^{90}Y-microsphere radioembolization: The method, clinical evidence and perspective

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Abstract
The current review unfolds the procedural steps and the clinical evidence for yttrium-90 (^{90}Y)-microspheres radioembolization. Radioembolization is part of the loco-regional therapeutic spectrum for liver malignancy and involves the invasive, intra-arterial delivery of microspheres carrying β-emitter isotopes in order to destroy cancerous tissue via ionizing radiation. The main steps of the therapeutic process are selection of eligible patients, angiographic workup, simulation scintigraphy, pre-treatment dosimetry, actual treatment and post-treatment imaging/dosimetry. Radioembolization is routinely applied in advanced stage hepatocellular carcinoma (HCC), yet its role is being investigated even in earlier stages. Prospective, randomized controlled trials did not verify increased overall survival of radioembolization over systemic treatment with sorafenib in HCC; however, it showed survival benefit in certain sub-groups and a favorable toxicity profile with fewer adverse events. Radioembolization is also applied in metastatic colon cancer showing tumoral liver responses, which however did not translate into an overall survival benefit. Data regarding applications of this method in other neoplasms, such as neuroendocrine tumors, breast cancer and melanoma are also presented. There are ongoing clinical trials to define the role of radioembolization within recent treatments algorithms, to determine optimal combinations of this treatment with systemic and targeted therapies and to decide the patients' sub-groups, who will benefit the most.

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Introduction

Radioembolization (selective internal radiation therapy-SIRT, or transarterial radioembolization-TARE) belongs to the therapeutic armamentarium for the loco-regional treatment (LRT) of liver malignancy either primary or metastatic. The LRT spectrum comprises ablative and intra-arterial treatment modalities, such as radio-frequency or micro-wave ablation (RFA or MWA), trans-arterial or chemo-embolization (TAE or TACE) and drug eluting bead-TACE (DEB-TACE). Recently, stereotactic body radiation therapy (SBRT) emerges as another effective alternative, whereas brachytherapy is less frequently applied.

During the last decade, SIRT exhibited a boom with ongoing and already published randomized clinical trials (RCT), continuous improvements in equipment and methodological aspects and development of new efficacious agents. The origin of SIRT dates back to the 50s. After the first pioneering efforts, it was nearly abandoned owing to the increased incidence of adverse events and lack of commercial interest; however it regained widespread clinical utility over the last two decades [1]. The pathophysiologic basis of SIRT lies to the preferential blood supply of liver malignancies by the hepatic artery, whereas normal liver parenchyma is mainly perfused by portal vein branches (nearly 70%), allowing for intra-arterial therapies to specifically target tumors while sparing normal parenchyma. Selective internal radiation therapy involves the selective, intra-arterial delivery of microspheres carrying β-emitter isotopes in order to eradicate cancerous tissue via ionizing radiation. Various agents have been applied, with different combinations of carriers and isotopes, such as phosphorus-32 (^{32}P) microspheres (resin, colloid, glass), iodine-131 (^{131}I)-lipiodol or rhenium-188 (^{188}Re)-labelled molecules. Nowadays, two different types of ^{90}Y-labelled microspheres have prevailed in common clinical practice: the resin microspheres (SIR-Spheres®, Sirtex Medical Ltd, North Sydney, Australia) and the glass-spheres (Theraspheres®, BTG International, London, UK). Both have "European Con-formity" mark (CE mark) and "Food and Drug Administration" (FDA) approval. Specifically, resin microspheres acquired FDA approval for metastatic colorectal cancer (mCRC) liver disease, and glass spheres for hepatocellular carcinoma (HCC), respectively;

however, both agents are invariably used for any of the above indications. Clinical results either with resin or glass spheres seem comparable [2]. There are, nonetheless, differences in physical properties: each resin microsphere carries much lower amount of radioactive ^{90}Y, compared with glass-spheres [1]. As a result, a larger number of resin microspheres needs to be administered. Amongst other potential agents, ^{166}Ho-labelled, biocompatible poly-L-lactic acid (PLLA) microspheres show promising initial clinical results and have been granted CE mark, yet no FDA approval [1].

Radioembolization - The procedure

Selective internal radiation therapy is a stepwise procedure, with proper selection of eligible patients being the first, indispensable step for future treatment success. Selected patients suffer neoplastic liver disease, deemed to be inoperable due to either disease extent or serious concurrent comorbidities, such as inadequate cardiac or pulmonary functional reserve. Patients need to have acceptable Performance Status (grades 0-1) and life expectancy (>3 months) as well as adequate functional liver reserve (no ascites, serum bilirubin ≤2mg/dL, serum albumin ≥3g/dL) and blood count (WBC> 2.500/μL, PLT>60000-100000/μL). The aforementioned cut-offs are recommended to minimize the risk of radioembolization induced liver disease (REILD). Protocol (selective vs whole liver therapy) and dose modifications may be applied to reduce incidence of REILD in borderline patients, especially in cirrhotics [3].

After patient selection, pre-therapy angiographic work-up follows to evaluate the specific vessels "feeding" the tumor. This is an integral part of the whole procedure because of the many existing anatomic variants in liver and upper abdominal vasculature. Some vessels, like gastroduodenal artery (GDA), are embolized in order to prevent backflow of microspheres to the gut, while any tumoral parasitic perfusion is occluded, if possible. Angiographic planning determines the arterial branches via which actual therapy will be performed. Once this has been decided, technetium-99m-macroaggregated albumin (^{99m}Tc-MAA) is delivered intra-arterially keeping the catheter in the same decided position as in future therapy. This serves as an accurate simulation of final treatment. Afterwards, the patient is transferred to the Nuclear Medicine Department for scintigraphic image acquisition. ^{99m}Tc-MAA simulation scintigraphy is essential for three reasons: a) to evaluate and quantify Lung-Shunt (L-S) in order to minimize the risk of radiation induced pneumonitis, which may occur in doses >30Gy. To prevent this complication, the administered dose may be appropriately reduced, whereas if L-S exceeds 20%, treatment should be canceled. Calculation of L-S based on single photon emission computed tomography/computed tomography (SPECT/CT) may differ from planar imaging, which usually overestimates it [4] (Figure 1) b) to seek for inadvertent leak to other organs, not appreciated by angiography, yet may be a significant source of severe side-effects. Single photon emission computed tomography/CT has, significantly, increased the accuracy for leak identification [5] (Figure 2) c) to estimate other essential parameters for dosage calculation, such as the perfused liver area by the target artery and the tumor to normal liver ratio. Usually, pre-therapy work-up and final treatment take place 1-2 weeks apart, however in centers with adequate experience and increased patient flow, they may be performed during the same day, reducing health costs and patients' inconvenience [6, 7].

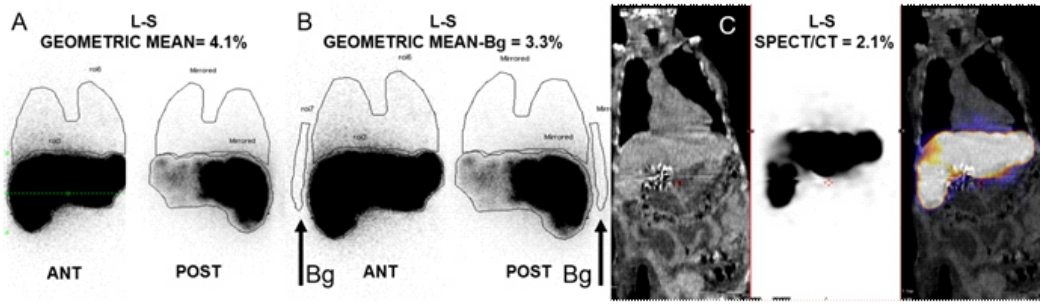

Figure 1. Estimation of Lung-Shunt (L-S) with planar and SPECT/CT imaging. Different values of L-S have been calculated, in the same patient, using planar imaging geometric mean (A), background corrected geometric mean (B) and SPECT /CT (C). In this case, different L-S values did not have clinical impact, however this does not apply as a general rule. Usually, planar imaging overestimates L-S.

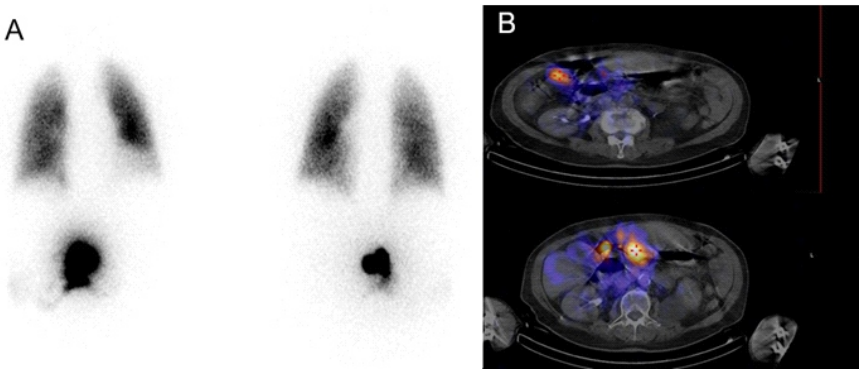

Figure 2. Significant Lung-Shunt precluding treatment. Planar images (A) of a patient with L-S>45%. The same patient had leak to the gut identified in SPECT/CT images (B) only. Single photon emission computed tomography/CT increases accuracy for leak identification.

The third step in SIRT is pre-treatment dosimetry, that is the calculation of the therapeutic dose to be administered. Tumoral dose is a pivotal factor for effective treatment response, whereas dose delivered to normal liver parenchyma determines treatment's tolerability. Unfortunately, prediction models for tumoral and liver doses are still imperfect. Technetium-99m-MAA distribution, on which pre-therapy dosimetry is based, is not identical with the actual distribution of therapeutic microspheres as verified by post treatment imaging (Figure 3). There have been efforts to overcome this discrepancy, including the development of sphere shaped ^{99m}Tc-MAA or starch-based microparticles labeled with positron emitters (like gallium-68 (^{68}Ga)) and the acquisition of scout doses of holmium-166 (^{166}Ho)-poly (L-lactic acid) microspheres [8]. Dose calculation methods are different for resin and glass spheres: in the former, an activity based empiric method based on body surface area is applied, whereas in the latter, a standardized dosimetric model largely based on uniformly absorbed dose to volume of perfused tissue within a fixed dose range is used [4]. Recently, a two-compartment partition model has been applied to provide accurate and personalized dosimetry. Single photon emission computed tomography/CT imaging is essential in this setting, since accurate estimations of perfusion area and tumor/liver ratio are requisites of this partition model.

Actual treatment follows the pre-therapy work-up and dosimetry. Hepatic angiography is performed with the catheter inserted in the predefined hepatic arterial branches, then the therapeutic agent is delivered via specifically designed apparatuses. Resin microspheres are administered with relatively slower rate, since a higher absolute number of microspheres is given compared with glass spheres. The procedure is performed under continuous angiographic assessment to evaluate for adverse backflow of microspheres, which could be the result of incidental sluggish blood flow. In highly experienced centers, SIRT may be performed as an outpatient procedure, with patients being discharged after few hours of hospital stay.

The final step is post-treatment dosimetry in order to estimate the doses delivered to the tumor and normal liver parenchyma. This is accomplished via post-treatment imaging of the actual distribution of the microspheres. Two methods are applied: a) SPECT/CT, using the Bremsstrahlung radiation produced by ^{90}Y, which is easier to perform, yet it yields less accurate results due to the nature of Bremsstrahlung radiation, b) PET/CT image acquisition, taking advantage of the internal positron production by ^{90}Y. This is limited by poor positron yield per decay (approximately 23/1,000,000 decays) requiring increased total acquisition time up to 40-45min. Regarding ^{166}Ho microspheres, post-therapy imaging may be performed either with SPECT/CT detecting γ-radiation emitted by holmium or with MRI making use of its paramagnetic properties.

For many years, evidence on SIRT was limited to observational and cohort studies of individual, dedicated centers with high expertise. This has changed, nowadays, with large-scale prospective studies and multi-center RCT evaluating the effectiveness and clinical utility of this modality in primary and metastatic liver cancer. The main evidence for SIRT is presented in the rest of the review, stratified by disease type.

Radioembolization - The evidence

Hepatocellular carcinoma (HCC)

Selective internal radiation therapy in HCC patients is continuously evolving and being applied with increasing frequency [9]. Initially, SIRT was performed in advanced stage patients (Barcelona Clinic Liver Cancer-BCLC stages B and C) failing TACE, prior to the initiation of Sorafenib treatment (Figure 4). Recently, with the advent of radiation lobectomy and segmentectomy, SIRT is applied at earlier stages competing with ablative treatment modalities (RFA, MWA) and TACE.

Liver transplantation (LT) is a viable treatment option in eligible stage A patients, who meet predefined criteria (Milan, etc.). These patients may need "bridging therapy" till LT to avoid interval disease progression, since time to final LT may be rather delayed. Usually, this is performed by applying abla-

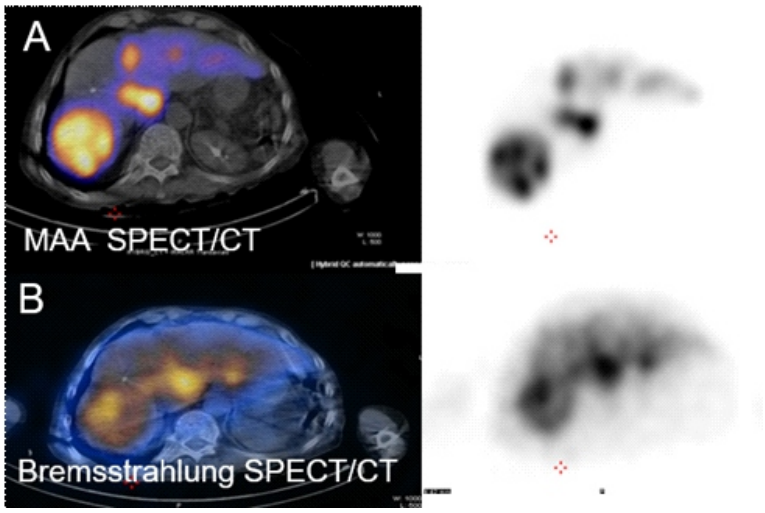

Figure 3. Pre-therapeutic and post-treatment imaging in a case of ^{90}Y-resin embolization. Actual distribution of ^{90}Y-resin microspheres (B) is not identical with ^{99m}Tc-MAA distribution (A).

tive modalities or TACE. Selective internal radiation therapy has recently been integrated in this setting showing encouraging results. In a recent study, complete pathologic responses in extracted livers post transplantation were higher after SIRT (75%) than after RFA (60%), TACE or SBRT [10]. In 172 post-transplantation patients, there was no significant survival difference between previous TACE or SIRT therapy, accounting for longer mean time to LT after SIRT compared with TACE (6.5 months vs 4.8 months, respectively) [11]. In phase II PREMIERE study, 45 out of 179 eligible patients were randomized to receive either SIRT or TACE with intent to LT. There was no survival difference up to LT (17.7 months for TACE, 18.6 months for SIRT), yet SIRT showed a decrease in transplantation drop list and a longer time to progression (TTP): 26 months vs 6 months for TACE [12]. The American Association for the Study of Liver Disease (AASLD) recommends that HCC patients, listed for LT, are treated with LRT to prevent tumor progression with no specific modality recommended over another as form of bridging therapy [13].

The concept of radiation lobectomy, targeting tumors in one liver lobe or more commonly serving as a bridge to surgical resection, was introduced in 2009 [14]. Some patients scheduled for hepatectomy, especially right lobectomy, undergo a bridging step towards resection, with prior portal vein embolization (PVE) in order to upsize future liver remnant (FLR). Portal vein embolization recanalizes blood flow to FLR (commonly the left lobe) so that it is adequately hypertrophied in order to support sufficient future liver function. Waiting for FLR hypertrophy after PVE, carries a risk of tumor progression, reported in 3%-38% of patients [15]. Alternatively to PVE, SIRT may be applied as radiation lobectomy, delivering eradicating doses to one liver lobe. Selective internal radiation therapy lobectomy has been shown to achieve contralateral lobe hypertrophy (average 21%-57%) in a relatively prolonged time interval (1-9 months) compared with PVE (nearly 1 month) [16]. Portal vein embolization attains higher volumes of FLR hypertrophy than SIRT [17], nonetheless a lower drop-out percentage is anticipated with SIRT, since the tumor itself is targeted within the therapeutic field of microspheres' distribution. In a systemic review, including 215 total patients, SIRT led to FLR hypertrophy ranging from 26% to 74% within time intervals of 1.5-9 months [18]. Beyond FLR hypertrophy, some authors consider radiation lobectomy as a "test of time" prior to surgery similar to the concept of neoadjuvant chemotherapy prior to surgical resection in other malignancies [15].

Another strategy, recently being used with increasing frequency, is SIRT segmentectomy with high doses directed to the liver segments, containing the tumor, like ablative techniques. Vouche et al. (2014) reported high median overall survival (OS) of 53.4 months in more than 100 patients, with a single lesion <5cm, who could not be treated with RFA [19]. In a recent study, 70 HCC patients, with tumors up to 5 cm not amenable to resection RF or LT, were treated with SIRT segmentectomy and followed for more than 10 years. Results were encouraging: median OS reached 6.7 years, while the majority (72%) of patients had no target lesion progression at 5 years. Results were better for smaller lesions <3cm with corresponding 5-year survival rate of 75% [20]. Retrospective comparison between SIRT and segmental TACE, in patients with single lesions <3cm, showed significantly higher tumor responses in SIRT vs TACE (92.1% vs 52.6%) and more favorable time to secondary therapy, yet there was no difference in OS [21]. The AASLD 2018 practice guidance states that LRT (TACE, RFA, TARE or SBRT) are recommended for BCLC stage A patients not amenable to resection or transplantation and does not favor any form of LRT over another, though evidence for TARE is still very weak [22].

Stage B patients are typically treated with TACE, yet SIRT is increasingly being applied and competes with TACE. The first randomized comparative study was the SIRTACE trial, which enrolled a small number of patients [23] and concluded that a

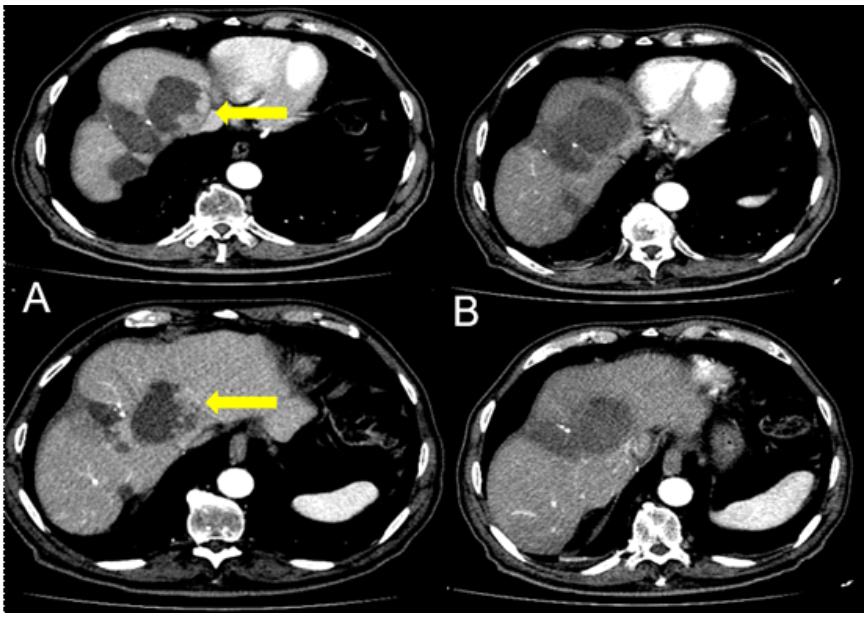

Figure 4. Treatment response after SIRT. (A) A patient with HCC, subjected to previous TACE, shows nodular enhancing lesions (arrow) in keeping with tumor recurrence. The patient was treated with SIRT. (B) Eleven months later, there was response to treatment with disappearance of previous lesions.

single SIRT session was both safe and effective compared with multiple TACE sessions. Selective internal radiation therapy vs TACE comparisons have been the subject of meta-analyses with contradictory results. A meta-analysis of 553 patients, in 5 studies, found no significant difference in 5-year survival between patients subjected to TACE or SIRT, though there was a trend for superior OS for TACE at 2 years (27% vs 18%, P=0.02) [24, 25]. In a recent, larger meta-analysis of 11 studies with 1,652 patients, SIRT showed superior 2-year OS, higher objective response (OR) rates and lower risk for adverse events [26]. Katsanos et al. (2017) studied the comparative effectiveness of different trans-arterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatment, including RCT only. Regarding OR and OS, SIRT was inferior only to the combinations of TACE plus radiotherapy or ablation, and superior to TACE alone as well as to all other combinations [27]. In another meta-analysis of 3 randomized studies, including 49 patients treated with SIRT and 48 with TACE, 1-year OS and progression free survival (PFS) were similar between SIRT and TACE. A greater proportion of patients underwent transplantation in the SIRT group (30% vs 20.8%), however this difference was not statistically significant [28]. The results of a randomized study, aiming to enroll 140 intermediate-stage HCC patients, who will be treated with either DEB-TACE or SIRT, are anticipated [29]. The AASLD suggests that LRT should be considered for intermediate-stage HCC patients who are not eligible for curative treatments and that there is need for more studies comparing TACE with SIRT. Patients who are ineligible for TACE/SIRT or experience disease progression should be considered for systemic treatment with sorafenib or newer agents like lenvatinib and regorafenib.

In advanced stages B and C, SIRT has been evaluated as alternative to sorafenib. Recently, two prospective RCTs did not meet their primary endpoint of increased OS of the SIRT arm over sorafenib; however, SIRT showed favourable toxicity profile, tolerability and quality of life. SARAH trial in France [30] randomized 467 patients to either SIRT or Sorafenib showing no significant difference in OS between treatments (median OS 8 months for the SIRT arm vs 9.9 months for Sorafenib); however SIRT showed higher tumor response rates (19% vs 2% for Sorafenib) and reduced incidence of adverse events. SIRveNIB study in Asia-Pacific reported similar results: no survival difference between treatments, higher tumor response rates for SIRT and reduced adverse events in the SIRT group (20.8% vs 35.2%) [31]. Results of a meta-analysis project combining data of both studies are anticipated [32]. After publication, these studies were subjected to remarks, comments [33] and criticism, which focused on four main topics. First, these studies were designed as superiority trials, a hypothesis which was not finally verified. Selective internal radiation therapy seems to be an effective alternative treatment, compared with sorafenib, in terms of OS; however, such an assumption cannot be inferred, since these studies were not planned as non-inferiority trials beforehand. The second limitation is the slight delay of SIRT administration at 21-29 days after randomization, compared with the immediate initiation of treatment in the sorafenib group. Third, a significant number of patients randomized to SIRT did not finally receive this treatment (22% in SARAH, 28.6% in SIRveNIB). Fourth, the multicenter nature of both studies (25 centers in SARAH, 11 in SIRveNIB) allowed for considerable dosimetric variation among centers regarding tumor doses. Thus, suboptimal doses may have been given in some cases affecting final clinical result. In a sub-analysis of the SARAH trial, OS was significantly longer in case of tumor doses exceeding 100Gy (14.1 months) compared with the sub-group receiving <100Gy (6.1 months, P=0.02) [34]. The AASLD finally concludes that current evidence does not show survival benefit of SIRT over sorafenib in advanced HCC. In the same setting, the results of the SORAMIC trial palliative cohort, comparing SIRT plus Sorafenib vs Sorafenib alone in 424 patients, have been announced [35]. Similarly to previous RCT, the addition of SIRT did not show superior OS over Sorafenib alone in either treated or intent-to-treat groups with median OS values in the range of 11-14 months. However, there was a survival benefit in certain sub-groups such as patients under 65 years of age, those with no alcoholic cirrhosis, and non-cirrhotics. The results of a similar large RCT (STOP-HCC) are anticipated [36].

Patients with main portal vein thrombosis (PVT) are deemed stage C. Surgery and TACE/TARE is not contraindicated in thrombosis limited to subsegmental/segmental portal vein branches in Child-Pugh A patients, whereas SIRT-only may be applied in case of lobar branch involvement [37]. Trans-arterial chemo-embolization induces increased incidence of side effects in these patients. According to a retrospective study in 151 patients (34 treated with SIRT, 117 with sorafenib), SIRT can be effectively performed in PVT: median OS was significantly higher for SIRT (18.8 months) vs sorafenib (6.5 months), even after comparing matched groups of patients (26.2 months for SIRT vs 8.7 months for sorafenib, P=0.054) [38]. Some cohort studies have shown better results of SIRT over sorafenib; however, this was not verified in sub-group analyses of SARAH and SIRveNIB trials. In a cohort of 185 patients with PVT treated with SIRT, results were encouraging with median OS ranging from 4 to 13.3 months dependent on different Child-Pugh classes [39]. In a recent meta-analysis, SIRT showed superior survival compared with sorafenib at all specified time intervals (6-month: 76% vs 54%, 3-year: 16% vs 7%), longer TTP and fewer grade 3 adverse events (9% vs 28%) [40]. A recent study, in 89 advanced HCC patients treated with SIRT, found that PVT did not affect survival; in nearly half of these patients, there was regression of PVT after SIRT [41]. The optimal treatment option for HCC patients with main PVT remains a matter of investigation yet.

A 10-year, US Survey (2003-2012) of the National Cancer Database identified 1,222 patients treated with SIRT, amongst 110,139 HCC patients. Corresponding post-SIRT survival rates ranged from 53.3% at 1 year to 15% at 5 years, while the age, tumor size and stage were the main factors associated with survival [9]. Recently, a highly-experienced center in TARE, at Northwestern University Chicago, came to a multidisciplinary decision to adopt TARE as the first-line transarterial LRT for HCC, based on their survival data in more than 1000 patients of various stages. They stated that their decision was informed by prospective data after 15 years of experience and by incrementally reported SIRT outcomes, applied as either neoadjuvant or definitive treatment and stratified by BCLC stages [42].

Intrahepatic cholangiocarcinoma (iCCC) shows increasing

incidence during the last years. In vast majority of cases (90%), it is found unresectable at first diagnosis with dismal prognosis and corresponding median survival of 8-11 months [43]. Therapeutic options are limited. Response to gemcitabine or gemcitabine plus cisplatin chemotherapy is poor. Trans-arterial chemo-embolization has been tried, yet carrying the risk of abscess formation exacerbated by disease nature and prior interventions like bilioenteric anastomosis, stenting or sphincterotomy [44]. Evidence for SIRT is limited to small cohort studies [45, 46], whereas no large-scale RCT have been conducted. Recent meta-analyses have reported median overall survival of 15-15.5 months after SIRT administration [47, 48], which is higher than historical survival rates and compares favorably with chemotherapy or TACE. Meta-regression analysis showed that the most significant determinants of longer survival were the presence of mass-forming type of iCCC, SIRT as the first-line therapy and the adoption of concomitant chemotherapy [48]. Results of ongoing trials comparing SIRT vs TACE and SIRT plus chemotherapy vs chemotherapy alone are awaited.

Metastatic colorectal cancer (mCRC) was one of the first applications of SIRT [1], being safe and effective even in older patients (>70-75 years-old). In the retrospective MORE study, SIRT proved to be equally effective in all age-groups and well-tolerated regardless of patients' age [49]. Selective internal radiation therapy has been applied in various clinical settings: combined with chemotherapy (1st, 2nd or 3rd line), as neo-adjuvant treatment prior to final surgery or as salvage therapy. Three large RCT have been conducted regarding the combination of SIRT with 1st line chemotherapy, in patients with liver-only or liver dominant disease: the SIRFLOX study with 530 patients (in Australia, Europe, Israel, New Zealand and USA) [50], the FOXFIRE with 364 patients (UK) [51] and the FOXFIRE-Global with 209 patients (worldwide). All 3 trials included 1,103 total patients, who were randomized to either FOLFOX alone or FOLFOX plus SIRT. Combined results showed no difference in OS between groups (median OS around 22-23 months), although there were better tumoral response rates and higher liver-specific PFS in the FOLFOX plus SIRT group; toxicities of any grade were more frequent in this group (54%) compared with FOLFOX alone (43%) [52]. Post-hoc analysis showed an added survival benefit of 4.9 months in patients with right-sided colon cancer with a corresponding reduction of 36% in the risk of death [53]. Apart from RCT, ongoing research registry studies, such as the RESIN study (USA), are collecting data from unresectable mCRC treated with SIRT, with principal objective to evaluate treatment response and secondary objectives to provide information about OS, TTP and related toxicity [54].

Selective internal radiation therapy is being evaluated as a consolidation therapy in mCRC patients, post induction chemotherapy. In this setting, there is an on-going, multicenter RCT (SIR-step) in Belgium comparing SIRT plus systemic therapy vs systemic therapy alone [55] and another multicenter (over 100 centers worldwide) RCT, aiming to enroll over 420 patients in order to compare SIRT plus 2nd line chemotherapy vs 2nd line chemotherapy alone [56]. Selective internal radiation therapy has also been tried as salvage treatment, after failure of 1st or 2nd line chemotherapy. A UK multicenter observational study evaluated the survival of patients, who have been treated with SIRT as salvage therapy. The median OS and PFS were 7.6 and 3.0 months respectively, with relatively low rates of grade 3 toxicity, in only 8% of patients [57]. After the results of this study, the National Health System (NHS) announced that SIRT will be routinely offered to patients with advanced colorectal cancer and metastatic liver disease not responding to previous chemotherapy. According to NCCN guidelines 2019, panel members reached to the consensus that SIRT is an effective option in specifically selected patients with liver dominant metastases and chemotherapy-refractory disease.

Metastatic neuroendocrine tumor (mNET)

Neuroendocrine tumor liver metastases are usually hypervascular, posing an ideal target for SIRT. Selective internal radiation therapy is frequently applied when previous treatments fail to halt tumor progression or to alleviate symptoms caused by hormone overproduction and circulation. Selective internal radiation therapy has already been applied in cohort studies with varying numbers of patients. The largest included 148 patients with satisfactory results of radiologic response (63%) and survival (median OS of 70 months) [58]. In 2012, a NET-Liver-Metastases Consensus Conference concluded that SIRT could be applied in mNET by virtue of fewer side effects and that it could substitute for TAE or TACE in patients with liver-only disease or those with limited extrahepatic metastases [59]. Recently, a systemic review assessing 846 total patients demonstrated high disease control rate of 86%, mainly achieving partial responses or cases of disease stabilization with a corresponding 3-year survival rate of 45% [60]. The largest, international, multicenter cohort study, in 244 patients, showed similar results: disease control rate exceeded 90% at 6 months, partial responses were above 25% and alleviation of symptoms was achieved in almost 80% of patients at the expense of few SIRT specific complications (<4%) [61]. Studies comparing SIRT with other LRT are sparse to draw definite results. In a retrospective comparative analysis of 192 patients, TACE showed significantly longer OS compared with DEB-TACE or SIRT, with 5-year survival rates of 28.2%, 18.5% and 10.3% respectively [62]. Recently, there is a trend for using intra-arterial ^{90}Y/^{177}Lu peptide receptor radionuclide therapy (PRRT) instead of ^{90}Y-microspheres. Due to the high abundance of tumor somatostatin receptors, a higher dose can be delivered using this approach, with considerably less renal toxicity that is of concern in systemic RPPT [8].

Breast cancer

Intra-arterial treatment of breast cancer liver metastases is most frequently applied in salvage setting after failure of previous chemotherapy. Treatment's efficacy has been reported in small cohort studies. Fendler et al. (2016) treated 81 patients, mainly with whole liver approach, to achieve partial metabolic responses in approximately half of them (52%) as evidenced by >30% decrease in positron emission tomography-fluorine-18-fluorodeoxyglucose (PET-^{18}F-FDG) uptake values [63]. In a recent analysis of cohort studies, including 355 patients overall, high disease control rate of 78% was reported [64]. There is a trend for increased hepatic toxicity in breast cancer patients treated with SIRT compared with other ma-

lignancies. Most of these patients are heavily pretreated, thus maintaining borderline hepatic reservoirs. Breast cancer liver metastases may not be an optimal target for SIRT, since they are not highly vascular compared with other malignancies or may maintain reduced vasculature as a result of previously applied anti-angiogenetic factors. Total tumor burden may be underestimated by CT scan, since a substantial proportion of liver metastases may be microscopic. Whole liver treatments carry greater risk for developing REILD. Comparisons of SIRT with other LRT are limited. A small retrospective study, in women with liver-dominant breast cancer disease, showed similar OS between SIRT (median OS 4.6 months) and TACE (median OS 4.6 months) with lower adverse events for SIRT (44% vs 71% for TACE, P=0.02) [65].

Ocular melanoma

Liver is the first and most common metastatic site of ocular (uveal) melanoma (92%). Prognosis in these patients is poor and has remained unchanged for many decades with median overall survival equal to 8 months [66] and death rate of 92% at 2 years [67]. Evidence for the efficiency of SIRT is limited, based on small, individual-center studies. In 2011, Consalves et al. reported median OS of 10.0 months and median PFS of 4.7 months in 32 patients treated with SIRT as salvage; survival was longer for patients with lower tumor burden [68]. Selective internal radiation therapy showed superior OS vs best supportive care in a comparative study in 58 patients: median OS of 19.9 vs 4.8 months respectively (P<0.0001) [69]. A small (18 patients), retrospective, nationwide Finnish study reported median OS of 13.5 months after SIRT, which compared favorably to the historical chemotherapy group (median OS 10.5 months, P=0.047) [70]. Results were better for patients who received SIRT as first-line treatment with median OS equal to 18.7 months [70]. Recently, SIRT is being tried combined with immunotherapy in small trials, reporting encouraging results [71]. There ongoing clinical trials comparing TACE with SIRT [72] and evaluating the combination of SIRT plus ipilimumab and nivolumab [73].

Many centers apply SIRT in liver metastases from other malignancies, like sarcomas [74], renal carcinoma [75], pancreatic [76], and various other tumors [77] but data are limited, based on small cohort studies, thus insufficient to draw robust conclusions.

In conclusion, nowadays, SIRT is an established, yet continuously evolving therapeutic modality. Its main strength is that it is well-tolerated, with fewer side effects compared to other treatments. Recently, evidence for SIRT, either supportive or not, comes from large, multi-center, prospective RCT, whereas ongoing trials may define the specific groups of patients, who will gain the greatest clinical benefit. In HCC, SIRT is routinely applied in advanced stages, however it is being tested even in earlier stages within the concept of SIRT segmentectomy. In mCRC, apart from use in salvage setting, it may be beneficial for certain sub-groups, such as patients with right colon cancer, combined with chemotherapy. There are certain components of the method, which may be improved, such as personalized and more accurate dosimetry, new agents applied in pretreatment planning like modified MAA particles, novel therapeutic bullets and efficient time reduction of the interval between initial work-up and actual treatment. Combination of SIRT with other therapeutic modalities and systemic therapies is of great interest, as well as its new role in the era of immunotherapy and targeted treatments. Compared with previous decade, evidence for SIRT is more robust and mature, additionally there are ongoing clinical trials to define the position of SIRT within modern treatment algorithms.

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