Internal Radiation Microspheres for Neuroendocrine Liver Metastases, *American Cancer Society, 113*, 921-929.	Prospective case series n=34 Mean follow-up=35.2 months	Post-SIRT complications included mild to severe abdominal pain, nausea, fever, lethargy lasting between 1 week and 1 month, radiation gastritis, duodenal ulcer, 1 early death because of liver dysfunction and pneumonia.	This study was included in the Frilling (2019) meta-analysis. More recent studies with larger samples were included.

		Symptomatic response was observed in 55% at 3 months and 50% at 6 months. Mean overall survival was 29.4 months and 50% has partial response or stable disease.	
Kukuk, G.M., Murtz, P., Traber, F., et al (2014). Diffusion-weighted imaging with acquisition of three b-values for response evaluation of neuroendocrine liver metastases undergoing selective internal radiotherapy. *Eur Radiol 24*, 267–276.	Retrospective case series n=10 3 months	Greater than 20% reduction in the longest diameter of each tumour in 39% (12/31) metastases. These metastases were in 4/10 patients.	Studies with prospective designs, longer follow up, more and standardised clinical outcomes and larger samples were included.
Lacin, S., Oz, I, Ozkan, K., et al., (2011). Intra-Arterial Treatment with 90Yttrium Microspheres in Treatment-Refractory and Unresectable Liver Metastases of Neuroendocrine Tumors and the Use of 111In-Octreotide Scintigraphy in the Evaluation of Treatment Response. *Cancer Biotherapy and Radiopharmaceuticals., 26,* 631-639.	Prospective case series n=13 Mean follow-up=17.4 months	One year survival was 84.7%, overall survival was 20 months and median survival was 18 months. All patients experienced postradioembolization syndrome (mild abdominal pain, nausea, fever) which subsided within 15 days.	More recent studies with larger samples were included.
Loree, J.M., Tadaaki, H.M., Kennecke, H.F. (2016). Case Report of Cirrhosis following Yttrium-90 Radioembolization for Pancreatic Neuroendocrine Liver Metastases, *Case Rep Oncol, 9*, 76–82	Case report n=1 Follow-up=49 months	Abdominal pain and nausea, biliary damage, postembolization oedema after one treatment. At approximately 49 months and after everolimus, liver	Studies with prospective designs, more clinical outcomes and larger samples were included.

		cirrhosis was diagnosed and attributed to 90Y SIRT treatments. The authors report this possible long-term complication should be considered when considering SIRT for people with good prognosis.	
Ludwig, J.M., McIntosh Ambinder, E., Ghodadra, A., et al., (2016). Lung Shunt Fraction prior to Yttrium-90 Radioembolization Predicts Survival in Patients with Neuroendocrine Liver Metastases: Single-Center Prospective Analysis, *Cardiovasc Intervent Radiol, 39,* . 1007-1014	Prospective case series n=44 Patients were enrolled between 2006 and 2012 and data were censored at 2014.	Median overall survival was 27.4 months (95%CI= 12.7 to 55.2). High lung shunt fraction was a statistically significant prognostic factor of overall survival (p=.003); people with lung shunt fraction greater than 10% had median overall survival of 4.8 months (95 %CI 2.87–26.73) whilst people with lung shunt fraction less than 10% had median overall survival of 42.8 months (95 %CI 18.47–59.73).	This study was included in the Frilling (2019) meta-analysis. Larger studies with more outcomes were included.
Maccauro, M., Follacchio, G.A., Spreafico et al., (2019). Safety and efficacy of combined Peptide Receptor Radionuclide Therapy and liver Selective Internal Radiation Therapy in a patient with metastatic neuroendocrine tumor. *Clin Nucl Med, 44*(4), e286-e288	Case report n=1 Follow-up= 16 months	PRRT followed by 2 SIRT treatments. From the end of PRRT and start of SIRT, the patient had 16 months of progression free survival. Liver and bone progression diagnosed at 16 months. No significant acute or delayed adverse effects or cumulative toxicity to	Studies with prospective designs, more clinical outcomes and larger samples were included.

		healthy liver parenchyma.	
Maker, A.V., August, C., Maker, V.K. & Weisenberg, E. (2016). Hepatectomy after Yttrium-90 (Y90) Radioembolization-induced Liver Fibrosis. *J Gastrointest Surg, 20*(4), 869–870.	Case report n=1 Last follow-up was not reported.	10 months after second SIRT treatment, the person was still symptomatic with flushing, diarrhoea, anxiety, myalgia, pain, and persistent night sweats, despite sandostatin administration. Histology showed Y90 induced fibrosis and microbeads in blood vessels around subsequently resected tumours which the authors believe demonstrates increased morbidity and mortality when resection previously radioembolised tumours.	Studies with prospective designs, more clinical outcomes and larger samples were included.
Mascarenhas, N.B., Mulcahy, M.F., Lewandowski, R.J. et al (2010). Hepatic Abscess After Yttrium-90 Radioembolization for Islet-Cell Tumor Hepatic Metastasis	Case report n=1 Last follow-up was not reported	Fever and abdominal pain after treatment which persisted with antibiotics. At 4-weeks post-treatment, an abscess in the treatment site was diagnosed. This was drained and several months after treatment the dominant hepatic metastases had decreased in size.	Studies with prospective designs, more clinical outcomes and larger samples were included.
Memon, K., Lewandowski, R.J., Mulcahy, M.F. et al., (2012). Radioembolization for Neuroendocrine Liver Metastases: Safety, Imaging and Long-term Outcomes. Int	Retrospective case series n=40	Overall survival at 1, 2 and 3 years was 73%, 63% and 45%. Two classifications for response rate were used: WHO measures	This study was included in the meta-analysis by Frilling

J Radiat Oncol Biol Phys, 83(3), 887–894.	Follow-up up to 3 years	size (CR: 1.2%, PR: 62.7%) and EASL measures necrosis (CR: 20.5%, PR: 43.4%). Fatigue (63%), nausea/ vomiting (40%), abdominal pain (18%), fever (8%), diarrhoea and weight loss (5%). Symptom remission was reported in 84% (21/25) of people after treatment.	(2019). Studies with prospective designs and larger samples were included.
Moir, J.A.G., Burns, J, Barnes, J. et al., (2015). Selective internal radiation therapy for liver malignancies. *BJS, 102,* 1533–1540.	Retrospective case series n=6 mNET (n=44 total) Median follow-up=10 months	Overall survival was 539 days (95%CI=350 to 617). Median percent change in tumour diameter was -30% (95%CI= -46 to -8; n=5). No significant difference in overall survival according to primary pathology (p=.065). No mNET patients required follow up resection.	Studies with prospective designs, larger samples and more outcomes specific to the group of interest were included.
Murthy, R., Kamat, P., Nunez, R., et al (2008). Yttrium-90 Microsphere Radioembolotherapy of Hepatic Metastatic Neuroendocrine Carcinomas after Hepatic Arterial Embolization. *J Vasc Interv Radiol, 19*, 145–151.	Retrospective case series n=8 Median follow-up= 9.5 months	Median overall survival was 14 months (range=3 to 15). Partial response was observed in 1/8 people, 50% (4/8) showed stable disease and 3/8 showed progressive disease in the liver. Disease progression was observed in 3/8. After 1 treatment, grade 2/3 abdominal pain was observed in 5/8 people, transient grade 1/2 fatigue in	Studies with prospective designs and larger samples were included.

		3/8, pyrexia in 1 person and grade 2 nausea in 1 person. No radiation induced liver disease was observed.	
Ozao-Choy, J., Friedman, M.L., Amanda, S.K. et al (2013). Radioembolization for Treatment of Liver Metastases From Neuroendocrine Tumors Correlation With Imaging and Biomarkers. *Pancreas 42*(2), 358-360.	Retrospective case series n=18 Median follow-up= 5 months	Of 19 evaluated procedures, 11% (2/19) resulted in complete response, 47% (9/19) partial response and 32% (6/19) stable disease. Disease progressed in 11% (2/19). Toxicities included: radiation gastritis (2/18), gastric ulcer (1/18), biliary stricture requiring drainage (1/18), portal hypertension with refractory ascites (1/18), zone 3 injury with necrosis consistent with radiation induced liver disease (1/18).	Studies with prospective designs, larger samples and more outcomes were included.
Ozkan, F., Peynircioglu, B., E.Cil, B., et al (2013). Transarterial Chemo and Radioembolization (Yttrium90) of Hepatic Metastasis of Neuroendocrine Tumors: Single Center Experience. International Journal of Hematology and Oncology, 23(1), 20-27.	Retrospective cohort n=14 (n=6 SIRT; n=8 TACE) Median follow-up=17 months	Mean overall survival was 14.5 months in the SIRT group and 16.8 months in the TACE group (p=0.09). Progressive disease in 17% (1/6) SIRT group and 71% (5/8) of TACE group at intermediate follow up (greater than 3 months). 75% of people who had SIRT and 57% of people who had TACE had relief of carcinoid symptoms. No major complications were	Study was included in the meta-analysis by Ngo (2021). Studies with prospective designs and larger samples were included.

		observed. One person who had SIRT had asymptomatic partial right portal vein thrombosis and almost all people had mild fatigue and fever. Grade 1 to 2 abdominal pain and nausea in 1/6 of the SIRT and 4/8 of the TACE group.	
Paprottka, P.M., Hoffmann, R.T., Haug, A., et al., (2012). Radioembolization of Symptomatic, Unresectable Neuroendocrine Hepatic Metastases Using Yttrium-90 Microspheres. *Cardiovasc Intervent Radiol, 35*, 334–342	Retrospective case series n=42 Mean follow-up=16.2 months	At 3 months, 22.5% had partial response, 75% had stable disease and 2.5% had progressive disease. At mean follow-up of 16 months, 95.2% of people were alive. Hypovascularisation or partial necrosis was observed in 97.5% of lesions. 36 of 38 people showed remission of symptoms at 3 months. No radiation induced liver disease was observed and no acute or delayed toxicity above grade 2.	This study was included in the meta-analysis by Frilling (2019). Other studies with prospective designs and larger samples were included in Table 2.
Paprottka, K.J., Schoeppe, F., Ingrisch, M., et al (2017). Pre-therapeutic factors for predicting survival after radioembolization: a single-center experience in 389 patients. Eur J Nucl Med Mol Imaging, 44, 1185–1193	Retrospective case series n=389 (n=56 mNETs) People had SIRT between January and February 2013 and	22/56 people with mNETs (60%) were alive at the end of follow-up. Compared to other tumour types mNET showed best survival rates at last follow up.	Studies with prospective designs, more clinical outcomes and larger samples of people with the indication of interest were included.

	followed up until December 2013.		
Peker, A., Cicek, O., Soydal, C., et al., (2015). Radioembolization with yttrium-90 resin microspheres for neuroendocrine tumor liver metastases. *Diagn Interv Radiol, 21,* 54–59.	Retrospective case series n=30 Mean= 23 months	Median overall survival was 39 months (95% CI= 13 to 65). One and 2-year survival rates were 71% and 45%. Complete remission was observed in 3%, partial response in 43%, stable disease in 37% and progressive disease in 17%. Post-radioembolization syndrome was observed in all people and resolved with treatment in 30 days. Radiation induced gastritis was observed in 2/30 people; 1 of those had persistent ulceration at 9 months.	This study was included in the meta-analysis by Frilling (2019). Studies with larger samples and prospective designs were included.
Prétot D, Engel-Bicik I, Kenkel D et al (2023). Outcome analysis in patients with metastatic gastroenteropancreatic neuroendocrine tumors receiving peptide receptor radionuclide therapy with Lu-177-DOTATATE. Journal of Gastrointestinal Oncology 14: 1204-1217.	Retrospective case series n=41 total (n=9 had SIRT) Range of follow-up= 21 to 248 months	This study assessed the outcome of PRRT therapy including the safety profile of giving PRRT after SIRT for people with mNETs of gastroenteropancreatic origin. Compared to people that did not have SIRT before PRRT, people who did have SIRT prior to PRRT had a mortality risk 4 times higher than patients without this treatment. There were no significant differences in quality	Few people who had SIRT were included in this analysis and people were not randomised to have SIRT or not before PRRT. This limits the validity of the conclusions.

		of life between both groups (p=0.3). Means of blood parameters did not significantly differ between patients with and without previous SIRT (p=0.2). The authors caveat the mortality finding by stating that people who had SIRT might have had more advanced or more aggressive disease than others; hepatic tumour load was higher in the SIRT group.	
Puleo, L., Agatem L., Bargellini, I., et al., (2022). Yttrium-90 transarterial radioembolization for liver metastases from medullary thyroid cancer, *European Thyroid Journal, 11,* e220130.	Prospective cohort study n=8 Mean follow-up=18 months	Two people were excluded from analysis because of liver injury and death due to disease progression. Significant reduction in tumour mass observed after 1, 4 and 12 months (p<.01).	Studies with larger samples, longer follow-up and more clinical outcomes were included.
Rajekar, H., Bogommana, K., Stubbs, R.S. (2011). Selective Internal Radiation Therapy for Gastrointestinal Neuroendocrine Tumour LiverMetastases: A New and Effective Modality for Treatment. *International Journal of Hepatology, 2011*, 404916.	Retrospective case series n=14 Up to 60 months	Median survival was 25 months. Partial response or stable disease in 100% of people. Carcinoid syndrome improved or resolved in 100% (10/10) instances. No treatment-related deaths or serious complications following SIRT. Anorexia and lethargy were experienced by all people. One person died 10	More recent studies with prospective designs, more and standardised clinical outcomes and larger samples were included

		months after second SIRT treatment but this was not considered 'obviously' related to treatment.	
Rhee, T.K., Lewandowski, R.J., Liu, D.M., et al., (2008). 90Y Radioembolization for Metastatic Neuroendocrine Liver Tumors: Preliminary Results From a Multi-institutional Experience. *Annals of Surgery, 247,* 1029-1035.	Prospective case series n=42 Every 3 months until end of study (between June 2001 and June 2006)	92% of people that had SIRT with glass microspheres and 94% who had SIRT with resin were classed as having partial response or stable disease at 6 months. Median survival was 22 months with glass and 28 months with resin (p=0.82). 6 people had grade 3 or 4 toxicity during follow up.	This study was included in the Frilling (2019) meta-analysis presented in Table 2.
Rodrigues-Lago, I., Carretero, C., Maite, H., et al (2013). Long-term follow-up study of gastroduodenal lesions after radioembolization of hepatic tumors. *World J Gastroenterol, 19*(19), 2935-2940.	Retrospective case series n=1 person with mNET (n=6 total) Follow-up= 29 months	Gastroduodenal ulcers were observed between 1 and 12 weeks after SIRT. The person with mNETs had multiple erosions in the duodenal bulb, severe mucositis in gastric fundus, body and antrum with mucosal friability and superficial ulcers 5 weeks after SIRT. The person reported abdominal pain (Grade 1), nausea and vomiting (grade 1). Microspheres were detected in biopsies. The patient was free from severe symptoms at the end of follow up.	Studies with prospective designs and larger samples were included.

Sangro, P., Bilbao, I., Fernandez-Ros, N. et al (2017). Pneumatocele during sorafenib therapy: first report of an unusual complication. *Oncotarget, 9*(5), 6652-6656.	Case study n=1 Follow-up= 5 years	A woman with pancreatic neuroendocrine tumours had SIRT. Her disease progressed after 9 months and required further intervention with Sorafenib. After this, pneumatocele were observed and the authors are unclear what the root cause of this was, but hypothesise it was Sorafenib.	Studies with prospective designs, more clinical outcomes and larger samples were included.
Saxena, A., Chua, T.C., Bester, L., et al., (2010). Factors Predicting Response and Survival After Yttrium-90 Radioembolization of Unresectable Neuroendocrine Tumor Liver Metastases: A Critical Appraisal of 48 Cases, *Annals of surgery, 251*(5), 910-916	Prospective case series n=48 Median follow-up=41 months	Median survival was 35 months. At follow-up, 15% (7/48) people had complete response, 40% (19/48) had partial response and 23% (11/48) had stable disease, 11% had progressive disease. One person showed grade 3 toxicity (cirrhosis, ascites) and died within 1 month of treatment. One patient developed biliary obstruction over the 6 month period.	Study is included in the Frilling (2019) meta-analysis in Table 2. More recent studies are also included.
Saxena, A., Chua, T.C., Zhao, J., Morris, D.L. (2012). Liver-Directed Therapy for Neuroendocrine Neoplasm Hepatic Metastasis Prolongs Survival Following Progression After Initial Surgery. *Journal of Surgical Oncology, 105,* 342–350.	Retrospective case series n=15 people who had SIRT (n=50 total)	Median progression free survival after SIRT was 18 months, following previous resection with or without ablation.	Studies with prospective designs, more clinical outcomes and larger samples in the group of interest were included.

	Median follow-up=29 months		
Schuttler, D., Mouroizis, K., Auernhammer, C.J. et al (2021). Development of severe intrapulmonary shunting in a patient with carcinoid heart disease after closure of a persistent foramen ovale: a case report. *European Heart Journal - Case Reports, 5*(12), 1–5.	Case report n=1 Follow-up=4 months	The patient had carcinoid heart disease. Four months after SIRT, disease progressed into the bone but symptoms of carcinoid syndrome (dyspnoea) were relieved.	Studies with prospective designs, more clinical outcomes and larger samples were included.
Shaheen, M., Hassanain, M., Aljiffry, M., et al (2011). Predictors of response to radio-embolization (TheraSphere®) treatment of neuroendocrine liver metastasis. *HPB, 14,* 60–66.	Retrospective case series n=25 Median follow-up=21.7 months	Previous surgery predicted greater change in percent tumour necrosis. 63% showed complete or partial response. 28% had grade 1–2 toxicities within 30 days of surgery. 2/25 people had grade 3 to 4 toxicity. One person died from bleeding from a perforated duodenal ulcer. Change in tumour necrosis was greatest for people who had previous surgical therapy indicating less bulky disease was a predictor of better response to SIRT.	This study was included in the meta-analysis by Frilling (2019). Studies with prospective designs and larger samples were included.
Sheheta, M., Yan, K., Itoh, S., et al., (2009). Splenomegaly and tumor marker response following selective internal radiation therapy for non-resectable liver metastases from neuroendocrine tumor. *Dokkyo Journal of Medical Sciences, 36*(3), 131-134.	Retrospective review of prospective database n=16 Splenic volume was measured 3	Oesophagal variceal bleeding due to portal hypertension, gastrointenstinal bleeding and duodenal ulceration causing death in one patient 9 months after treatment. Long-term splenomegaly and portal hypertension	Studies with prospective designs, more clinical outcomes and larger samples were included. As this is an old article, the

	months after SIRT.	may be important complications of SIRT.	methods of SIRT may have evolved since.
Simon, N., Warner, R.R.P., Baron, M. et al., (1968). Intra-arterial irradiation of carcinoid tumors of the liver. *The American journal of roentgenology, radium therapy, and nuclear medicine, 102*(3), 552-561.	Retrospective case series n=5 Followed up to 19 months	Two people died from side effects of extrahepatic irradiation. Two people had remission of carcinoid symptoms in the short term (up to 6 months and 10 months respectively) but later showed recurrence of symptoms. One person made complete recovery.	As this is an old article, the methods of SIRT may not reflect current practice. Studies with prospective designs, more clinical outcomes and larger samples were included.
Singla, S., LeVea, C.M., Pokuri, V.K., et al., (2016). Ki67 score as a potential predictor in the selection of liver directed therapies for metastatic neuroendocrine tumors: a single institutional experience. *J Gastrointest Oncol, 7*(3), 441-448	Case series. n=72 (n=44 SIRT) Median follow-up=54.5 months	No significant difference in overall survival between SIRT and TACE when used without selection (median= 69, 82 months, respectively; p=0.47). There was significant interaction between Ki-67 score and liver-directed treatment benefit.	This study was included in the meta-analyses by Ngo (2021) and Frilling (2019). Studies with more clinical outcomes and larger samples were included.
Smits, M.L.J., van den Hoven, Rosenbaum, C.E.N.M., et al (2013). Clinical and Laboratory Toxicity after Intra-Arterial Radioembolization with 90Y-Microspheres for Unresectable Liver Metastases. *PLoS ONE, 8*(7): e69448.	Retrospective case series n=6 people with mNETs (n=59 people in total)	Median overall survival was 40.3 months (95% CI = 0 to 107.9). Median time to progression for the target lesion was 36.4 months (95% CI= 0 to 88.7) and 11.7 months (95% CI= 0 to 24.8)	Studies had more people in the group of interest, prospective designs and more information about the

	Follow-up until death end of study period (2009-2012).	overall. Grade 1 to 2 toxicity observed in majority of patients (fatigue, loss of appetite, pain/ discomfort in upper abdominal quadrant, nausea/vomiting, fever). No grade 3 or 4 toxicity was observed. No serious treatment-related complications.	mNET subgroup.
Sommer, W.H., Celeen, F., Garcia-Albeniz, X., et al., (2013). Defining predictors for long progression-free survival after radioembolisation of hepatic metastases of neuroendocrine origin. *Eur Radiol, 23,* 3094–3103	Retrospective case series n=45 Median=303 days	Median progression free survival was 727 days (95 % CI, 378–964). Best response to SIRT in terms of longer progression free survival was predicted by hypervascular metastases, Ki-67 less than 2% and low neuron specific enolase level.	Studies with prospective designs, longer follow-up, more clinical outcomes and larger samples were included.
Soulen MC, Teitelbaum MC, Mick R, et al (2023). Integrated Capecitabine-Temozolomide with Radioembolization for Liver-Dominant G2 NETs: Long-Term Outcomes of a Single-Institution Retrospective Study. Cardiovascular and interventional radiology, 47: 60-68.	Retrospective case series n=37 Follow-up= up to 60 months	This study examined the effects of using Capecitabine–Temozolomide (CapTem) with SIRT. Overall response rate in the liver was 72% with a disease control rate of 100%. Median progression free survival was 36 months (95% CI= 25 to 45 months). Median overall survival was 41 months (95% CI= 24 to 87 months) from initiation of CapTemY90 therapy and 130 months (95%	Larger prospective studies with more clinical outcomes were included in the main evidence. This study did not isolate the effects of SIRT alone but provides context for combination therapies that could

		CI= 56 to 172 months) from initial diagnosis. The authors conclude the combination of CapTem and SIRT showed durable control of grade 2 mNETs for substantially longer than expectations for embolotherapy or chemotherapy alone.	be used in practice.
Stella M, van Rooij, Lam MGEH et al (2023). Automatic healthy liver segmentation for holmium-166 radioembolization dosimetry. EJNMMI Research 13: 68.	Secondary analysis of a single-arm trial n=31 people (n=66 procedures) Follow-up=12 months	This article reports the results of a secondary analysis of the HEPAR PLuS trial, and compares the relationship between automatic and manual liver segmentation methods and their relationship with hepatotoxicity. The findings indicate that an automated protocol for liver segmentation is a reliable alternative to the manual method. The authors highlight the importance for optimising dosimetry and prevention of long-term toxicity, especially in people with mNETs who have longer survival expectancies than people with other types of cancer in the liver that have SIRT.	The main clinical outcomes from this clinical trial were included in a publication in the main evidence.
Su, Y.K., Mackey, R.V., Riaz, A., (2017). Long-Term Hepatotoxicity of Yttrium-90 Radioembolization as Treatment of Metastatic	Retrospective case series n=54	Development of cirrhosis-like morphology was more common in people who had whole-liver	Larger and more recent studies reporting similar long-

Neuroendocrine Tumor to the Liver, *J Vasc Interv Radiol, 28,* 1520–1526		treatments than unilobar; 56.4% (22/39) of people who had whole-liver SIRT developed cirrhosis-like morphology. Median time to cirrhosis-like morphology was 1.8 years (range 0.7 to 7.2 years).	term toxicity were included.
	Retrospective case series n=93 Median follow-up= 15 months		The toxicities in this study focus on laboratory not clinical toxicity. Another study from 2018 that focuses on long term clinical side effects of SIRT has been included.
Tsang, E.S., Loree, J.M., Davies, J.M., et al., (2020). Efficacy and Prognostic Factors for Y-90 Radioembolization (Y-90) in Metastatic Neuroendocrine Tumors with Liver Metastases. *Canadian Journal of Gastroenterology and Hepatology, 2020,* 5104082	Retrospective case series n=49 Data collected between Jun 2011 and Jan 2017	Median overall survival was 27.2 months (95%CI 8 to 47). Partial response (53%), stable disease (33%), and progressive disease (12%) was observed. Grade 3-4 biochemical toxicities (2%) and grade 3 abdominal pain (6%) were observed. Grade 1 toxicities included fatigue (4%), gastric ulceration (2%), and odynophagia (2%).	Studies with prospective designs and larger samples of the group of interest were included.

Tudela-Lerma, M, Orcajo-Rincon, J., Ramon-Botella, E. et al., (2021). Efficacy and safety of Yttrium-90 radioembolization in the treatment of neuroendocrine liver metastases. Long-term monitoring and impact on survival. *Revista Española de Medicina Nuclear e Imagen Molecular, 40*, 82–90.	Retrospective case series n=15 5 years	No patient developed postembolisation syndrome or carcinoid syndrome after treatment. There were no vascular complications associated with the procedure. At 6 months, 78.6% presented partial response and 21.4% stable disease, there was no progression or complete response. Survival at 3 and 5 years was 73% in both cases.	Studies with prospective designs and larger samples of the group of interest were included.
Turkmen, C., Ucar, A., Poyanly, A et al. (2013). Initial Outcome After Selective Intraarterial Radionuclide Therapy with Yttrium-90 Microspheres as Salvage Therapy for Unresectable Metastatic Liver Disease, *Cancer and Radiotherapy Biopharmaceuticals, 28*(7), 534-540	Retrospective case series n=12 mNET (n=61 total) Mean=11 months	Median overall survival was not reached. Mean overall survival was 29 months (SD=3).	Studies with prospective designs, more clinical outcomes and larger samples of the group of interest were included.
Xing, M., Lahti, S., Kokabi, N., et al. (2016). 90Y Radioembolization Lung Shunt Fraction in Primary and Metastatic Liver Cancer as a Biomarker for Survival, *Clinical Nuclear Medicine, 41*(1), 21–27	Retrospective case series N=73 mNET patients (n=366 total) Every 3 months until death	People with low lung shunt fraction (less than 10%) had significantly longer overall survival. Overall survival was 33 months for people with low (less than 10%) lung shunt fraction, compared with 9.1 months in people with high (greater than or equal to 10%) lung shunt fraction ($p< 0.001$).	Studies with prospective designs, more clinical outcomes and larger samples of the group of interest were included.

Yang, T.X., Hua, T.C., Morris, D.L., (2012). Radioembolization and chemoembolization for unresectable neuroendocrine liver metastases: A systematic review, *Surgical Oncology, 21,* 299-308.	Systematic review for SIRT and TARE n=12 SIRT studies with 423 patients (n=37 studies in total) median follow-up was reported in 8 of 12 studies ranged from 9.4 months to 42 months (median=22.9)	The objective response rate was 63.1% (range= 12.5-100%) for SIRT, compared to 58.4% (range= 11.1- 89%) of those treated with TACE. More people who had SIRT had stable disease (32.8% versus 22 %), while less had progressive disease (3.6% versus 8.7%). The clinical response rates were similar in patients treated with SIRT and TACE (85% versus 88.5%) Median survival for SIRT was 28 months (range= 14 to 70 months). Rates of major complication were similar. Radioembolisation may allow downstaging of liver metastases and subsequent radiofrequency ablation, liver resection or bridge to transplantation, allowing for a complete response.	A more recent systematic review explicitly comparing SIRT with TARE with meta-analyses was included in table 2.
Yilmaz, E., Engin, M.N., Ozkan et al., (2020). Y90 selective internal radiation therapy and peptide receptor radionuclide therapy for the treatment of metastatic neuroendocrine tumors: combination or not? *Nuclear medicine communications, 41*(12), 1242-1249.	Retrospective case series n=27 (n=15 SIRT, n=12 SIRT and PRRT)	Objective response or stable disease was observed in 87% (13/15) people in the SIRT only group and 67% (8/12) in the SIRT and PRRT group. Median OS was 34.9 months in SIRT only group and	Studies with prospective designs, more clinical outcomes and larger samples of the group of interest

	Mean= 32 months	67.5 months in the SIRT plus PRRT group (=0.22). Mean progression free survival was 53.1 in the SIRT only group and 27.2 in the SIRT plus PRRT group (p=0.56).	were included.
Zubiri, L., Bilbao, J.I., Rodriguez, J., Sangro, B., (2018). Selective internal radiation therapy: an effective treatment for hormonal syndromes in pancreatic neuroendocrine tumors. Hepat. Oncol, 5(2).	Case reports n=2 24 to 28 months after treatment	Two people with severe carcinoid syndrome that was refractory to other treatments were successfully treated with SIRT. One person had no side effects, was asymptomatic for 2 years and showed decrease in lesion vascularity. One person's symptoms were brought under control after treatment and ongoing octreotide. They experienced mild hypertransaminasemia 2 months after treatment. Their tumour showed complete response at 8 months which was maintained until their death 28 months after treatment.	Studies with prospective designs, more clinical outcomes and larger samples of the group of interest were included.
Zuckerman, D.A., Kennard, R.F., Roy, A., et al., (2019). Outcomes and toxicity following Yttrium-90 radioembolization for hepatic metastases from neuroendocrine tumors- a single institution experience. *J*	Retrospective case series n=59 Mean=2 years	Median overall survival was 31 months, and the 1- and 2-year overall survival was 80.4% and 65.6%, respectively. Median hepatic progression free survival and	Larger, prospective studies with longer follow-up were included.

Gastrointest Oncol, 10(1), 118-127		overall progression-free survival were 18 and 13 months, respectively. Three patients died of hepatic failure that was possibly therapy-related. Preliminary data regarding dose to normal liver is suggestive of a relation between dosimetry and toxicity.	