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Executive Summary

Background and research question:

Selective internal radiotherapy (SIRT) is a treatment option for patients with primary and secondary liver malignancies, such as hepatocellular carcinomas (HCC) or metastases from colorectal cancer (mCRC), neuroendocrine tumours or breast cancer. This technique involves the injection of radionuclides (e.g. jodine-131, rhenium-188, yttrium-90) directly into the liver artery. If yttrium-90 is used, small particles the so called microspheres are used to deliver the radioactive substance. Two yttrium-90 products are commercially available: resin-microspheres (SIR-Spheres®) and glass-microspheres (TheraSphere®). Due to differing blood supply of healthy liver tissue and tumour, the microspheres lodge directly in the tumour and can deliver radiation predominantly to the tumour.

SIRT: radionuclides injected directly into liver artery

2 yttrium-90 products commercially available: SIR-Spheres®, TheraSphere®

The research question of this review was whether SIRT using yttrium-90 microspheres is an efficacious and safe therapy in comparison to other treatment options for non-resectable, non-ablatable HCCs and mCRC.

research question: SIRT for hepatocellular carcinoma and liver metastases from colorectal cancer

Methods:

A systematic literature search, in addition to a hand search and literature provided by the manufacturers as well as the applicant resulted in 900 references overall.

overall 900 references

Inclusion criteria for efficacy were prospective controlled trials and for safety prospective studies with ≥50 patients.

Results:

2 studies, both reporting on TheraSphere®, were included for efficacy of SIRT for the treatment of HCC. One trial showed improvements in median overall survival for the SIRT group, but this might be explained due to different baseline characteristics of the two groups. Another study, which included 28 patients, showed only partly improved results for quality-of-life.

2 efficacy studies for TheraSphere®…

For efficacy of SIRT for mCRC, 3 randomized controlled trials, all using SIR-Spheres®, were included but a judgment on efficacy was hampered as results deviated, different comparators were used and additional therapies were allowed.

3 for SIR-Spheres®

Data on safety was considered in 8 studies overall. It seems that careful patient selection is crucial for a safe treatment with SIRT. Overall, the safety profile of this intervention is acceptable.

for safety another 8 studies included

Conclusion and recommendation:

The evidence for TheraSphere® for the treatment of HCC does not currently allow a definite statement on efficacy. An inclusion in the catalogue of benefits is not currently recommended.

TheraSphere® not currently recommended

The evidence indicates that treatment of mCRC with SIR-Spheres® is more efficacious and as safe as other treatment options. An inclusion in the catalogue of benefits is therefore recommended with restrictions and a re-evaluation should be conducted in 2015.

SIR-Spheres® for mCRC recommended with restriction

1 Technology

1.1 Background

1.1.1 Primary liver cancer

hepatocellular carcinoma 3rd most common cause of cancer-related death

Primary liver cancer comprises several different entities, such as hepatocellular carcinomas (HCC) and cholangiocarcinomas. Of those, HCC is the most common form of malignant hepatobiliary diseases and it is the third most common cause of cancer-related death worldwide [1]. Risk factors include hepatitis B and/or hepatitis C virus infections, alcohol abuse or cirrhosis [1, 2]. On average men are 3.7 times more frequently affected than women and median age at diagnosis ranges from between 50 and 60 years [1]. In Austria, 785 patients were newly diagnosed with liver cancer in 2008 [3].

risk factors: hepatitis, alcohol,…

most often diagnosed at late stage of disease

median survival of 6-20 months

Because the liver has a large functional reserve and there are few specific symptoms associated with HCC, HCCs are usually diagnosed at a late stage of the disease. This results in a median survival of 6 to 20 months after diagnosis [1] and a 5-year survival rate of only 3% to 5% [4]. To establish prognosis, many different systems exist (e.g. TNM-system, the Okuda-system and the CLIP score), but none of them is commonly accepted. However, all of these systems incorporate four characteristics crucial for survival: the severity of underlying liver disease, the size of the tumour, the extension of the tumour into adjacent structures, and the presence of metastases [5].

surgery and liver transplantation are potentially curative treatment options, but only rarely an option

Potentially curative therapies include resection of the liver if function is adequate, or, if cirrhosis is more advanced, liver transplantation [4]. But these therapies are often not an option, either because of the extent of the tumour, the location of the tumour or because of compromised liver function or reduced performance status [2].

other options: local non-surgical methods or embolization

Treatment options for un-resectable HCCs are local non-surgical methods like ablation techniques or embolization. Radiofrequency ablation (RFA) and percutaneous ethanol injection belong to the first category. Both techniques induce tumour necrosis, either by using an alteration in temperature (radiofrequency ablation) or by exposing the tumour to chemicals (percutaneous ethanol injection). RFA is usually indicated for singular tumours with a diameter of <4 cm [6].

multiple tumours most often treated with transarterial chemoembolisation

Multiple tumours in the liver or larger tumours can be treated using embolizing methods: embolizing particles ± chemotherapy or iodine 131- labelled lipiodol are directly injected into the liver artery [2]. Transarterial chemoembolisation (TACE) is most often used for large un-resectable HCCs which cannot be treated with other techniques such as RFA [7]. In contrast to bland embolization (synonymous: transarterial embolization) where only embolic particles are injected in the hepatic artery, TACE includes the additional injection of a chemotherapeutic drug [2]. Systemic chemotherapy is not usually used for the treatment of HCC, because this cancer is most often refractory to chemotherapy and tolerability of this toxic therapy is limited by any underlying liver dysfunction [1]. However, sorafenib, a molecular targeted therapy, offers a systemic treatment option and is recommended for un-resectable tumours, for patients not eligible for surgery due to co-

morbidities or performance status, or for patients with metastatic disease [2].

1.1.2 Liver metastases

colorectal carcinomas metastasize to liver in 50%

Liver metastases from primary tumours are very common, including metastases from breast cancer, neuroendocrine tumours or pancreatic cancer [4]. As 50% of all patients suffering from colorectal cancer (CRC), which is the third most common cancer in women and the fourth in men, will eventually develop metastases in the liver, hepatic metastases from CRC are very frequent [4]. 5-year survival rates of patients diagnosed with liver metastases are less than 5% [4].

non-resectable metastases most often treated with systemic chemotherapy

other methods: hepatic arterial chemotherapy

If metastases are confined to the liver, patients might be cured with surgical resection [8]. But similar to HCCs, only the minority of patients, that is less than 10% with metastatic disease, are candidates for surgery, either because of the tumour size, the location of the tumour or due to liver dysfunction. In this palliative setting, systemic chemotherapy (e.g. FOLFOX = oxaliplatin, leucovorin, 5-fluorouracil (5-FU), capecitabine or FOLFIRI = irinotecan, leucovorin, 5-FU, capecitabine) [9] is then the standard therapy for metastatic CRC (mCRC). For these patients, local therapies offer an alternative treatment option to systemic chemotherapy [8]. These local therapies include the above mentioned ablation techniques such as RFA, or, hepatic arterial chemotherapy (HAC)[8]. During HAC, chemotherapeutic drugs are injected directly into the liver artery which allows higher concentrations of the drug in the liver than with systemic chemotherapy. But, in order to delay disease progression outside the liver, HAC might also be combined with systemic chemotherapy [8].

1.2 Description of the intervention

SIRT = radionuclides directly injected into liver artery

„Selective Internal Radiotherapy"(SIRT), also called radioembolization, is a technique which specifically delivers radiation to hepatic malignancies. The underlying rationale is that healthy liver tissue is connected to the portal vein, whereas malignancies are mostly supplied by the liver artery [8, 10].

2 Y-90 products are commercially available: SIR-Spheres®, TheraSphere®

radiation predominately delivered to liver, therefore higher radiation doses possible

Using a catheter, or a permanent implanted liver port [11], several radionuclides such as yttrium-90 (Y-90), jodine-131 or rhenium-188 can be delivered into the hepatic artery [12]. In the case of Y-90, two products are commercially available (see Table 1.2-1), made either of resin (SIR-Spheres®) or glass (TheraSphere®). These radioactive particles, the so called microspheres, are delivered into the hepatic artery and get trapped in the capillary bed [10, 13]. Y-90 is a pure β-emitter and has a mean tissue penetration of 2.5mm [10]. Radiation can therefore be delivered predominantly to the tumour while simultaneously sparing normal liver tissue, allowing higher radiation doses than conventional radiotherapy [10]. Requirements for the targeted delivery are an exact positioning of the catheter and a pretherapeutic dosimetry to exclude shunting to the extrahepatic circulation.

Table 1.2-1: Characteristics of commercially available Y-90 microsphere products [4, 10, 12]:

Brand name	SIR-Spheres®	ThereSphere®
Matrix material	resin	glass
Diameter (µm)	20 - 60	20 - 30
Activity/sphere (Becquerel)	50	2,500
Average number of particles delivered	40-60 million	1.2-8 million
Activity delivered	depending on body surface area and tumour volume	depending on the target dose and the patient's liver mass
Maximal prescribed dose (Giga Becquerel)	3	20
Licensed in Europe	yes	yes

licensed in Europe and the US

Both products are approved in Europe [12], but in the US, SIR-Spheres® are only approved in combination with adjuvant HAC with floxuridine for the treatment of un-resectable liver metastases from primary CRC since 2002 [14]. TheraSphere® is approved under the humanitarian device exemption for radiation treatment or as neoadjuvant therapy prior to surgery for patients with un-resectable HCC since 1999 [15]. The device exemption was expanded to patients suffering from HCC who additionally have a partial or branch portal vein thrombosis in January 2007 [16].

patient selection for SIRT

Basic requirements for patients deemed eligible for SIRT are an adequate liver function (e.g. bilirubin ≤2mg/dl, liver enzymes < 5 times upper normal limit) and a liver-dominant tumour burden [12]. A detailed patient history is necessary, because previous chemotherapy might be associated with higher rates of complications associated with SIRT [17, 18]. Due to the embolic effect of SIR-Spheres®, portal vein thrombosis [4] has to be excluded prior to therapy with *resin*-microspheres. Moreover, aberrant vessels to the gastrointestinal tract which could distort the targeted delivery of the microspheres directly to the tumour and which would lead to radiation exposure of organs such as the gallbladder, or the stomach, need to be embolized before SIRT [4, 10, 13]. In addition, excessive exposure of the lungs to radiation has to be avoided in order to reduce adverse events such as radiation-induced pneumonitis.

Proposed eligibility criteria for SIRT are thus:

- un-resectable primary or metastatic hepatic disease with liver dominant tumour burden and life-expectancy ≥ 3 months
- an acceptable lung shunt fraction (≤20 Gray for resin, ≤30 Gray for glass microspheres)
- an adequate liver function
- absence of portal vein thrombosis (only SIR-Spheres®)
- a good performance status [19-21].

rigid pre-treatment work-up necessary

Therefore a rigid pre-treatment work-up is necessary: pre-treatment blood work to evaluate the liver function [10] and a CT/MRI scan to assess the tumour volume and the extent of extrahepatic disease and to exclude portal vein thrombosis are required [22]. In addition, an angiogram is necessary to

map out the blood supply to the liver and thus ensure the delivery route [10, 22]. To avoid excessive shunting of the radioactive microspheres to the lungs, a scan with a nuclear tracer (technetium 99 labelled macroaggregated albumin) has to be performed [4, 22].

microspheres injected into liver artery using a catheter

If the patient has been found to be eligible for SIRT, a catheter is placed under fluoroscopic control in the hepatic artery through an incision in the groin and the microspheres are then injected in the artery [23]. Another option to administer the microspheres is via a permanent hepatic port. Usually, only one treatment is delivered, but especially in patients with HCC and a compromised liver reserve, several treatments can be administered [22]. Even though the intervention can be performed as an outpatient procedure [10, 23, 24], patients are usually discharged 2 days after the intervention in Austria and Germany [20].

in-patient stay for 2 days

In summary, treatment delivery and planning of SIRT requires a multidisciplinary team of experts including (interventional) radiologists, nuclear medicine specialist, oncologists and surgeons and it is thus a resource intense intervention.

1.3 Indication and therapeutic aim

SIRT for primary liver cancer and metastatic liver cancer, life expectancy ≥ 3 months

As already mentioned above, SIRT is indicated for patients with large, unresectable hepatic primary cancer or metastatic cancer and liver-dominant tumour burden and a life expectancy ≥ 3 months [10, 25]. This includes, besides HCC and mCRC, many other tumours such as cholangiocarcinomas or metastases from breast cancer, pancreatic cancer or neuroendocrine tumours [16, 26].

different indications for HCC…

For the most common malignancies (HCC, mCRC) many indications exist.

More specifically for HCC, SIRT might also be used:

- for non-resectable, non-ablatable HCCs
- as bridge to transplant by allowing more time to wait until transplantation or,
- to downstage the tumour either to within transplant criteria if patients do not fulfil transplantation criteria initially, or to enable resection or to allow partial liver hepatectomy [7, 17, 23, 27].

and mCRC possible

For mCRC, several indications are also possible:

- after failure of first-line chemotherapy
- in combination with (systemic) chemotherapy as first-line therapy
- as salvage therapy after failure of several lines of chemotherapy for patients with mCRC [25, 28].

Therefore, SIRT therapy has, besides some exceptions (downstaging), a palliative intention with the therapeutic aim of prolonging survival, delaying disease progression and maintaining or achieving good quality-of- life (QoL).

1.4 Estimated volumes of services and costs

Based on the documents submitted by the applicant, about 20 procedures are performed each year at this hospital. No estimates are available for Austria in general. Since treatment planning and delivery of SIRT requires a multidisciplinary team and a department for nuclear medicine and interventional radiology, only specialised tertiary care hospitals qualify.

according to applicant: 20 procedures/year

No information regarding the costs of any microsphere product was mentioned on the application submitted, but some evidence from Germany suggests a price of € 14,000.- for the microsphere products [20].

no cost estimates submitted, but some evidence that cost might be about € 14,000

2 Literature search and selection of literature

2.1 Research question

PICO-question

Based on the application submitted to the Ministry of Health (MoH) the research question was:

Does SIRT using Y-90 microspheres in patients with non-resectable, non-ablatable primary liver cancer or with metastatic liver tumours lead to better clinical outcomes and fewer adverse effects than alternative treatment options?

After scoping the literature, this overall research question was narrowed down to the two most common malignancies[1]. The research questions were thus:

1. Does SIRT using Y-90 microspheres in patients with non-resectable, non-ablatable HCC lead to improved clinical outcomes (survival, progression, quality of life, tumour response) and fewer adverse events than TACE, HAC, sorafenib or best supportive care?

   efficacy/safety of SIRT for HCC

2. Does SIRT using Y-90 microspheres in patients with non-resectable, non-ablatable liver metastases from colorectal carcinoma lead to improved clinical outcomes (survival, progression, quality of life, tumour response) and fewer adverse events than systemic chemotherapy, HAC or best supportive care?

   efficacy/safety of SIRT for mCRC

2.2 Inclusion criteria

study inclusion criteria

Inclusion criteria for the identification of relevant references are displayed in table 2.2-1.

Table 2.2-1: Inclusion criteria

Population	non-resectable, non-ablatable HCC/ mCRC
Intervention	selective internal radiotherapy using Y-90 microspheres (± systemic chemotherapy or HAC)
Control	HCC: • TACE, HAC • Sorafenib • best supportive care mCRC: • HAC • systemic chemotherapy • best supportive care Safety: any

[1] Due to the large number of entities, methodological and feasibility considerations necessitated to restrict the research question.

Outcomes	• survival • quality-of-life • progression • tumour response • adverse events
Study design	Efficacy: prospective controlled studies Safety: prospective controlled studies, prospective studies ≥ 50 patients

2.3 Literature search

systematic literature search in databases and websites

A systematic literature search was conducted between 28.-31.01.2011 in the following databases:

- Medline via Ovid
- Embase
- Cochrane Central Register of Controlled Trials
- NHS-CRD-HTA (INAHTA)

literature search yielded 852 hits

The systematic search was not limited to specific publication dates and yielded after deduplication 852 references. The detailed search history can be found in the appendix.

hand search: 136 hits

overall 900 references

The manufacturers of the two technologies (SIR-Spheres®, TheraSphere®) submitted an additional 9 relevant studies, a hand search identified 136 references and the applicant submitted 4 articles. Overall after deduplication, 900 hits/studies were found.

.

2.4 Literature selection

literature selection

900 references were considered for inclusion overall. The literature selection was done by two independent researches. In case of disagreement a third researcher was involved to establish consensus. The study selection process is displayed in figure 2.4-1:

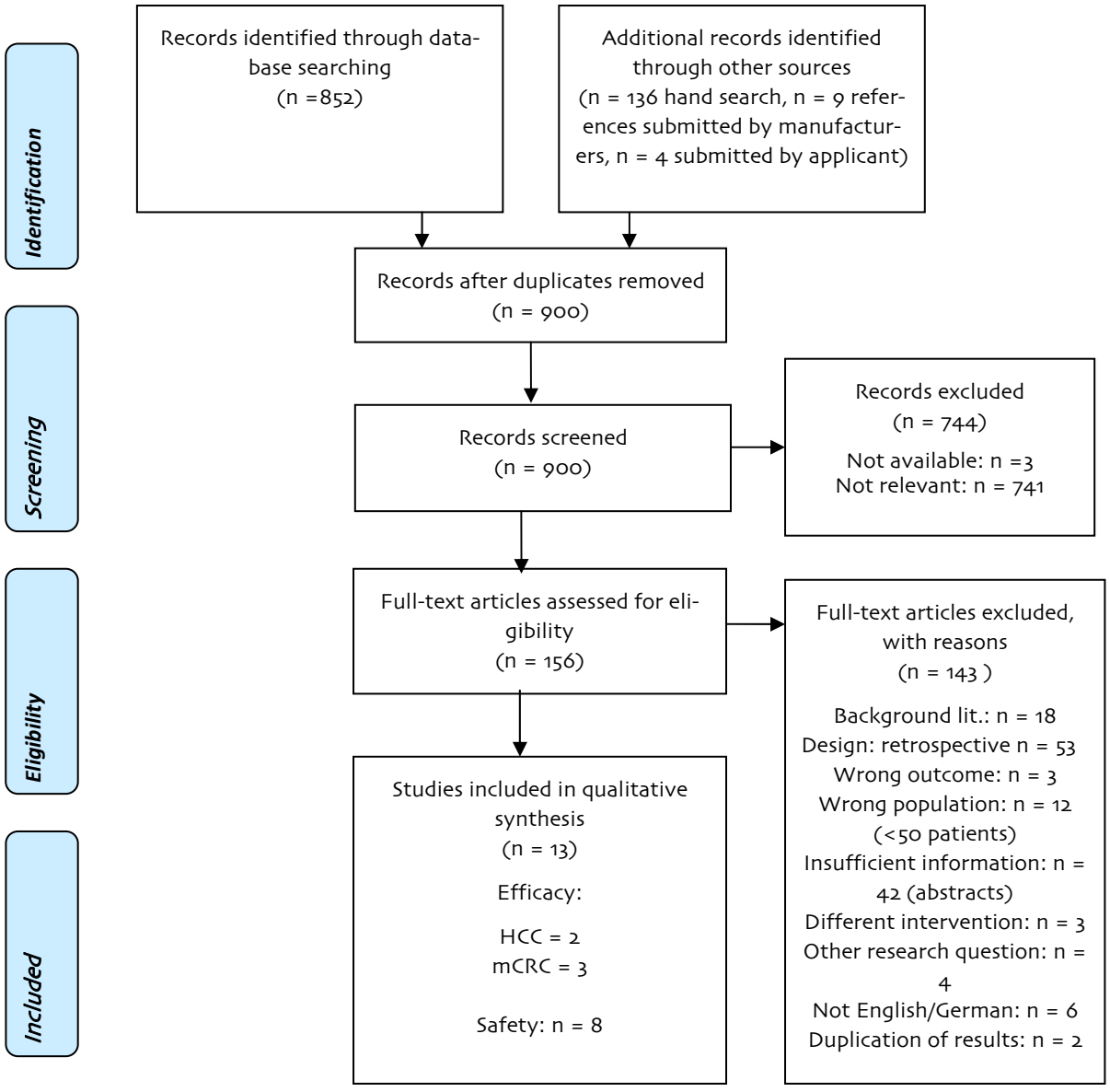

Figure 2.4-1: Literature selection process (PRISMA Flow Diagramme)

3 Study quality

study quality assessment

Assessment of the internal validity of studies was done by two researchers independently. Different results were discussed in order to achieve consensus. A third person was involved in cases of uncertainty. The internal manual of the LBI-HTA describes the quality criteria in detail [29].

4 Data extraction

data extraction

Data extraction was done by a single researcher. A second researcher independently double-checked the data for correctness and completeness.

4.1 Description of study results

13 studies included overall

13 studies were included overall [30-42]. For efficacy of SIRT for HCC, two studies on TheraSphere® were found [30, 31]; for safety 5 studies [32-36] were included, where all but 1 [36] assessed TheraSphere®.

3 randomized controlled trials (RCTs), all using SIR-Spheres® were identified for efficacy of SIRT for mCRC [37-39]. Data on safety were extracted from 3 publications [40-42]. Of those, 2 used SIR-Spheres® [40, 41] und 1 [42] TheraSphere®.

HCC:

2 prospective controlled trials for efficacy for HCC

2 comparative and prospective studies using TheraSphere® were found for efficacy (see table 4.1-1) [30, 31].

The study conducted by *Carr et al.* [30] enrolled two sequential cohorts: the first, which was recruited between 1992 and 2000, consisted of 691 patients whom were treated with TACE. The second cohort (2000 – 2005) comprised 99 patients treated with TheraSphere®. The second non-randomized study [31] assessed QoL in 28 patients overall.

outcomes considered

Outcomes which were considered in this review included:

- Survival: median overall survival (OS), survival rates
- Progression: time to disease progression (TTP)
- Tumour response: partial response (PR) , complete response (CR), stable disease (SD), progressive disease (PD)
- Quality-of-life (QoL)
- Adverse events (AEs)

Outcomes which were considered as relevant for formulating the recommendations are:

- OS
- TTP
- PR, CR, SD, PD
- QoL
- Adverse events: adverse events grade ≥3, treatment-related deaths

OS and QoL were chosen because the therapeutic aim in this setting is to prolong life and/or to increase QoL. Time to disease progression and tumour response as measured by tumour area are clearly surrogate outcomes but a change in tumour size is an important outcome if tumours can be downsized, consequently allowing liver transplantation in previously ineligible patients. Time to disease progression is relevant if SIRT is used as a bridge-to-transplant.

mCRC:

3 RCTs for efficacy for mCRC

3 RCTs [37-39], all using SIR-Spheres®, were included for efficacy of SIRT for the treatment of mCRC. The study characteristics and the results are summarized in table 4.1-3.

All 3 comparative trials evaluated SIR-Spheres® for mCRC and can essentially be regarded as industry-sponsored [37-39]. Sample size ranged from 21 [37] patients to 70 patients [38]. 2 trials [37, 39] compared SIR-Spheres® + systemic chemotherapy to systemic chemotherapy alone, whereas the third trial used HAC as a comparator [38]. Enrolled patients differed between the trials as they included untreated [37], as well as patients previously treated for their metastatic disease [39]. Similarly, presence of extrahepatic disease at time of randomisation was an exclusion criterion in two studies [38, 39], whereas *van Hazel et al.* [37] also included patients with extrahepatic disease.

outcomes considered

Outcomes which were considered in this review included:

- Survival: OS , survival rates
- Progression: TTP, time to hepatic disease progression (TTHP)
- Tumour response: CR, PR, SD, PD, serum CEA changes
- QoL
- Adverse events

Outcomes which were considered as relevant for formulating the recommendations are:

- OS
- TTP
- PR, CR, SD, PD
- QoL
- Adverse events grade ≥3, treatment-related deaths

Improvements in OS and QoL are again the most important outcomes for patients with mCRC. Tumour response and TTP are surrogate parameters but they can provide some information on the intervention's activity.

Safety:

for safety: 8 uncontrolled trials, 5 for HCC, 3 for mCRC

Safety issues related to SIRT concerning HCC was the topic of 5 uncontrolled studies [32-36] (see Table 4.1-2). In 4 studies, glass-microspheres were used [32-35], whereas only one used resin microspheres [36]. Sample sizes ranged from 71 [36] to 291 patients [33].

3 studies which met our inclusion criteria were found which assessed mCRC [40-42] (see table 4.1-4). SIR-Spheres® were used in 2 [40, 41] and TheraSphere® in 1 study [42]. Sample size ranged from 50 [40] to 140 patients [41] and all trials evaluated patients previously treated with chemotherapy.

Table 4.1-1: Comparative studies for efficacy of SIRT for the treatment of HCC

Author, Year [Reference]	Carr 2010 [30]	Steel 2004 [31]
Country	USA	USA
Sponsor	US National Institutes of Health	American Cancer Society
Study period	C: 1992 – 2000 I: 2000 - 2005	NR
I(ntervention)	glass microspheres	glass microspheres
Indication	unresectable HCC	unresectable HCC
Administration of intervention	median dose: NR; single dose TheraSphere, 30% received a 2nd treatment	single dose TheraSphere
C(omparator)	TACE (125mg/m² of body surface area cisplatin) + Gelfoam sponge particles/biospheres	HAC (cisplatin 125mg/m² every 6 weeks)
Study design	open-label, cohort study	prospective, non-randomized study
Number of patients	790, I 99 vs C 691	28, I 14 vs C 14
Mean age of patients	NR	59
Patient characteristics	male: I 70% vs C 75% PVT: I 28% vs C 42%	male: I 64% vs C 79%
Inclusion	unresectable HCC, not amenable to RFA, hepatic transplantation	HCC
Exclusion	ECOG PS 0-1	current suicidal ideation, current psychosis, health too poor to complete questionnaire
Follow up (months)	NR	NR
Outcome		
Median survival	I 11.5 months (95%CI 8 – 16 months) vs C 8.5 months (95%CI 8 – 10 months), p< 0.05	NR
Survival rate	NR	NR
Tumour response measured by tumour area (criteria used)	WHO	-
	CR: I 3% vs C 5% PR: I 38% vs C 55% SD: I 35% vs C 29% PD: I 23% vs C 11%	NR
Median time to disease progression	NR	NR
QoL	NR	FACT-Hep instrument: 3 months follow-up: I vs C functional well-being (p<0.001), overall health-related quality of life (p<0.001) 6 months follow-up: I vs C: higher functional well-being (p<0.04)
Treatment related deaths	NR	NR
overall AEs	NR	NR
Grade 1-2	NR	NR
Grade ≥3	NR	NR
Notes	difference in survival may be explained by the selection of patients who had milder disease in the SIRT group	

Abbreviations used: PVT = portal vein thrombosis, ECOG PS = Eastern Cooperative Oncology Group Performance Status, NR = not reported, CI = confidence interval, WHO = World Health Organisation, FACT-Hep = Functional Assessment of Cancer Therapy- Hepatobiliary

Table 4.1-2: Uncontrolled studies for safety of the efficacy of SIRT for the treatment of HCC

Author, Year [Reference]	Kulik 2008 [32]	Salem 2010 [33]	Hilgard 2010 [34]	Atassi 2008 [35]	Lau 1998 [36]
Country	USA	USA	Germany	USA	Hong Kong
Sponsor	MDS Nordion (grants to individual authors)	MDS Nordion (research support to individual authors)	NR	one author acts as an advisor to MDS Nordion	NR
Study period	NR	January 2004 – December 2008	November 2006 – March 2009	2001 - 2006	October 1992 – December 1995
Intervention	glass microspheres	glass microspheres	glass microspheres	glass microspheres	resin-based microspheres
Indication	HCC	unresectable HCC	unresectable HCC	unresectable HCC	unresectable HCC
Administration of intervention	median dose 134 Gy, 1 -3 treatments	median dose 103 Gy, mean 1.8 treatments	mean dose 120 Gy, mean 1.5 treatments	NR	median dose 5.6 to 13 GY, 1 – 5 treatments
Study design	open-label, phase II	prospective longitudinal cohort study	observational cohort study	prospective safety study	prospective observational study
Number of patients	108	291	108	190	71
Mean age of patients (years)	69	65	65	NR	55 median
Patient characteristics	male: 69% PVT: 34% Child Pugh A/B: 54%/27%	male: 77% PVT: 43% previously treated: 13% Child Pugh A/B: 45%/52%	male: 80% PVT: 31% previously treated: 38% Child-Pugh A: 77% BCLC stage B/C: 47%51%	NR	male: 87% men previously treated: 28%
Inclusion	ECOG ≤2	ECOG ≤2, extrahepatic disease, portal vein thrombosis	HCC of BCLC C tumour stage, or with BCLC A/B if not eligible for selective TACE, ECOG ≤2)	ECOG 0-3	Karnofsky PS >70%
Exclusion	significant extrahepatic disease	NR	extrahepatic disease	life expectancy <3 months	extrahepatic disease
Follow up (months)	NR	31 months	NR	laboratory follow-up >300 days	NR
Outcomes					
Median survival (months)	193 – 670 days (dependent on presence of portal vein thrombis/location of portal vein thrombosis, presence of cirrhosis)	2. 5 months to 47.4 months (dependent on staging based on UNOS, Child-Pugh, PVT, tumour stage)	16.4 months (95%CI 12.1 months to NR)	NR	9.4 months (range 1.8 to 46.4 from diagnosis)
Survival rate (%)	NR	NR	at 1 year: 59%	NR	NR
Tumour response measured by tumour area (criteria used)	WHO	WHO	RECIST	_	-

Author, Year [Reference]	Kulik 2008 [32]	Salem 2010 [33]	Hilgard 2010 [34]	Atassi 2008 [35]	Lau 1998 [36]
	PR 42% CR: 0% SD: 35% PD: 23%	overall response rate: 42%	30/60/90 days after treatment: CR or PR: 3%/10%/16% SD: 90%/80%/74% PD: 7%/10%/10%	NR	NR
Median time to disease progression	NR	7.9 months (95% CI 6.0 to 10.3 months)	10.0 months (95% CI 6.1-16.4 months)	NR	NR
QoL	NR	NR	NR	NR	NR
Treatment-related deaths (%)	1 % (1/108)	0%	0%	0%	1% (1/71)
AEs overall	with/without cirrhosis: elevated bilirubin: 40%/4% ascites: 18%4% hepatic encephalopathy: 4%/0%	NR	NR	symptomatic and asymptomatic toxicities: 15%	low grade fever 14% nausea/vomiting/abdominal pain: 17%
Grade 1 – 2	NR	fatigue: 57% diarrhoea/nausea/vomiting/abdominal pain/anorexia: 2% - 23% elevated liver enzymes: 55% - 77%	fatigue syndrome: 61% abdominal pain: 56%	NR	NR
Grade ≥3	with/without cirrhosis: elevated bilirubin: 2% - 26%/0% - 4% ascites: 15%/4% hepatic encephalopathy: 1%/- ascites: 4%/-	elevated liver enzymes: 4% - 19%	lymphopenia: 11-60% bilirubin toxicities: 3-20%	elevated liver enzymes: 2%- 7%	0%
Notes		34% received treatment with curative intent after SIRT	AEs grade 3/4 depending on values at baseline		6% (4/71) became resectable

Abbreviations used: Gy = Gray, PVT = portal vein thrombosis, ECOG = Eastern Cooperative Oncology Group, PS = Performance Status, BCLC = Barcelona Liver Cancer Clinic NR = not reported, CI = confidence interval, WHO = World Health Organisation, UNOS = United Network for Organ Sharing, RECIST = Response Evaluation Criteria In Solid Tumors, HRQL= health related quality of life

Table 4.1-3: Comparative studies for efficacy of SIRT for the treatment of mCRC

Author, Year [Reference]	Van Hazel 2004 [37]	Gray 2001 [38]	Hendlisz 2010 [39]
Country	Australia	Australia	Belgium
Sponsor	Sirtex Medical Limited	Sirtex Medical Limited	Sirtex Medical Limited
Study period	NR	1991 - 1997	December 2004 – November 2007
Intervention	resin microspheres + systemic chemotherapy (5-fluorouracil 425mg/m²/day + leucovorin 20 mg/m²/day for 5 consecutive days every 4 weeks)	resin microspheres + HAC (12 day cycles 0.3 mg/kg/day floxuridine for 18 cycles)	resin microspheres + systemic chemotherapy (5-fluorouracil 225mg/m²/days for 14 consecutive days, followed by 5-fluorouracil 300mg/m²/day for 14 days every 3 weeks)
Tumour stage	1st line therapy	1st- 2nd line therapy	salvage therapy
Administration of intervention	single dose of resin microspheres, mean activity 2.25 GBq, transfemoral catheter	single dose of resin microspheres, mean activity 2.16 GBq, delivered by a permanent hepatic port	single dose of resin microspheres, median activity 1.79 GBq
Comparator	systemic chemotherapy (5-fluorouracil 425mg/m²/day + +leucovorin 20 mg/m²/day for 5 consecutive days every 4 weeks)	HAC (12 day cycles of 0.3 mg/kg/day floxuridine for 18 cycles)	systemic chemotherapy (5-fluorouracil 300mg/m²/days for 14 consecutive days every 3 weeks)
Study design	RCT, phase II	RCT, phase III	RCT, open-label, phase III
Number of patients randomized	21, I 11 vs C 10	70, I 36 vs C 34	44, I 21 vs C 23
Mean age of patients (years)	I 64 vs C 65	I 59 vs C 62	I 62 vs C 62
Patient characteristics	male: I 91% vs C 80% extrahepatic metastases: I 18% vs C 30%	male: I 78% vs C 76% previous chemotherapy: I 15% vs C 14%	male: I 48% vs C 78% previous chemotherapy: I 100% vs C 100%
Inclusion	liver metastases from CRC ± extrahepatic disease not treatable with resection or locally ablative therapy, WHO performance status <3	liver metastases from CRC not treatable with resection or locally ablative therapy, WHO performance status <3, previous systemic chemotherapy for the treatment of metastases was allowed	liver metastases from CRC not treatable with resection or locally ablative therapy, resistant or intolerant to standard chemotherapy (FU, oxaliplatin, and irinotecan), ECOG PS<3,
Exclusion	previously treated metastases, cirrhosis, portal hypertension, central nervous system metastases	extrahepatic disease, previous radiotherapy to the liver, cirrhosis	extrahepatic disease, liver cirrhosis >Child-Pugh B, liver abscess, partial/total thrombosis of the portal vein, prior HAC with fluorouracil, floxuridine or other chemotherapeutic regimens
Median Follow up	NR	Minimum follow-up of 3.5 years	25 months
Results			
Median survival (months)	I 29.4 months vs C 12.8 months HR = 0.33 95%CI 0.12 to 0.91, p=0.025	I 17.0 months vs C 15.9 months HR = 1.41 95%CI 0.86 to 2.34, p= 0.18	I 10.0 months vs C 7.3 months HR =0.92, 95%CI 0.47 to 1.78, p = 0.80
Survival rate (%)	NR	1 year: I 72% vs C 68% 2-years: I 39% vs C 29% 3-years: I 17% vs C 6% 5-years: I 3.5% vs C 0%	NR

Author, Year [Reference]	Van Hazel 2004 [37]	Gray 2001 [38]	Hendlisz 2010 [39]
Tumour response measured by tumour area (criteria used)	RECIST	non standardized criteria [2]	RECIST
	CR: I 0% vs C 0% PR: I 73% vs C 0% SD: I 27% vs C 60% PD: I 0% vs C 40% Comparison between groups p<0.001	CR: I 6% vs C 0% PR: I 39% vs C 18% SD: I 36% C 38% PD: I 8% vs C 24% Difference between groups p=0.01	CR: I 0% vs C 0% PR: I 10% vs C 0% (p=0.22) SD: I 76% vs C 35% (p=0.001) PD: I 10% vs C 61% Non-evaluable: I 5% vs C 4%
Tumour response measured by CEA	NR	CR: I 42% vs C 26% PR: I 31% vs C 21% SD: I 6% vs C 29% PD: I 3% vs C 18%[3]	NR
Median time to hepatic disease progression (months)	NR	log-rank measured for tumour area: p<0.01[4]	I 5.5 months vs C 2.1 months HR = 0.38 95%CI 0.20 to 0.72; p = 0.003
Median time to tumour progression (months)	I 18.6 months vs C 3.6 months, p<0.0005	NR	I 4.5 months vs C 2.1 months HR = 0.51 95%CI 0.28 to 0.94, p = 0.03
QoL	at 3 months: patient reported (FLIC questionnaire): no differences between groups, p=0.96 Physician reported (Spitzer index): no difference, p=0.98	3-monthly intervals: self Assessment Scale by Priestmann and Baum: no significant differences between groups	NR
Treatment related deaths, % (number of events)	I 9% (1/11 pts) vs C 0% pts	0%	0%
Overall AEs	NR	NR	NR
Grade 1 – 2, %	NR	liver function tests (number of events): I 300 vs C 207 nausea/diarrhoea: I 44% vs C 32%	NR
Grade ≥3, %	overall (number of events): I 13 vs C 5 cirrhosis: I 9% vs C 0% nausea/vomiting/gastritis/diarrhoea/mucositis: I 9% -36% vs C 10% granulocytopenia: I 27% vs C 0%	overall (number of events): I 23 vs C 23 elevated liver enzymes: I 3 -39% vs C 0% 35% nausea/vomiting/diarrhoea: I 0% vs C 3% Hb: I 0% vs C 3%	overall I 5% vs C 27%
Notes	once protocol treatment ceased, further cancer-specific treatment, including non-protocol chemotherapy, was allowed to best manage patient care	initially designed for 95 pts, but only 74 pts were enrolled, study therefore underpowered for original primary outcome (survival), changed to response and time to disease progression Once protocol treatment ceased, further cancer-specific treatment, including non-protocol chemotherapy was allowed	10 patients cross-over to SIR treatment, 6 patients from the control group received further therapies (cetuximab + chemotherapy, chemotherapy alone), 9 patients in the intervention group received further treatment (e.g. cetuximab + chemotherapy, chemotherapy alone)

Abbreviations used: GBq = Giga Becquerel, ECOG = Eastern Cooperative Oncology Group, PS = Performance Status, NR = not reported, CI = confidence interval, WHO = World Health Organisation, PS = performance status, RECIST = Response Evaluation Criteria In Solid Tumors, HR = Hazard ratio

[2] PR: decrease of tumour size ≥50%, CR: disappearance of all tumour lesions, PD: increase in cross-sectional tumour area, by 25% or more over the nadir, development of new lesions in the liver ; NC: decrease in tumour volume

[3] CR: decrease in serum CEA into the normal range, PR: decrease of serum CEA by ≥50%

[4] Measured as an increase in cross-sectional tumour area/volume by ≥25%, development of new liver lesions, increase in serum CEA by ≥25% over nadir

Table 4.1-4: Uncontrolled studies for safety of SIRT for mCRC

Author, Year [Reference]	Cosimelli 2010 [40]	Chua 2010 [41]	Mulcahy 2009 [42]
Country	Italy	Australia	USA
Sponsor	SIR-Spheres provided by Sirtex	NR	one author acts as an advisor to MDS Nordion
Study period	May 2005 – August 2007	March 2006 - May 2009	2003 - 2007
Intervention	resin microspheres	resin microspheres	glass microspheres
Indication	salvage therapy	salvage therapy	salvage therapy
Administration of intervention	single dose, median activity 1.7 GBq	mean activity 1.8 GBq	mean number of treatments 1.9, median activity 2.37 GBy
Study design	prospective, multi-centre, phase II	prospective database collection	open-label, expanded use protocol
Number of patients	50	140	72
Mean age of patients (years)	64	64	61
Patient characteristics	male: 74% previous chemotherapy: 100%	male: 63% Previous chemotherapy: 94%	male: 65% previous chemotherapy: 94%
Inclusion	unresectable CRC liver metastases, limited extrahepatic disease, progressive liver disease following systemic standard chemotherapy, ECOG PS ≤2	unresectable CRC liver metastases, ECOG PS ≤2, prior/concomitant chemotherapy allowed	liver-dominant unresectable CRC metastases, ECOG PS ≤2
Exclusion	previous HAC	NR	significant extrahepatic disease, life expectancy <3 months
Median Follow-up	11 months	9 months	26.2 months
Outcome			
Median overall survival (months)	12.6 months (95%CI 7.0 to 18.3 months)	9 months (95%CI 6.4 to 11.3 months)	14.5 months (95%CI 9.6 to 21.9 months)
Survival rate (%)	1-year: 50% 2-years: 20%	1-year survival rate: 42% 2-year survival rate 22% 3-year survival rate 20%	5 year survival rate: 30% (from time of cancer diagnosis)
Tumour response measured by tumour area (criteria used)	RECIST	RECIST	WHO
	CR 2% PR 22% SD 24% PD 44%	CR 1% PR 31% SD 31% PD 37%	PR 40% SD 45% PD 15%
Median time to hepatic disease progression	2.8 months	NR	15.4 months (95% CI 5.4 to 18 months)
Median time to tumour progression	3.7 months (95%CI 2.6 to 4.9 months)	NR	NR
QoL	anxiety levels were significantly reduced (p<0.01) at 6 week follow-up	NR	NR
Treatment related deaths (%)	2 (4%) probably treatment related deaths	0	0
Overall AEs	NR	intestinal ulceration: 1%, abdominal pain: 14%	NR
Grade 1 -2	total: 22% leucocytosis: 2% jaundice/nausea/fatigue/fever/chronic pain: 2%-10% gastrointestinal ulcers: 4%	NR	fatigue/abdominal pain/nausea/fever/diarrhoea 4% - 61% gastrointestinal ulceration 1%
Grade ≥3	0%	NR	elevated liver enzymes: 6% - 13%

Author, Year [Reference]	Cosimelli 2010 [40]	Chua 2010 [41]	Mulcahy 2009 [42]
Notes	14 pts received subsequent chemotherapy, downstaging enabling resection 4%	34% had concomitant or post radioembolisation chemotherapy after SIRT Single factor for better response was chemo SIRT	

Abbreviations used: GBq = Giga Becquerel, ECOG PS = Eastern Cooperative Oncology Group, PS = Performance Status, NR = not reported, CI = confidence interval, WHO = World Health Organisation, RECIST = Response Evaluation Criteria In Solid Tumors

4.2 Efficacy

HCC:

2 studies using TheraSphere®

SIRT in comparison to TACE in study of low quality

improvement of OS, but not for tumour response

2 trials were found which both assessed glass microspheres for the treatment of non-resectable HCC (see table 4.1.-1) [30, 31]. *Carr et al.* [30] compared in two sequential cohorts TheraSphere® to TACE with cisplatin and embolizing particles. Median OS was significantly improved in the SIRT group (I 11.5 months vs C 8.5 months, $p < 0.05$). But the study suffers from methodological weaknesses and even the authors themselves mention that the statistically significant difference in OS is most likely explained by differences in baseline characteristics with patients allocated to the SIRT group having milder disease than those in the control group. Tumour response showed inferior results for SIRT.

QoL was outcome in study with small sample size: only partly improved

QoL outcomes were assessed in a small group of patients (I 14 pts vs C 14 pts) [31] comparing glass-microspheres to HAC. Functional well-being, as well as overall health related QoL (HrQL) at 3 months showed improved outcomes for patients treated with microspheres. After 6 months, however, only the positive effective on functional well-being persisted in patients treated with SIRT ($p<0.04$). But due to the small sample size, these findings have to be interpreted with caution.

uncontrolled studies provide limited evidence

Furthermore, 5 uncontrolled studies [32-36] provide limited evidence on efficacy of SIRT for the treatment of HCCs (see table 4.1-2). In the 4 studies with glass-microspheres, median OS varied substantially as results between 2.5 months and 47 months were found and outcomes for tumour response differed too. But these discrepancies can be explained as these numbers represent results for rather heterogeneous patients (e.g. different tumour stage, ± extrahepatic disease). The only study [36] with SIR-Spheres® showed a median OS of 9.6 months.

mCRC:

Overall 3 RCTs with SIR-Spheres® were included in this report [37-39]. Two trials, where the majority of patients received SIRT as first-line therapy [37, 38], showed somehow varying results (see table 4.1-3). The study conducted by *van Hazel* [37] comprised only 21 patients and showed improvements in median OS for patients treated with SIRT + chemotherapy in comparison to patients treated with systemic chemotherapy only (HR=0.33, p=0.025). In contrast, the other study [38] did not demonstrate favourable results for OS in the SIRT group. But similarities were found for outcome measures such as tumour response and time to (hepatic) disease progression, where, for example, a partial response was achieved more often after the delivery of SIR-Spheres® (I 39%-73% vs C 0%-18%). Both studies report statistically significant differences in TTP in favour of patients treated with SIRT. However, when compared to systemic chemotherapy or HAC, neither trial demonstrated any difference in QoL, indicating that, if QoL is not improved, addition of SIRT does at least not worsen QoL.

3 RCTs evaluating SIR-Spheres® as 1st-line therapy and salvage therapy

2 studies for 1st –line therapy

differing comparators,

results for OS varied

similar results for tumour response and time to disease progression

However, the trial is open to criticism, since, in addition to the small sample size, the chemotherapy regimen used in the *van Hazel* trial no longer reflects standard chemotherapy [37]. Furthermore, patients in both RCTs received non-protocol chemotherapy once protocol treatment ceased. Also, extra-hepatic disease is generally regarded as exclusion criterion for the delivery of SIRT [10, 12, 20], but one of the trials incorporated patients with disease outside the liver [37]. Moreover, the trial conducted by *Gray et al.* [38] was initially designed to enrol 95 patients, but due to slow accrual only 74 patients finally entered the trial. Therefore, the initial primary outcome, OS, was underpowered and was thus changed to tumour response and TTP.

but chemotherapy does not reflect standard therapy anymore

additional, non-protocol chemotherapy was allowed

Hendlisz et al. [39] evaluated SIR-Spheres® + 5-fluorouracil (5-FU) in patients with unresectable liver metastases resistant or intolerant to standard chemotherapy in comparison to 5-FU only. With a difference of only 2.7 months, OS was not statistically significant, but as in the trials mentioned above, better results for SIRT + chemotherapy were found for TTP. No difference was found for partial responses (p=0.22), but disease control rates (PR + SD) were improved for patients receiving both, i.e. SIRT and chemotherapy, compared to patients treated with chemotherapy alone. (p=0.001). Nonetheless, these numbers have to be interpreted with caution, since 10 patients crossed-over to the SIRT group, and, overall, 15 patients received further therapies.

for salvage therapy: 1 RCT

no difference for OS, improved TTP and disease control rate

Some additional evidence might be derived from 3 uncontrolled trials [40-42] which were primarily included for the safety analysis (see table 4.1-4). As none of them are of a comparative study design, no final conclusions on efficacy can be drawn. Overall, 262 previously treated patients were either treated with glass or resin-microspheres. When SIR-Spheres® [40, 41] were used, median OS ranged from 9 to 12.6 months; TTP was about 4 months [40]. PR was seen in 22% [40] to 31% [41]. One study reports additionally that anxiety levels were significantly reduced after 6 weeks [40]. The only study where TheraSphere® was used for the treatment of mCRC [42], reported a median OS of 14.5 months and PR was observed in 40% of all patients.

additional evidence from 3 uncontrolled studies

4.3 Safety

HCC

HCC: grade 1+2 AEs in 77%

Safety-related outcomes were only reported in the uncontrolled studies (see table 4.1-2). In the 4 studies which used glass-microspheres [32-35] grade 1/2 AEs occurred in up to 77% of patients [33].The most common AEs were elevated liver enzymes, fatigue and abdominal pain. One study reported, that out of 108 patients, 1 patient (i.e. 1%) had died due to treatment-related AEs [32]. Most common AEs of grade ≥3 were liver dysfunctions which occurred in 2% - 26%, but these differences might be explained due to dissimilarities between the study populations (e.g. ± liver cirrhosis). Lymphopenia was reported in one study [34] in 11% to 60% of patients.

1% treatment-related deaths, most common AEs grade ≥3: liver dysfunction

Lau et al. [36] investigated resin-microspheres for HCC and also reported 1 treatment-related death (=1%). Nausea, vomiting and abdominal pain of any grade were each seen in 17%; higher grade AEs were not reported.

mCRC:

AEs from 6 studies overall

Overall 6 studies (3 RCTs, 3 uncontrolled studies) reported safety outcomes for patients with mCRC treated with SIRT (glass and resin) (see table 4.1-3 und 4.1-4) [37-42]. All but one [42] used SIR-Spheres®.

grade ≥3 liver dysfunctions most common

Within the RCTs, 1 treatment–related death due to sepsis (=9%, 1 out of 11 patients) was observed [37]. The most common adverse events of higher grades were liver dysfunctions which occurred in 3% to 39% in the SIRT group and in 0% to 35% in the control group. Other, non-hepatic AEs of grade ≥ 3 included diarrhoea (I 18% vs C 10%) and vomiting/nausea (I 9% vs C 10%). Because all 3 RCTs also allowed further non-protocol therapy it is difficult to clearly state which AEs are attributable to SIRT and which to chemotherapies.

others: diarrhoea, nausea

uncontrolled studies reported 2 treatment-related deaths (liver-/kidney failure)

Gastrointestinal ulcerations in uncontrolled studies which used SIR-Spheres® were seen in up to 4%. *Cosimelli et al.* [40] reported 2 deaths possibly related to the therapy: one due to kidney failure and the other due to liver failure [40]. AEs of grade ≥3 were either not reported or did not occur.

Grade 1+2 AEs in the only study with TheraSphere® [42] were reported in 61%. Most common AEs of grade ≥3 were elevated liver enzymes (13%).

5 Quality of evidence

GRADE approach for quality of evidence

The GRADE approach was used to assess the quality of evidence [43]. The GRADE system classifies the quality of evidence in one of four grades:

- High quality: further research is very unlikely to change our confidence in the estimate of effect
- Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimates
- Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low quality: any estimate of effect is very uncertain.

The GRADE approach was applied to the research question and is displayed in table 5.1. and 5.2. As efficacy outcomes for HCC were only found for TheraSphere®, safety outcomes were only included for those studies which assessed glass-microspheres. Similarly, because all RCTs on SIRT for mCRC had used SIR-Spheres®, only safety outcomes of those studies which had used the resin-microspheres were incorporated in the tables.

For the treatment of HCC, the overall strength of evidence for TheraSphere® is very low; the one for safety is good. The strength of evidence for SIR-Spheres® for mCRC is overall low; the one for safety is good.

Table 5-1: Evidence profile for comparative efficacy and safety for SIRT (TheraSphere®) for HCC

No of studies/patients	Design	Limitations	Consistency of results	Directness	Effect size	Other modifying factors	Strength of evidence
Outcome: median survival							
1/790	sequential cohort study	serious limitations[1]	-	yes	I (99 pts) 11.5 months vs C (691 pts) 8.5 months, p< 0.05	-	very low
Outcome: time to disease progression							
-	-	-	-	-	-	-	-
Outcome: tumour response							
1/790	sequential cohort study	serious limitations[1]	-	yes	CR: I 3% vs C 5% PR: I 38% vs C 55% SD: I 35% vs C 29% PD: I 23% vs C 11%	-	very low
Outcome: QoL							
1/28	prospective non-randomized	some limitations[2]	-	yes	some improvements (HrQL and functional well-being) after 3 months after 6 months: only for functional well-being	sparse data	very low
Outcome (safety): treatment related deaths							
4/697	prospective, uncontrolled	no serious limitations	yes	yes	1%	-	good
Outcome (safety): adverse events grade ≥3							
4/697	prospective uncontrolled	no serious limitations	yes	yes	hepatic: 2% - 26% non-hepatic AEs:1% - 60%	heterogeneous population	good

1= baseline characteristics not balanced, patient recruitment during different time periods, follow-up period not reported

2= no information whether investigators were blinded, possible selection bias, median follow-up not reported

Table 5-2: Evidence profile: comparative efficacy and safety of SIRT (SIR –Spheres®) for mCRC

No of studies/patients	Design	Limitations	Consistency of results	Directness	Effect size	Other modifying factors*	Strength of evidence
Outcome 1st line: median survival							
2/91	RCTs	no serious limitations	no	yes	I 29.4 months vs C 12.8 months (95%CI 0.12 – 0.91, P=0.025) in 21 pts I 17 months vs C 15.9 months (95%CI 0.86 to 2.34), p=0.18) in 70 pts	sparse data/imprecise results, other confounding factors, underpowered for OS	low
Outcome salvage: median survival							
1/44	RCT	some limitations[1]	-	yes	I 10.0 months vs C 7.3 months (95%CI 0.47 to 1.78, p = 0.80)	sparse data/imprecise results, other confounding factors	very low
Outcome 1st-line: time to tumour progression							
1/21	RCT	no serious limitations	-	yes	I 18.6 months vs C 3.6 months, p<0.0005	sparse data, other confounding factors	low
Outcome salvage: time to tumour progression							
1/44	RCT	some limitations[1]	-	yes	I 4.5 months vs C 2.1 months, p=0.03	sparse data/imprecise results, other confounding factors	very low

Outcome 1st-line: tumour response							
2/91	RCTs	no serious limitations	yes	yes	CR: I 0-6% vs C 0% PR: I 39-73% vs C 0-18% SD: I 27-36% vs C 38-60% PD: I 0-8% vs C 24-40%	sparse data, other confounding factors, limited external validity	moderate
Outcome salvage: tumour response							
1/44	RCT	some limitations[1]	-	yes	CR: I 0% vs C 0% PR: I 10% vs C 0% SD: I 76% vs C 35% PD: I 10% vs C 61%	sparse data, other confounding factors	very low
Outcome 1st line: QoL							
2/91	RCTs	no serious limitations	yes	yes	no difference between I and C	sparse data, other confounding factors	moderate
Outcome salvage: QoL							
-	-	-	-	-	-	-	-
Outcome (safety): treatment related deaths							
3/135	RCTs	no serious limitations – serious limitations[1]	yes	yes	I 0% - 9% vs C 0%	other confounding factors	moderate- good
2/190	prospective, uncontrolled	no serious limitations	yes	yes	0% - 4%	-	good
Outcome (safety): adverse events grade ≥3							
3/135	RCTs	no serious limitations – some limitations[1]	yes	yes	hepatic: I 3% -39% vs C 0% - 35% extra-hepatic: 0% -36% vs C 0% - 10%	other confounding factors	moderate -good
1/50	prospective, uncontrolled	no serious limitations	-	-	hepatic: 0% non-hepatic: 0%	sparse data	moderate

1 = unclear allocation concealment, no information about blinding of investigators, unclear ITT

6 Discussion

Even though SIRT using Y-90 - microspheres is the oldest transarterial therapy which has been described for the treatment of liver tumours, its use has only increased during the last decade [12]. Even though SIRT is most often used for HCC and liver metastases from CRC, several other cancers such as metastases of breast cancer or neuroendocrine tumours or cholangiocarcinomas might also be treated with SIRT. Nonetheless, even within the two main indications, SIRT might be used in various setting such as 1st- line therapy, as bridge-to-transplant or as salvage therapy. In spite of the various possible indications and a plethora of studies, there are a surprisingly few controlled trials.

SIRT oldest transarterial therapy, but use increased only recently

for many tumours and indications but controlled trials rare

As all comparative trials for mCRC used SIR-Spheres®, judgements on efficacy can only be made for resin-microspheres. Even though 3 RCTs were found which assessed SIR-Spheres® for mCRC [37-39], a conclusive judgement on efficacy is difficult, since, in addition to some methodological concerns, these trials are rather heterogeneous, because settings, populations and comparators varied. Consequently, the results for different outcomes are ambiguous. Indeed, one study showed significantly improved outcomes for median OS [37] whereas 2 other trials, one using SIRT as 1st-line therapy [38], the other as salvage therapy [39], found no differences. Clear conclusions on the effect of SIRT on OS are also hampered as patients were allowed to receive non-protocol chemotherapy once protocol treatment ceased, or patients crossed-over to SIRT therapy. On the other hand, for outcomes, such as tumour response and progression, somehow consistent results, favouring patients treated with SIR-Spheres® were found. Likewise, there is some indication that if QoL is not improved, addition of SIRT to other therapies at least does not compromise QoL. But criticism can be expressed, as, for example, no data on the efficacy of SIRT in comparison to current chemotherapy regimens for the treatment of mCRC exist [11] as 2 trials [37, 39] used a chemotherapy regimen which cannot be considered as standard-therapy any longer. In addition, extrahepatic disease is generally regarded as an exclusion criterion for the delivery of SIRT [10, 12, 20], but one of the trials incorporated patients with disease outside the liver [37], a fact which might not impact on tumour response but might distort outcomes such as QoL or OS.

judgements on SIRT for mCRC only for SIR-Spheres®

different indications and comparators

despite 3 RCTs, judgements on efficacy difficult, because different results for OS, no comparison to state-of-the art chemotherapies,

further chemotherapies were allowed, cross-over

some evidence for improved outcomes such as tumour response

Data on efficacy of SIRT for HCC was only found for TheraSphere® [30, 31]. The available comparative evidence from 2 studies of diminished methodological quality and with small numbers of patients is rather weak. Therefore, a definite statement on efficacy is currently not possible.

for HCC, only studies using TheraSphere®

but due to weak evidence, definite statement on efficacy not possible

Regarding safety, it seems that careful patient selection and an extensive pre-treatment work-up, allow the frequency of serious adverse events to be minimized (see chapter 1.2.). The majority of AEs associated with SIRT were of grade 1 or 2. More severe AEs, include treatment-related deaths (in 1%- 9%). More frequent were liver dysfunctions: those of grade≥3 occurred in the controlled trials in 39% of patients in the SIRT group in comparison to 35% in the control group. The uncontrolled studies report liver dysfunctions in up to 26%. Radiation-induced, sometimes life threatening AEs such as radiation pneumonitis/cholecystitis or gastrointestinal ulcerations were reported infrequently in up to 4%.

most common AEs: liver dysfunctions

pneumonitits, cholezystitis/ulcerations in 4%

conflicting evidence reflected in differing recommendations by expert groups

The lack of unequivocal evidence is also reflected in differing recommendations by expert groups [7, 8, 19, 44, 45] and institutions [11, 16]. Therefore, high-quality studies with comparators relevant to daily practice are needed to clearly define the role of SIRT for the treatment of various liver tumours [7, 8, 26].

several on-going studies for SIR-Spheres®

only 1 phase III study for TheraSphere®

But in fact, many trials are on-going [25, 46]: examples for SIR-Spheres® include the FOXFIRE trial (until December 2014), an independent, investigator-led trial, which will compare 1st-line systemic chemotherapy in addition to SIR-Spheres® with systemic chemotherapy alone [47], or, for the same indication, the SIRFLOX trial (estimated study completion date December 2012) [48]. For TheraSphere®, on the other hand, only one RCT (NCT00109954) was found on ClinicalTrials.gov with the intention of comparing SIRT with TACE, but no information is given about when results can be expected. This comparison is of great interest, as due to some overlap in patient eligibility between SIRT and TACE, it is unclear how to choose between SIRT and TACE. But some authors suggest that SIRT might be preferred over TACE in patients with branch or lobar portal vein thrombus [7, 49].

no precise cost-effectiveness analyses available

Concerning cost-effectiveness, a report published by the Australian "Medical Services Advisory Committee" had modelled cost-effectiveness of SIR-Spheres® but due to the surrounding uncertainties (no comparison to current treatment regimens, impact on OS) no precise estimated were possible [11]. The documents submitted to the MoH state that some cost savings might be associated with SIRT as this intervention usually requires fewer treatment sessions and can thus reduce hospitals stay in comparison to other treatment options (e.g. TACE).

limitations of this report

indications for efficacy of SIR-Spheres® for mCRC, no conclusive judgment for TheraSphere® for HCC

Limitations of our study might be that due to the inclusion criteria, many studies reporting outcomes on SIRT were not considered in this review. However, as it is rather unlikely that any relevant comparative trial for efficacy has been missed, we are confident with our estimates on efficacy. Regarding safety issues, the limitation to prospective studies comprising only ≥ 50 patients seems to be justified for the very short time-frame in which we had to operate. But it can also be considered a means to improve the quality of evidence included, as only centres which perform SIRT interventions frequently might be able to accrue these numbers of patients. Retrospective studies, even with large sample sizes, were excluded due to methodological concerns.

In summary, there are some indications that selected patients suffering from mCRC can benefit from SIR-Spheres®. In the context of HCC, despite an acceptable safety profile, the efficacy of SIRT currently remains unknown.

7 Recommendation

Table 7-1 and 7-2 represent the scheme on which the recommendation is based. The option chosen is marked.

Table 7-1: Scheme for recommendation based on the evidence available for SIRT (TheraSphere®) for the treatment of HCC

		Inclusion in the catalogue of benefits is recommended.
		Inclusion in the catalogue of benefits is recommended with restrictions.
X		Inclusion in the catalogue of benefits is currently not recommended.
		Inclusion in the catalogue of benefits is not recommended.

Reasoning:

The available evidence is *currently not sufficient* to accurately assess efficacy and safety of SIRT using TheraSphere® for the treatment of HCC (unresectable, unablatable) in comparison to other available treatment options (TACE, HAC, Sorafenib, best supportive care). A re-evaluation is recommended, but it remains unknown when results of high-quality trials will become available.

Table 7-2: Scheme for recommendation based on the evidence available for SIRT (SIR-Spheres®) for the treatment of mCRC

		Inclusion in the catalogue of benefits is recommended.
X		Inclusion in the catalogue of benefits is recommended with restrictions.
		Inclusion in the catalogue of benefits is currently not recommended.
		Inclusion in the catalogue of benefits is not recommended.

Reasoning:

The available evidence *indicates* that SIRT using *SIR-Spheres®* for the treatment of mCRC (unresectable, unablatable) is *more efficacious than/ as safe* as other available treatment options (HAC, systemic chemotherapy with 5-FU/leucovorin) under specific circumstances (careful patient selection, multidisciplinary team, selected centres), but new studies will probably change our effect estimates. Therefore, an inclusion in the catalogue of benefits is recommended with restrictions and a re-evaluation is recommended in 2015, after completion of the SIRFLOX/FOXFIRE trials.

8 Appendix

Cochrane Suchstrategie am 31.Jänner 2011

#1	MeSH descriptor Liver Neoplasms explode all trees
#2	liver NEAR/3 cancer*
#3	"hepatic neoplasm"
#4	"hepatic neoplasms"
#5	"hepatic cancer"
#6	"hepatic cancers"
#7	"liver metastasis"
#8	liver metastases
#9	"hepatic metastasis"
#10	"hepatic metastases"
#11	metastas*s NEAR/3 liver
#12	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
#13	"Selective internal radiation therapy"
#14	"Selective internal radiotherapy"
#15	"Selected internal radiation therapy"
#16	"Selected internal radiotherapy"
#17	SIRT
#18	SIR-Sphere*
#19	SIRTex
#20	Therasphere*
#21	"radiolabeled microsphere"
#22	"radiolabelled microsphere"
#23	"radiolabeled microspheres"
#24	"radiolabelled microspheres"
#25	"radio-labeled microsphere"
#26	"radio-labelled microsphere"
#27	"radio-labeled microspheres"
#28	"radio-labelled microspheres"
#29	MeSH descriptor Yttrium Radioisotopes explode all trees
#30	"Yttrium 90"
#31	Yttrium90
#32	Y90
#33	"Y 90"
#34	MeSH descriptor Microspheres explode all trees
#35	Radioemboli*ation
#36	Radioisotope* NEAR/5 Therap*
#37	(#13 OR #14 OR #17 OR #18 OR #19 OR #20 OR #23 OR #24 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36)
#38	(#12 AND #37)
#1	MeSH descriptor Liver Neoplasms explode all trees

#2	liver NEAR/3 cancer*
#3	"hepatic neoplasm"
#4	"hepatic neoplasms"
#5	"hepatic cancer"
#6	"hepatic cancers"
#7	"liver metastasis"
#8	liver metastases
#9	"hepatic metastasis"
#10	"hepatic metastases"
#11	metastas*s NEAR/3 liver
#12	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
#13	"Selective internal radiation therapy"
#14	"Selective internal radiotherapy"
#15	"Selected internal radiation therapy"
#16	"Selected internal radiotherapy"
#17	SIRT
#18	SIR-Sphere*
#19	SIRTex
#20	Therasphere*
#21	"radiolabeled microsphere"
#22	"radiolabelled microsphere"
#23	"radiolabeled microspheres"
#24	"radiolabelled microspheres"
#25	"radio-labeled microsphere"
#26	"radio-labelled microsphere"
	58 Hits

CRD Suchstrategie am 31.Jänner 2011

"Selective internal radiation therapy"
"Selective internal radiotherapy"
"Selected internal radiotherapy"
"Selected internal radiation therapy"
SIRT
SIR-Sphere*
SIRTex
Therasphere*
"radiolabeled microsphere"
"radiolabelled microsphere"
"radiolabelled microspheres"
"radiolabeled microspheres"
"radio-labeled microspheres"
"radio-labeled microsphere"
"radio-labelled microsphere"
"radio-labelled microspheres"
MeSH Yttrium Radioisotopes QUALIFIERS AD TU ST RE EXPLODE 1 2
"Yttrium 90"
"Yttrium90"
"Y 90"
"Y90"
MeSH Microspheres EXPLODE 1
Radioemboli*ation
Radioembolisation
Radioembolization
Radioisotope* NEAR Therap*
#1 OR #5 OR #6 OR #8 OR #17 OR #18 OR #21 OR #22 OR #25 OR #26
"Selective internal radiation therapy"
"Selective internal radiotherapy"
"Selected internal radiotherapy"
"Selected internal radiation therapy"
SIRT
SIR-Sphere*
SIRTex
Therasphere*
"radiolabeled microsphere"
"radiolabelled microsphere"
"radiolabelled microspheres"
"radiolabeled microspheres"
"radio-labeled microspheres"
"radio-labeled microsphere"
"radio-labelled microsphere"
"radio-labelled microspheres"

MeSH Yttrium Radioisotopes QUALIFIERS AD TU ST RE EXPLODE 1 2
"Yttrium 90"
"Yttrium90"
"Y 90"
"Y90"
MeSH Microspheres EXPLODE 1
Radioemboli*ation
Radioembolisation
Radioembolization
Radioisotope* NEAR Therap*
#1 OR #5 OR #6 OR #8 OR #17 OR #18 OR #21 OR #22 OR #25 OR #26
"Selective internal radiation therapy"
"Selective internal radiotherapy"
"Selected internal radiotherapy"
"Selected internal radiation therapy"
SIRT
SIR-Sphere*
SIRTex
Therasphere*
"radiolabeled microsphere"
"radiolabelled microsphere"
25 Hits

Embase Suchstrategie am 28. Jänner 2011

#47.	#13 AND #46	734
#46.	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #39 OR #40 OR #41 OR #42 OR #45	8,638
#45.	#43 AND #44	398
#44.	'radioisotope'/exp	501,026
#43.	'yttrium'/exp	3,169
#42.	therasphere*	103
#41.	'radioisotope therapy'/exp	6,238
#40.	radioemboli?ation	302
#39.	#35 AND #38	401
#38.	#36 OR #37	24,267
#37.	microspheres	18,560
#36.	'microsphere'/exp	15,984
#35.	#31 OR #32 OR #33 OR #34	4,023
#34.	'y 90'	961
#33.	y90	102
#32.	yttrium90	12
#31.	'yttrium 90'/exp	3,401
#29.	'radio-labelled microspheres'	15
#28.	'radio-labeled microspheres'	22
#27.	'radiolabelled microspheres'	189
#26.	'radiolabeled microspheres'	700
#25.	'radio-labelled microsphere'	4
#24.	'radio-labeled microsphere'	6
#23.	'radiolabelled microsphere'	48
#22.	'radiolabeled microsphere'	213
#20.	sirtex	99
#19.	'sir-spheres'	109
#18.	'sir-sphere'	16
#17.	sirt	329
#16.	'selected internal radiation therapy'	1
#15.	'selective internal radiation therapy'	137
#14.	'selective internal radiotherapy'	35
#13.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	148,305
#12.	metastas* NEAR/4 liver	45,345
#11.	'liver metastasis'/exp	25,439
#10.	'hepatic metastases'	4,510
#9.	'hepatic metastasis'	1,930
#8.	'liver metastases'	11,459
#7.	'liver metastasis'	27,561
#6.	'hepatic neoplasms'	535
#5.	'hepatic neoplasm'	180

#4.	liver NEAR/4 cancer*	116,892
#3.	'liver neoplasms'	2,628
#2.	'liver neoplasm'	537
#1.	'liver tumor'/exp	133,450

Medline Suchstrategie am 28.Jänner 2011

1	exp Liver Neoplasms/ (105396)
2	(liver adj3 cancer*).mp. (11207)
3	hepatic neoplasm*.mp. (555)
4	hepatic cancer*.mp. (667)
5	liver metastas#s.mp. (12903)
6	hepatic metastas#s.mp. (5054)
7	(metastas#s adj3 liver).mp. (15160)
8	1 or 2 or 3 or 4 or 5 or 6 or 7 (114494)
9	Selective internal radiation therapy.mp. (87)
10	Selective internal radiotherapy.mp. (15)
11	Selected internal radiation therapy.mp. (1)
12	SIRT.mp. (202)
13	SIR-Sphere*.mp. (45)
14	SIRTex.mp. (7)
15	Therasphere*.mp. (29)
16	radiolabel?ed microsphere*.mp. (1015)
17	radio-label?ed microsphere*.mp. (41)
18	exp Yttrium Radioisotopes/ (1683)
19	Yttrium 90.mp. (968)
20	Yttrium90.mp. (14)
21	Y90.mp. (104)
22	Y 90.mp. (203)
23	19 or 20 or 21 or 22 (1198)
24	exp Microspheres/ (19054)

9 References

1. UpToDate - 18.3. *Epidemiology and etiologic associations of hepatocellular carcinoma*. 2010 [cited 2011 08.February]; Available from: http://www.uptodate.com/contents/epidemiology-and-etiologic-associations-of-hepatocellular-carcinoma?source=see_link.
2. National Comprehensive Cancer Network, *Practice Guidelines in Oncology - v.2.2010 - Hepatobiliary Cancers.* 2010.
3. Statistik Austria. *Krebserkrankungen - Leber*. 2010 [cited 2011 03.March]; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/leber/index.html.
4. Bult, W., et al., *Microsphere radioembolization of liver malignancies: current developments.* The Quarterly Journal of Nuclear Medicine & Molecular Imaging, 2009. **53**(3): p. 325-35.
5. UpToDate - 18.3, *Staging and prognostic factors in hepatocellular carcinoma.* 2010.
6. UpToDate - 18.3, *Overview of treatment approaches for hepatocellular carcinoma.* 2010.
7. UptoDate - 18.3. *Nonsurgical therapies for localized hepatocellular carcinoma: Transarterial embolization, radiotherapy, and radioembolization*. 2010 [cited 2011 09.February]; Available from: http://www.uptodate.com/contents/nonsurgical-therapies-for-localized-hepatocellular-carcinoma-transarterial-embolization-radiotherapy-and-radioembolization?source=search_result&selectedTitle=4~15#H1248650419.
8. UpToDate - 18.3, *Nonsurgical treatment strategies for colorectal cancer liver metastases.* 2010.
9. UpToDate - 18.3. *Systemic chemotherapy for nonoperable metastatic colorectal cancer: Treatment recommendations*. 2010 [cited 2011 13.March]; Available from: http://www.uptodate.com/contents/systemic-chemotherapy-for-nonoperable-metastatic-colorectal-cancer-treatment-recommendations?source=search_result&selectedTitle=2~58#H46.
10. Ahmadzadehfar, H., et al., *Radioembolization of liver tumors with yttrium-90 microspheres.* Seminars in Nuclear Medicine, 2010. **40**(2): p. 105-21.
11. Medical Services Advisory Committee, *SIR-Spheres for the treatment of non-resectable liver tumours*. 2005, Medical Services Advisory Committee (MSAC): Canberra.
12. Hilgard, P., et al., *[Selective internal radiotherapy (radioembolization) and radiation therapy for HCC--current status and perspectives].* Zeitschrift fur Gastroenterologie, 2009. **47**(1): p. 37-54.
13. Dezarn, W.A. and W.A. Dezarn, *Quality assurance issues for therapeutic application of radioactive microspheres.* International Journal of Radiation Oncology, Biology, Physics, 2008. **71**(1 Suppl): p. S147-51.
14. U.S. Food and Drug Adminstration. *SIR-Spheres®- P990065*. 2009 [cited; Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=p990065.
15. U.S. Food and Drug Adminstration, *TheraSphere® - H980006*. 1999.
16. CIGNA Healthcare coverage Position, *Radioembolization with Yttrium-90 (90Y) Microspheres*. 2010.

17. Riaz, A., et al., *Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review.* Journal of Vascular & Interventional Radiology, 2009. **20**(9): p. 1121-30; quiz 1131.
18. Salem, R. and K.G. Thurston, *Radioembolization with 90 yttrium microspheres: A state-of-the-art brachytherapy treatment for primary and secondary liver malignancies - Part 1: Technical and methodologic considerations.* Journal of Vascular and Interventional Radiology, 2006. **17**(8): p. 1251-1278.
19. Kennedy, A., et al., *Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium.* International Journal of Radiation Oncology, Biology, Physics, 2007. **68**(1): p. 13-23.
20. Antoch, G., et al., *[Selective internal radiotherapy (SIRT) for hepatocellular carcinoma].* Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin, 2010. **182**(8): p. 660-70.
21. Coldwell, D., et al., *General selection criteria of patients for radioembolization of liver tumors: An international working group report.* American Journal of Clinical Oncology, 2010.
22. Kennedy, A., et al., *Radioembolization for the treatment of liver tumors: General principles.* American Journal of Clinical Oncology, 2010.
23. Riaz, A., et al., *Yttrium-90 radioembolization using TheraSphere in the management of primary and secondary liver tumors.* The Quarterly Journal of Nuclear Medicine & Molecular Imaging, 2009. **53**(3): p. 311-6.
24. Carretero, C., et al., *Gastroduodenal injury after radioembolization of hepatic tumors.* American Journal of Gastroenterology, 2007. **102**(6): p. 1216-20.
25. Kennedy, A.S., et al., *Radioembolization (yttrium-90 microspheres) for primary and metastatic hepatic malignancies.* Cancer Journal, 2010. **16**(2): p. 163-75.
26. Vente, M.A., et al., *Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis.* European Radiology, 2009. **19**(4): p. 951-959.
27. Jelic, S. and G.C. Sotiropoulos, *Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2010. **21 Suppl 5**: p. v59-64.
28. Hong, K., et al., *Salvage therapy for liver-dominant colorectal metastatic adenocarcinoma: comparison between transcatheter arterial chemoembolization versus yttrium-90 radioembolization.* Journal of Vascular & Interventional Radiology, 2009. **20**(3): p. 360-7.
29. Gartlehner, G., *Internes Manual. Abläufe und Methoden*, LBI-HTA, Editor. 2007, LBI-HTA: Vienna.
30. Carr, B.I., et al., *Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study.* Cancer, 2010. **116**(5): p. 1305-14.
31. Steel, J., et al., *Quality of life in patients diagnosed with primary hepatocellular carcinoma: hepatic arterial infusion of Cisplatin versus 90-Yttrium microspheres (Therasphere).* Psycho-Oncology, 2004. **13**(2): p. 73-9.
32. Kulik, L.M., et al., *Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis.* Hepatology, 2008. **47**(1): p. 71-81.

33. Salem, R., et al., *Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes.* Gastroenterology, 2010. **138**(1): p. 52-64.
34. Hilgard, P., et al., *Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival.* Hepatology, 2010. **52**(5): p. 1741-9.
35. Atassi, B., et al., *Biliary sequelae following radioembolization with Yttrium-90 microspheres.* Journal of Vascular & Interventional Radiology, 2008. **19**(5): p. 691-7.
36. Lau, W.Y., et al., *Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90yttrium microspheres.* International Journal of Radiation Oncology, Biology, Physics, 1998. **40**(3): p. 583-92.
37. Van Hazel, G., et al., *Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer.* Journal of Surgical Oncology, 2004. **88**(2): p. 78-85.
38. Gray, B., et al., *Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer.* Annals of Oncology, 2001. **12**(12): p. 1711-20.
39. Hendlisz, A., et al., *Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy.* Journal of Clinical Oncology, 2010. **28**(23): p. 3687-94.
40. Cosimelli, M., et al., *Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases.* British Journal of Cancer, 2010. **103**(3): p. 324-31.
41. Chua, T.C., et al., *Radioembolization and systemic chemotherapy improves response and survival for unresectable colorectal liver metastases.* Journal of Cancer Research and Clinical Oncology, 2011. **137**(5):865-73.
42. Mulcahy, M.F., et al., *Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres.* Cancer, 2009. **115**(9): p. 1849-58.
43. Atkins, D., et al., *Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group.* BMC Health Serv Res, 2004. **4**(1): p. 38.
44. National Comprehensive Cancer Network, *Colon Cancer - Version 3.2011.* 2011, NCCN.
45. Schmiegel, W., et al., *S3-Leitlinie „Kolorektales Karzinom" Ergebnisse evidenzbasierter Konsensuskonferenzen am 6./7. Februar 2004 und am 8./9. Juni 2007 (für die Themenkomplexe IV, VI und VII) S3-Guideline „Colorectal Cancer" 2004/2008.* Z Gastroenterol, 2008. **46**: p. 1–73.
46. Nicolay, N.H., et al., *Liver metastases from colorectal cancer: radioembolization with systemic therapy.* Nature Reviews Clinical Oncology, 2009. **6**(12): p. 687-97.
47. International Standard Randomised Controlled Trial Number Register. *FOXFIRE: An open-label randomised phase III trial of 5-Fluorouracil, OXaliplatin and Folinic acid +/- Interventional Radio-Embolisation as first line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer* 2011 [cited 2011 07.March]; Available from: http://www.controlled-trials.com/ISRCTN83867919.
48. ClinicalTrials.gov. *FOLFOX Plus SIR-SPHERES MICROSPHERES Versus FOLFOX Alone in Patients With Liver Mets From Primary Colo-*

rectal Cancer (SIRFLOX). 2010 [cited 2011 07.March]; Available from: http://clinicaltrials.gov/ct2/show/NCT00724503?term=NCT00724503&rank=1.

49. Sangro, B., et al., *Radioembolization for hepatocellular carcinoma: A review of the evidence and treatment recommendations.* American Journal of Clinical Oncology, 2010.