MINI-HTA

SIR-Spheres® Y-90 resin microspheres for the treatment of chemotherapy refractory or chemotherapy intolerant liver metastases from colorectal cancer

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Contributions

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Abbreviations
Adverse events (AEs)
Alanine Transaminase (ALT)
Alkaline Phosphatase (ALP)
Aspartate Aminotransferase (AST)
Best Supportive Care (BSC)
Carcinoembryonic Antigen, Abbreviated (CEA)
Colorectal Cancer (CRC)
Common Terminology Criteria For Adverse Events (CTCAE)
Computed Tomography (CT)
Cost-effectiveness Analysis (CEA)
Diagnosis-related group (DRG)
Eastern Cooperative Oncology Group (ECOG)
European Organisation for Research and Treatment of Cancer questionnaire on satisfaction of cancer inpatients (EORTC IN–PATSAT 32)
European Society for Medical Oncology (ESMO)
European network for health technology assessment (EuNetHTA)
EuroQol five dimensions questionnaire (EQ-5D))
Evaluation Criteria In Solid Tumours (RECIST)
Extrahepatic Disease (EHD)
Fluorodeoxyglucose (FDG)
Fluorouracil (FU)
Health-Related Quality of Life (HRQL)
Incremental Cost-Effectiveness Ratio (ICER)
Interquartile range (IQR)
Italian Agency Of Medicines (AIFA)
Italian Agency Of National Health Services (Age.Na.S)
Italian Association of Clinical Engineers (AIIC),
Italian Association of Hospital Pharmacists SIFO),
RadioEmbolization Induced Liver Disease (REILD)
Medical Device (MD)
Metastatic Colorectal Cancer (mCRC)
Magnetic Resonance Tomography (MRI)
National Health Service (NHS)
Out-of-Pocket (OOP)
Overall Survivor (OS)
Positron Emission Tomography (PET)
Photon Emission Computed Tomography (SPECT)
Progression Free Survival (PFS)
Quality-Adjusted Life Years (QALYs)
Quality of life (QoL)
Randomized clinical trial (RCT)
Response Criteria In Solid Tumors (PERCIST)
Selective Internal Radiation Therapy (SIRT)
SIR-Spheres® Y-90 Resin Microspheres (SIRTEX)
Time to Liver Progression (TTLP)
Time to Progression for any site (TTP)
Treatment Response (TR)
Yttrium-90 (90 Y)
Preface

The working team of the Postgraduate School of Health Economics and Management (Altems) of the Università Cattolica del Sacro Cuore, has produced the current health technology assessment (HTA) report on SIR-Spheres® Y-90 resin microspheres (SIRTEX) in the treatment of liver metastases from colorectal cancer, in order to provide an overview of the current and potential impact of the use of this technology within the Italian context.

In order to do so, a systematic review of existing literature has been performed. Evidence has been selected in accordance with pre-defined inclusion criteria and summarized based on the HTA domains under the framework of the European network for health technology assessment (EuNetHTA) Core Model®.

Coherent with the HTA approach, an expert advisory board was established with the aim of providing their expertise for the integration of evidence coming from the existing literature. The advisory board was made up of clinicians who are experienced with treating their patients with radioembolization using Y-90 microspheres, a bioethicist who is experienced both in HTA ethical domain and in clinical ethics, representatives of the Italian Association of Clinical Engineers (AIIC), the Italian Association of Hospital Pharmacists (SIFO), and the Italian Ministry of Health.

The Advisory Board met at the initial stage of this research project, just after the construction of the search string and the presentation of some preliminary statements of the multidimensional impact of this technology based on existing literature. Feedback received was integrated with the evidence presented in this document. The first draft of this report was submitted to the Advisory Board for external review. Comments received were utilized to further improve the document before dissemination.

Americo Cicchetti
Director of ALTEMS
Executive summary

Background
Colorectal cancer (CRC) is one of the most frequent cancers in the Western countries. In Italy, the epidemiology of CRC is very heterogeneous across regions. In 2015, the standardized incidence was 52/100.000 inhabitants whereas the standardized prevalence was 355/100.000 among 0-99-year-old individuals. About 50% of patients with CRC develop liver metastases, but of these only 25% are resectable. Surgical resection is the treatment of choice for resectable colorectal metastases. For unresectable metastatic CRC (mCRC), systemic medical therapy (chemotherapy) is the first-choice treatment, but local therapy such as loco-regional radiotherapy and ablative procedures, may be associated in an attempt to prolong survival or to palliate symptoms (e.g. pain). Radioembolization, also known as Selective Internal Radiation Therapy (SIRT) is a form of intra-arterial brachytherapy used to treat primary liver cancer and liver metastases.

Objective
The aim of this report is to provide an overview of the clinical, economic, organizational and ethical impact of SIRT using SIR-Spheres® Y-90 resin microspheres in the treatment of liver metastases from colorectal cancer in patients with unresectable, liver-dominant metastatic colorectal cancer who are chemotherapy-refractory or chemotherapy-intolerant. This study poses a particular focus on the Italian setting.

Methods
A systematic literature review was performed by querying 5 search engines namely, PubMed, Scopus, EBSCO, CRD, GIN. After the identification of duplicates, two reviewers blindly screened the records retrieved against some pre-defined inclusion/exclusion criteria. The selected studies were summarized narratively, following a simplified version of the EuNetHTA Core Model ® 2.1. Also, in order to get a deeper understanding of the use of this technology in Italy and its impact on clinical and economic outcomes a multidisciplinary advisory board with experts was established. They were asked to provide their opinion on some issues, considered of paramount importance within the Italian jurisdiction. The opinions provided where integrated in the current document. The list of issues discussed by the advisory board is reported in Appendix 3.
The experts Advisory Board also committed in reviewing the first draft of the current document.

**Results**
The most recent ESMO guidelines (2016) recommend SIRT as a treatment option for patients with liver-limited disease failing the available chemotherapeutic options. However, further evidence is now being generated upon the use of this technology in earlier treatment lines.

**Safety**
Most of studies evaluate SIRT as a second or further line treatment. Only one phase III comparative study allowed evaluating the safety profile of SIRT. In this study combination of SIRT with fluorouracil (FU) has not resulted in increased grade 3 and 4 toxicities, which were more common in patients receiving monotherapy. In general, common adverse events following the radioembolization were grade ≥ 3 fatigue, abdomen pain and vomiting. Further adverse events where associated with the implantation of the Y-90 microspheres (gastro duodenal ulcers). In a longer timespan after SIRT, the most common adverse event was grade 3 increase in bilirubin. In clinical studies, treatment-related deaths were rare. Two studies reported no difference in terms of toxicities across different age cohorts (comparison between less than 70 and over 70-year-old patients).

**Efficacy**
In clinical studies, Overall Survival (OS), Treatment Response (TR), Time to Progression for any site (TTP), Time to Liver Progression (TTLP) and Progression Free Survival (PFS) were assessed. In the phase III pivotal multicenter randomized clinical trial (RCT), where SIRT was compared to 5-FU, the study met its primary endpoint by showing a significant improvement in TTLP in favor of the SIRT arm. There was a trend to improved OS; however, this was confounded by cross-over. In two retrospective comparative studies, SIRT was associated with significantly longer OS than Best Supportive Care (BSC). In a systematic review, median OS was 12 months ([8.3–36]).
In the pivotal study, SIRT significantly increased TTLP and TTP compared to BSC. A median time to intra-hepatic progression of 9 months ([6–16]) was reported in a systematic review.
PFS was reported in 6 studies, included in the mentioned review, and ranged from 3.9 to 9.2 months for Y-90 resin microspheres treatment combined with chemotherapy.
Finally, for Y-90 resin microspheres treatment combined with chemotherapy, response rates reported in 11 studies, ranged from 8% to 90%; moreover, for SIRT
alone, the average reported value of patients with complete radiological response, partial response and stable disease was 0% ([0–6%]), 31% ([0–73%]) and 40.5% ([17–76%]), respectively.

**Organizational aspects**
In order to safeguard safety and quality of care, SIRT should be provided in specialized centers and all the patients’ flow should be managed by a multidisciplinary team. Literature, as well as experts, suggests that a “hub and spoke” net of services providing SIRT could be a viable option to guarantee access to this technology in a more equitable way across jurisdictions. On the other hand, the lack of a specific diagnosis-related group (DRG) tariff accounting for the cost of the device could be seen as the major obstacle to a fair diffusion of this technology. No specific investment is necessary to set the technology in hospitals.

**Costs and economic evaluation**
Three economic evaluations exploring the cost-effectiveness of SIRT are currently available. So far, full evidence on the cost-effectiveness profile of SIRT procedure for the management of patients with mCRC chemorefractory or intolerant to chemotherapy, is available for the UK and France and demonstrates the cost-effectiveness of SIRT procedure compared to BSC in the target population. The same decision model used in previous studies is being adapted to the Italian context.

**Ethical Aspects**
Evidence on ethical aspects connected to the implementation of SIRT is poor, since there are no ethical analyses previously performed on this technology. Thus, the ethical analysis provided in this report was performed on the basis of the clinical, economic and organizational literature as well as of the other chapters of the present report. However, it should be noticed that, given the current recommendation of European Society for Medical Oncology (ESMO), this technology is recommended for a population of patients with a very poor prognosis, and thus it may satisfy a large area of unmet clinical need. Finally, effectiveness/safety and QoL/HRQoL profiles are potentially positive from a beneficience/non maleficence point of view. On the other hand, adequate and realistic information should be provided to the patient. However, the technology seems to be well accepted by patients and professionals.

From distributive justice perspective – other issues arise from the cost of the procedure and the need of concentrating the delivery in specialized centers for
organizational purposes. This can actually represent an obstacle to patients’ equal access. On the other side, the introduction of SIRT in clinical routine would allow a reduction in hospital admissions, so from the patients’ perspective these improvements may result in better QoL, while from the payers’ perspective this could change the structure of direct healthcare costs.

The lack of definitive conclusions on cost-effectiveness analyses (CEA) and on sustainability of this technology for the Italian NHS do not allow for definitive conclusions to be drawn in relation to distributive justice issues, however the first available data suggest a potentially positive CEA profile.

**Recommendations**

SIRT using SIR-Spheres Y-90 resin microspheres appears to be a clinically effective and cost-effective option for the treatment of mCRC patients who are chemotherapy refractory or chemotherapy intolerant. The implementation of this technology is recommended in hospital centers with adequate technological infrastructure and appropriate personnel training. Compliance with the treatment protocol is important for the success of the procedure. Further research is needed to recommend the use of SIRT in earlier treatment lines.
Objective

The aim of this report is to provide – using HTA methodology - an overview of the clinical, economic, organizational and ethical impact of use of SIRT using SIR-Spheres® Y 90 resin microspheres in the treatment of liver metastases from colorectal cancer in patients with unresectable, liver-dominant metastatic colorectal cancer who are chemotherapy-refractory or chemotherapy-intolerant. This study poses a particular focus on the Italian setting.
Methods

In order to achieve the aim of this research both a literature review and a field research were performed.

The literature review

Definition of the research question

The research question was made explicit by using the PICO model including the population under study (P), the intervention being assessed (I), the comparator (C), and the outcomes of interest (O). Table 1, describes the PICO model underlying this research.

Table 1. PICO table.

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with unresectable, liver-dominant metastatic colorectal cancer who are chemotherapy-refractory or chemotherapy-intolerant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>SIR-Spheres® Y-90 resin microspheres</td>
</tr>
<tr>
<td>Comparator</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>Outcomes</td>
<td>• Effectiveness (Overall survival, Progression free survival, HRQL, Resection Rate)</td>
</tr>
<tr>
<td></td>
<td>• Safety (Adverse Events, Side effects)</td>
</tr>
<tr>
<td></td>
<td>• Economic Impact (costs, cost-effectiveness)</td>
</tr>
<tr>
<td></td>
<td>• Organizational impact (Investments, training, Patients flow, Workflow)</td>
</tr>
<tr>
<td></td>
<td>• Ethical Implications (at individual, social, institutional level)</td>
</tr>
</tbody>
</table>

Search Strategy

Five databases were queried to gather evidence needed to conduct the current assessment. The list of databases utilized is reported below:

1. PubMed;
2. Scopus;
3. EBSCO, including Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessments, NHS Economic Evaluation Database;
4. CRD Database, including DARE, Health Technology Assessments, NHS Economic Evaluation Database;
5. GIN (Guidelines International Network) database.
The search string launched on PubMed and Scopus as well as the key words utilized in the other databases are fully reported in Appendix 1. No temporal limits where imposed to our search strategy, but only pieces of evidence published in Italian or English language and reporting the key words in the title and/or abstract were included.

Further evidence was identified though manual search. Moreover, data concerning the technical features of the technology where provided by the manufacturer.

**Inclusion/Exclusion criteria**

Records retrieved though the search strategy was considered eligible unless they met one or more of the following exclusion criteria:

- Not relevant to the technology under study;
- Not relevant to the condition under study;
- Neither English nor Italian language;
- Type of study not relevant (case report, editorial, preclinical study);
- Not sufficient information on any of the aspects under study.

**Study selection process**

Records retrieved where classified into an Excel worksheet containing for each record an ID number, the database in which it was found, indication of whether it was a duplicate or not, first author, year of publication, title, reference citation, link to the abstract, name of the reviewer who selected it, a drop down menu indicated whether it was to be included or excluded, a drop down menu with the reasons of exclusion, some drop down menus listing the HTA domains for whom the paper could be considered relevant. Figure 1 reports a screenshot of this tool.

**Figure 1. Study selection worksheet.**

The first screening, based on title and abstract, was done by two senior researchers blindly, while two junior researchers extracted data from the selected studies.

**Reporting of results**

Results of this review have been discussed narratively. Grade scale was used to assess the quality of the evidence of primary study included in this report. Evidence has been organized based on selected items of the EuNetHTA Core Model® 2.1
Appendix 2 reports the list of items considered in the current analysis.

**Field research**

In order to get a deeper understanding of the use of this technology within the Italian setting, a multidisciplinary expert advisory board was established. In the first meeting experts were presented with some preliminary statements based on a quick review of evidence coming from the search strategy. They were asked to provide their opinion on some issues, considered of paramount importance within the Italian jurisdiction.

The opinions provided were integrated in the current document. Particularly relevant issues were discussed within boxes. The list of issues discussed by the advisory board is reported in Appendix 3.

The expert advisory board also committed to reviewing the first draft of the current document.
Results

Our search strategy produced 171 results overall. After deletion of 62 duplicates, 109 abstracts were reviewed. Of these 39 records were excluded based on title/abstract for reporting a non-relevant study design (9), for reporting on a different technology (20), for reporting on another condition (9), for being neither in English nor in Italian language.

Another 33 records were identified through a manual search. One hundred-three studies eventually met our inclusion criteria.

After selection studies were summarized and evidence reports was used to discuss assessment elements reported in Appendix 2.

The study selection process is depicted in Figure 2.

Figure 2. Study selection process.
1. Health problem and current use or the technology

1.1. Target Condition

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in Europe and a leading cause of death both in Europe and worldwide. In 2012, there were 447,000 new cases of CRC in Europe with 215,000 deaths and worldwide, there were 1.4 million new cases with 694,000 deaths (van Cutsem, 2016). CRC is one of the most frequent cancers in the Western countries.

In Italy, the estimated standardized prevalence rate of 2015 is 355/100,000 individuals aged 0-99. The standardized incidence rate, for the same year, is 52/100,000 at a national level. The epidemiology of colorectal cancer in Italy is characterized by a remarkable interregional gradient as depicted in Figures 1.1 and 1.2. In 2015, the disease-related mortality rate has been 16/100,000 in the 0-99-year-old population. The highest mortality rate has been recorded in Friuli Venezia Giulia (19/100,000), while the lowest rate has been recorded in Puglia (ISS, 2015).

Liver metastases from CRC develop in 50% of patients but only 25% of those are considered to have resectable metastases. The five-year survival rate after surgery is 20% to 40% (Chiarolla et al., 2014).

After liver resections for CLM, Abbass et al. (2011) have observed that the 10-year survival has included between 12% and 28%, while Kanas et al. (2012) have estimated a median 5-year survival rate of 38% ([16%, 74%]) (Abbass et al, 2011; Kanas et al 2012).
Figure 1.1. Prevalence of CRC in Italy, 2015. Source: ISS, 2015.

Figure 1.2. Incidence of CRC in Italy, 2015. Source: ISS, 2015.
1.2. **Target Population**

1.2.1. **Features of the target population**

According to the most recent ESMO Guidelines (2016) over the last decade, the clinical outcome for patients with mCRC has improved greatly due not only to an increase in the number of patients being referred for and undergoing surgical resection of their localized metastatic disease but also to a more strategic approach to the delivery of systemic therapy and an expansion in the use of ablative techniques. This reflects the increase in the number of patients that are being managed within a multidisciplinary team environment and specialist cancer centers, and the emergence over the same period not only of improved imaging techniques but also prognostic and predictive molecular markers (van Cutsem et al., 2016).

For patients with colorectal liver metastases, the treatment strategy should be directed towards complete resection whenever possible, with both ‘oncological’ (prognostic) and ‘technical’ (surgical) criteria being considered when evaluating patients for surgery. However, prospective evaluations do not exist either for ‘oncological’ or for ‘technical’ criteria, and for many of these, there is no (international) consensus.

The ‘technical’ definitions of resectable colorectal liver metastases proposed by the most recent ESMO guidelines (2016) consider the disease technically resectable as long as complete macroscopic resection is feasible, while maintaining at least a 30% future liver remnant or a remnant liver to body weight ratio >0.5 (e.g. >350 g of liver for a 70 kg patient). Computed tomography (CT) scans and magnetic resonance imaging (MRI) are considered the best methods to detect and evaluate liver metastases.

In the case of unresectable disease, systemic therapy is delivered with the aim of allowing the resection of technically unresectable colorectal metastases (conversion therapy), (van Cutsem et al., 2016). Patients with unresectable metastases from primary CRC are usually considered for systemic chemotherapy. In case of tumor progression, the patient can be considered for second-line chemotherapy or liver-directed treatment in case of limited extra hepatic disease. The current alternatives are: systemic chemotherapy including oxaliplatin or irinotecan combined with 5-FU, and sometimes a biological compound (Avastin®, Vectibix®, or Erbitux®) or/and a regional chemotherapy such as hepatic artery chemotherapy (HAC), (Chiarella et al., 2014; Rizell et al. 2010).

For patients with liver-limited metastases failing the available chemotherapeutic options, radioembolisation with Y-90 resin microspheres has been shown to prolong the time to tumor progression in the liver (van Cutsem et al., 2016).

The algorithm depicted in Figure 1.3 summarizes the treatment options for patients with liver metastasis from primary CRC cancer.
Both cetuximab and panitumumab have shown efficacy in the third-line/salvage-therapy setting in patients with RAS wildtype tumors, and are equally active as single agents. The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients. Any activity in patients with BRAF-mutant tumors seems to be limited to patients with chemorefractory mCRC. There is no unequivocal evidence to support administration of the alternative EGFR antibody, if a patient is refractory to the other.

The multi-targeted kinase inhibitor regorafenib has reported activity versus placebo plus best supportive care in two phase III trials (Grothey et al., 2013; Li et al., 2015). Regorafenib has demonstrated a significant improvement in OS in patients pre-treated with all available cytotoxics and bevacizumab and EGFR antibodies and can be proposed as a standard treatment in this setting (Grothey et al., 2013). However, some concerns over safety have raised some doubt as to whether the labelled dose (160 mg/day 1–21 q4 weeks) is the optimal dose. For this reason, frequent and close monitoring for regorafenib toxicity is recommended (van Cutsem et al., 2016).

The selection process of patients referred for SIRT involves several aspects to be taken into account. Patients considered for SIRT should have (Ahmadzadehfar et al., 2010):

- unresectable hepatic primary or metastatic cancer;
- liver-dominant tumor burden;
- a life expectancy of at least 3 months;
Contraindications for SIRT include:

- pretreatment angiogram indications of flow to the gastrointestinal tract—such as those visualized by the pretreatment Tc-MAA scan—which cannot be corrected by catheter embolization techniques;
- an excessive shunting to the lungs as quantified by the Tc-MAA scan that would result in 30 Gy lung dose on a single administration;
- excessive tumor burden with limited hepatic reserve or biochemical evidence of reduced liver function as potentially indicated by elevated levels of bilirubin (widely suggested cut-off: 2 mg/dL);
- markedly abnormal synthetic and excretory liver function test (LFTs);
- significantly altered international normalized ratio or partial thromboplastin time, or reduced serum albumin;

1.2.2. **Size of the target population**

Box 1.1 summarizes experts’ estimation of the size of the target population.

**Box 1.1 Experts’ estimation of the size of the target population.**

**Size of the target population**

According to the Italian National Institute of Public Health, in Italy 52,000 new cases of colorectal cancer were diagnosed\(^1\). Of these, about 30% exhibit liver metastatic disease. These patients are eligible for first-line chemotherapy, but approximately 15% of them will achieve surgically operable disease. The remaining 85% will receive second-line chemotherapy. Again, 85% of patients will not become eligible for surgery and, thus undergo third-line chemotherapy. About 30% of the third-line patients are chemorefractory and about 90% of them will be eligible for SIRT procedure as a third-line option (3380), and the remaining 10% will be considered not eligible for SIRT due to physical or technical contraindications. Moreover, after third-line treatment, at any further treatment line the target population decreases by 15% due to the availability of other options\(^2\).

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1. Italian National Institute of Public Health ([http://www.epicentro.iss.it/temi/tumori/registri.asp](http://www.epicentro.iss.it/temi/tumori/registri.asp)). Last access: February 23\(^{rd}\).

**Current management**

The primary aim of treating CRC liver metastases is to decrease the lesions’ size and spread. Surgical resection is the treatment of choice for resectable colorectal metastases. However, only 10 to 25 percent of patients with isolated liver metastases are eligible for resection because of anatomical constraints, inadequate hepatic functional reserve or concurrent medical co-morbidities such as poor performance status and cardiac failure. For unresectable metastatic disease, systemic medical therapy (chemotherapy) is the first-choice treatment, but local therapy such as locoregional radiotherapy and ablative procedures, may also be utilized in an attempt to prolong survival or to palliate symptoms (e.g. pain).

Selective internal radiation therapy (SIRT), also known as radioembolisation, is a form of intra-arterial brachytherapy used to treat primary liver cancer and liver metastases. SIRT uses resin microspheres including the β-emitter Yttrium-90 (Y-90) (Chiarolla et al., 2014).

Potential treatment options available for patients with unresectable, liver-dominant mCRC who are chemotherapy-refractory or chemotherapy-intolerant are summarized in Table 1.1 (NCCN 2016 Van Cutsem et al., 2014; Adam et al., 2009).

### Table 1.1: Potential treatment options available for patients with unresectable, liver-dominant mCRC (Sources: NCCN 2016; Van Cutsem et al., 2014; Adam et al., 2009)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACE</td>
<td>Infusion of chemotherapy directly to the liver through hepatic artery catheterization delivery of DEBIRI.</td>
<td>NCCN: Category 3 Recommendation ESMO: No reference</td>
</tr>
<tr>
<td>External beam liver radiation</td>
<td>Radiation therapy directed at the liver through three-dimensional conformal radiation therapy SBRT or IMRT.</td>
<td>NCCN: Category 3 recommendation ESMO: No reference</td>
</tr>
<tr>
<td>SIRT (radioembolisation)</td>
<td>Infusion of radiotherapy directly to the liver through hepatic artery catheterization delivery of radioactive microspheres. Resin or glass microspheres loaded with Y-90.</td>
<td>NCCN: Category 2A recommendation ESMO: Category B recommendation For Y-90 resin microspheres.</td>
</tr>
</tbody>
</table>
1.3. Utilization

1.3.1. Current use of technology at a national level

An independent survey performed by the Italian Agency of National Health Services (Age.Na. S) and involving 19 Italian centers performing SIRT revealed that all these are equipped with the appropriate technology such as CT, Angiography, PET/CT and SPECT and with all key professional figures required. The survey, published in 2014, revealed that SIRT was used as 1st-line in only 21.2% of cases, meaning that that chemotherapy still represents the best option as 1st-line treatment. The majority of hospitals (54.5%) declared to provide SIRT in one session, while only two hospitals in two sessions and the remaining three of them in one or two sessions. All these centers employ SIR-Spheres® Y-90 resin microspheres (SIRTEX) to perform SIRT.

As discussed in the subsequent sections of the current document, the number of sessions in which SIRT is provided is driven by cost issues and by the extension of metastatic disease, as well as the necessity to reduce the technical complications potentially related to several sessions, different vascular supply of liver metastases and different response of each metastatic nodule to chemotherapy.

Fifty percent of liver involvement is the highest acceptable threshold in all hospitals. Overall, the current patient selection threshold is higher than in the past. Even if decisions on the way to employ SIRT is basically driven by existing protocols, the number of centers employing it in earlier early therapeutic lines (2nd, 3rd) has been increasing over years. Overall 47 out of 61 (68,9%) patients treated during the study time horizon, received SIRT as a second-fourth-line treatment, while the remaining 14 patients (31,1%) received SIRT as an over-fourth-line treatment. As a matter of fact, emerging SIRT centers initially selected patients in more advanced lines of treatment, also for testing feasibility and safety at each respective clinical site. So far, the number of patients treated annually per center is relatively small with no more than 12 patients treated per year (Chiarolla et al., 2014).

The most recent ESMO guidelines (2016) recommend SIRT as a treatment option for patients with liver-limited disease failing the available chemotherapeutic options. Moreover, radioembolisation with Y-90 resin microspheres (and chemoembolization) of colorectal liver metastases in earlier treatment lines is considered as an interesting strategy as ‘consolidation treatment’ but should be limited to clinical trials (van Cutsem et al., 2016).
Box 1.2 summarizes experts’ opinion on the place in therapy of SIRT.

### Box 1.2. Place in therapy of SIRT according to experts’ opinion.

**Place in therapy of SIRT using Y-90 resin microspheres in patients with mCRC**

So far, SIRT has been used as a palliative treatment of patients refractory or intolerant to chemotherapy. Thus, it has been considered as a third or fourth line treatment. Safety and efficacy of SIRT using Y-90 resin microspheres, has been investigated in a pivotal trial whose results were published in 2010 (Hendlisz et al, 2010³). In that study the technology demonstrated promising health outcomes and an acceptable tolerability profile. However, since that time the treatment pattern for patients with liver metastases from primary CRC has dramatically changed and the proportion of patients treated with biological agents is now much greater than in the past.

Also, a new molecule, regorafenib, has been approved for reimbursement by the Italian Agency of medicines. This molecule, which has not been approved in Germany or in the UK, is currently used as a third-line treatment in mCRC in Italy. These forthcoming changes should be taken into account when investigating the economic impact of SIRT procedure. Moreover, this technology is expected to produce a much higher incremental benefit if used in earlier lines of treatment. Used as a first line treatment in this population, SIRT would allow a progression free survival in the liver (PFS₂) of 7.9 months. Probably, the best place in therapy for this technology would be the maintenance of first line treatment. The availability of robust evidence of OS is an important issue to be addressed in order to support the use of SIRT as first line treatment.

Multidisciplinary assessment of each patient is important to ensure that only suitable patients are selected for treatment with SIRT.

1.3.2. **Local-Regional utilization patterns**

The survey performed by Age.Na.S revealed that many different Italian hospital centers perform SIRT on a small number of patients. In some cases, these may have been part of study protocols for formal scientific investigations. This may explain the irregular pattern of provision of the therapy (Chiarolla et al., 2014).

A more rational use of resources would involve concentration of all patients in a smaller number of qualified hospitals doing higher volumes of SIRT and accruing experience with the technique.

Box 1.3 summarizes experts’ opinion on the cross-regional differences characterizing the use of SIRT across the Italian territory.

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³ Further detail on this study is provided in the Efficacy and Safety Sections.
Box 1.3. Cross-regional differences in the use of SIRT in Italy

Cross-regional differences in the use of SIRT in Italy

The delivery of SIRT is very heterogeneous across the Italian territory. An important North-South gradient in the distribution of centers performing SIRT can be observed. However, if under the equity point of view this can induce differences in patient’s access to services, on the other hand, it is important to concentrate the delivery of this treatment in highly specialized centers. The identification and the certification of minimum volumes should be set as standards to guarantee a minimum level of quality.

The share of target population that is able to receive SIRT is strongly affected by the possibility of adopting a hub-and spoke organization of centers, which would provide patients with the chance to be treated also in spoke centers. However, also for spokes, minimum quality requirements need to be defined and observed.
2. Technical features of the technology

2.1. Technical Features

The new minimally invasive treatment options for primary and metastatic liver cancer technologies include radiofrequency ablation, cryoablation, percutaneous ethanol ablation, chemoembolization (TACE) and selective internal radiation therapy (SIRT).

SIRT uses microspheres (particles) made of resin, loaded with the isotope Yttrium-90 (Y-90) beta emitter, which are infused through a catheter directly into the hepatic arteries (Lewandowski et al. 2009).

Y-90, a pure beta emitter, with a physical half-life of 64.2 hours (2.68 days) with a mean tissue penetration of 2.5 mm and a maximum range of 11 mm (Jakobs et al., 2016; Wang et al., 2013; Stubbs et al. 2004; Stubbs et al. 2004a; Stubbs et al. 2004b). The SIRT procedure is based on the fact that intrahepatic malignancies derive their blood supply almost entirely from the hepatic artery and newly formed arterial vessels inside the cancerous tissue. The microspheres are injected selectively into the appropriate hepatic artery and subsequently become lodged in the microvasculature surrounding the tumor. Very high irradiation doses are delivered to the tumor, whereas the surrounding normal liver parenchyma is less affected by the radiation (Vente et al., 2009).

SIR-Spheres® Y-90 resin microspheres consist of millions of resin microspheres with an average diameter of about 32 microns ([20 – 60] microns) loaded with Y-90. Typically about 30-40 million Y-90 resin microspheres (1.0 – 1.5 GBq) are delivered in a treatment (Lewandowski et al., 2009).

The microspheres are suspended in sterile water so that they can be delivered by injection (Kennedy et al., 2007) and have a specific activity of 50 Bq per microsphere at the time of calibration. SIR-Spheres® Y-90 resin microspheres have a specific gravity of 1.6 g/ml which means that they become easily suspended in the blood flow when administered allowing optimal distribution in the microvasculature supplying the tumor(s). This device has a 24-hour shelf life. The technical features of SIR-Spheres® Y-90 resin microspheres are summarized in Table 2.1.
Table 2.1. Summary of the technical features of the technology. Sources: Authors’ elaboration from Ahmadzadehfar et al., 2010.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SIR-Spheres® Y-90 resin microspheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Sirtex Medical Ltd, Australia</td>
</tr>
<tr>
<td>Material</td>
<td>Resin</td>
</tr>
<tr>
<td>Radionuclide</td>
<td>90Y</td>
</tr>
<tr>
<td>Size of particle</td>
<td>35 μm</td>
</tr>
<tr>
<td>Activity per particle</td>
<td>50 Bq</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.6 g/ml</td>
</tr>
<tr>
<td>No. of spheres per 3-GBq Vial</td>
<td>40-80 million</td>
</tr>
<tr>
<td>Embolization</td>
<td>Moderate</td>
</tr>
<tr>
<td>Relative pressure for infusion</td>
<td>Low</td>
</tr>
<tr>
<td>Contrast injection during infusion</td>
<td>Possible</td>
</tr>
</tbody>
</table>

The SIRT procedure as well as the equipment needed in the centers where SIRT is utilized is discussed in the organizational domain. However, the principle of SIRT is based on the preferential vascular distribution of radioactive microspheres within the tumor vasculature, which allows delivery of high doses of y-90 with relative sparing of normal liver parenchyma. Before SIRT is undertaken, meticulous coeliac and superior mesenteric angiography is conducted to map the hepatic arterial tree and to detect and occlude, using microcoil embolization, every collateral vessel that arises from the hepatic artery that could lead to extrahepatic deposition of microspheres. During a second hepatic arterial catheterization conducted separately after the therapy-planning arteriography, Y-90 resin microspheres suspended in sterile water are injected under intermittent fluoroscopic visualization, alternating with 5% glucose and contrast medium, to assess for preserved antegrade hepatic arterial flow (Jakobs et al. 2016; Hipps et al., 2013; Garrean et al., 2007).

2.2. Regulatory status

2.3. Indications for which the technology received Marketing Authorization

SIR-Spheres® by Sirtex Medical Ltd obtained the CE mark in 2002 for the treatment of inoperable liver tumors, and received FDA premarket approval(PMA) for the treatment of hepatic metastases secondary to CRC in 2002.

2.3.1. Reimbursement status of the technology

In Italy, no specific DRG tariff exists for the reimbursement of SIRT. Centers providing SIRT utilize different ICD-9-CM codes to identify this procedure.
As a result, different centres get different reimbursement for the delivery of SIRT. DRG codes typically used in current practice are:

- DRG 409: radiotherapy (€1,471);
- DRG 191: pancreas and liver treatment and shunt with complications (€13,929)
- DRG 192: pancreas and liver treatment and shunt without CC (€9,558).

Lombardy is, so far, the only Italian region with a higher fee (€10,000) for DRG 409 for SIRT, to be applied in case of use of microspheres implantation in patients with hepatocellular carcinoma.

In some cases, SIRT is reimbursed by dedicated financed projects (such as clinical investigations) or directly by the patient (out of pocket) (Chiarolla et al., 2014).

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*Decreto del Ministero della Salute, October 18th 2012, published on the Official Gazette on January 20th 2013 (Attachment 1).*
3. Safety

3.1. Patient’s safety

Maleux et al. (2016), in a retrospective study, have assessed the technical outcomes of patients after SIRT using Y-90 resin microspheres as a salvage therapy for patients with chemorefractory liver-only or liver-dominant colorectal metastases. From January 2005 to January 2014, all the patients selected for SIRT to treat chemorefractory colorectal liver metastases were identified. In total 71 patients finally underwent catheter-directed Y-90 resin microsphere infusion into the hepatic artery 25 days (SD: 13 days) after angiographic workup. At 30-day toxicity, adverse events included: fatigue (n = 39; 55%), abdominal discomfort (n = 33; 47%), nausea (n = 5; 7%), fever (n = 14; 20%), diarrhoea (n = 6; 9%), liver function abnormalities and elevated bilirubin (transient) (n =3; 4%). Gastric ulcer was found in five patients (7%). A late complication was radioembolization-induced portal hypertension (REIPH) in three patients (4%). The authors have concluded that SIRT using Y-90 resin microspheres for chemorefractory colorectal liver metastases has an acceptable safety profile (Maleux et al, 2016).

Kennedy et al 2016 in a study have conducted a retrospective analysis of 160 elderly (≥ 70 years) and 446 younger (< 70 years) consecutive patients from 11 US centers who received SIRT using Y-90 resin microspheres between July 2002 and December 2011. A further analysis was conducted in 98 very elderly patients (≥75 years). SIRT appeared to be equally well tolerated in the elderly and younger patients, with no statistically significant differences in reporting of events by age for any grade (P= 0.433) or grade 3 events (P= 0.615), although gastrointestinal events (any grade) were less likely to be reported in the elderly patients than in the younger patients. Common grade 3+ events reported in the elderly and the younger patients were abdominal pain (3.1% vs. 6.1%), gastritis or duodenitis (1.3% vs. 0.2%), nausea (0.6% vs. 1.3%), vomiting (1.3% vs. 1.3%), fatigue (5.6% vs. 4.5%), ascites (1.3% vs. 2.0%), hyperbilirubinemia (3.8% vs 2.7%), and RE-induced liver disease (REILD) (1.3% vs. 0.2%), respectively. Similar findings for grade 3 events were also observed in the analyses of the very elderly, with the exception of grade 3+ abdominal pain, which was less likely to be reported in elderly (1.0% vs. 6.1%; p=0.029). The most common event overall was mild to moderate fatigue, which tended to be more frequent in the elderly patients than in the younger patients (41.3% vs 34.5%), but between-
group differences were not statistically significant. Overall, the reporting of liver-function related adverse events was low and not statistically significantly different compared with the younger cohorts in the analyses of either the elderly or the very elderly (Kennedy et al., 2016).

Srnivas et al. 2016 aimed to assess the safety of Y-90 glass and Y-90 resin microspheres in 28 patients undergoing SIRT for liver-dominant mCRC. Most adverse events were mild and occurred within a month of the first Y-90 treatment. Other side effects were abdominal pain that resolved without surgical intervention and liver toxicities which were similar among two groups (Srnivas et al., 2016).

The study by Jakobs et al. (2016) evaluated the safety of SIRT using Y-90 resin microspheres for unresectable chemorefractory liver metastases from mCRC in 104 patients. The analysis demonstrated a good profile of tolerability of the procedure. It was observed that the most common adverse events a day after the procedure were fatigue (14.4%) and abdominal pain (8.7%) while after 3 months was grade 3 increases in bilirubin (5.0%). Gastric ulcer due to the suspected extrahepatic deposition of microspheres was reported in three patients (2.9%) and cholecystitis in two (1.9%); all occurred early following radioembolization and resolved with treatment. Regarding liver-related events, raised bilirubin (all grades) was recorded in 26.9% of patients at baseline, increasing to 50.0% of patients at month 3 post-radioembolization. At baseline 43.9% of patients and at 3 months post procedure 72% of them experienced raised aspartate aminotransferase (AST) levels (all grades) (Jakobs et al. 2016).

A prospective, randomized, multicenter international trial was conducted by Van Hazel et al. (2016) to assess the safety of SIRT using Y-90 resin microspheres in addition to standard fluorouracil, leucovorin and oxaliplatin based chemotherapy in patients with previously untreated metastatic colorectal cancer. Moreover, 73.4% and 85.4% of patients in control versus SIRT experienced grade ≥3 adverse events. Hematologic toxicities were reported at a higher rate in SIRT compared with control (P <.05). It was observed some cases of grade ≥ 3 gastric or duodenal ulcers and one of grade 4 ulcer. Also, 1.9% of control group and 3.7% of SIRT patients were reported grade 5 adverse events of any causality. Four treatment-related grade 5 adverse events were attributed to chemotherapy (two cardiac-related events in control, and one respiratory failure and one febrile neutropenia in SIRT), two were attributed to SIRT (hepatic failure and radiation hepatitis), and one was attributed to both chemotherapy and SIRT (hepatic failure in SIRT). Serious adverse events were reported less frequently in control patients (41.6%) than in SIRT patients (54.1%; p=0.005). The authors showed that five patients experienced SIRT-related hepatotoxicity (radiation hepatitis or hepatic failure). Both cases of radiation hepatitis, one of which was fatal, occurred 2 to 3 months after SIRT and were treated with low–molecular-weight heparin, diuretics, and corticosteroids. Two
patients experienced fatal hepatic failure, one case occurring 5 days after SIRT and the other case > 2 years after SIRT (Van Hazel et al., 2016).

Retrospective observational study by Damm et al. (2016) evaluated the safety of SIRT. They observed in most patients adverse events of grade 3 or 4. One patient displayed pleural effusion requiring thoracocentesis. Symptomatic gastric or duodenal ulcers occurred in three patients with subsequent endoscopic interventions. Seven patients developed radiation induced RILD with ascites requiring paracentesis (n=6), in one case associated with liver failure without tumor progression (n=1). One patient underwent cholecystectomy after developing radiation-induced cholecystitis (Damm et al., 2016)

The safety of SIRT using Y-90 resin microspheres in patients with unresectable and chemorefractory colorectal cancer liver metastases was evaluated by Sofocleous et al. (2015). The authors were observed that 60% of patients reported self-limited fatigue that lasted up to 14 days, seven patients experienced significant hyperbilirubinemia while five grade 3 abdominal pain. Twenty-nine patients (55%) retained their pre-procedural ECOG performance status when evaluated at 1 and 3 months after radioembolization. Eight patients (15%) had a transient decline in status at 1 month by 1 grade that resolved at 3 months after radioembolization. Nine patients (17%) had sustained decline by 1 grade (2 with evidence of disease progression within the first 3 months) (Sofocleous et al., 2015).

The study by Kennedy et al. 2015 evaluated the safety associated with SIRT using Y-90 resin microspheres in patients with mCRC. Adverse events were monitored from the day of the first SIRT procedure up to 184 days (6 months) in 606 patients considered in the study. The most common adverse events a week after the procedure were fatigue (all grades: 43.7%; grade ≥3: 5.8%), abdominal pain (39.3%; 6.1%), nausea (28.4%; 1.3%) and vomiting (10.6%; 1.5%). These events were transient and managed with medication. 1.7% of patients experienced gastrointestinal ulcerations (grade ≥3) while 0.5% of them experienced grade ≥3 radioembolization induced RILD and 0.8% a grade ≥3 hepatic failure. Analyses of baseline laboratory parameters revealed that a high proportion of patients had mild-to-moderate (mostly grade 1 or 2) changes before Y-90 radioembolization including: alkaline phosphatase (ALP) (all grades: 59.3%; grade 3: 3.0%); AST (49.8%; 1.5%), albumin (33.7%; 1.4%) and hemoglobin (40.1%; 0.7%) (Kennedy et al., 2015).

Golfieri et al. (2015) assessed the safety of SIRT using Y-90 resin microspheres. The whole sample experienced side effects within the first 24 hours of the procedure and these were transient and managed with medical therapy. 23% of patients reported mild fever, 17% abdominal pain and 6% asthenia. Subsequent adverse events thought to be related to the non-target distribution of Y-90 resin microspheres were radioembolization-induced RILD (grade 1 ulceration, 2 %),
radiation gastritis (grade 2 ulcerations, 2%) and gastric ulcer (grade 3 ulcerations, 2%) (Golfieri et al., 2015).

Cohen et al. (2014) analyzed the safety of capecitabine with the combination of SIRT using Y-90 resin microspheres. 37.5% of patients experienced non-hematologic toxicities included transaminases/ALP elevation or nausea, 33.3% grade 3 lymphopenia, 29% abdominal pain or fatigue or hand-foot syndrome or rash/desquamation. The latter was more common at higher doses of capecitabine (≥750 mg/m²). Grade 1/2 changes in creatinine, bilirubin and albumin only occurred with higher doses of capecitabine (≥750 mg/m²) and with the first SIRT procedure, while transaminases and ALP elevations were reported across all doses and cycles of treatment. These side effects were mild, except for one patient who reported grade 3 nausea and another with grade 3 diarrhea in the first two cycles (Cohen et al., 2014).

Another study, conducted by Saxena et al. (2014), reports that SIRT using Y-90 resin microspheres is a safe procedure. Between 2006 and 2013, 302 patients underwent resin-based Y-90 SIRT for unresectable chemorefractory colorectal cancer liver metastases have been included. One hundred fifteen (38%) developed clinical toxicity after treatment; most complications were minor (grade I/II) and resolved without active intervention (Saxena et al., 2015).

In a retrospective study, Tohme et al. (2014) have evaluated the tolerability outcomes among elderly (≥70 years) and younger patients (<70 years) with liver-dominant mCRC who received SIRT using Y-90 resin microspheres as salvage therapy. From 2002 to 2012, 107 consecutive patients with unresectable mCRC treated with SIRT after failing first- and second-line chemotherapy have been included in a study, of which, 44 elderlies and 63 younger patients. SIRT was equally well tolerated in both groups and common procedure-related adverse events (fatigue, nausea and/or vomiting, abdominal pain, fever, and increased bilirubin) were predominately of mild-to-moderate intensity and of short duration. Post-treatment hepatic toxicity was assessed between the elderly and younger patients and found to be relatively mild in both groups. No patient had fulminant hepatic failure after treatment. One patient in each group developed a late (after 30 days) grade 4 toxicity that was related to a biliary stricture and resolved with endoscopic retrograde cholangiopancreatography and stenting. No patients developed post-treatment gastric or duodenal ulceration (Tohme et al., 2014).

Sofocleous et al. (2014) conducted a prospective, single-center phase I study to evaluate the safety of SIRT for liver-predominant metastases of colorectal cancer in patients with progression after hepatic arterial and systemic chemotherapy. 19 patients with liver-predominant metastases of colorectal cancer progression received SIRT in 24 sessions after hepatic arterial and systemic chemotherapy. The probable or possible causes of all events were attributed at the time of their
occurrence. Total of 16 patients (84%) reported ≥ 1 grade 1 or 2 adverse events (side effects) and 3 patients (16%) had no adverse events. Transient fatigue/weakness, abdominal pain, and distension were common across all 3 groups. Transient dyspnea and loss of appetite or anorexia were reported by patients in cohort 3 and resolved by 4 weeks. This study demonstrated that SIRT with Y-90 resin microspheres appeared to be safe and well tolerated in patients who had progressed following prior hepatic arterial and systemic chemotherapy (Sofocleous et al. 2014).

Raval et al. (2014) have conducted a review focused on the use of Y-90 microsphere therapy in the treatment of liver metastases from CRC, including a comprehensive review of published clinical trials and prospective studies conducted so far. Generally, the adverse events reported are fever, lethargy, decreased appetite, and fatigue following therapy. Uncommon serious adverse events included radiation-induced gastric ulcers, lymphocytopenia, jaundice, cholecystitis, lung toxicity, hepatic abscess, radiation hepatitis, and liver failure. In four studies included the radioembolization has been used as first line therapy for hepatic colorectal metastases and in Table 3.1 shows the features of only study not included in our report.

Table 3.1: Studies included where the radioembolization with Y-90 resin microspheres has been used as first line therapy for hepatic colorectal metastases.

<table>
<thead>
<tr>
<th>Author</th>
<th>N Patients</th>
<th>Trial Design</th>
<th>Treatment</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray et al</td>
<td>70</td>
<td>Prospective, Phase III, Randomized</td>
<td>Y 90 Radioembolization plus chemotherapy vs chemotherapy alone.</td>
<td>Higher incidence of grade III elevation of ALP in the group that received Y 90 Radioembolization plus. No overall difference in the incidence of grade 3-4 toxicities among two groups.</td>
</tr>
</tbody>
</table>

In 2 studies the radioembolization has been used as second- or third-line therapy and Table 3.2 reports the features of the only study not included in our report.

Table 3.2: Studies included where the radioembolization with Y-90 resin microspheres has been used as second or third line therapy for hepatic colorectal metastases.

<table>
<thead>
<tr>
<th>Author</th>
<th>N Patients</th>
<th>Trial Design</th>
<th>Treatment</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim et al</td>
<td>30</td>
<td>Prospective study</td>
<td>Y-90 Radioembolization</td>
<td>Duodenal/gastric ulcer in 13%. A death related to radiation hepatitis.</td>
</tr>
</tbody>
</table>

This review included seven studies on the use of Y-90 as salvage therapy for chemorefractory patients. Their summary is not reported because these studies are already included in our report.
The authors have concluded that Y-90 microsphere therapy is being increasingly used for treatment of patients with colorectal metastases to the liver. Patients who have failed systemic chemotherapy appear to benefit from this therapy. Concurrent use of Y-90 microspheres in first and second line chemotherapy is currently being investigated. Future trials need to focus on identifying specific target populations who may benefit most from this therapy (Raval et al., 2014).

In a retrospective study, Kalva et al. (2014) have reported the safety outcomes of SIRT using Y-90 microspheres when it used as salvage therapy for chemotherapy-resistant liver metastases from colorectal cancer. Forty-five patients with hepatic metastases from colorectal cancer underwent SIRT after failure of systemic chemotherapy, have been included. Twenty-three patients (51%) had no toxicities, whereas 6 patients (13%) had grade 3 toxicities, and no patients had grade 4 toxicities. The authors have concluded that SIRT as a salvage therapy for chemotherapy-resistant hepatic metastases from colon cancer was safe (Kalva et al, 2014).

The retrospective study by Zarva et al. (2014) assessed the safety of repeated SIRT with Y-90 resin microspheres in patients with extensive primary and secondary liver tumors after failure of the first SIRT treatment. 21 patients (12 women, 9 men; mean age, 61.0 years [34–75]) with nonresectable advanced liver tumors were repeatedly treated by radioembolization. Total numbers of adverse events in treatment cycle 1 were 22 events for patients with HCC and 35 for all other patients. Total numbers of adverse events in treatment cycle 2 were 27 events for patients with HCC and 44 for all other patients. No grade IV or grade V events were recorded after initial or repeated radioembolization procedures. In treatment cycle 1, adverse events of grade I, II, and III were reported for 75%, 50%, and 13% (respectively) of the patients with HCC and for 92%, 38%, and 8% of all other patients. In treatment cycle 2, the respective numbers of patients were 100%, 25%, and 0% for the patients with HCC and 92%, 54%, and 8% of all other patients. Most frequent adverse events were ascites, elevation of bilirubin or liver enzymes, and decrease of serum albumin levels. However, despite that increase, all bilirubin values remained within normal limits. No radioembolization-induced RILD was observed in any of the patients. Three patients showed reversible grade III to IV toxicities according to laboratory values, which returned to pretreatment levels after 6 weeks. In 1 patient, a treatment-related duodenal ulcer occurred. In advanced liver tumors, repeated whole-liver treatments with 90Y radioembolization showed an acceptable toxicity profile (Zarva et al., 2014).

Two protocol studies (Gibbs et al. 2014 and Dutton et al. 2014) reported only safety measures: adverse events and serious adverse events. They will be collected and rated according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0.
and the relationship to protocol therapy will be rated as none, unlikely, possible or probable (Gibbs et al. 2014; Dutton et al. 2014).

The retrospective study by Fendler et al. 2013 aimed to analyze the safety and the prognostic value of several 18F-FDG PET response parameters in predicting the survival of CRC patients on SIRT for hepatic metastases. Eighty patients with hepatic metastases of colorectal cancer were treated with SIRT. Three months after SIRT, increased liver toxicity was found for 33 patients according to serum bilirubin level and 28 patients according to serum ALT activity. Increased bilirubin and ALT toxicities were reported in fourteen patients while in 19 patients, toxicity grades increased by 2 or 3 on the basis of bilirubin level, ALT level, or ascites 3 months after SIRT (Fendler et al., 2013).

Sexena et al. (2013) was performed a systematic review whose secondary objectives were to evaluate the safety profile of Y90 radioembolization of unresectable CRCLM refractory to systemic therapy. Twenty studies comprising 979 patients were examined. The overall acute toxicity rate ranged from 11 to 100 % (median 40.5 %). Most cases of acute toxicity were mild (Grade I or II) (median 39 %; 7–100 %) which resolved without intervention. The number of previous lines of chemotherapy (≥3), poor radiological response to treatment, extra-hepatic disease and extensive liver disease (≥25 %) were the factors most commonly associated with poorer overall survival. (Sexena et al., 2013)

Bester et al (2012) in a retrospective study have evaluated the safety of patients with chemotherapy-refractory liver metastases treated with Y-90 resin microspheres. While 339 patients with chemotherapy-refractory liver metastases underwent Y-90 microspheres radioembolization at a single institution between 2006 and 2011, 232 patients were referred back to their treating physician for conservative treatment or best supportive care. Adverse events were assessed at the time of treatment and at 1 and 3 months after treatment. the incidence and severity of adverse events with radioembolization were low and readily medically manageable. Adverse events at the time of radioembolization were minor (grade 1 abdominal pain, nausea, and vomiting) and occurred in 75 patients (22%; calculated based on adverse events occurring 0–24 hours after radioembolization only). Grade 1 abdominal pain was the most commonly reported adverse event immediately after radioembolization and occurred in 51 of these patients (15%). Grade 1 abdominal pain and lethargy were the most commonly reported minor adverse events 1 month after radioembolization. Abdominal pain was reported by 62 patients (18%), and lethargy was reported by 41 patients (12%). At the 3-month follow-up after radioembolization, there were 11 reported cases (3.2%) of ulceration (duodenal or gastric), with three cases being severe (grade 3 ulceration) and eight cases being moderate (grade 2 ulceration); 10 cases (2.9%) of radiation-induced liver disease, with one case being severe (grade 3 radiation-induced liver disease, which was
complicated by the development of high obstruction of the common bile duct) and the other cases being moderate (grade 2); and six (1.8%) reported adverse events (all grade 2) involving the gallbladder (e.g., cholecystitis). (Bester et al., 2012)

Seidensticker et al (2012) in a retrospective study, have evaluate overall survival after radioembolization or best supportive care (BSC) in patients with chemotherapy-refractory liver dominant mCRC. This was a matched-pair comparison of patients who received radioembolization plus BSC or BSC alone for extensive liver disease. Twenty-nine patients who received radioembolization were retrospectively matched with a contemporary cohort of 500 patients who received BSC from 3 centers in Germany. Treatment-related adverse events following radioembolization included: grade 1–2 fatigue (n=20, 69%), grade 1 abdominal pain/nausea (n=14, 48.3%), and grade 2 gastrointestinal ulcerations (n=3, 10.3%). Three cases of grade 3 radiation-induced liver disease were symptomatically managed.

Cosimelli et al. (2010) evaluated the tolerability of a single hepatic intra-arterial injection of Y-90 resin microspheres in patients with unresectable, chemotherapy refractory CRC liver metastases. The nature and severity of all adverse events were assessed and recorded from the time of the initiation of protocol treatment up to 3 months after treatment. At the time of their occurrence, adverse events were attributed as being definitely, probably, possibly, unlikely or not related to radioembolization. The analysis demonstrated that adverse events were mild or moderate within the first 48 h from the procedure, after a month and 2–3 months after treatment (Cosimelli et al., 2010).

Two studies (Ahmadzadehfar et al., 2010 and Welsh et al., 2006) showed adverse events related to use of SIRT. The first reported serious complications when microspheres were inadvertently deposited in excessive amounts in organs other than the liver. It was observed conditions including gastrointestinal ulceration/bleeding, gastritis/duodenitis, cholecystitis, pancreatitis, and radiation pneumonitis. One important complication was affection of the non-tumorous hepatic parenchyma by radiation. The latter showed that toxicity was usually mild, including fatigue, anorexia, nausea, abdominal discomfort, and slight elevations of liver function tests. About one-third of patients will report mild fatigue, fever, abdominal discomfort, or nausea that was readily managed with analgesics, antiemetics, and H2 blockers or proton pump inhibitors. Up to 50% might experience Grade 1–2 fatigue or nausea. Nearly all acute toxicities were resolved by 3 weeks. In rare instances, peptic ulcers could develop as a result of microspheres entering the gastric or duodenal arterial circulation, highlighting the importance of proper technique and patient selection. Other less commonly observed complications of SIRT included radiation-induced liver damage, including veno-occlusive disease,
coagulopathy, and radiation hepatitis, radiation pneumonitis, pancreatitis, and cholecystitis (Ahmadzadehfar et al., 2010; Welsh et al., 2006).

Hendlisz et al. (2010) conducted a prospective, multicenter, randomized phase III trial in patients with unresectable, chemotherapy-refractory liver-limited mCRC comparing arm A (fluorouracil [FU] protracted intravenous infusion 300 mg/m² days 1 through 14 every 3 weeks) and arm B (SIRT plus intravenous FU 225 mg/m² days 1 through 14 then 300 mg/m² days 1 through 14 every 3 weeks) until hepatic progression. Patients randomly assigned to two arms. The authors assessed the safety of intra-arterial SIRT using Y-90 resin microspheres in liver-limited mCRC among patients for whom all other evidence-based treatments had failed. Toxicity analysis was conducted in 43 patients (22 in arm A and 21 in arm B). Two patients (both in arm A) were never treated and so were not evaluated for toxicity. Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after SIRT plus FU treatment. Adverse events: gastrointestinal (nausea, vomiting, etc.), pain, constitutional (fever, fatigue), dermatological (skin), pulmonary, neurological, cardiac arrhythmia, other toxicities. In general, the incidence and severity of adverse events with SIRT are low and manageable, provided that standard safety procedures are followed. More patients experienced grade 3 toxicities in the FU-only arm. This difference was probably largely due to lower efficacy and more rapidly progressive disease in the FU arm because the nature of the adverse events were essentially indistinguishable from those due to disease progression. SIRT with Y-90 resin microspheres plus FU was well tolerated (Hendlisz et al., 2010).

The retrospective study by Hoffmann et al. 2010 analyzed, whether patients suffering from extensive hepatic metastatic disease treated with SIRT could become suitable candidates for radiofrequency ablation. Forty-six patients bearing an extensive hepatic metastatic disease were treated with SIRT. In 3 patients, major complications (2/3 gastric ulceration and 1/3 oedematous pancreatitis) and in 24 patients minor complications occurred (acute abdominal/epigastric pain and/or nausea). 93.5% of patients experienced no severe side-effects from the treatment while 52.2% of them experienced acute abdominal/epigastric pain and/or nausea immediately after SIRT. Almost all of patients suffered from a weak post-radiation syndrome presenting with lethargy and fatigue for up to 6 weeks after the treatment. The study demonstrated that SIRT was well tolerated (Hoffmann et al., 2010).

The purpose of the study by Cianni et al. (2009) was to evaluate the toxicity of CRC liver metastasis treatment with SIRT using Y-90 resin microspheres in 41 patients with no response to chemotherapy through 3-year experience. Twelve hours after the procedure, it was observed in five patients mild abdominal pain or nausea while a person experienced grade 2 cholecystitis after 25 days. Two patients reported
grade 2 gastritis, 4 and 6 weeks after treatment, respectively, and were also treated with medical therapy. It was observed a patient with grade 4 hepatic failure 40 days after treatment, probably due to radiation-induced hepatitis (Cianni et al., 2009). Harris et al. (2009) observed, in a review, adverse events were gastrointestinal (nausea, abdominal pain) or slightly elevated liver enzymes and they were transient. Late toxicities had been rare, but gastrointestinal mucosal ulceration, liver abscess formation, cirrhosis, and cholecystitis related to treatment had been reported (Harris et al., 2009).

In the review of Van De Wiele et al. (2009), phase I and II studies, on SIRT treatment performed in patients suffering from liver metastases as well as in patients suffering from multinodular asymptomatic unresectable HCC with a well-preserved liver function had consistently reported a favorable safety profile for Y-90 resin microspheres therapy; only a limited number of patients develop gastrointestinal ulceration or bleeding (Van De Wiele et al., 2009).

Van Hazel et al. (2009) evaluated the maximum-tolerated dose of irinotecan chemotherapy in combination with SIRT using Y-90 resin microspheres in fluorouracil-refractory patients with CRC hepatic metastases. Twenty-five irinotecan-naïve patients who had experienced relapse after previous chemotherapy were enrolled onto three dose-escalating groups. Irinotecan was administered at 50, 75, or 100 mg/m² on days 1 and 8 of a 3-week cycle for the first two cycles, and full irinotecan doses (i.e., 100 mg/m²) were administered during cycles 3 to 9. SIRT was administered during the first chemotherapy cycle. In the group treated with irinotecan (50 mg/m²) one patient reported jaundice 7 weeks after the initiation of treatment, grade 4 bilirubin and ALP and grade 3 AST. One patient presented with a perianal abscess and grade 4 thrombocytopenia 5 weeks after the initiation of treatment while another experienced grade 3 diarrhea and alopecia during cycle 1 of chemotherapy. In group treated with irinotecan (70 mg/m²) it was observed different adverse events. One patient reported grade 3 leukopenia and neutropenia in cycle 1 and grade 3 leukopenia after cycle 3. Another patient developed grade 3 thrombocytopenia and elevated ALP during cycle 2 and grade 3 leukopenia in cycle 3. A third patient reported grade 3 hyperbilirubinemia a week after being withdrawn from the study because of progressive disease detected during cycle 3. A fourth patient experienced grade 3 leukopenia during cycle 7, and a fifth patient reported grade 3 fatigue that began at the conclusion of cycle 1; this developed into grade 4 fatigue after the second cycle of treatment, at which point the patient was found to have progression of disease. In the group treated with irinotecan (100 mg/m²) one patient developed deep vein thrombosis at the conclusion of cycle 3. A second patient experienced grade 3 constipation during the first week of the first cycle. A third patient experienced grade 3 diarrhea during the first cycle and grade 3 abdominal pain that resulted from SIRT. A fourth patient
experienced grade 3 neutropenia and leukopenia that resulted in a delay of administration of cycle 4 chemotherapy. Concomitant use of SIRT plus irinotecan did not reach a maximum-tolerated dose (Van Hazel et al., 2009). The study by Jakobs et al. (2007) aimed to analyze the feasibility and the safety of single-session, whole-liver SIRT in patients with non-resectable, otherwise non-responding liver cancer. 39 patients with non-resectable, otherwise non-responding primary or secondary liver cancer received SIRT. Patients previously treated with intravenous chemotherapy were either non-responding or had to abandon chemotherapy due to toxicity-effects. Overall SIRT treatment was well tolerated. Thirty-six of 39 patients experienced no severe side-effects from the treatment. Two patients developed an (actinic) gastric ulcer and one patient an edematous pancreatitis. Twenty-four patients (61%) experienced acute abdominal/epigastric pain and/or nausea immediately after SIRT administration, but symptoms were manageable with analgesics and antiemetics. Almost all suffered from post-embolization syndrome consisting of low-grade fever, loss of appetite, lethargy and fatigue for up to 6 weeks following the treatment. No clinical evidence presented for radiation pneumonitis or radiation induced RILD. The study showed that SIRT was well tolerated.

Jiao et al., (2007) evaluated the safety of SIRT in management of unresectable liver metastases. Twenty-one patients who had failed to respond to conventional treatment including chemotherapy, intra-arterial chemoembolization for hepatocellular carcinoma or local ablative treatment received Y-90 microspheres consisting of liver metastases from colorectal primary and non-colorectal primaries, and primary liver tumors. Most patients developed minor degrees of nausea and abdominal pain that resolved spontaneously except in one patient who required hospital admission for analgesia. Four patients developed major post-SIRT complications: 1 cholecystitis followed by fibrosis and portal hypertension confirmed on biopsy and TC scan; 1 peptic ulceration in the lesser curvature of the stomach confirmed on endoscopy and 2 radiation hepatitis. The patient with gastric ulcer had a prior embolization of the gastroduodenal artery for upper gastrointestinal bleeding.

Sharma et al. 2007 analyzed the safety of SIRT using Y-90 resin microspheres in combination with oxaliplatin, fluorouracil, and leucovorin chemotherapy. Grade 3 abdominal pain was reported in five patients, two of whom had microsphere-induced gastric ulcers. The dose-limiting toxicity was grade 3 or 4 neutropenia, which was recorded in 12 patients. One episode of transient grade 3 hepatotoxicity was reported (Sharma et al., 2007).

The study by Stubbs et al, 2006 assessed the safety of SIRT in the management of 100 patients with extensive colorectal liver metastases. In particular, the authors reported adverse events after the use of SIRT. Mild liver pain and/or nausea was
experienced at the time of receiving SIRT in virtually all patients, but was readily manageable with i.e. narcotics and anti-emetics. Van Hazel et al., (2004) conducted a randomized trial to compare the response rate, time to progressive disease, and toxicity of a regimen of systemic fluorouracil/leucovorin chemotherapy versus the same chemotherapy plus a single administration of SIR-Spheres Y-90 resin microspheres in patients with advanced colorectal liver metastases. Twenty-one patients with previously untreated advanced colorectal liver metastases, with or without extrahepatic metastases, were randomized into the study: 5-fluorouracil 425 mg/m$^2$/day plus leucovorin 20 mg/m$^2$/day for 5 consecutive days and repeated at 4 weekly intervals versus the same chemotherapy plus a single administration of Y-90 resin microspheres that was administered on the 3rd or 4th day of the second cycle of chemotherapy. There were more grade 3 and 4 toxicity events in patients receiving the combination treatment. One patient in the combination arm died from chemotherapy induced neutropenic sepsis after the fourth chemotherapy cycle. Four patients developed transient abdominal pain at the time of injection of the Y-90 resin microspheres that resolved with narcotic analgesia. One patient treated with SIRT plus chemotherapy developed a liver abscess in the site of a necrotic tumor mass following treatment and recovered quickly after drainage of the abscess. One patient developed radiation induced liver cirrhosis. As this patient weighed 43 kg, treatment with 2.5 GBq of Y-90 activity was considered excessive. As a result of this experience, future patients were treated with an amount of Y-90 resin microspheres that was calculated from the size of the patient and tumor (Jakobset al., 2007).
Table 3.3: Primary studies about safety outcomes of the use of Y-90 resin microspheres.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Intervention and Comparator</th>
<th>Treatment Line</th>
<th>Type of study</th>
<th>Nr of patients</th>
<th>Follow up</th>
<th>Outcome</th>
<th>Quality of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maleux</td>
<td>2016</td>
<td>Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>71 patients</td>
<td>30-day</td>
<td>• fatigue (n = 39; 55%), abdominal discomfort (n = 33; 47%), nausea (n = 5; 7%), fever (n = 14; 20%), diarrhea (n = 6; 9%), liver function abnormalities elevated bilirubin (transient) (n = 3; 4%), gastric ulcer (n = 5; 7%), REIPH (n=3;4%)</td>
<td>Low</td>
</tr>
<tr>
<td>Kennedy</td>
<td>2016</td>
<td>Y-90 resin microspheres</td>
<td>Either first or further treatment line</td>
<td>Retrospective study</td>
<td>NA</td>
<td>NA</td>
<td>Redoembolization was equally well tolerated in the elderly and younger patients. There were no differences between cohorts and any grade adverse events (P = .433) or grade 3+ events (P = .482). Common grade 3+ events reported were: • abdominal pain (3.1% vs. 6.1%) • gastritis or duodenitis (1.3% vs. 0.2%) • nausea (0.6% vs. 1.3%) • vomiting (1.3% vs. 1.3%) • fatigue (5.6% vs. 4.5%), ascites (1.3% vs. 2.0%), hyperbilirubinemia (3.8% vs.2.7%), REILD (1.3% vs. 0.2%)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Srinivas</td>
<td>2016</td>
<td>Y-90 resin vs Y-90 glass</td>
<td>Second or further treatment line</td>
<td>Retrospective observational study</td>
<td>18 patients</td>
<td>3 months</td>
<td>Most adverse events were mild. Side effects were abdominal pain and liver toxicities that were similar among two groups.</td>
<td>Moderate/low</td>
</tr>
<tr>
<td>Jakobs</td>
<td>2016</td>
<td>Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Retrospective observational study</td>
<td>104 patients</td>
<td>Until death</td>
<td>The most common adverse events a day after the procedure were fatigue (14.4%) and abdominal pain (8.7%)</td>
<td>Moderate/low</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment Details</td>
<td>Phase</td>
<td>Study Type</td>
<td>Patients</td>
<td>Follow-up</td>
<td>Key Findings</td>
<td>Risk Level</td>
<td></td>
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<tr>
<td>Van Hazel 2016</td>
<td>FOLFOX6 VS Y-90 resin microspheres plus FOLFOX6</td>
<td>First</td>
<td>RCT</td>
<td>530</td>
<td>Until death or for a maximum of 5 years</td>
<td>After 3 months it was grade 3 increases in bilirubin (5.0%)</td>
<td>Moderate/high</td>
<td></td>
</tr>
<tr>
<td>Damm 2016</td>
<td>Y-90 resin microspheres</td>
<td>Second</td>
<td>Retrospective observational study</td>
<td>106</td>
<td>6 months (median value)</td>
<td>73.4% versus 85.4% of patients in control versus SIRT experienced grade 3 adverse events</td>
<td>Low/Moderate</td>
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<td></td>
<td>Serious adverse events and hematologic toxicities were reported less frequently in control patients (41.6%) than in SIRT patients</td>
<td>Low/Moderate</td>
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<tr>
<td>Sofocleous 2015</td>
<td>Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Retrospective observational study</td>
<td>53</td>
<td>15 weeks (median value)</td>
<td>Most patients experienced adverse events of grade 3 or 4 (gastric or duodenal ulcers, radiation induced liver disease)</td>
<td>Low/Moderate</td>
<td></td>
</tr>
<tr>
<td>Kennedy 2015</td>
<td>Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Retrospective observational study</td>
<td>606</td>
<td>8.6 months (median value)</td>
<td>66% of patients reported self-limited fatigue</td>
<td>Low/Moderate</td>
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<td>Seven patients experienced significant hyperbilirubinemia</td>
<td>Low/Moderate</td>
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<td>Five patients reported grade 3 abdominal pain</td>
<td>Low/Moderate</td>
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</tr>
<tr>
<td>Golfieri 2015</td>
<td>Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Prospective case series</td>
<td>52</td>
<td>7 months (median value)</td>
<td>The most common adverse events a week after the procedure were fatigue (all grades: 43.7%; grade 3: 5.8%), abdominal pain (39.3%; 6.1%), nausea (28.4%; 1.3%) and vomiting (10.6%; 1.5%)</td>
<td>Low</td>
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<td>23% of patients reported mild fever, 17% abdominal pain and 6% asthenia</td>
<td>Low/Moderate</td>
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<tr>
<td>Cohen 2014</td>
<td>Capecitabine plus Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Prospective single-center, phase I study</td>
<td>24</td>
<td>6 months (median value)</td>
<td>Adverse events occurred 24 hours after the procedure</td>
<td>Moderate/low</td>
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<td>37.5% of patients experienced non-hematologic toxicities, 33.3% grade 3 lymphopenia, 29% abdominal pain or fatigue or hand-foot syndrome or rash/desquamation</td>
<td>Moderate/low</td>
<td></td>
</tr>
<tr>
<td>Saxena 2014</td>
<td>Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>302</td>
<td>NA</td>
<td>Hematologic events were generally mild</td>
<td>Low/Moderate</td>
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<td>38% developed clinical toxicity after treatment; most complications were minor (grade I/II) and resolved without active intervention</td>
<td>NA</td>
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</tr>
<tr>
<td>Tohme 2014</td>
<td>Y-90 resin microspheres</td>
<td>Either first or further treatment line</td>
<td>Retrospective study</td>
<td>107</td>
<td>NA and 30 days</td>
<td>Radioembolization was equally well tolerated in both groups</td>
<td>Moderate</td>
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<td>One patient in each group developed a late (after 30 days) grade 4 toxicity</td>
<td>Moderate</td>
<td></td>
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<tr>
<td>Study</td>
<td>Y-90 resin microspheres</td>
<td>Treatment Line</td>
<td>Study Type</td>
<td>Patients</td>
<td>Duration (Median, Range)</td>
<td>Adverse Events</td>
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</table>
| Sofocleous 2014       | Y-90 resin microspheres | Second or further | Prospective single-center phase I study | 19 patients | 31.2 months after SIRT (median duration, range 19-4.5 months) | • Total of 16 patients (84%) reported ≥ 1 grade 1 or 2 adverse events (side effects)  
• 3 patients (16%) had no adverse events |
| Kalva 2014             | Y-90 resin microspheres | Second or further | Retrospective study | 45 patients | NA | • 23 patients had no toxicities  
• 6 patients had grade 3 toxicities  
• no patients had grade 4 toxicity |
| Zarva 2014             | Repeated Y-90 resin microspheres | Second or further | Retrospective study | 21 patients | 10 months (median duration, range 5-38 months) | • Total numbers of adverse events in treatment cycle 1 were 22 events for patients with HCC and 35 for all other patients  
• Total numbers of adverse events in treatment cycle 2 were 27 events for patients with HCC and 44 for all other patients. No grade IV or grade V events |
| Fendler 2013           | Y-90 resin microspheres | Second or further | Retrospective study | 80 patients | Follow-up at 3 months | • Toxicity grades increased by 2 or 3 on the basis of bilirubin level, ALT level, or ascites |
| Bester 2012            | Y-90 resin microspheres | Second or further | Comparative retrospective study | 339 patients | Follow-up at after the treatment, 1 and 3 months | • Adverse events at the time of radioembolization were minor (grade 1 abdominal pain, nausea, and vomiting) and occurred in 75 patients (22%; calculated based on adverse events occurring 0–24 hours after radioembolization only). Grade 1 abdominal pain was the most commonly reported adverse event immediately after radioembolization and occurred in 51 of these patients (15%).  
• Grade 1 abdominal pain and lethargy were the most commonly reported minor adverse events 1 month after radioembolization. Abdominal pain was reported by 62 patients (18%), and lethargy was reported by 41 patients (12%). |
<table>
<thead>
<tr>
<th>Author</th>
<th>Y-90 resin microspheres</th>
<th>Treatment Line</th>
<th>Study Type</th>
<th>Number of Patients</th>
<th>Follow-up</th>
<th>Treatment-related adverse events following radioembolization included:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seidensticker, 2012</td>
<td>Second or further treatment line</td>
<td>Comparative retrospective study</td>
<td>29 patients both groups</td>
<td>After the treatment</td>
<td>• Treatment-related adverse events following radioembolization included:</td>
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<tr>
<td></td>
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<td></td>
<td>• grade 1–2 fatigue (n = 20, 69%)</td>
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<td>• grade 1 abdominal pain/nausea (n = 14, 48.3%)</td>
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<td></td>
<td></td>
<td>• grade 2 gastrointestinal ulceration (n = 3, 10.3%)</td>
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<td>• Three cases of grade 3 radiation-induced liver disease were symptomatically managed.</td>
</tr>
<tr>
<td>Cosimelli 2010</td>
<td>Second or further treatment line</td>
<td>Prospective, multi-center phase II trial</td>
<td>50 patients</td>
<td>11 months (median value)</td>
<td>• Adverse events were mild or moderate within the first 48 h from the procedure, after a month and 2–3 months after treatment</td>
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</tr>
<tr>
<td>Hendlisz, 2010</td>
<td>Second or further treatment line</td>
<td>Open-label, randomized, phase III clinical trial</td>
<td>44 patients</td>
<td>Median follow-up was 24.8 months</td>
<td>• Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after radioembolization plus FU treatment</td>
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</tr>
<tr>
<td>Hoffmann 2010</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>46 patients</td>
<td>Patients were routinely followed every 3 months after SIRT</td>
<td>• In 3 patient’s major complications and in 24 patient’s minor complications occurred</td>
<td></td>
</tr>
<tr>
<td>Clanni 2009</td>
<td>Second or further treatment line</td>
<td>Retrospective observational study</td>
<td>44 patients</td>
<td>8 weeks</td>
<td>• Twelve hours after the procedure, five patients experienced mild abdominal pain or nausea</td>
<td></td>
</tr>
<tr>
<td>van Hazel 2009</td>
<td>Second or further treatment line</td>
<td>Phase I, dose-escalation study</td>
<td>25 patients</td>
<td>Based on duration of cycles</td>
<td>• Grades 3 to 4 events were seen in three of six patients at 50 mg/m², in five of 13 patients at 75mg/m² and in four of six patients at 100mg/m²</td>
<td></td>
</tr>
<tr>
<td>Jakobs 2007</td>
<td>Second or further treatment line</td>
<td>Clinical trial</td>
<td>39 patients</td>
<td>Patients were followed repeatedly every 2–3 months after SIRT</td>
<td>• Thirty-six of 39 patients experienced no severe side-effects from the treatment</td>
<td></td>
</tr>
<tr>
<td>Sharma 2007</td>
<td>First line</td>
<td>Open-label, nonrandomized phase I clinical</td>
<td>20 patients</td>
<td>Until death</td>
<td>• Two patients developed an (actinic) gastric ulcer and one patient an edematous pancreatitis</td>
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<td></td>
<td>• Twenty-four patients (61%) experienced acute abdominal/epigastric pain and/or nausea immediately after SIRT administration</td>
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<td></td>
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<td>• Grade 3 abdominal pain was reported in five patients</td>
</tr>
</tbody>
</table>
with FOLFOX4 trial

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of Studies included</th>
<th>Intervention and Comparator</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiao LR, 2007</td>
<td>21 patients</td>
<td>Second or further treatment line</td>
<td>Clinical trial</td>
<td>6 weeks together with follow-up imaging with CT and PET after therapy</td>
</tr>
<tr>
<td>Stubbs 2006</td>
<td>100 patients</td>
<td>First line</td>
<td>Clinical trial</td>
<td>12 months</td>
</tr>
<tr>
<td>Van Hazel 2004</td>
<td>21 patients</td>
<td>First line</td>
<td>Randomized Phase 2 Trial</td>
<td>Every 3 months</td>
</tr>
</tbody>
</table>

Table 3.4: Reviews about safety outcomes of the use of Y-90 resin microspheres.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of Studies included</th>
<th>Intervention and Comparator</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raval 2014</td>
<td>14</td>
<td>SIRT with Y90 microsphere alone or in combination with chemotherapy</td>
<td>Adverse events</td>
<td>Y-90 therapy in combination with first line chemotherapy is safe.</td>
</tr>
<tr>
<td>Harris 2009</td>
<td>6</td>
<td>SIRT in combination with chemotherapy</td>
<td>Adverse events</td>
<td>Acute toxicities are limited to gastrointestinal (nausea, abdominal pain) or slightly elevated liver enzymes while late toxicities have been rare</td>
</tr>
<tr>
<td>Sexena 2013</td>
<td>20</td>
<td>Y90 radioembolization of unresectable CRCLM refractory to systemic therapy</td>
<td>Adverse events</td>
<td>SIRT is a safe treatment of CRCLM in the salvage setting and should be more widely utilized.</td>
</tr>
<tr>
<td>Van De Wiele 2009</td>
<td>15</td>
<td>SIRT alone or in combination with chemotherapy</td>
<td>Adverse events</td>
<td>SIRT resulted well tolerated</td>
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3.2. Safety risk management

3.2.1. Can different organizational settings increase or decrease harms?

The optimal treatment strategies for patients with mCRC are evolving rapidly with improved clinical outcomes being achieved when the treatment approaches for individual patients are discussed within a multidisciplinary team of experts who meet regularly as a tumor board to review mCRC cases. Ideally, patients should be treated either in specialist cancer centers or, alternatively, where this is not possible, as part of a network of individuals dedicated to the management of CRC with an established referral route between their site or center and a specialist cancer center (virtual multidisciplinary teams). Wherever possible, multidisciplinary teams should provide the opportunity to register patients for the local and/or national registries with extreme/unusual patients’ details just noted, to provide information on the diversity of patients seen (van Cutsem et al., 2016). In order to achieve high levels of safety, SIRT should ideally be undertaken at centers that employ a multidisciplinary approach to planning, delivering and reviewing cancer treatment, or upon referral from a multidisciplinary team familiar with the procedure. In particular, multidisciplinary team members should be consulted with regard to the likely interactions between SIRT and any prior, concurrent or planned biological, chemotherapeutic, locoregional ablative, surgical or external beam radiation therapies. All candidates for SIRT should preferably be discussed by a multidisciplinary team – regardless of the referring clinician or center – and should remain under team review both during and after treatment (Wang et al., 2010).

3.2.2. How can one reduce safety risks for patients

Patient’s selection and assessment

Many studies emphasize the importance of patients’ selection in order to minimize risks connected to SIRT (Wang et al. 2010; Welsh et al., 2006). More in detail, in order to prevent serious toxicity associated with the potent antitumor efficacy, meticulous pretreatment evaluation is of particular importance. Improvements in predicting dosimetry will help optimize treatment and patient selection. Nuclear medicine procedures are essential for planning, performing, and monitoring of SIRT (Ahmadzadehfar et al., 2010). The patient’s renal status should be adequate to accommodate any concurrent chemotherapy that is part of the treatment plan, as well as for the use of contrast agents during the diagnostic and the therapeutic angiogram.
Hemodialysis patients may be treated with SIRT, but dialysis has to be planned and timed before and after the intervention.

One important aspect for patient selection before SIRT is the general clinical condition, as described by the Eastern Cooperative Oncology Group (ECOG) or Karnofsky performance score. Patients with a significantly reduced performance status are at a higher risk of developing severe side effects, including radiation-induced liver failure.

Biliary integrity with regard to potential ascending infections of the liver is another aspect for patient selection. Patients with recurrent infections of the bile system should be evaluated with special scrutiny before potential SIRT, as the intervention may be a substantial risk for increased infectious complications.

Portal hypertension should be viewed critically together with liver function and the proportion of liver involved by the tumor (segment, unilobar, bilobar).

Regarding the patient medication at the time of evaluation, attention should be paid to antiangiogenic drugs, such as bevacizumab. These drugs should be discontinued in an adequate time frame before the pretreatment angiogram, for example, at least 2-4 weeks, in order to avoid vascular complications during the angiogram, such as dissection or rupture and bleeding, and optimize treatment efficiency at the later SIRT.

Finally, prior to infusion, it is necessary to exclude patients with significant shunt (>20%) between the liver and lung and with any shunt between the liver and the gastrointestinal tract, in order to avoid the risk of radiation pneumonitis and/or gastritis (Sutcliffe et al., 2011; Liu et al., 2003).

**Patient’s treatment**

For better tolerance of SIRT, some premedications are advisable (Ahmadzadehfar et al., 2010):

- **Gastrointestinal ulcer prophylaxis**: due to the possibility of small unrecognized arterial vessels coursing to the gastrointestinal system, the routine use of prophylactic antulcer medications (proton pump inhibitors such as omeprazole or pantoprazole or H2-blockers such as ranitidine) should be initiated 1 week before SIRT and continuation for at least 4 weeks post-treatment is advised in all patients. In a recent study, Raval et al. (2014) confirmed that the use of proton pump inhibitors in patients undergoing SIRT prevented gastrointestinal side effects while peri-procedural steroids avoided the development of fatigue or chronic liver injury.

- **Antinausea prophylaxis**: antiemetics (e.g., ondansetron or granisetron) are recommended before and after SIRT to reduce post-treatment nausea.
- Post embolization syndrome prophylaxis: fever, malaise, and lethargy can occur because of the radiation injury and embolic effect of the SIRT on the tumor neovasculature. Oral corticosteroids (e.g., dexamethasone 4 mg BID) are recommended for 3 days starting at the day of treatment. Additionally, intravenous high-dose steroids immediately before treatment are helpful for tolerance.
- Pain control: oral analgesia may be required for 1 week following treatment to relieve pain from radiation injury, and liver capsular pain from tumor edema.
- Control of embolization symptoms: slow infusion of an i.v. analgesia (e.g., pethidine) and a corticosteroid during therapy with SIR-spheres could be helpful against embolization symptoms.

The retrospective study by Dhabuwala et al, 2005 aimed to determine whether the pattern of uptake of $^{99m}$Tc-MAA after arterial injection by colorectal liver metastases was predictive of tumor response after SIRT. When analyzing 58 patients with colorectal hepatic metastases receiving SIRT, authors found that if the adverse effects of anorexia and lethargy relate to the damage of normal liver tissue, as seemed possible, then a smaller dose of SIRT using Y-90 resin microspheres might be better tolerated without compromising anti-tumor efficacy (Dhabuwala et al, 2005).

Finally, a recently published evaluation also suggests that there is potential for improved safety with the replacement of sterile water with 5% glucose for the administration of SIR-Spheres Y-90 resin microspheres. In this retrospective, single-center case series, 78 SIRT procedures using 5% glucose compared with sterile water were associated with a significantly lower incidence of stasis (28% versus 11%; p=0.02) and mild-to-moderate abdominal pain (1.8% versus 44%; p<0.001) (Ahmadzadehfar et al, 2013).

**Patient’s Follow up**

Follow-up schedules after treatment vary depending on the treatment plan of each patient. Continuous monitoring of liver function tests is recommended to determine the outcome of treatment. This includes monitoring for stabilization in liver function tests due to the control of disease.

A biweekly assessment to rule out RILD is recommendable in the first 2 months after SIRT.

Abdominal and whole-body imaging should be performed for evaluation of response and evaluation of extrahepatic metastases with a sequence that differs according to tumor type and individual treatment plan (Ahmadzadehfar et al., 2010).
Box 3.1 summarizes experts’ opinion on how different organizational settings can increase or decrease harms.

**Box 3.1. Experts’ opinion on how different organizational settings can increase or decrease harms.**

**Organizational settings affecting safety.**

Performing a good preliminary work-up is the best strategy to improve patients’ safety, also through an appropriate selection of patients to be treated with SIRT. However, also organizational features do play a central role. For this reason, the selection of centers allowed to perform SIRT is of paramount importance to guarantee a certain level of quality. Moreover, even if the treatment itself is generally well tolerated by the patients, a wash-out time span should be observed when SIRT is delivered as a third line treatment in order to control potential interactions with previous treatments. Finally, a potential issue for safety, strongly related to the organization of care, concerns the continuity of care for patients who receive treatment outside their home town. Indeed, the management of follow up for these patients can be problematic. In order to enhance safety, a reference consultant oncologist should be identified for the surveillance of these patients in their home town and appropriate patient information materials should be provided.
4. Efficacy

4.1. Mortality and morbidity
Maleux et al. (2016) in a retrospective study have assessed the technical and clinical outcomes, OS and prognostic factors for prolonged survival after Y-90 radioembolization as a salvage therapy for patients with chemorefractory liver-only or liver-dominant colorectal metastases. From January 2005 to January 2014, all the patients selected for SIRT to treat chemorefractory colorectal liver metastases were identified. In total 71 patients finally underwent catheter-directed Y-90 microspheres infusion into the hepatic artery. Median time to progression in the liver was 4.4 months. Estimated survival at 6 and 12 months was 65% and 30%, respectively, with a 50% estimated mOS after 8.0 months in this group of chemorefractory patients. The authors have concluded that Y-90 resin microspheres for chemorefractory colorectal liver metastases have an acceptable survival profile with a 50% estimated survival after 8.0 months (Maleux et al., 2016).

Jakobs et al. (2016) evaluated efficacy of SIRT using Y-90 resin microspheres for unresectable chemorefractory liver metastases from mCR. The results showed a median OS of 10.2 months, which did not differ significantly by gender or age. The authors studied survival in relation to response. If patients had a complete response to prior chemotherapy, survival was 23 months while if they had a partial response or stable disease, it was 13 months. Moreover, if durability of response to radioembolization extended to ≥6 months, median survival was 17.1 months (95 % [13.7, 23.7]) compared with 5.8 months (95 % [13.7, 23.7]) in patients who had disease progression within 6 months of treatment. Furthermore, it was observed an improvement of survival (15.0 vs 6.7 months) in patients with a positive trend in CEA serum levels (≥30% reduction) at 3 months post-radioembolization (Jakobs et al., 2016).

A randomized, multicentre trial was conducted by Van Hazel et al. (2016) in patients with previously untreated metastatic colorectal cancer. Chemotherapy naïve patients with liver metastases plus or minus limited extrahepatic metastases were randomly assigned to receive either modified FOLFOX (mFOLFOX6; control) or mFOLFOX6 plus SIRT using Y-90 resin microspheres plus or minus bevacizumab. The addition of SIRT to chemotherapy demonstrated a similar median PFS at any site compared with in the control group (10.7 months vs 10.2 months). Conversely, median PFS in the liver was better in SIRT in the control group (20.5 months vs 12.6 months). Also for objective response rates there was the same situation shown in
progression free survival. At any site objective response rates were similar (76.4% vs 68.1%) while in the liver was higher in SIRT arm (78.7) than in the control group (68.8%). Control group reported A greater number of patients with disease progression were reported in the control group (77% vs 52.4%) (Van Hazel et al., 2016).

A retrospective observational study by Kennedy et al. (2016) compared the survival of 160 elderly (≥ 70 years) and 446 younger (< 70 years) patients who received SIRT using Y-90 resin microspheres between July 2002 and December 2011. The authors analysed OS, with similar results between the two groups (9.3 months for elderly and 9.7 months for younger patients). The study also considered 35 patients who had received no previous chemotherapy. For these, median survival was better for younger (25.2 months) than elderly patients (11.9 months) (Kennedy et al., 2016).

Damm et al. (2016) analysed the efficacy of radioembolization in 106 patients with liver metastases from CRC. All patients had failed at least one chemotherapy regimen (bevacizumab, cetuximab, capecitabine, mitomycin and 5-FU). The median OS was 6.7 months after the first radioembolization while the median PFS was 3.5 months. The authors determined prognostic score according to CEA and CA19-9 serum levels, hepatic tumor load and Karnofsky index were further processed to form a prognostic score. For patients with 0 points, median survival was 13.4 months, 8.3 months for those with 1 point, 5.8 months for those with 2 points and 4.0 months for those with 3 points (Damm et al., 2016).

The Post-SIR-Spheres Surgery Study (P4S) is an international, multicentre, retrospective study specifically designed to assess outcomes of liver resection or transplantation following SIRT using Y-90 resin microspheres. Data were collected from 100 patients, 30 of whom received SIRT treatment for liver metastases secondary to CRC. Median (IQR) time from last SIRT to surgery was 3.6 (4.0) months. 10 (33.3%), 12 (40.0%) and 8 (26.7%) patients received no-lines, 1-line or >1-line of pre-SIRT chemotherapy, respectively; 11 (37%) received post-SIRT chemotherapy. Resection was major (3 segments) in 24 (80%) patients, and extended (5 segments) in 12 (40%) patients. Patients with >1-line of pre-SIRT chemotherapy were more likely to undergo extended resection (75% vs 40% and 17% in patients receiving no-lines and 1-line, respectively). Complete resection was achieved in 24 (80.0%) patients, R1 in 5 (16.7%) and R2 in 1 (3.3%). Post-operative (any Clavien-Dindo-grade) complications were observed in 20 (66.7%) patients, and post-operative liver failure in 7 (23.3%) patients (grade 3+ in 5 [16.7%]). Cumulative 30-day and 90-day all-cause mortality from first hepatic surgery was 1 (3.3%) and 3 (10.0%), respectively. No deaths appeared directly related to prior SIRT. Median survival was 29.3 ([0.9-71.0]) months, 39.4 ([19.3-69.4]) months and 11.6 months post-surgery in patients receiving no-lines, 1-line or >1-line of pre-SIRT chemotherapy, respectively. The authors concluded that complications in resected mCRC patients following SIRT
appear similar to published studies. OS was encouraging in patients with 1-line of pre SIRT chemotherapy (Shon et al., 2016).

Moir et al. (2015) examined radiological (CT/MRI according to Response Evaluation Criteria in Solid Tumours (RECIST)) and biological (α-fetoprotein, CEA, carbohydrate antigen 19-9, chromogranin A) response in 44 patients treated with SIRT. 31 patients reported radiological response with a median reduction in sum of diameters (SOD) in hepatocellular carcinoma (-24.1) and neuroendocrine tumours (-30.0) and median increase in SOD in colorectal cancer (4.9). Biological response was assessed in 17 patients, with a reduction in 12, a mixed response in two and no improvement in three. In addition to response, the authors calculated median OS that resulted equal to 292 days. It was observed a higher number of patients who survived 6 months after the procedure (71%) than after 12 months (41%) (Moir et al., 2015).

Sofocleous et al. (2015) have assessed the efficacy and factors that affect outcomes of SIRT using Y-90 resin microspheres in patients with unresectable and chemorefractory colorectal cancer liver metastases. From September 2009 to September 2013, 53 patients underwent radioembolization at a median of 35 months after the diagnosis. Multivariate analysis showed that CEA levels at the time of SIRT ≥ 90 ng/ml (P = 0.004) and microscopic lymphovascular invasion of the primary tumor (P = 0.002) were independent predictors of decreased OS. Median LPFS was 4.7 months. At 4 to 8 and 12 to 16 weeks after radioembolization, most patients (80% and 61%, respectively) had stable disease; additional evaluation using PET Response Criteria in Solid Tumors (PERCIST) led to reclassification in 77% of these cases (response or progression). No deaths were noted within the first 30 days. Within the first 90 days after radioembolization, 4 patients (8%) developed liver failure and 5 patients (9%) died, all with evidence of disease progression. SIRT in the salvage setting was well-tolerated, allowed the administration of additional therapies and led to a median overall survivor (OS) of 12.7 months. Evaluation using PERCIST was more likely than RECIST to document response or progression compared with the baseline assessment before radioembolization (Sofocleous et al., 2015).

A retrospective chart review of patients undergoing SIRT was performed by Henry et al. (2015). Demographic, clinic-pathologic, operative, and long-term outcomes variables were collected. Independent pathologic review of tumour necrosis and normal liver tissue grading of fibrosis and inflammation after resection was performed. Data are expressed as medians and ranges. Between 2004 and 2011, SIRT was delivered to 106 patients with primary and metastatic disease of the liver, of whom 9 patients with metastatic disease ultimately underwent resection. RE was previously administered to the right liver in five, the left liver in one, and to the whole liver in three. Two patients had a second RE performed before resection. Six of the nine patients had previously received several infusions of cytotoxic therapy.
The operations occurred at a median of 115 [56-245] days after SIRT and included right lobectomy (n=5), left lobectomy (n=1), left-lateral sectionectomy (n=1), and bilobar wedge resections (n=2). Extrahepatic sites were resected in three patients. Median blood loss was 900 ml. Grade 3 or higher complications occurred in seven cases (78 %). Follow-up was complete all nine patients. Three patients (33 %) died within 30 days of resection. All those surviving the operative period had disease recurrence (time to recurrence: 202 [54-315] days), and all have since died (overall survival: 584 [127-1230] days). Review of resected specimens demonstrated median tumour necrosis of 70 % ([20-90%]). The authors have concluded that in this small cohort of highly selected and heavily pre-treated patients, long-term survival in patients undergoing resection after SIRT appears possible, but the operations may carry substantial risks-highlighting the importance of careful patient selection for these resections (Henry et al., 2015).

The study by Fendler et al. (2015) studied 100 CRC patients treated with SIRT between October 2003 and August 2010 at the Department of Nuclear Medicine, University Hospital of the Ludwig Maximilian University (LMU) in Munich that were taken as the training set, and 25 CRC patients treated with SIRT between November 2008 and March 2011 at the Department of Nuclear Medicine at the University Hospital Bonn in Germany who were taken as the validation set. The mean OS was longer in the training cohort (60 weeks) compared with the validation cohort (54 weeks). No significant difference was seen in survival rates between the training and validation sets using log-rank tests (p=0.51). In the validation cohort, 9 patients had a score of ≤57 points, with a predicted 1-year survival ≥68 % according to the nomogram. Median OS for this subgroup was 93 weeks. Nine patients had 57 to 152 points, with a predicted 1-year survival ranging between 61 and 35 % according to the nomogram. Median OS for this subgroup was 30 weeks. Seven patients had a score ≥209 points, a predicted 1-year survival <15 %, and a true median OS of 16 weeks (Fendler et al., 2015).

A prospective case series by Golfieri et al. (2015) evaluated 52 patients with mCRC who were treated at a single centre following a median of 2 lines of chemotherapy. The authors evaluated response rate and survival. Response rate resulted better after 3 months compared with that after 6 months (59% vs 28.6%). The proportion of patients with extrahepatic disease (EHD) increased from 32.5 % (12 of 52 patients) at baseline to 38.5 % (20 of 52 patients) and 37.2 % (19 of 51 patients) at 1 and 3 months after treatment, respectively; most of whom had disease progression of target lesions at 1 (70.0 %) and 3 months (94.7 %). Survival resulted equal to 11.0 months and it was determined by the tumour response at 3 months (p=0.044) and best tumour response (p<0.001). Finally, it was prolonged after SIRT using Y-90 resin microspheres in patients with fewer liver metastases, a lower tumour burden in the
liver, less extensive liver involvement and good performance status (Golfieri et al., 2015).

In a retrospective study, Kalva et al. (2014) have reported the outcomes of SIRT when it used as salvage therapy for chemotherapy-resistant liver metastases from colorectal cancer. Forty-five patients with hepatic metastases from CRC underwent Y-90 SIRT after failure of systemic chemotherapy, and have been included. Twenty-three patients (51%) had no toxicities, whereas 6 patients (13%) had grade 3 toxicities, and no patients had grade 4 toxicity. The authors have concluded that y-90 SIRT as a salvage therapy for chemotherapy-resistant hepatic metastases from colon cancer was safe (Kalva et al., 2014). [Only abstract availability]

Saxena et al. (2014) have reported that SIRT using Y-90 resin microspheres is an efficacious procedure. Between 2006 and 2013, 302 patients who underwent resin-based Y-90 SIRT for unresectable, chemorefractory colorectal cancer liver metastases were evaluated. After 7.2 months of 293 patients who were followed up beyond 2 months, complete response to treatment was observed in 2 patients (1%), partial response in 111 (38%), stable disease in 96 (33%), and progressive disease in 84 (29%) (Saxena et al., 2015).

Kalva et al. (2014) in a retrospective study have assessed safety outcomes of SIRT when used as salvage therapy for chemotherapy-resistant liver metastases from CRC. 45 patients with hepatic metastases from CRC underwent Y-90 SIRT after failure of systemic chemotherapy, have been included. Per RECIST, 1 patient (2%) had partial response, 34 (71%) had stable disease, and 6 (13%) had progressive disease. PET response was seen in 46% of patients with 2 patients (4%) demonstrating complete and 22 (42%) demonstrating partial metabolic response. The median survival was 186 days (95% CI, 149-277 d). Response on PET was the only independent predictor of superior overall survival. Patients who had response on PET following Y-90 therapy had a median OS of 317 days (10.6 mo) (95% CI, [193, 564]), whereas patients with no response on PET had a median OS of 163 days (5.4 mo) (95% CI, [64, 283]). The authors have concluded that Y-90 SIRT is a salvage therapy for chemotherapy-resistant hepatic metastases from colon cancer (Kalva et al., 2014).

Cohen et al. (2014) conducted a prospective single-centre, phase I study on capecitabine in combination with SIRT using Y-90 resin microspheres in patients with advanced unresectable liver-dominant cancer. They considered as outcome: response rate, time to progression and overall survival. 70.8% of sample had stable disease, 16.7% of patients reported partial response while 12.5% was in progression. The median time to progression and OS was 6.4 months and 8.1 months, respectively (Cohen et al., 2014).

In a retrospective study, Tohme et al. (2014) have evaluated the overall median survival among elderly (≥70 years) and younger patients (<70 years) with liver-
dominant mCRC who received radioembolization as salvage therapy. From 2002 to 2012, 107 consecutive patients with unresectable mCRC treated with SIRT after failing first- and second-line chemotherapy have been included in a study, of which, 44 elderlies and 63 younger patients. No significant difference was found with regard to overall median survival between younger [8.4 months; 95% CI, [6.2, 10.6] or elderly patients (8.2 months; 95% CI [5.9, 10.5]) p=0.667). The presence of EHD at the time of RE was associated with a significantly worse median survival in both groups. The authors have concluded that radioembolization with Y-90 resin microspheres appears to be as effective for the elderly as it is for younger patients with mCRC (Tohme et al., 2014).

The review of Raval et al. (2014) showed that Y-90 therapy in combination with first line chemotherapy may improve tumour response rates. The procedure improved survival, in particular median value was 4–6months. Y-90 therapy was recommended for chemorefractory patients with liver-only or liver-predominant disease and in patients who did not wish to have systemic chemotherapy. The use of Y 90 was not recommended in patients with extensive extra-hepatic disease or extensive bilobar hepatic involvement (Raval et al., 2014).

The retrospective study by Zarva et al. (2014) evaluated the OS of repeated SIRT with resin microspheres in patients with nonresectable advanced liver tumors. The study recruited 21 patients (12 women, 9 men; mean age, 61.0 years) with unresectable advanced liver tumors (breast cancer liver metastases, n=7; colorectal liver metastases, n=5; hepatocellular carcinoma, n=8; cholangiocellular carcinoma, n=1) were repeatedly treated by SIRT. The authors showed that median OS resulted equal to 18 months (Zarva et al., 2014).

Sofocleous et al. (2014) conducted a prospective study to assess the efficacy of SIRT for liver-predominant metastases of CRC in patients with progression after hepatic arterial and systemic chemotherapy. The study recruited 19 patients who had received a mean of 2.9 prior lines of chemotherapy and ≥1 line of HAC. PFS and median OS was 2 months (95% CI, [1.1, 2.9] months) and median LPFS was 5.2 months (95% CI, [3.3 6.4] months). OS was 14.9 months (95% CI, [6.4, 25.6] months) (Sofocleous et al., 2014).

The review by Hipps et al. (2013) assessed the response following SIRT. A literature review was undertaken detailing SIRT in the treatment of colorectal liver metastases comparing staging methods, criteria, and response. A search was performed of electronic databases from 1980 to November 2011. Nineteen studies were analysed including randomised controlled trials, clinical trials, meta-analyses, and case series. Ten studies were already analysed in this paper (Wong et al, 20002; Murthy et al, 2005; Kennedy et al, 2006; Boppudi et al, 2006; Jakobs et al, 2007; Sharma et al, 2007; van Hazel et al, 2009; Hoffmann et al, 2010; Cosimelli et al, 2010; Stubbs et al, 2006). The others were evaluated below. Chua et al, 2011 evaluated the
role of SIRT and systemic chemotherapy as a combined modality therapy for unresectable colorectal liver metastases in Australia. 140 patients with unresectable colorectal liver metastases were analysed to assess OS. The median OS was 9 (95% CI [6.4, 11.3]) months with a 1, 2, and 3-year survival rate of 42, 22, and 20%, respectively. Combined modality therapy improved overall survival. Response following treatment was complete in two patients (1%), partial in 43 patients (31%), stable in 44 patients (31%), and 51 patients (37%) developed progressive disease. Combining chemotherapy with SIRT was associated with a favorable treatment response (p=0.007). Combined modality therapy improved tumor response rates. The study by Kosmider et al, (2011) analysed the efficacy of SIRT with Y-90 resin microspheres plus systemic chemotherapy as a first-line treatment for liver metastases from CRC. Clinical outcomes were evaluated retrospectively among 19 patients with unresectable liver metastases from CRC who had a good performance status and a low burden of EHD and were eligible for SIRT. Concurrent treatment with 5-fluorourail/leucovorin (n=7) or 5-fluorourail/leucovorin/oxaliplatin (FOLFOX; n=12) was started 3-4 days before single treatment with SIRT. Overall response rate according to the RECST was 84% (two complete responses and 14 partial responses). The study confirmed the effectiveness of SIRT plus systemic chemotherapy for mCRC. Nace et al, 2011 assessed the efficacy of the use of SIRT with Y-90 resin microspheres as salvage therapy for liver-dominant mCRC. A retrospective review of consecutive patients with unresectable mCRC who were treated with Y-90 after failing first and second line systemic chemotherapy. Fifty-one patients underwent Y-90 treatments. Using RECIST criteria, either stable disease or a partial response was seen in 77% of patients. The treatment was an important therapeutic option to patients who have failed first and second line chemotherapy. Mancini et al, 2006 aimed to evaluate clinical response in 35 patients with unresectable colorectal liver metastases submitted to SIRT. Preliminary results were available in terms of clinical response after 6 weeks: 12.5% had a partial response, 75% a stable disease, while progression of disease, was observed in 12.5% of the patients. Intra-arterial microspheres could represent a good therapeutic option for patients with progressing liver metastases only, after two lines of systemic chemotherapy. Lim et al, 2005 evaluated the efficacy of SIRT with Y-90 resin microspheres in patients with previously untreated CRC received concurrent 5FU, other patients with CRC received 5-FU at investigator discretion and all other patients received Y-90 resin microspheres alone. Forty-six patients were enrolled between January 2002 and June 2003 in three Australian centres. The study assessed the response to treatment. There were 12 partial responses, of which 10 were in patients with CRC. 28% of patients had stable disease. The median duration of response for all patients was 8.6 months ([2-21]). In this study, treatment with
SIR-Spheres demonstrated effectiveness, mostly in patients with CRC. Gray et al, 2001 conducted a phase III randomized clinical trial on 74 patients with bilobar unresectable liver metastases from CRC. This trial was designed to measure any increased patient benefit by adding a single administration of SIR-Spheres Y-90 resin microspheres to a regimen of regional hepatic artery chemotherapy administered as a 12-day infusion of floxuridine and repeated at monthly intervals (36 patients), vs the same chemotherapy alone. The partial and CR rate was significantly greater for patients receiving SIR-Spheres when measured by tumour areas (44% vs 17.6%, P=0.01), tumour volumes (50% vs 24%, P=0.03), and carcinoembryonic antigen (CEA) (72% vs 47%, P=0.004). The combination of a single injection of SIRT and HAC was substantially more effective in increasing tumour responses than the same regimen of HAC alone. Anderson et al, 1992 reported a significant response rate for stable disease of 86% (Hipps et al., 2013).

The retrospective study by Fendler et al. 2013 recruited eighty patients with hepatic metastases of CRC, treated with SIRT. It was observed 1 death within 12 weeks after SIRT; this patient died shortly after follow-up examination, most likely because of rapid progression of the disease. The patient had undergone multiple chemotherapies, hemicolectomy, and splenectomy before SIRT and presented with lymph node metastasis and a 25%-50% metastatic tumour burden in the liver. Overall, median survival after SIRT was 60 weeks. Median survival after the initial diagnosis of CRC was 195 weeks. Median survival of patients with response according to metabolic volume and total lesion glycolysis plus progressive disease according to RECIST was 69 weeks (46–92 weeks) versus 73 weeks (20–126 weeks) for patients plus any response according to RECIST. Changes in metabolic volume and total lesion glycolytic rate as measured by FDG PET predicted survival in patients with hepatic metastases from CRC (Fendler et al., 2013).

Soydal et al. 2013 aimed to evaluate tumour response using FDG PET/CT in patients who received SIRT for colorectal liver metastases. Thirty-five patients who received SIRT treatment for unresectable CRC liver metastases in hospital setting. The authors reported mean OS time and it was 12.7±8.0 months ([3–31] months) (Soydal et al., 2013).

Rosenbaum et al. (2013) in a systematic review have evaluated the available data on tumour response and survival after 90Y radioembolization for this group of patients.

The search yielded 13 relevant articles for systematic review on Y-90 resin microspheres as monotherapy and 13 relevant articles on Y-90 resin microspheres combined with chemotherapy. For Y-90 radioembolization as monotherapy, tumour response rates were reported in 10 studies with a total of 545 patients. Response rates (defined as complete response and partial response) ranged from 18% to 46%. Disease control rates (i.e., complete response, partial response, and stable disease)
ranged from 29% to 90%. Progression-free survival was reported in 6 studies and ranged from 3.9 to 9.2 mo. For 90Y radioembolization treatment combined with chemotherapy, responses were reported in 11 studies with a total of 388 patients. Response rates ranged from 8% to 90% (Rosenbaum et al., 2013).

Melucci et al. (2013) conducted a prospective multicentre phase II trial of SIRT in chemorefractory liver-dominant mCRC. 50 patients with unresectable, histologically proven CRC liver metastases and limited extra-hepatic disease, in progression following standard systemic chemotherapy. Of the 50 patients included in the study, 29 pre-Y-90 therapy and 15 post-Y-90 liver biopsy specimens available. In 13 matched patients, 5 presented biomarker variations pre-and post-SIRT therapy and 8 no biomarker variations. Of clinical interest, 6 of the latter patients (75%) presented progression disease whereas all the 5 patients showing changes in biomarker expression had partial response or stable disease. Nevertheless, the limited number of patients did not allow to determine whether these changes may really affect survival. Although analysis was conducted in a very limited number of cases, these changes appeared strictly related to the response to SIRT and might deserve further investigation on a larger series of patients. (Melucci et al., 2013)

Saxena et al. (2013) examined the radiological response, overall survival and progression-free survival of patients who underwent Y-90 radioembolization of unresectable CRCLM refractory to systemic therapy. Twenty studies comprising 979 patients were examined. Patients had failed a median of 3 lines of chemotherapy ([2–5]). After treatment, the average reported value of patients with complete radiological response, partial response and stable disease was 0% ([0–6%]), 31% ([0–73%]) and 40.5% ([17–76%]), respectively. The median time to intra-hepatic progression was 9 months ([6–16]). The median overall survival was 12 months ([8.3–36]). (Saxena et al., 2013)

The study by Fahmueller et al. (2012), 49 CRC patients suffering from liver metastases were treated with SIRT. All patients had primarily been treated with surgical resection and adjuvant chemotherapy (fluorouracil, folinic acid, oxaliplatin and/or irinotecan) and developed metachronous liver metastases lateron. Blood samples were prospectively and consecutively taken from 49 CRC patients with extensive hepatic metastases before, three, six, 24 and 48 hours after SIRT. When evaluating therapy response 3 months after SIRT, 14 patients out of 49 showed stable disease or partial remission (no progression) while the remaining 35 patients either deceased within time to staging (n=10), developed progressive disease in the liver (n=19) or in other organs. Panels of biochemical markers were helpful to stratify pretherapeutically CRC patients for SIR-therapy and to early estimate the response to SIRT-therapy (Fahmueller et al., 2012).

Bester et al. (2012) in a comparative retrospective study have evaluated the efficacy of patients with chemotherapy-refractory liver metastases treated with Y-90 resin
microspheres. While 339 patients with chemotherapy-refractory liver metastases underwent 90Y microspheres radioembolization at a single institution between 2006 and 2011, 51 patients were referred back to their treating physician for conservative treatment or best supportive care. OS was determined for the whole treated cohort and the standard-care cohort, as well as for the treated CRC group and the treated non-CRC group. For the whole treated cohort, the median OS after the first treatment with Y-90 microsphere radioembolization was 12.0 months [95% CI, [10.7, 14.5] p<0.001], and there was a significant improvement in OS in those patients treated with SSM compared with the standard care cohort (Bester et al., 2012).

Martin et al. (2012) have conducted a retrospective study to assess the efficacy in patients with refractory mCRC who underwent SIRT. Patients with unresectable mCRC with liver metastases treated at the Ohio State University were included in this analysis. Demographic data, CEA values, observed toxicities, and information on prior therapies were collected. Twenty-four patients were included. Of the patients, 54% had extrahepatic disease; 67% had bilobar involvement. Five patients had a CEA response. Median PFS and OS were 3.9 months (95% CI, [2.4-4.8] months) and 8.9 months (95% CI, [4.2-16.7] months), respectively. Patients older than 65 years had improved PFS (4.6 vs. 2.4 months) and OS (14 vs. 5.5 months) vs. younger patients, likely due to receipt of Y-90 treatment earlier in their disease course. The authors concluded that Y-90 SIRT is active in selected patients with refractory mCRC and with liver metastases. In patients with extensive extrahepatic disease, Y-90 should be used in combination with chemotherapy. CEA may be a predictor of efficacy (Martin et al., 2012).

Fifty-one patients with chemotherapy-refractory CRC liver metastases have been included in a study conducted by Leoni et al. (2012). The aim of this study was to evaluate target lesions response, safety and median survival in patients with liver metastases refractory to systemic chemotherapy from CRC treated with SIRT. All 51 patients enrolled had received, before SIRT, at least 3 lines of systemic chemotherapy; the majority of them had more than 5 hepatic lesions (53%) whose median size was 61 mm ([11-130]) with a median tumour volume of 272cm3. Median survival after SIRT was 8.5 months ([1-64 months]). Response rate of target lesions was 53% at 1 month, 41% at 3 months, 29% at 6 months and 36% at 9-12 months. Progression rate of target lesions was 18% at 1 month, compared to 89% in non-target lesions at the same time of follow up. In the majority (90%) of patients with minimal EHD, a 6 months EHD progression was observed. After SIRT two patients became eligible for surgery (hepatic resection) and one for radiofrequency ablation. The authors have concluded that the results confirm the effectiveness of the use of SIRT in a salvage setting, in a population of patients with liver metastases from CRC refractory to systemic chemotherapy (Leoni et al., 2012).
Seidensticker et al (2012) in a comparative retrospective study, have evaluated OS after radioembolization or best supportive care (BSC) in patients with chemotherapy-refractory liver dominant metastatic colorectal cancer (mCRC). This was a matched-pair comparison of patients who received radioembolization plus BSC or BSC alone for extensive liver disease. Twenty-nine patients who received radioembolization were retrospectively matched with a contemporary cohort of 500 patients who received BSC from 3 centres in Germany. Patients in both groups had a similar performance status (Karnofsky index, median 80% [60–100%]). Compared with BSC alone, radioembolization with Y-90 resin microspheres prolonged survival (median, 8.3 vs. 3.5 months; p<0.001) with a hazard ratio of 0.3 (95% CI [0.16–0.55]; p<0.001) in a multivariate Cox proportional hazard model. (Seidensticker et al., 2012)

The study by Kosmider et al. (2011) analysed the PFS and OS of SIRT plus systemic chemotherapy as a first-line treatment for liver metastases from CRC. Clinical outcomes were evaluated retrospectively among 19 patients with unresectable liver metastases from CRC who had a good performance status and a low burden of EHD (EHD) and were eligible for SIRT. Median PFS time was 10.4 months and median OS time was 29.4 months. For patients with disease confined to the liver, PFS improved (10.7 months vs 3.6 months; p=0.09), with significant prolongation of OS (median, 37.8 months vs 13.4 months; p=0.03) compared with those who had EHD. The study confirmed the effectiveness of SIRT plus systemic chemotherapy for metastatic CRC. Nace et al, 2011 assessed the efficacy of the use of SIRT with Y-90 resin microspheres as salvage therapy for liver-dominant mCRC. A retrospective review of 51 patients with unresectable mCRC who were treated with Y-90 after failing first and second line systemic chemotherapy. Overall median survival from the time of first Y-90 treatment was 10.2 months (95% CI, [7.5, 13.0]). The absence of EHD at the time of treatment with Y-90 was associated with an improved survival, median survival of 17.0 months (95% CI,[6.4, 27.6]), compared to those with EHD at the time of treatment with Y-90, 6.7 months (95% CI, [2.7, 10.6]). The treatment was an important therapeutic option to patients who have failed first and second line chemotherapy. Gray et al, (2001) conducted a phase III randomized clinical trial on 74 patients with bilobar nonresectable liver metastases from CRC. This trial was designed to measure any increased patient benefit by adding a single administration of SIR-Spheres to a regimen of regional hepatic artery chemotherapy administered as a 12-day infusion of floxuridine and repeated at monthly intervals (36 patients), vs the same chemotherapy alone. The median time to disease progression in the liver was significantly longer for patients receiving SIR-Spheres in comparison with patients receiving HAC alone, when measured by either tumour area (9.7 vs 15.9 months, p=0.001), tumour volumes (7.6 vs 12.0 months, p=0.04), or CEA (5.7 vs 6.7 months, p=0.06). The median OS was 17 months vs 15.9 months. The combination of
a single injection of SIR-Spheres and HAC was substantially more effective in increasing progression-free survival than the same regimen of HAC alone. The patients treated with Y-90 showed a good survival (13.8 months). Anderson et al. (1992) reported a good median survival of 11 months (Kosmider et al., 2011). Whitney et al. (2011) analysed 44 patients who had received SIRT using Y-90 resin microspheres for unresectable hepatic malignancies. The use of SIRT for the treatment of metastases in the liver could successfully downstage the lesions to allow for surgical resection in patients with amenable predictors, and could provide a significantly better prognosis in these patients. One patient had progression of disease in the lungs following resection, histologically confirmed as metastatic rectal carcinoma. The median survival was 2 years (Whitney et al., 2011).

Gulec et al. (2011) investigated the relationship between functional tumour parameters (FTV and TLG) and clinical outcomes in 20 patients with CRC liver metastases undergoing SIRT. The median survival in the study group was 14.8 months ([2.0–27.7 months]). The median survival for patients with pre-treatment FTV values of above and below 200 cc were 11.2 and 26.9 months, respectively (p<0.05). The median survival for patients with 4-week posttreatment FTV values of above and below 30 cc were 10.9 and 26.9 months, respectively (p<0.05). The median survival for patients with pre-treatment TLG values of above and below 600 g were 11.2 and 26.9 months, respectively (p<0.05). The median survival for patients with 4-week posttreatment TLG values of above and below 100 g were 10.9 and 26.9 months, respectively (p<0.05). Pre-treatment and posttreatment FTV and TLG showed very strong association with survival (Gulec et al., 2011).

Hendlisz et al. (2010) conducted a prospective, multicentre, randomized phase III trial in patients with unresectable, chemotherapy-refractory or chemotherapy intolerant liver-limited mCRC comparing arm A (fluorouracil [FU] protracted intravenous infusion 300 mg/m² days 1 through 14 every 3 weeks) and arm B (SIRT plus intravenous FU 225 mg/m² days 1 through 14 then 300 mg/m² days 1 through 14 every 3 weeks) until hepatic progression. Patients were randomly assigned to two arms. Overall response rates in arms A and B were 0% and 9.5, respectively, and disease control rates (partial response and stable disease) were 35. The study met its primary endpoint with Y-90-resin microspheres plus FU significantly improving TTLP and TTP compared with FU alone. There was no significant difference in median OS between the treatment arms: 7.3 months for arm A (two patients alive at the time of analysis) and 10.0 months for patients in arm B. The OS result was confounded by crossover as 10/23 patients in arm A received SIRT on progression. This procedure was a valid therapeutic option for chemotherapy-refractory liver-limited mCRC (Hendlisz et al., 2010).

The study by Dudeck et al. (2010) assessed diffusion-weighted imaging (DWI) for early prediction of tumour response in patients with colorectal liver metastases
following SIRT. Forty-one metastases were evaluated in 21 patients, age 62.9 ± 9.9 years. All patients underwent MRI including breath-hold echo planar DWI sequences. Imaging was performed before therapy (baseline MRI), 2 days after SIRT (early MRI) as well as 6 weeks later (follow-up MRI). Thirty-three metastases (80.5%) were rated as responding lesions (RL), in which tumour volume decreased significantly by 31.3±21.3% ([3.7, 270.4] cm³) on follow-up MRI 6 weeks after SIRT (p < 0.0001). For these lesions, ADC increased significantly by 21.4 ± 16.4%. On early MRI performed 2 days following SIRT, no significant changes in total volume were found either for RL (14.0±8.0%; mean value: 58.8±85.0 cm³; [6.8, 444.7] cm³; p=0.21) or for NRL (mean value: 28.4±27.8 cm³; 5.2±3.5%; [6.3, 91.6] cm³; p=0.53). Conversely, in RL a significant decrease in ADC of 10.7±8.4% was found (p<0.0001). DWI was capable of predicting therapy effects of SIRT in patients with colorectal hepatic metastases as early as 2 days following treatment (Dudeck et al., 2010). Cosimelli et al. (2010) assessed the efficacy of a single hepatic intra-arterial injection of Y-90 resin microspheres in 50 patients with unresectable, chemotherapy refractory CRC liver metastases as the sole or dominant site of disease. Patients with liver disease progression following standard systemic chemotherapy (including FOLFOX and FOLFIRI regimens) were recruited following multidisciplinary review from four centres in Italy between May 2005 and August 2007. By intention-to-treat analysis using RECST, 1 patient (2%) had a complete response, 11 (22%) partial response, 12 (24%) stable disease, 22 (44%) progressive disease; 4 (8%) were non-evaluable. Median overall survival was 12.6 months (95% CI, 7.0–18.3); 2-year survival was 19.6% (Cosimelli et al., 2010). Ahmadzadehfar et al. (2010) conducted a review about efficacy and safety of SIRT. In particular, the authors evaluated the efficacy of SIRT in hepatic metastasized CRC in 12 studies (6 were already analysed in this study: Van Hazel et al, 2004; Sharma et al, 2007; Mancini et al, 2006; Gray et al, 2001). Kennedy et al. (2006) conducted a review of 208 patients in the United States treated with Y-90 resin microspheres in liver brachytherapy. Median survival is 10.5 months for responders but only 4.5 months in nonresponders. Radioactive microspheres produced an encouraging median survival. Partial responses were found in 74 of 208 patients (35.5%), stable disease or minor response was found in 114 of 208 patients (55%), and progressive disease was found in 21 of 208 patients (10%). PET scans showed response in 176 of 208 patients (85%) and no response or progression in 31 of 208 patients (15%). Radioactive microspheres produced a significant objective response rate. The retrospective study by Stubbs et al. (2006) assessed the OS of patients treated with Y-90 resin microspheres and HAC5-FU. The combination of these treatments reported a median OS of 11 months. The prospective study by Van Hazel et al. (2009) evaluated the efficacy of irinotecan+SIRT in 25 patients with hepatic metastasized CRC. The median time to disease progression was 6 months while the median OS
was 12 months. Gray et al. (2001) showed in a group of 70 consecutive patients with advanced liver metastases from CRC who were treated with 1 or 2 injections of SIR-spheres followed by hepatic HAC. Mean and median survival for patients with metastases confined to the liver was 14.5 and 13.5 months from the time of SIRT. The addition of SIRT significantly improved progression-free survival. This study demonstrated a high response rate (74%).

The prospective study by Van Hazel et al. (2009) evaluated the efficacy of irinotecan+SIRT in 25 patients with hepatic metastasized CRC. The response rate was 47%. This study demonstrated a moderate response rate. Gray et al. (2001) showed in a group of 70 consecutive patients with advanced liver metastases from CRC who were treated with 1 or 2 injections of SIR-spheres followed by hepatic HAC and an objective response rate of 72% (PR+CR) when measured by CEA. The study showed a significant improvement in response rate with the addition of SIRT using Y-90 resin microspheres (Van Hazel et al., 2005).

Van Hazel et al. (2009) evaluated the maximum-tolerated dose of irinotecan chemotherapy in combination with SIRT using Y-90 resin microspheres in fluorouracil-refractory patients with CRC hepatic metastases. Twenty-five irinotecan-naive patients who had experienced relapse after previous chemotherapy were enrolled onto three dose-escalating groups. Irinotecan was administered at 50, 75, or 100 mg/m² on days 1 and 8 of a 3-week cycle for the first two cycles, and full irinotecan doses (i.e., 100 mg/m²) were administered during cycles 3 to 9. SIRT was administered during the first chemotherapy cycle. The authors reported median PFS and survival of patients. The median PFS was 6.0 months, from 1.6 to 11.4 months. The median PFS in the liver was 9.2 months ([1.6, 25.8]). Patients with disease confined to the liver at the time of study entry had a marginally improved PFS (median, 6.1 months; [1.6, 10.8] months). The median survival was 12.2 months ([2.8, 60.0] months). None of the deaths were considered by the investigators to be related to either treatment modality. At the time of manuscript preparation, three patients, all of whom had disease initially confined to the liver, were still alive (Van Hazel et al., 2009).

A retrospective observational study by Cianni et al. (2009) analysed the response rate, PFS and survival of patients treated with SIRT. 41.5% of patients reported a partial response, 36.2% stable disease, 19.5% progressive disease and 4.8% complete response. The median survival was 354 days and the progression-free survival was 279 days (Cianni et al., 2009).

Campbell et al. (2009) analyzed a patient-specific single SPECT based method of dose calculation for treatment planning of SIRT. The study recruited 12 patients with inoperable metastatic liver cancer from primary colon cancer, treated with Y-90 resin microspheres. Many patients who have been treated with SIRT have now lived longer than their initial prognosis indicated. Their metastatic disease had regressed,
or the progression had slowed or arrested (Campbell et al., 2009). In the review of Harris et al. 2009, response rates to SIRT ranged from 35% to 73%. The progression of disease occurred in about 10% of patients, and there have been few reports of complete response (Harris et al., 2009). In the meta-analysis of Vente et al. (2009), for mCRC, response rate was 79% for Y-90 resin microspheres combined with 5-fluorouracil/leucovorin (5-FU/LV), and 79% when combined with 5-FU/LV/oxaliplatin or 5-FU/LV/irinotecan, and in a first-line setting 91%. The median survival from diagnosis of mCRC ranged from 10.8 to 29.4 months. Median survival from microsphere treatment varied between 7.1 and 21.0 months, and median survival from diagnosis or recurrence was 9.4–24.0 months (Vente et al., 2009). The study by Flamen et al. (2008) developed a predictive dosimetric model for SIRT and validated it by correlating results with the metabolic treatment response. All patients were enrolled in a phase III clinical research trial comparing the efficacy of SIRT combined with 5FU in continuous infusion to infusional 5FU alone in end-stage patients with only liver metastases of CRC. All patients were refractory to two or more lines of standard chemotherapy (including 5FU-leucovorin). Fluorouracil (5FU) was associated to SIRT. Only the 10 patients who were randomized into the SIRT+5FU arm were considered for analysis. The patients received 225 mg m−2 5FU during 2 weeks starting on the day of SIRT, followed after a one week of rest by 5FU 300 mg m−2 during 2 weeks on three. The median metabolic response was around 50% and it was highly variable among lesions. Eleven lesions had an increase in TLG (28%), 28 (72%) a decrease. The median lesion TLG reduction was 48%. This value justifies the use of 50% as the cut-off between a subgroup with poor (n=20) versus good response (n=19). Integrated multimodality imaging allows prediction of metabolic response post SIRT using Y-90 resin microspheres, and should be used for patient selection (Flamen et al., 2008).The study by Gulec et al. (2007) assessed the dose response of tumour in patients with liver malignancies who underwent SIRT with Y-90 resin microspheres. The results showed that 67.5% of sample had complete response, partial response, and stable disease. In particular, the tumour response rate was 100% for patients with neuroendocrine tumours compared with lower value of CRC and HCC (47% and 80%, respectively). Median tumour absorbed doses for responders and non-responders were 107.8 Gy and 76.9 Gy respectively. The lowest tumour absorbed dose producing a detectable response was 40 Gy (Gulec et al., 2007). Two studies (Jiao et al., 2007 and Szyszko et al., 2007) reported the same results. These studies evaluated the efficacy of SIRT in management of unresectable liver metastases. Twenty-one patients who had failed to respond to conventional treatment including chemotherapy, intra-arterial chemoembolization for hepatocellular carcinoma or local ablative treatment received Y-90 resin microspheres consisting of liver metastases from colorectal primary and non-colorectal primaries, and primary liver tumours. The authors analysed the mortality
and the survival of patients. Seven patients died at follow-up from progressive EHD (33%): 1 pancreatic, 1 unknown origin and 5 colorectal primaries. Three patients are alive with a stable disease at 24 months post therapy. When comparing colorectal with non-colorectal liver metastases, although statistically there was no difference, the survival curve would favour the non-colorectal liver metastases due to the fact that 50% of patients with colorectal liver metastases also had extrahepatic disease. Further analysis showed that patients with EHD had a poor short-term survival when compared with those without extrahepatic disease, 83% dying within 5 months. Moreover, the authors evaluated the response rate, that was 57% of patients for stable EHD prior to receiving Y-90 microspheres. In these patients, although the live disease improved or remained stable after SIR-Spheres treatment, there was progression of extrahepatic disease, in particular of lung metastases. Patients with EHD did badly when compared with those without extrahepatic involvement, indicating SIRT had no impact on EHD or disease progression. SIRT should be considered for patients with advanced liver cancer. It had a significant effect on RILD in the absence of EHD (Jiao et al., 2007; Szyszko et al., 2007) Sharma et al. 2007 designed a phase I study to assess the efficacy of SIRT using Y-90 resin microspheres with concomitant FOLFOX chemotherapy in patients with mCRC. The study design was an open-label, nonrandomized phase I clinical trial with escalation of the oxaliplatin dose administered for the first three cycles. Partial responses were demonstrated in 18 patients and stable disease in two patients. One patient had a complete response in liver metastases and a partial response in lung metastases. Patients suffering from CRC liver metastases, the median time to progression was 6.5 months ([3-20] months). Response was assessed by tumour-markers and CT imaging. According to CT imaging, progressive liver disease was detected in 24% of patients 2–4 months after SIRT. Stable disease or partial response was noted in 14 patients. Progressive liver disease was detected in only 17% of patients 5–8 months after SIRT. The remaining 10 patients showed stable disease or partial response. 20% of patients reported progressive disease 9–10 months after SIRT. According to tumour markers, 18% of patients presented with serum CEA levels higher than pre-treatment levels 2–4 months after SIRT. At 5–7 months after treatment 33% of patients presented with elevated tumour markers compared with those data
acquired prior to treatment. By 8–9 months, serum CEA levels were higher than pre-treatment levels in 5 (50%) of 10 patients. In 1, 3 and 3 patients 2–4, 5–7 and 8–9 months after SIRT an increase of tumour marker levels was associated with an extrahepatic tumour progression. SIRT was a promising, liver-targeted approach for patients with otherwise treatment-refractory liver tumours (Jakobs et al., 2007).

A study by Boppudi et al. (2006) was undertaken in 54 patients to evaluate CT changes after SIRT for advanced CRC and to compare these with tumour marker (CEA) changes to determine how best to assess whether a response has occurred. CT scans were carried out before treatment and at 3-monthly intervals thereafter. At the time of writing, 51 of the 54 patients had died between 1.25 and 51.7 months (median 14.1 month) after SIRT. Three patients remain alive between 40.3 and 73.3 months after SIRT. Median life expectancy after SIRT was 15.6 months. The study compared the CEA changes to determine how best to assess whether a response has occurred. In particular, serum CEA level was increased above normal in 92.5% of patients before SIRT while after SIRT it was observed a median reduction of 89% within 2 months. 70% of patients had a reduction of 75% or more in CEA levels within 2 months (CEA responders), and 30% had a reduction of less than 75% in CEA levels within 2 months (CEA non-responders). Progressive disease indicated by a progressive increase in tumour size on CT scanning was always associated with a progressive rise in CEA levels (Boppudi et al., 2006).

The study by Stubbs et al. (2006) assessed the response rate of SIRT in the management of 100 patients with extensive colorectal liver metastases. Although the reductions in tumour size on CT scanning were not generally as impressive as the CEA falls, progressive liver disease was seen in only 5 of 79 patients (6.3 %) after 3 months and in only 14 of 65 patients (21.5%) after 6 months. Treatment-related morbidity occurred in 11 patients: morbidity resulting from the SIRT occurred in 7 (8%) of those who received treatment through a portacath and 4 (31%) of those who were treated through a femoral catheter. Four people died in the first 6 weeks post-SIRT, 6 more died by 3 months post-SIRT and a total of 25 died by 6 months post-SIRT.

Van Hazel et al (2004) conducted a randomized trial to compare the response rate and time to progressive disease of a regimen of systemic fluorouracil/leucovorin chemotherapy versus the same chemotherapy plus a single administration of SIR-Spheres in patients with advanced colorectal liver metastases. Twenty-one patients with previously untreated advanced colorectal liver metastases, with or without extrahepatic metastases, were randomized into the study: 5-fluorouracil 425 mg/m2/day plus leucovorin 20 mg/m2/day (FU/LV) for 5 consecutive days and repeated at 4 weekly intervals versus the same chemotherapy plus a single administration of SIR-Spheres that was administered on the 3rd or 4th day of the second cycle of chemotherapy. In the study, it was observed that there was one
treatment related death in the combined treatment group (SIR-Spheres plus Fluorouracil/Leucovorin Chemotherapy). This patient received four cycles of chemotherapy and experienced chemotherapy induced neutropenia with each cycle despite progressive chemotherapy dose reductions. On the fourth occasion, he rapidly deteriorated and died from sepsis associated with the neutropenia. So, the one treatment related death in this study was due to the chemotherapy rather than the SIRT. Patients treated with the combination of SIR-Spheres plus chemotherapy had a median survival of 29.4 months compared to 12.8 months for patients treated with chemotherapy alone (p=0.025). Moreover, in this study, the response rate was evaluated using RECIST criteria. Although several patients in the chemotherapy arm showed some diminution in tumour size with treatment, no patient qualified for a response. No complete responses were recorded in either group. The response rate for 11 patients receiving the combination treatment was significantly greater than for 10 patients receiving chemotherapy alone (First Integrated Response; 10 PR, 1 SD vs. 0 PR, 6 SD, 4 PD, P<0.001 and Best Confirmed Response; 8 PR, 3 SD vs. 0 PR, 6 SD, 4 PD P<0.001). The time to progressive disease was significantly longer for patients treated with the combination of SIRT plus chemotherapy (18.6 months vs 3.6 months). This trial demonstrated that the addition of a single administration of SIR-Spheres to a regimen of systemic fluorouracil/leucovorin chemotherapy significantly increased both treatment related response, time to progressive disease, and survival (Van Hazel et al, 2004).

The retrospective study by Dhabuwala et al. (2005) aimed to determine whether the pattern of uptake of 99mTc-MAA after arterial injection, by colorectal liver metastases was predictive of tumour response after SIRT. 58 patients with colorectal hepatic metastases received SIRT. Uptake was classified as "hot" in 37 patients (Group 1) and "equivocal" or "cold" in 21 (Group 2). The authors analysed the response rates in these groups and the survival. The response rate was higher in tumour regression compared with stable disease and progressive disease. The first group reported a greater number of patients in three states of disease compared with the other group. Median survival from diagnosis of liver metastases for all patients is 14.1 months ([1.9-91.4]) and from treatment is 11 months ([1.0–50.2]). For Group 1 the median survival from diagnosis of liver metastases is 16 months ([1.9-91.4]) while for Group 2 was 14.1 months ([5.4-75.8]). In Group 1 median survival time from treatment is 11 months ([1.0-48.5]) while for Group 2 it was 12.3 months ([1.9-50.2]) (Dhabuwala et al., 2005).

Retrospective series and a few early trials demonstrated improved response rates (as high as 44%) and time to disease progression in the liver (15.9 months) in patients treated with Y-90 resin microspheres in combination with intrahepatic chemotherapy as compared to microspheres alone. Clinical trials combining systemic chemotherapy with SIRT demonstrated overall response rates of 48% to
63% but resulted in a greater incidence of myelosuppression (Pwint et al, 2010). The response rate to SIRT was sufficiently high to make it likely that the treatment will have some useful impact on the management and survival of patients with this disease (Stubbs et al, 2004). SIRT represented an effective means of controlling liver metastases from colorectal adenocarcinoma. Clinical trials have demonstrated improved local control of disease and survival with relatively low toxicity (Welsh et al, 2006).

4.1.1. **Treatment-related mortality.**

Some studies reported the number of deaths after SIRT with Y-90 microspheres. In three papers some patients died 30 days after the procedure. Two patients died within 30 days of SIRT (Moir et al., 2015), 1.9% of younger patients and 2% of the elderly died after 30 days (Kennedy et al., 2016) and 12 people died in the study by Kennedy et al. (2015). In Cosimelli et al. (2010) one patient died 40 days after treatment from acute renal failure and another responding patient died 60 days after treatment due to liver failure. In Kennedy et al. (2016), mortality rate did not differ significantly between younger patients (<70 years) and elderly patients (≥ 70 years) on day 60 (10 [6.3%] vs 27 [6.1%]), or day 90 after the procedure (29 [18.1%] vs 56 [12.6%]). 37 patients (6.1%) and 14% (85 patients) died 60 and 90 days after the procedure, respectively (Kennedy et al., 2015).
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Intervention and Comparator</th>
<th>Treatment Line</th>
<th>Type of study</th>
<th>Nr of patients</th>
<th>Follow up</th>
<th>Outcome</th>
<th>Quality of studies</th>
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</table>
| Maleux   | 2016 | Y-90 resin microspheres      | Second or further treatment line | Retrospective study        | 71 patients    | 6 and 12 months  | • Median time to progression in the liver was 4.4 months  
  • Estimated survival at six and 12 months was 65% and 30%, respectively, with a 50% estimated survival after 8.0 months in this group of chemorefractory patients. | Moderate/low      |
| Jakobs   | 2016 | Radioembolization with Y-90 resin microspheres | Second or further treatment line | Retrospective observational study | 104 patients | Until death | • The results showed median OS of 10.2 months  
  • If patients had a complete response to prior chemotherapy, survival was 23 months while if they had a partial response or stable disease, it was 13 months | Moderate/low      |
| Van Hazel| 2016 | Modified FOLFOX (mFOLFOX6) plus SIRT (SIRT) plus or minus bevacizumab vs mFOLFOX6 | First line | RCT | 530 patients | Until death or for a maximum of 5 years | • The addition of SIRT to chemotherapy demonstrated a similar median PFS at any site compared with control group (10.7 months vs 10.2 months)  
  • At any site, also ORRs were similar (76.4% vs 68.1%) | High/moderate     |
| Kennedy  | 2016 | Y-90 resin microspheres      | Either first or further treatment line | Retrospective study | 606 (160 elderly ≥ 70 years and 446 younger < 70 years) | NA | OS was similar between elderly and younger patients: (9.3 months (95% confidence interval [CI], 8.0-12.1) and 9.7 months (95% CI, 9.0-11.4) (P = .335)) | Moderate          |
| Damm R   | 2016 | Radioembolization with SIRT  | Second line                     | Retrospective observational study | 106 patients | 6 months (median value) | • The median OS was 6.7 months after the first radioembolization  
  • The median PFS was 3.5 months | Moderate/low      |
<p>| Schon    | 2015 | SIRT                         | Second or further treatment line | International, multicentre, and | 100 patients, 30 of whom received SIRT | NA | Median survival was 29.3 (0.9 e 71.0) months, 39.4 (19.3 e 69.4) months and 11.5 (1.6-nr) months post-surgery in | NA                |</p>
<table>
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<tr>
<th>Authors</th>
<th>Procedure</th>
<th>Treatment Line</th>
<th>Study Design</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Moir 2015</td>
<td>SIRT</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>44 patients</td>
<td>10 months (median value)</td>
<td>• 31 patients reported radiological response while 17 biological response response. • Median OS was 292 days</td>
</tr>
<tr>
<td>Sofocleous 2015</td>
<td>Radioembolization (RE) using Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>53 patients</td>
<td>30 days and 90 days</td>
<td>• RECIST had stable disease • PERCIST led to reclassification in 77% of these cases • No deaths were noted within the first 30 days. • Within the first 90 days after radioembolization, 4 patients (8%) have developed liver failure and 5 patients (9%) died, all with evidence of disease progression.</td>
</tr>
<tr>
<td>Henry 2015</td>
<td>Radioembolization (RE)</td>
<td>First or further treatment line</td>
<td>Retrospective study</td>
<td>106 patients</td>
<td>NA</td>
<td>The operations occurred at a median of 115 (56-245) days after RE and included right lobectomy (n=5), left lobectomy (n=1), left-lateral sectionectomy (n=1), and bilobar wedge resections (n=2).</td>
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<tr>
<td>Fendler 2015</td>
<td>SIRT in training set vs SIRT in validation set</td>
<td>Second or further treatment line</td>
<td>Retrospective observational study</td>
<td>125 patients</td>
<td>60 weeks (mean value for training set) and 54 weeks (mean value for validation set)</td>
<td>The mean OS was longer in the training cohort (60 weeks) compared with the validation cohort (54 weeks)</td>
</tr>
<tr>
<td>Golfieri 2015</td>
<td>Radioembolization with Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Prospective case series</td>
<td>52 patients</td>
<td>7 months (median value)</td>
<td>• Response rate resulted better after 3 months compared with that after 6 months (59% vs 28.6%) • Survival resulted equal to 11.0 months</td>
</tr>
<tr>
<td>Saxena 2014</td>
<td>Y-90 radioembolization</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>302 patients</td>
<td>7.2 months</td>
<td>• Complete response to treatment was observed in 2 patients (1%), partial response in 111 (38%), stable disease in 96 (33%), and progressive disease in 84 (29%).</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>First or further treatment</td>
<td>Study Type</td>
<td>Sample Size</td>
<td>Follow-up</td>
<td>Median OS</td>
</tr>
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</tr>
<tr>
<td>Kalva 2014</td>
<td>Y-90 radioembolization</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>45</td>
<td>NA</td>
<td>• The median survival was 186 days (95% CI, 149-277 d).</td>
</tr>
<tr>
<td>Cohen 2014</td>
<td>Capecitabine (375, 600, 750, 900 and 1000 mg/m2 b.i.d.) with the combination of radioembolization</td>
<td>Second or further treatment line</td>
<td>Prospective single-centre, phase I study</td>
<td>24 patients</td>
<td>6 months (median value)</td>
<td>• 70.8% of sample had stable disease, • The median time to progression and OS was 6.4 months and 8.1 months, respectively</td>
</tr>
<tr>
<td>Tohme 2014</td>
<td>Radioembolization</td>
<td>Either first or further treatment line</td>
<td>Retrospective study</td>
<td>107 (44 elderly (&gt;70) and 63 younger patients (&gt;70))</td>
<td>NA and 30 days</td>
<td>• Median OD between younger [8.4 months; CI, [6.2 10.6] or elderly patients (8.2 months; CI [5.9-10.5], P = 0.667).</td>
</tr>
<tr>
<td>Zarva 2014</td>
<td>Repeated radioembolizations</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>21 patients</td>
<td>10 months (range 5-38 months)</td>
<td>• Median OS was 18 months after first radioembolization</td>
</tr>
<tr>
<td>Sofocleou 2014</td>
<td>SIRT in 24 sessions</td>
<td>Second or further treatment line</td>
<td>Prospective single-centre phase I study</td>
<td>19 patients</td>
<td>31.2 months after SIRT (median duration, range 19-4.5 months)</td>
<td>• Median LPFS, PFS, and OS after SIRT were 5.2 months, 2.0 months, and 14.9 months, respectively</td>
</tr>
<tr>
<td>Fendler 2013</td>
<td>SIRT</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>80 patients</td>
<td>3 months</td>
<td>• Overall median survival after SIRT was 60 wk</td>
</tr>
<tr>
<td>Soydal 2013</td>
<td>Y-90 resin microspheres</td>
<td>First or further treatment line</td>
<td>Ongoing study</td>
<td>38 patients</td>
<td>The mean follow-up period for the remaining 35 patients was 18.3±60.3 months (range: 3-38 months) after SIRT</td>
<td>• Mean OS time was 12.7 ± 8.0 months</td>
</tr>
<tr>
<td>Author</td>
<td>Treatment</td>
<td>Treatment Line</td>
<td>Study Type</td>
<td>Study Size</td>
<td>Biomarkers and Response Details</td>
<td>Risk Level</td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Melucci 2013</td>
<td>Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>50 patients</td>
<td>Biomarkers expression and response to 90Y-RE therapy, liver metastases biopsies were taken 8–21 days prior to 90Y-RE and 2 months post-90Y-RE. In 13 matched patients, 5 presented biomarker variations pre- and post-90Y-RE therapy and 8 no biomarker variations.</td>
<td>Moderate/Low</td>
</tr>
<tr>
<td>Fahmueller 2012</td>
<td>SIRT</td>
<td>Second or further treatment line</td>
<td>Cohort study</td>
<td>49 patients</td>
<td>3 months after therapy. Pretherapeutical levels of CYFRA 21-1, CEA, cancer antigen 19-9 (CA 19-9), asparate-aminotransferase (AST) and lactate dehydrogenase (LDH) as well as 24 hours values of nucleosomes were significantly higher in patients suffering from disease progression (N = 35) than in non-progressive patients (N = 14). Concerning overall survival, CEA, CA 19-9, CYFRA 21-1, CRP, LDH, AST, choline esterase (CHE), gamma-glutamyl-transferase, alkaline phosphatase, and amylase (all 0 h, 24 h) and nucleosomes (24 h) were found to be prognostic relevant markers in univariate analyses.</td>
<td>Moderate/Low</td>
</tr>
<tr>
<td>Martin 2012</td>
<td>Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>34 patients</td>
<td>Median PFS and OS were 3.9 months (95% CI, 2.4-4.8 months) and 8.9 months (95% CI, 4.2-16.7 months). Five patients had a CEA response. Median PFS and OS were 3.9 months (95% CI, 2.4-4.8 months) and 8.9 months (95% CI, 4.2-16.7 months).</td>
<td>Low</td>
</tr>
<tr>
<td>Bester 2012</td>
<td>Y-90 resin microspheres</td>
<td>Second or further treatment line</td>
<td>Comparative retrospective study</td>
<td>232 patients</td>
<td>Follow-up at after the treatment, 1 and 3 months. The median OS after the first treatment with 90Y microsphere radioembolization was 12.0 months (95% CI, 10.7-14.5 mo).</td>
<td>Moderate/Low</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Treatment Line</td>
<td>Study Type</td>
<td>Patients</td>
<td>Follow-Up</td>
<td>Key Findings</td>
</tr>
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</tbody>
</table>
| Leoni 2012 | Y-90 microspheres radioembolization | Second or further treatment line | Retrospective study | 51 patients | 1, 3, 6 months | • Median survival after RE was 8.5 months (1-64 months).  
• Response rate of target lesions was 53% at 1 month, 41% at 3 months, 29% at 6 months and 36% at 9-12 months. |
| Seidensticker 2012 | Y-90 resin microspheres | Second or further treatment line | Comparative matched-pair retrospective study | 29 patients both groups | After the treatment | • Compared with BSC alone, radioembolization prolonged survival (median, 8.3 vs. 3.5 months; P<0.001 with a hazard ratio of 0.3 (95% [0.16–0.55]; P<0.001) |
| Gulec 2011 | Y-90 microspheres radioembolization | NA | Prospective, phase II clinical trial | 20 patients | Median follow-up of 16.5 months (range 2–27.7 months) | • The median survival in the study group was 14.8 months (range 2.0–27.7 months) |
| Hendlisz 2010 | Radioembolization with 90Y-resin microspheres plus FU vs FU alone | Second or further treatment line | Open-label, randomize, phase III clinical trial | 44 patients | Median follow-up was 24.8 months | • Median TTLP was 2.1 and 5.5 months in arms A and B, respectively  
• Median time to tumour progression (TTP) was 2.1 and 4.5 months, respectively  
• Median OS was 7.3 and 10.0 months in arms A and B, respectively |
| Dudeck 2010 | SIRT | Second or further treatment line | Prospective trial | 21 patients | 6 weeks after SIRT (follow-up MRI; mean 45.4±11.5 days) | • DWI was capable of predicting therapy effects of SIRT in patients with colorectal hepatic metastases as early as 2 days following treatment |
| Cosimelli 2010 | Radioembolization with 90Y microspheres | Second or further treatment line | Prospective, multi-centre phase II trial | 50 patients | 11 months (median value) | • Treatment response resulted independent of performance status, number of metastases, metastases size, liver involvement, previous anti-angiogenic agents or previous resection  
• The median PFS was 3.7 months  
• Median OS was 12.6 months |
<p>| van Hazel 2009 | Irinotecan in combination with radioembolization | Second or further treatment line | Phase I, dose-escalation study | 25 patients | Based on duration of cycles | • Eleven (48%) of 23 patients had a partial response, and nine patients (39%) had stable disease |</p>
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Treatment</th>
<th>Line of Treatment</th>
<th>Study Type</th>
<th>Study Parameters</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cianni 2009</td>
<td>Radioembolization with Y-90</td>
<td>Second or further treatment line</td>
<td>Retrospective observational study</td>
<td>44 patients</td>
<td>8 weeks</td>
<td>The median progression-free survival was 6.0 months, The median survival was 12.2 months</td>
</tr>
<tr>
<td>Campbell 2009</td>
<td>Treatments Y-90 SIRTs</td>
<td>Second or further treatment line</td>
<td>Retrospective study</td>
<td>12</td>
<td>Approximately 3 months after 90Y microsphere therapy</td>
<td>41.5% of patients reported a partial response and 36.2% stable disease, The median survival was 354 days, The median PFS was 279 days</td>
</tr>
<tr>
<td>Flamen 2008</td>
<td>SIRT combined with 5FU</td>
<td>NA</td>
<td>Phase III clinical research trial</td>
<td>8</td>
<td>End of cycles</td>
<td>The tumor dose calculated with the patient-specific method was more predictive of response in liver-directed 90Y</td>
</tr>
<tr>
<td>Gulec 2007</td>
<td>Y-90 resin microspheres</td>
<td>NA</td>
<td>Retrospective observational study</td>
<td>40 patients</td>
<td>19 weeks (mean value)</td>
<td>Tumor response rate was 100% for patients with neuroendocrine tumours compared with lower value of CRC and HCC (47% and 80%, respectively)</td>
</tr>
<tr>
<td>Jiao 2007</td>
<td>SIRT with Y-90 microspheres</td>
<td>Second or further treatment line</td>
<td>Clinical trial</td>
<td>21</td>
<td>Clinical and biochemical assessment with tumour markers was performed at 6 weeks together with follow-up imaging with CT and PET at 6-8 weeks after therapy</td>
<td>57% of patients had stable EHD prior to receiving their SIR-Spheres</td>
</tr>
<tr>
<td>Szyszko 2007</td>
<td>Value of FDG PET in assessing the response to SIRT as compared to CT</td>
<td>Second or further treatment line</td>
<td>Clinical trial</td>
<td>21</td>
<td>Follow-up was done with FDG PET and CT at 6 weeks, and 6-monthly thereafter</td>
<td>The survival curve would favour the non-colorectal liver metastases due to the fact that 50% of patients with colorectal liver metastases also had extrahepatic disease</td>
</tr>
<tr>
<td>Author</td>
<td>Procedure</td>
<td>Line of Treatment</td>
<td>Study Design</td>
<td>Duration</td>
<td>Follow-up Interval</td>
<td>Outcomes</td>
</tr>
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</tbody>
</table>
| Sharma 2007     | Radioembolization with Y-90 resin microspheres | First line             | Open-label, nonrandomized phase I clinical trial | 20 patients with metastatic CRC | Until death | • Median PFS was 9.3 months, and median time to progression in the liver was 12.3 months  
• Partial responses were demonstrated in 18 patients and stable disease in two patients | Moderate/low  |
| Jakobs 2007     | SIRT with Y-90 microspheres | Second or further treatment line | Clinical trial | 39 | Follow-up every 2–3 months after SIRT | • The median survival for the MBC (breast-cancer metastases) group and the mixed group (other cancers) is 3.7 and 2.2 months, respectively | Moderate/low  |
| Boppudi 2006    | SIRT                    | NA                | Evaluation study | 54 | Every 3 months | • Median life expectancy after SIRT was 15.6 months | Low           |
| Stubbs RS, 2006 | SIRT with Y-90 resin microspheres | First line             | Clinical trial | 100 | 12 months | • Only 5 of 80 patients (6.25%) scanned at 3 months showed disease progression  
• Survival was significantly more in those who experienced a good tumour marker response and in those who were slow to develop extrahepatic disease | Intermediate/low |
| Van Hazel 2004  | SIRT Fluorouracil/Leucovorin Chemotherapy Vs Fluorouracil/Leucovorin Chemotherapy Alone | First line             | Randomized Phase 2 Trial | 21 | Every 3 months | • Median survival was significantly longer for patients receiving the combination treatment (29.4 months vs 12.8 months) | High / Moderate |
| Dhabuwala 2005  | SIRT                    | NA                | Retrospective study | 58 patients | 11.6 months (range 1 – 50.2) | • Median survival from diagnosis of liver metastases for all patients is 14.1 months and from treatment is 11 months (range 1.0 –50.2) | Moderate/low  |
Table 4.2: Reviews about efficacy outcomes of the use of Y-90 resin microspheres

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of Studies included</th>
<th>Intervention and Comparator</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raval 2014</td>
<td>14</td>
<td>SIRT with Y-90 microsphere alone or in combination with chemotherapy</td>
<td>Response rate, PFR and overall survival</td>
<td>Y-90 therapy in combination with first line chemotherapy may improve tumor response rates</td>
</tr>
<tr>
<td>Hipps 2013</td>
<td>19</td>
<td>SIRT</td>
<td>Response to radioembolisation</td>
<td>The most common modality to assess response to radioembolisation was a CT scan performed at 3 months after treatment. Response rates varied across the studies and also depended on the criteria used to judge response. Although PET-CT has been shown to have limitations in detecting small metastases, this review suggests that PET-CT is a more sensitive modality.</td>
</tr>
<tr>
<td>Rosenbaum 2013</td>
<td>26</td>
<td>Y-90 resin microspheres as monotherapy and Y-90 resin microspheres combined with chemotherapy</td>
<td>Progression-free survival and tumor response rates</td>
<td>For Y-90 radioembolization as monotherapy, tumor response rates were reported in 10 studies with a total of 545 patients. Response rates (defined as complete response and partial response) ranged from 18% to 46%. Disease control rates (i.e., complete response, partial response, and stable disease) ranged from 29% to 90%. Progression-free survival was reported in 6 studies and ranged from 3.9 to 9.2 mo. For 90Y radioembolization treatment combined with chemotherapy, responses were reported in 11 studies with a total of 388 patients. Response rates ranged from 8% to 90%.</td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Malignancy Type</td>
<td>Procedure Description</td>
<td>Outcomes</td>
</tr>
<tr>
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</tr>
<tr>
<td>2014</td>
<td>Sexena</td>
<td>CRCLM</td>
<td>Y-90 radioembolization of unresectable CRCLM refractory to systemic therapy</td>
<td>Radiological response, overall survival and progression-free survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The average reported value of patients with complete radiological response, partial response and stable disease was 0 % (range 0–6 %), 31 % (range 0–73 %) and 40.5 % (range 17–76 %), respectively. The median time to intra-hepatic progression was 9 months (range 6–16). The median overall survival was 12 months (range 8.3–36).</td>
</tr>
<tr>
<td>2010</td>
<td>Pwint</td>
<td>ND</td>
<td>Regional Hepatic Chemotherapies: portal venous infusion (PVI) of 5-fluorouracil (5-FU), intra-arterial chemotherapy HAI, chemoembolization, and SIRT</td>
<td>Survival rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Regional therapy may have a role in combination with systemic chemotherapy, in patients with metastatic disease, However, further larger randomized trials with modern systemic chemotherapy regimens will be needed to anchor HAI therapy more firmly in the therapeutic mainstream for CRC.</td>
</tr>
<tr>
<td>2010</td>
<td>Ahmadzadehfa</td>
<td>ND</td>
<td>SIRT</td>
<td>Response to treatment</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Treatment refractory tumors will frequently respond to this potent therapeutic modality due to the extraordinary local radiation doses achieved.</td>
</tr>
<tr>
<td>2009</td>
<td>Vente MAD</td>
<td>30</td>
<td>Radioembolization with Y-90 microspheres alone or in combination with chemotherapy</td>
<td>Response rate and survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In mCRC, 90Y-RE delivers high response rates, especially if used neoadjuvant to chemotherapy. In HCC, 90Y-RE with resin microspheres is significantly more effective than 90Y-RE with glass microspheres</td>
</tr>
<tr>
<td>2006</td>
<td>Welsh JS</td>
<td>ND</td>
<td>SIRT</td>
<td>Survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinical trials have demonstrated improved local control of disease and survival.</td>
</tr>
</tbody>
</table>
4.2. Change in management

The studies addressing the impact of SIRT on hospitalizations, reported a short length of stay for patients undergoing SIRT. Soydal et al. (2013) observed 35 patients who received SIRT treatment for unresectable liver metastases CRC in hospital setting. There was no case of hospitalization after an overnight stay, and all the patients were managed by their family physicians at home with symptomatic relief including antiemetics, H2 antagonists, and nonsteroid analgesics after radioembolization (Soydal et al. 2013). Another 7 studies, reported that patients undergoing SIRT stayed overnight and were discharged the day after SIRT (Kennedy et al., 2016, Kennedy et al., 2015; Hendlisz A et al., 2010; Van Hazel et al., 2009; Sharma et al., 2007; Garrean et al., 2007; Van Hazel et al., 2004).

Only 3 studies reported a length of stay of 2 or more days after SIRT (Stubbs et al., 2016; Dudeck et al., 2010; Pini et al., 2010).

Box 4.1 summarizes experts’ opinion on the change in patients’ management introduced by the use of SIRT in the Italian context.

**Box 4.1. Changes in management introduced by SIRT according to experts’ opinion.**

**Change in management.**

Compared to standard chemotherapy or best supportive care, the use of SIRT introduces important changes in patient management. Indeed, according to the experts’ panel, a more systematic introduction of SIRT in clinical practice would allow a better management of patients.

After the work-up phase, which is usually performed in inpatient setting with a mean length of stay of two nights, SIRT is typically administered in one or, rarely, two hospital admissions with a length of stay >1 day per hospital admission. Thus, compared to chemotherapy, which is usually performed in day hospital, the length of stay increases at least of five days. Patients usually stay overnight in nuclear medicine or in Interventional radiology ward. However, standard chemotherapy usually requires 8-10 admissions. Moreover, the good tolerability of SIRT, would avoid the hospitalizations relating to the management of side effects usually associated with conventional chemotherapy.
4.3. Function

Only a few studies investigate the impact of SIRT on patients’ Quality of life (QoL). Welsh et al. (2006) reported that, in a pivotal study including 74 patients with mCRC, there was no difference in quality of life for patients receiving SIR-Spheres in comparison to patients receiving hepatic artery chemotherapy alone ($p = 0.96$, for difference, when QoL was assessed by patients and $p=0.98$ when QoL was assessed by physicians).

Comparing Y-90 resin microspheres plus Fluorouracil/Leucovorin chemotherapy versus Fluorouracil/Leucovorin chemotherapy alone in advanced CRC patients, van Hazel et al. (2004) found no difference in quality-of-life over a 3-month period between the two treatments when rated by patients or physicians. The number of quality of life assessments in the chemotherapy only arm diminished after 3 months due to disease progression. Changes in the quality of life were almost identical in both arms. This was also the case for physician rated quality of life. This lack of variation was mainly due to the fact that most patients were still receiving chemotherapy during this 3-month period. The quality of life of patients is not compromised in the short term by the addition of SIRT (van Hazel et al., 2004). In a more recent study, the same authors concluded that the combination of an oral form of irinotecan in combination with SIRT could potentially improve patient’s quality of life (Hazel et al., 2009).

In their review, Cosimelli et al. (2012), found that patients’ mean HADs scored ‘8’ for anxiety and ‘9’ for depression, indicating borderline pre-treatment levels of anxiety and depression. Six weeks after radioembolisation, patients’ anxiety levels were significantly reduced ($p<0.01$); with no significant change in depression score (Cosimelli et al., 2012).
5. Organizational Aspects

5.1. Health delivery process

5.1.1. Procedure and workflow

Description of SIRT procedure
A patient being considered for SIRT will be admitted for a workup procedure before the treatment (Lewandowski et al., 2009). The pre-treatment workup consists of the following steps:

1. Angiography:
   • identify the hepatic vasculature feeding the tumour(s) to ensure that the blood supply to the tumour(s) is suitable for highly selective injection;
   • identify hepatic vascular connections to the Gastro Intestinal (GI) tract to ensure that these are sufficiently small to avoid radiation pneumonitis or radiation gastritis.

2. Injection of macro aggregated albumin labelled with Technetium-99m (99mTc-MAA): this is a diagnostic injection predicting the distribution of microspheres. Since there are limits to the exposure of lungs to shunted microspheres, a 99mTc-MAA study demonstrates the degree of hepatopulmonary shunting and the connections between liver vascularization and gastro intestinal tract that could result in delivery of radiation to non-target tissue.

3. Single SPECT scan using a gamma camera:
   • demonstrate the degree of lung shunting;
   • confirm avoidance of GI tract shunting;
   • map the deposition of MAA in target lesions and confirm the degree to which healthy tissue will be spared by radiation.

4. Review of SPECT scan:
   • calculate the lung shunt and confirm that it is below the acceptable threshold;
   • determine if SIRT is the appropriate treatment option;
   • establish the appropriate dose for the patient.

If SIRT is confirmed as the appropriate treatment option, the treatment date is defined. This allows precise calibration of delivered radioactivity dose.
Under local anesthesia patients are injected with radioactive microspheres, that are designed to embolise into small vessels around the metastases, usually via a transfemoral catheter into the branches of the hepatic artery. The target areas can be defined using Technetium-99m micro aggregated albumin ($^{99m}$Tc MAA) planar nuclear scan, CT or $^{99m}$Tc MAA SPECT. Angiographic mapping of the hepatic vascular tree can define the liver and tumour partitions further before radioembolization, including the extra hepatic connections and tumour vessels (Lau WY et al., 2012). The workup can be performed in outpatient setting. The administration of SIRT using Y-90 resin microspheres is predominately performed in a single session. Box 5.1. provides further detail on set up of SIR-Spheres Y-90 resin microspheres.
Box 5.1. Set up of SIR-Spheres Y-90 resin microspheres.

### Delivery box set up for SIR-Spheres Y-90 resin microspheres

The delivery box contains mainly 4 different drips and a glass box. Once opened, the operator should remove the sterile delivery set from package and maintain in a field that ensures sterile fluid pathway at a minimum. At the beginning of the process, the operator should not remove the needle sheets from the two needles in order to help preserve needles sterility. This delivery set should be assembled in close proximity to the patient and placed on an elevated surface at the patient’s side. Before assembling the delivery set, the operator should check that all the components, especially the lock connections lines are tight. Each line is identified by a color-coded tag with an associated letter to ensure correct placement in the glass box provided. A stopcock can be used to facilitate the device assembly. The risk of erroneous assembly is mitigated by the instructions and colour-tagged signs. The holes where the drips pass through are colour-tagged and marked with letters (A, B, C, D) as well. Moreover, there is also a control knob to fix the three-way stopcock and to control the liquid flow. Furthermore, on the “B” and “D” lines there are one-way valves fitted to prevent any possibility of SIR-Spheres microspheres refluxing into either of the syringes.

The delivery box contains also a retaining ring which can contain the SIR-Spheres vial. Once placed the vial, the operator should remove the cap from the top of the vial holder, discard the swab in a designated waste container as it may be contaminated. The vial septum must be swabbed and the sides of the hole in the top of the vial holder with an alcohol wipe. The alcohol swab should be discarded in a designated waste container as it may be contaminated as well. Now, the needles can be inserted into the septum of the vial, care must be taken when inserting needles not to contaminate them. If contamination occurs, the delivery set must be discarded and a new one needs to be used. The first cover to remove is from the “C” needle. Once removed, the C-line needle must be inserted through the centre of the septum aiming at the base of the vial, being careful not to scrape the vial side walls until it penetrates approximately ten millimetres below the surface of the water in the vial. The operator should make sure that the distance between any puncture holes in the vial is at least two millimetres. The microspheres that are delivered to the patient must be decanted from the top of the vial so the suspension remains diluted and does not obstruct the catheter. At this point, the D-line needle can be removed and inserted through the septum. Any puncture holes in the vial must be at least two millimetres apart. The needle must be pushed deep into the vial until the point of the needle rests at the base of the vial. It is important that this needle goes to the bottom of the vial so when the water is injected it will swirl the microspheres into a thin suspension. Finally, place the lid into the delivery box. At this point, the delivery set is ready for administration of the Y-90 microspheres. When it is fully assembled, injecting water in the recommended pulsing motion from the syringe on line D will cause the microspheres to swirl into a suspension pass into line C and then into lane A that is connected to the patient.
**Treatment Planning**

Therapy planning includes definition of the target volume for the treatment and assuring the safety of the procedure. The combination of morphological imaging (CT and MRI) with functional imaging, preferably obtained using combined imaging modalities (PET/CT, SPECT/CT), provides the most reliable information for determining which parts of the liver need to be treated. Depending on the distribution of the liver malignancies, either right, left, or both liver lobes should be treated. Figure 5.1 depicts the preferred treatment planning, according to the distribution of liver malignancies.

**Dose calculation and adjustment**

There are 2 methods for prescribed activity determination (Ahmadzadehfar et al., 2010):

1. “Body Surface Area Method”, which consists of adjusting the activity implanted according to the size of the tumour within the liver and the size of the patient. Method is recommended for patients having concurrent systemic chemotherapy or for particularly small patients.

2. The partition method involves implanting the highest possible activity to the tumour while maintaining radiation dose to sensitive tissues, such as the lung and the normal liver. This model relies on accurate information relating to the degree of lung shunting, liver mass, tumour mass, and tissue/normal ratio (T/N) ratio. Measurements needed are the volume of tumour and normal liver determined from a CT scan and the proportion of Tc-MAA activity that lodges in the tumour, normal liver, and lung.

The activity prescribed can be reduced if the hepatic function is compromised. There are no accepted guidelines as to how much the activity should be reduced, if a patient’s liver function or estimated reserve is only good enough to be a candidate. Generally, more experienced users reduce the dose by 30% for patients with poorer liver function, but who are still candidates for this approach according to established eligibility criteria. The amount of Y-90 should also be reduced according to the dose adjustment of lung shunt if the percentage lung shunting is greater than 10% (Ahmadzadehfar et al., 2010).

Dhabuwala et al. (2005), performed a retrospective study aimed at determining whether the pattern of uptake of 99mTc-MAA after arterial injection, by colorectal liver metastases was predictive of tumour response after SIRT. 58 patients with

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5 Further detail on dose calculation adjustment can be found on the Sirtex training materials (http://foxfireglobal.sirtex.com/sites/foxfireglobal.sirtex.com/files/user/trn-rw-04_for_eu-au_nz_and_asia.pdf) and Ahmadzadehfar et al., 2010.
colorectal hepatic metastases received SIRT. From the assessment of these patients, authors concluded that if the adverse effects of anorexia and lethargy relate to the damage of normal liver tissue, as seemed possible, then a smaller dose of SIR-spheres® might be better tolerated without compromising anti-tumour efficacy (Dhabuwala et al., 2005).

Assessment of treatment response
Soydal et al., 2013 aimed to evaluate tumour response using FDG PET/CT in patients who received SIRT with Y-90 resin microspheres for colorectal liver metastases. Thirty-five patients received SIRT treatment for unresectable CRC liver metastases in hospital setting. Response was evaluated according to the change in total lesion glycolysis (ΔTLG). The mean ΔTLG was 43±35 ([0 100]). An 18F-FDG PET/CT scan with calculation of ΔTLG before and at the sixth week after SIRT might play an important role in evaluating early tumour response and survival expectancy in these patients and helped decide whether these patients should be referred to other treatment modalities or to follow-up.

5.1.2. Education and training of the staff
Patients eligible to receive SIRT should be referred to a centre with specific training and considerable experience in the various technologies for the treatment of liver metastases and safe delivery of the radioactive microspheres (Harris et al., 2009). SIRT must be provided by professionals who have received appropriate education and training (Jacobs et al., 2007; Welsh et al., 2006). In particular, it is strongly recommended that all interventional radiologists who contemplate adopting SIRT should consult a clinical mentor experienced in the technique. The initial instruction should ideally take place at centres of excellence compliant with guidelines prepared by appropriate professional bodies (Wang et al., 2010).

At the moment of implementation, education is provided free of charge by the manufacturer. Box 5.2. briefly describes the structure of the training manual provided by Sirtex.

Box 5.2. Description of the training manual.

<table>
<thead>
<tr>
<th>The training manual</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Sirtex training manual provides all the necessary information about the correct utilization of the technology. It is divided in seven different sections. The first three sections contain general recommendations and indications for use (structure, functions and calibration). Moreover, there is an overview of the regulatory aspects (Australia, EU and USA), and information relative to technical and scientific features like warnings, precautions, contraindications, possibility of adverse events (post-operative or delayed serious events) and other considerations. Section four offers a brief summary about the hepatic vascular anatomy and on dealing with abnormalities. The following parts are more focused on technical aspects. First, there is a section providing information</td>
</tr>
</tbody>
</table>
on the dose preparation procedure and the dose calibration. Furthermore, this section provides also a step-by-step example. Second, more technical data regarding the prescribed activity calculation for the right lobe treatment are provided, pointing out either the BSA method (body surface area) in order to calculate the prescribed activity or the cases where it is necessary a reduction in the standard dose. In fact, quoting the manual, “several authors have identified a number of: 1) tumour characteristics; and 2) risk factors for the development of radio embolization induced liver disease (REILD) that may necessitate a reduction in the prescribed activity of SIR-Spheres microspheres from that determined using the BSA method”. After the information about the implant of the sir-spheres, the manual focuses on the radiation, listing data about the regulation, facility requirements, physical requirement and other aspects like, shielding, equipment and check lists. Additionally, the last two sections provide evidence on radiation safety either with SIRT or radiation safety with the patient. Moreover, a section dedicated to deal with contamination is specified. Finally, appendices are provided with other valuable information. Specifically, the appendices include: 1) radiation dosimetry and effects; 2) estimated effective dose; 3) patient documentation; 4) radiation and training requirements checklist; 5) radiation exposure during dose preparation; 6) radiation exposure for staff implanting the device; 7) implantation room set-up; 8) partition model for prescribed activity calculation.

Thus, to summarize, the aim of this manual is to provide data on: requirements for personnel and facilities, product clinical properties and use of the device, including patient selection and dosimetry; calculation and preparation of individual radiation doses, implant procedures, potential post-op reactions and suggested management, radiation safety product ordering. All the sections are accompanied by explanatory tables or figures; moreover, more materials for physicians or institution are available on the Sirtex website. The company is also focused on the pharmacovigilance procedure, providing an efficient reporting system.

5.2. Process-related Costs

5.2.1. Processes related cost to purchasing and setting up the technology

Equipment needed

All SIRT procedures must be performed by an expert radiologist, under aseptic conditions in an interventional radiology/ theatre setting (Moir et al., 2015). In order to be able to perform SIRT, a Hospital Centre must fulfil the following conditions (Chiarolla et al., 2014):

1. Presence of a tumour board to discuss patients with CRC liver metastases;
2. Presence of a nuclear Medicine Unit with license to store and dispose of Yttrium-90 and a hot lab to prepare the activity;
3. Presence of a planar gamma camera and/or SPECT-CT to perform the Technetium-99m labelled MAA scan after the pre-treatment work-up procedure and the Bremsstrahlung scan after SIRT administration;
4. Presence of interventional radiology suite, equipped with an angiography, also licensed to use Yttrium-90 within interventional procedures;
5. Presence of a license for authorized users to administer Yttrium-90 microspheres;
6. Presence of a medical Physics Unit with facility to perform Yttrium-90 dosimetric calculations and manage radiation protection before, during and after the procedure.

However, the organizational and technological requirements listed above are, generally, already owned by hospitals for performing other procedures, thus they do not represent a specific investment in order to perform SIRT.

**Human resources needed**

According to ESMO guidelines (2016), clinical decisions upon the treatment of mCRC should be discussed within a multidisciplinary team. An ideal multidisciplinary team should include access to both a colorectal surgeon and a specialist hepatobiliary and/or, liver surgeon as necessary, with the obligatory inclusion of a pathologist and a diagnostic radiologist, as well as radiation and medical oncologists. An interventional radiologist/nuclear physician may also be included as appropriate, as the role of ablative treatments gains increasing importance (van Cutsem et al., 2016).

In terms of human resources and skills needed to perform the procedure, many studies state that SIRT must be performed by a multidisciplinary team, and report on the composition of the team in the clinical practice (Paprottka et al., 2011; Ahmadzadehfaret al., 2010; Wang et al., 2010; Nicolay et al., 2009).

Table 5.1 reports the composition, the aim of multidisciplinary teams performing SIRT in different settings, as well as authors suggestions on the means of coordination among professionals.

<table>
<thead>
<tr>
<th>First Author, year</th>
<th>Setting</th>
<th>Composition</th>
<th>Aim</th>
<th>Coordination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paprottka 2011</td>
<td>Germany</td>
<td>Radiation oncologists, nuclear medicine physicians, interventional radiologists, medical oncologists, surgeons, and hepatologists</td>
<td>Define patient’s eligibility for SIRT</td>
<td>Collegial assessment of the patient</td>
</tr>
<tr>
<td>Ahmadzadehfaret 2010;</td>
<td>Germany</td>
<td>Not reported</td>
<td>Clinical evaluation, imaging, pre-treatment angiogram, and treatment simulation with Tc-99m, therapy, and follow-up.</td>
<td>Treatment form</td>
</tr>
</tbody>
</table>
At least three of: hepatic surgeon, medical oncologist, radiation oncologist, nuclear medicine physician, pain physician or anaesthetist, gastroenterologist/hepatologist, medical physicist/radiation safety officer. Dedicated oncology nursing staff.

Planning, delivering and reviewing cancer treatment, or upon referral from a multidisciplinary team familiar with the procedure.

**Table 5.2 Professionals involved in providing SIRT. Sources: authors’ elaboration from Chiarolla et al., 2014.**

<table>
<thead>
<tr>
<th>Professional</th>
<th>Work up</th>
<th>SIRT procedure</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Involved</td>
<td>Median time (mins)</td>
<td>Involved</td>
</tr>
<tr>
<td>Oncologist</td>
<td>YES</td>
<td>45 [20-60]</td>
<td>NO</td>
</tr>
<tr>
<td>Interventional Radiologist</td>
<td>YES</td>
<td>60 [30-120]</td>
<td>YES</td>
</tr>
<tr>
<td>Medical Physicist</td>
<td>YES</td>
<td>45 [5-90]</td>
<td>YES</td>
</tr>
<tr>
<td>Nurse</td>
<td>YES</td>
<td>60 [30-180]</td>
<td>YES</td>
</tr>
<tr>
<td>Radiology Technician</td>
<td>YES</td>
<td>60 [45-120]</td>
<td>YES</td>
</tr>
<tr>
<td>Radiologist</td>
<td>NO</td>
<td>-</td>
<td>NO</td>
</tr>
</tbody>
</table>

5.2.2. **Budget impact**

Age.Na.S performed a budget impact analysis, using data coming from a survey involving 19 Italian centres performing SIRT. When possible, cost drivers were identified based on experts’ answers to the survey and multiplied for unitary costs; otherwise tariffs where considered as proxy of costs.
During 2012 the number of patients that received SIRT was 25 (and 35 procedures). We calculated the total cost of the SIRT procedure adding the costs of diagnostic work-up, treatment and follow up. The median cost is 15,229 Euros ranging from 13,582 to 17,370 Euros. The costs of an individual dose of SIR-Spheres Y-90 resin microspheres is €12,000. Total cost of the SIRT treatment in 2012 is 533,015 Euros (35 procedures) (Chiarolla et al., 2014).

The cost reimbursed by the Regional Health Services for SIRT is remarkably below the actual cost of the device and the procedure. In the light of the ever-stringent budget constraint, this mismatch represents an obstacle to a wide access to this procedure.

Lombardy is, so far, the only Italian region providing reimbursement, beside DRG 409 for radioembolization, with an additional fee to be applied in case of use of Y-90 microspheres implantation in patients with Hepatocellular carcinoma.

However, the acknowledgement of a supplemental fee for the purchase of the device, as well as the chance of setting some kind of producer-purchaser agreements based on volumes and the homogenisation of the purchase procedures emerged as possible steps towards a more equitable access to this technology in the advisory board meeting.

### 5.3. Management

This section investigates the opportunities and barriers relating to the introduction of SIRT in the clinical practice. Statements reported here mainly arose from the consultation of the experts’ advisory board involved in this project. Table 5.3, reports opportunities and barriers as emerged from the discussion.

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The technology is well accepted by professionals.</td>
<td>• Need of identifying reference centres.</td>
</tr>
<tr>
<td>• There is clinical evidence supporting the technology</td>
<td>• Lack of a specific DRG tariff covering the cost of the procedure.</td>
</tr>
<tr>
<td>• Patient’s follow up is easier and less costly than chemotherapy.</td>
<td>• Presence of budget caps, defined by national law, for the purchase of MD.</td>
</tr>
<tr>
<td>• May be better accepted by patients, for not requiring infusion and not being associated with typical side effects of chemotherapy</td>
<td>• Need of reliable scales to access the expected benefit of treatment.</td>
</tr>
</tbody>
</table>
5.4. Culture

5.4.1. *How is the technology accepted?*

The advisory board meeting provided interesting insights on the acceptability of the technology from the professionals. As a matter of fact, clinicians involved in the advisory board expressed great trust in the potentialities of this technology, and consider it as a good treatment option even as a first line treatment. Also, clinicians expressed the wish to be able to rely soon also on robust evidence concerning the OS of patients receiving SIRT.

Furthermore, according to the experts’ panel, a more systematic introduction of SIRT in clinical practice would allow a better management of patients resulting in less hospital admissions (SIRT is typically administered in one or, rarely, two hospital admissions after the work up phase) and in the avoidance of side effects usually related to conventional chemotherapy. While from the patients’ perspective these improvements may result in better quality of life, from the payers’ perspective this could dramatically change the structure of direct healthcare costs.

Concerning the acceptability of the technology to the patients, in their review, Cosimelli et al. (2012), found that patients were satisfied with healthcare providers’ interpersonal and technical skills as well as the information provided on the treatment. Patients showed a good compliance to physicians’ advice (mean score of 8 on a visual analogue scale where ‘0’ is a low and ‘10’ is a high compliance score) (Cosimelli et al., 2012).
6. Costs and economic evaluation

6.1. Resource utilization

General costs associated with the management of the target condition

MCRC is characterized by a significant economic burden. A study conducted in the US examined health care costs and utilization by initial CRC stage at diagnosis and the number of lines of treatment received by patients with mCRC, starting by a large insurance administrative database. A total of 598 patients were included. At initial diagnosis, 91 patients had stages 0 to III CRC, 310 patients had stage IV CRC, and 197 patients had an unknown stage of CRC. The mean unadjusted total cost per patient (medical + pharmaceutical costs) was $252,200; outpatient hospital visits (excluding radiation and surgery) contributed most to the total cost, at a mean cost of $71,334. Hospitalization costs, with or without surgery (mean, $56,862), accounted for 33% of the $176,135 unadjusted mean cost for medical services (ambulatory visits, emergency department visits, laboratory/radiology services, and inpatient admission). Chemotherapy and biologics were also costly (mean, $31,112 and $38,276, respectively). A general linear model analysis of estimated 4-year total costs showed that both CRC stage at diagnosis and the number of lines of treatment after metastasis had a statistically significant association with cost (P<0.001). Variables that had a statistically significant association with cost (P<0.05) were sex, age group, and follow-up Charlson Comorbidity Index score after metastases (Chastek et al., 2013).

Another study from the US revealed that the annual cost for patients with mCRC in the follow-up period averaged $97,031 more for mCRC cases than for controls. The main cost drivers for mCRC were hospitalizations ($37,369) and specialist visits ($34,582), which included chemotherapy administration (Paramore et al., 2006).

A large Finnish cost-of-illness study highlighted a similar cost pattern along the disease progression. The total costs for the cross-sectional six-month period were €22,200 in the primary treatment state, €2,106 in the rehabilitation state, €2,812 in the remission state, €20,540 in the metastatic state, and €21,146 in the palliative state. Most of the costs were direct medical costs. The informal care cost was highest per patient in the palliative care state, amounting to 33% of the total costs. The productivity costs varied between disease states, constituting 19-40% of the total costs, and were highest in the primary treatment state (Färkkilä et al., 2015).
Terminal metastatic CRC patients are those consuming the highest amount of healthcare resources. Mittmann et al. (2014) estimated that patients approaching death received an average of 8 home care visits at Canadian $800 within a 30-day time horizon. Home care costs were highest in the month before death. Male sex, a history of moderate or high utilization of health care services, and hospitalization were associated with lower home care costs. Overall, patients with advanced CRC who were approaching death were found to require a moderate level of home care support, resulting in costs of about $5,000 over the 6-month time horizon (Mittmann et al., 2014).

**Private costs and productivity losses**

Using regression methods, Hanly et al. (2013) only focused on costs beared by patients and their families within the Irish setting. In the diagnosis and treatment phase, weekly informal care costs per person were reported in the table below.

<table>
<thead>
<tr>
<th>Table 6.1. Regression results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly informal care costs per person</strong></td>
</tr>
<tr>
<td><strong>Hospital based costs</strong></td>
</tr>
<tr>
<td><strong>Domestic-based time costs</strong></td>
</tr>
<tr>
<td><strong>Domestic-based Out-of-Pocket (OOP) costs</strong></td>
</tr>
<tr>
<td><strong>Ongoing costs included domestic-based time costs</strong></td>
</tr>
<tr>
<td><strong>Domestic-based OOP costs</strong></td>
</tr>
</tbody>
</table>

The approximate average first year informal care cost was €29,842, of which 85% was time costs, 13% OOP costs and 2% travel costs. Significant cost predictors included carer age, disease stage, and survivor age (Hanly et al., 2013).

**Costs of the technology**

The only study investigating the cost-effectiveness of SIRT using Y-90 resin microspheres compared to supportive care in the perspective of the Italian NHS was published by Cosimell et al. in 2013. Further detail on the study is provided in the cost-effectiveness section below. Concerning the identification, measurement and valorization of resources taken into account for the cost-effectiveness analysis, authors only considered direct healthcare costs, and in particular: costs for treatment acquisition, pre-treatment work-up and delivery of microspheres, and chemotherapy received in addition to, instead of, or after, SIRT. In addition, costs of
managing adverse events (AEs) and a cost of death were included. Costs were
obtained from a University Hospital in Bologna, the Italian Agency of Medicines
(AIFA), and the literature. Although this study could provide interesting estimates
of the overall cost of the technology within the Italian context, so far it is only
available as a poster, and from incremental values it is not possible to extrapolate
the overall per patient annual cost.

### 6.2. Measurement and estimation of outcomes

Health-Related Quality of Life (HRQOL) is measured as part on the ongoing SIR-
Spheres clinical trial programme. These data will allow for a more comprehensive
assessment of the impact of SIR-Spheres on HRQL of patients with liver-dominant
mCRC. Early analyses from the SIRFLOX trial suggest that the most important
determinant of HRQL (measured by EuroQoL five dimensions questionnaire (EQ-
5D)) in patients with liver-dominant mCRC is the progression status of the disease
and the efficiency of the healthcare setting (Schon et al., 2015).

### 6.3. Examination of costs and outcomes: cost-effectiveness

Pennington et al., compared Y 90-resin microspheres compared to best supportive
care (BSC) in patients with inoperable liver-dominant chemotherapy-refractory
mCRC from a UK perspective. Survival data from a comparative retrospective
cohort study was analysed and used in a state-transition cost-effectiveness model,
using quality-adjusted life years (QALYs) gained as the measure of effectiveness.
The model incorporated costs for the SIRT procedure, monitoring, further
treatment, adverse events, and death. Utility values, reflecting patient quality-of-
life, were taken from a published source. SIRT using Y90 resin microspheres
compared to BSC improved OS by a mean of 1.12 life years and resulted in a cost per
QALY gained of £28,216. In sensitivity analysis, this varied between £25,015-£28,817
(Pennington et al, 2015).

Using the same model structure, Taieb et al. (2015) assessed the cost-effectiveness
of SIRT with SIR-Spheres 90Y resin microspheres compared to best supportive care
(BSC) from the perspective of the national health service in France. The model
included costs for treatment acquisition, pre-treatment work-up and delivery of
microspheres, and chemotherapy. Additionally, costs of managing adverse events
and a cost of death were included. Utility data were taken from a recent NICE
economic evaluation in mCRC. A wide range of sensitivity analyses were performed
on utility, OS and costs. The one-way sensitivity analysis varied each parameter
between its lower and upper bound and investigated the effect on the cost per
QALY. The probabilistic analysis simultaneously sampled each parameter from its
appropriate distribution (beta for utilities, normal for costs and multivariate normal for survival curve parameters) for 1,000 simulations and investigated the uncertainty around the cost per QALY. The scenario analysis explored alternative parametric curves for overall survival, alternative sources for utility values and alternative assumptions for the proportion of time spent in the pre- and post-progression health states. The results have demonstrated that the use of 90Y-resin microspheres is a cost-effective option in the treatment of patients with chemotherapy-refractory liver-dominant mCRC in France (Taieb et al, 2015).

Cosimelli et al. (2013) have investigated the use of Y-90 resin microspheres to treat liver metastases resulting from CRC. A retrospective cohort study found a survival advantage from SIRT compared to standard care in chemotherapy-refractory patients. This study was used in combination with other sources to model the cost-effectiveness of SIRT vs BSC in this indication. A state-transition model was developed, with three health states, based on survival outcomes from a retrospective cohort study in chemotherapy refractory mCRC comparing yttrium-90 resin microspheres vs. BSC. The model was developed from the perspective of the National Health Service in Italy. The model included costs for treatment acquisition, pre-treatment work-up and delivery of microspheres, and chemotherapy received in addition to, instead of, or after, SIRT. In addition, costs of managing AEs and a cost of death were included. Costs were obtained from the University Hospital in Bologna, the AIFA, and the literature. Utility data was not available from the study, so was taken from a recent NICE economic evaluation in the same indication. SIRT increased survival resulting in a life-year gain of 1.35 (2.12 vs 0.98) life years and a QALY gain of 0.83 (1.52 vs 0.70). The costs of SIRT, monitoring and further treatment were greater in the SIRT arm with partial cost-offset through a reduction in adverse events. Overall, SIRT lead to an increase in costs of €24,626 (€39,973 vs €15,347), resulting in a cost/QALY of €29,850. Probabilistic sensitivity analysis showed a 97% chance of SIRT being cost-effective at a threshold of €50,000/QALY. The authors concluded that the analysis demonstrates that SIRT using Y 90 resin microspheres has the potential of being a cost-effective option in the treatment of patients with chemotherapy-refractory liver metastases resulting from CRC.

6.4. Heterogeneity
Available economic evaluations did not investigate the effects of heterogeneity on the cost effectiveness of SIRT.
<table>
<thead>
<tr>
<th>Author Year</th>
<th>Intervention and Comparator</th>
<th>Type of study</th>
<th>Type of analysis</th>
<th>Study perspective/Country</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penninington 2015</td>
<td>SIR-Spheres Y-90 resin microspheres vs BSC</td>
<td>Model-based economic evaluation.</td>
<td>Cost-utility</td>
<td>Third Party Payor / UK</td>
<td>The cost per QALY gained was £28,216. In sensitivity analysis, this varied between £25,015-£28,817. In an area of large unmet need, treatment with (90)Y-resin microspheres offers a clinically effective and cost-effective treatment option.</td>
</tr>
<tr>
<td>Taieb 2015</td>
<td>SIR-Spheres Y-90 resin microspheres vs BSC</td>
<td>Model-based economic evaluation.</td>
<td>Cost-utility</td>
<td>Third Party Payor / France</td>
<td>The cost per QALY was €30,610. The results have demonstrated that the use of 90Y-resin microspheres is a cost-effective option in the treatment of patients with chemotherapy-refractory liver-dominant mCRC in France.</td>
</tr>
<tr>
<td>Cosimelli 2013</td>
<td>Resin microspheres of Y-90 associated with chemotherapy vs best supportive care (BSC)</td>
<td>Model-based economic evaluation.</td>
<td>Cost-utility</td>
<td>Third Party Payor / Italy</td>
<td>SIRT lead to an increase in costs of €24,626 (€39,973 vs €15,347), resulting in a cost/QALY of €29,850. Probabilistic sensitivity analysis showed a 97% chance of SIRT being cost-effective at a threshold of €50,000/QALY.</td>
</tr>
</tbody>
</table>
7. Ethical Aspects

7.1. Beneficence/Non maleficence

The new ESMO guidelines, recommend SIRT using Y-90 resin microspheres as a third line treatment for chemorefractory and chemo intolerant patients with liver metastases from primary colorectal cancer (van Cutsem et al., 2016). For patients, being able to undergo SIRT means having a further chance of surviving cancer. Cosimelli et al. (2010) in their study measured patients QoL before SIRT and 6 weeks after treatment. They administrated cancer and site-specific questionnaires to 14 patients (out of 50 patients who were included in the study). The interpersonal and technical skills of healthcare operators and the information they provided on treatment were evaluated and the authors state they were judged positively by patients (European Organisation for Research and Treatment of Cancer questionnaire on satisfaction of cancer inpatients (EORTC IN–PATSAT 32)). Compliance was good (mean 8 out of a 10-point scale, were 10 is the maximum score). Anxiety and depression levels before treatment were borderline, but anxiety decreased significantly after 6 weeks, while the depression score did not change. According to the authors the results show good overall QoL with SIRT (Cosimelli et al., 2010).

7.2. Autonomy

Treatment options for mCRC patients are limited and for this reason, these patients can be considered particularly vulnerable; this population is defined by Pennington et al. (2015) as having a large unmet need (Pennington et al., 2015). For this reason, a realistic information about “strengths” and “weaknesses” of the technology in object is required for making the patient able to adequately consent to the therapy. As underlined by Chiarolla et al. (2014), this point is relevant from the ethical point of view with particular reference to patients’ expectations and hopes, also considering that these persons are human subjects at a very vulnerable time in their lives. Nevertheless, patients’ attitude toward this treatment is usually positive and its side effects are regarded as tolerable (Chiarolla et al., 2014).
7.3. Justice and equity

The relatively high cost of the technology, however considered cost-effective, along with the lack of a specific reimbursement within the Italian NHS, could be perceived as an obstacle to patients’ equal access to care.

Box 7.1. summarises experts’ opinion on the obstacles to patients’ equal access to SIRT.

**Box 7.1. Experts’ opinion on the obstacles to patients’ equal access to SIRT.**

The obstacles to patients’ equal access to SIRT

The presence of budgetary caps to the purchase of medical devices within public hospitals is perceived as an obstacle to equal access to this technology for patients in need. In particular, only hospitals can decide to assign a specific share of their medical devices (MDs) budget to this technology and the imbalance between supply and demand may impede patient access to the technology.

Finally, other aspects with potential ethical and social relevance emerged during the advisory board discussion. Those aspects are listed in Box 7.2.

**Box 7.2. Potential ethical issues emerging from the advisory board discussion.**

**Further ethical issues**

- Since this is a third line treatment, there is an issue with cross over in clinical studies.
- The disease imposes high indirect and intangible costs to patients and their family (Hanly et al., 2013).
- Patients should be adequately informed when undertaking this treatment.
- In order to safeguard safety and quality of care, the treatment should be delivered only in centres adequately experienced and equipped; however, these “centralization” choices should be adequately justified to patients.

Finally, effectiveness/safety and HRQoL profiles are potentially positive from a beneficience/non maleficence point of view. Further and robust evidence concerning the OS of patients receiving SIRT is required. On the other hand, an adequate and realistic information should be provided to the patient.

Regarding justice issues, we have to consider organizational and economic issues. About the first ones, (cf. also p. 91 of the report) “according to the experts’ panel, a more systematic introduction of SIRT in clinical practice would allow a better management of patients resulting in less hospital admissions […] while from the patients’ perspective these improvements may result in better quality of life, from
the payers’ perspective this could dramatically change the structure of direct healthcare costs”.

About economic issues, the relatively high cost of the technology can represent an obstacle to patients’ equal access to care. Despite first data suggesting a positive cost-effectiveness (CEA) profile, further robust evidence is required on the incremental cost-effectiveness ratio (ICER) of the technology is required, as well as specific reimbursement within the Italian National Health Service (NHS). Once economical sustainability is ascertained, organizational requirements (and sustainability) for an effective delivery of the technology in the Italian regional context should also be assessed in an equity perspective.
References


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Flamen P, Vanderlinden B, Delatte P, Ghanem G, Ameye L, Van Den Eynde M, Hendliz A. Multimodality imaging can predict the metabolic response of unresectable


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### Appendix 1. Search strategy

<table>
<thead>
<tr>
<th>Database</th>
<th>Keywords/Search String</th>
<th>Filters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pubmed</strong></td>
<td>(((((&quot;trans arterial radio embolization&quot;) OR (((SIRT) OR TARE) OR Trans Arterial Radio embolization)) OR (((&quot;yttrium-90 resin microspheres&quot;) OR (&quot;Radiation Therapy&quot;) AND &quot;resin microspheres&quot;)))) OR (((&quot;Selective internal radiation therapy&quot;) AND &quot;yttrium-90 resin microspheres&quot;)) OR (((&quot;Yttrium&quot;[Mesh]) AND &quot;Microspheres&quot;[Mesh]) AND &quot;Radiotherapy&quot;[Mesh]))))))</td>
<td>Language: English, Italian; Field: Title/Abstract</td>
</tr>
<tr>
<td><strong>Scopus</strong></td>
<td>(((((&quot;trans arterial radio embolization&quot;) OR (((SIRT) OR TARE) OR Trans Arterial Radio embolization)) OR (((&quot;yttrium-90 resin microspheres&quot;) OR (&quot;Radiation Therapy&quot;) AND &quot;resin microspheres&quot;)))) OR (((&quot;Selective internal radiation therapy&quot;) AND &quot;yttrium-90 resin microspheres&quot;)) OR (((&quot;Yttrium&quot;[Mesh]) AND &quot;Microspheres&quot;[Mesh]) AND &quot;Radiotherapy&quot;[Mesh]))))))</td>
<td></td>
</tr>
<tr>
<td><strong>EBSCO, CRD, GIN</strong></td>
<td>Liver metast* AND (trans arterial radio embolization, SIRT, yttrium-90 resin microspheres).</td>
<td>N.A.</td>
</tr>
</tbody>
</table>
## Appendix 2. Framework of analysis

<table>
<thead>
<tr>
<th>Domain</th>
<th>Topic</th>
<th>Issue</th>
</tr>
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</table>
| Health Problem and Current Use of the Technology (CUR) | Target Population | What is the target population in this assessment? (<A0007>)
| | | How many people belong to the target population? (<A0023>)
| | Target Condition | What is the disease or health condition in the scope of this assessment? (<A0002>)
| | | What are the known risk factors for the disease or health condition? (<A0003>)
| | | What is the natural course of the disease or health condition? (<A0004>)
| | | What are the symptoms and the burden of disease or health condition for the patient? (<A0005>)
| | Current Management of the Condition | How is the disease or health condition currently managed according to published guidelines and in practice? (<A0025>)
| | Utilisation | For which health conditions and populations, and for what purposes is the technology used? (<A0001>)
| | | How much are the technologies utilised? (<A0011>)
| | | What kind of variations in use are there across countries/regions/setting? (<A0012>)
| Description and technical characteristics of technology (TEC) | Features of the technology | What is this technology and the comparator(s)? (<B0001>)
| | | What is the claimed benefit of the technology in relation to the comparators? (<B0002>)
| | Regulatory Status | For which indications has the technology received marketing authorisation or CE marking? (<A0020>)
| | | What is the reimbursement status of the technology? (<A0021>)
| Safety (SAF) | Patient's safety | How safe is the technology in relation to the comparator(s)? (<C0008>)
| | | How does the frequency or severity of harms change over time or in different settings? (<C0004>)
| | Safety risk management | Can different organizational settings increase or decrease harms? (<C0061>)
| | | How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)? (<C0062>)
| Efficacy (EFF) | Mortality | What is the expected beneficial effect of the technology on mortality? (<D0001>)
| | Morbidity | How does the technology affect progression (or recurrence) of the disease or health condition? (<D0006>)
| | Change-in management | How does use of the test change physicians’ management decisions? (<D0021>)
| | | How does the technology modify the need for hospitalization? (<D0010>)
| | Function | What is the effect of the technology on return to previous living conditions? (<D0015>)
| Organisational | Health delivery process | How does the technology affect the current work
| aspects (ORG) | Process-related costs | Management | Culture | Costs and economic evaluation (ECO) | Resource utilization | Measurement and estimation of outcomes | Examination of costs and outcomes | Characterising heterogeneity | Ethical aspects |
|--------------|-----------------------|------------|---------|-----------------------------------|----------------------|----------------------------------------|--------------------------------|----------------------------|----------------|}
| processes? (G0001) | What are the processes related to purchasing and setting up the new technology? (G0006) | What management problems and opportunities are attached to the technology? (G0008) | How is the technology accepted? (G0010) | What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)? (E0001) | What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)? (E0002) | What is(are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)? (E0005) | What are the estimated differences in costs and outcomes between the technology and its comparator(s)? (E0006) | To what extent can differences in costs, outcomes, or ‘cost effectiveness’ be explained by variations between any subgroups using the technology and its comparator(s)? (E0011) | Beneficence/nonmaleficence |}
|             | What are the likely budget impacts of implementing the technologies being compared? (G0007) |  |  |  |  |  |  |  | Autonomy | Is the technology used for patients/people that are especially vulnerable? (F0005) | Does the implementation or use of the technology affect the patient’s capability and possibility to exercise autonomy? (F0004) | Is there a need for any specific interventions or supportive actions concerning information in order to respect patient autonomy when the technology is used? (F0006) | Justice and Equity | How does implementation or withdrawal of the technology affect the distribution of health care resources? (F0012) | Are there factors that could prevent a group or person from gaining access to the technology? (H0012) |
## Appendix 3. Topics discussed by the advisory board

<table>
<thead>
<tr>
<th>Domain</th>
<th>Topics for discussion</th>
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</table>
| CUR    | 1. Are there any drugs used in Italy for mCRC? What peculiarities? Size of consumption?  
2. What is the impact of mCRC on hospitalization rates in Italy?  
3. What is the diffusion of TACE and external radiotherapy in Italy?  
4. What is the potential place in therapy for SIRT?  
5. Among patients with mCRC what percentage should be treated with SIRT?  
6. What are the likely cross regional differences in terms of diffusion and access? |
| SAF    | 1. How are side effects from SIRT managed?  
2. Apart from staff training, what other organizational feature can affect patients’ safety?  
3. Is there the necessity of any specific monitoring system? If so at what institutional level?  
4. How different treatment planning strategies can affect patients’ safety? And what about dose splitting? |
| EFF    | 1. What is the potential effect of SIRT on the disease symptoms?  
2. What are the chances for patients to return to their normal life?  
3. How does the patient’s pathway change with the introduction of SIRT?  
4. What is the impact of SIRT on the hospitalization rates?  
5. How does the patient’s autonomy change? |
| ORG    | 1. What are the facilitators and barriers to implementation?  
2. How is the technology accepted by healthcare professionals?  
3. What communication with the patient is needed?  
4. Beside the doctor, what other professional are involved in delivering SIRT?  
5. What is the follow up after patients’ discharge?  
6. How does the patient flow change with SIRT?  
7. What are the pros and cons of different treatment planning strategies?  
8. What are the users’ legal and cultural barriers? |
| ECO    | 1. How to compute the treatment costs?  
2. What role for societal costs?  
3. How can cost-effectiveness change across different patients’ sub-populations? |
| ETH    | 1. What is the impact of SIRT on patient’s autonomy?  
2. Are there particular questions concerning information and communication?  
3. Are there potential obstacles to uniform access?  
4. Are there potential cultural barriers on the patient side?  
5. The alternative is a palliative treatment strategy. Does this arise ethical issues? |