Radioembolization: An update on current practice and recent developments

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Introduction

Since the 1950s, when it became clear that hepatic tumors derive their blood supply primarily from the hepatic artery and normal hepatic parenchyma primarily receives it blood from the portal vein, there has been growing interest into hepatic artery-directed treatments (1).
Dr. Irving Ariel was the first to describe the technique of radioembolization in 1965. Via a groin puncture and femoral artery access, ^{90}Y loaded ceramic microspheres were administered through a catheter in the celiac artery (2). This therapy provided symptomatic improvements, but was not without complications. One patient experienced paresis of the right leg, while another patient became paraplegic. Five decades later and after the publication of multiple large multicenter studies, this technique eventually evolved into radioembolization and has become mainstream clinical practice performed in hospitals worldwide.
To date three types of microspheres have gained European CE market approval. Resin ^{90}Y-microspheres in 2002 (SIR-Spheres, SIRTeX Medical Ltd., Australia), glass ^{90}Y-microspheres in 2006 (TheraSphere, Boston Scientific, US) and ^{166}Ho-microspheres in 2015 (QuiremSpheres, Quirem Medical, The Netherlands).
Since the last review on radioembolization in this journal in 2016, data from large randomized multicenter trials have been published that have changed the playing field (3). Based on these data, guidelines have been adjusted that confirm that radioembolization is a valuable tool in treatment of hepatic malignancies. This paper will give an overview and future outlook of the current state of radioembolization treatment for three types of tumors.

Microspheres

^{90}Y-microspheres

In the early beginnings of radioembolization, non-selective tracer distribution and subsequent non-target microsphere deposition in distal organs caused major side effects, including gastrointestinal ulceration, radiation cholecystitis and radiation pneumonitis (liver-lung shunts). Myelotoxicity was also a major side effect reported. This was due to the unstable binding of the isotope ^{90}Y to the microspheres and detrimental leaching of ^{90}Y from the plastic or ceramic spheres used at that time (4). This eventually led to the development of new generation glass and resin ^{90}Y-microspheres in the early 1980's. In phase I trials and subsequent dose escalation studies the safety and early efficacy of glass ^{90}Y-microspheres in patients with hepatocellular carcinoma (HCC) and resin ^{90}Y-microspheres in patients with metastatic colorectal cancer (mCRC) was demonstrated (5). As a result of these studies (and subsequent studies), both glass and resin ^{90}Y-microspheres are currently approved for treatment of unresectable liver tumors on the European market.

^{166}Ho-microspheres

A relatively new type of microspheres used for radioembolization are ^{166}Ho-microspheres that are radioactive loaded bio-resorbable poly-L-lactic acid (PLLA) microspheres containing the isotope ^{166}Ho (see also table 1). These microspheres were initially developed at the UMC Utrecht in the Netherlands and are now a commercial product (Quiremspheres™, Terumo). Like ^{90}Y, ^{166}Ho is a high-energy beta-emitting isotope that can be used for tumor irradiation. Furthermore, it has imaging properties, through the emission of gamma photons and due to its paramagnetic properties. This allows visualization of its distribution in the liver and quantification of the absorbed tumor on SPECT/CT and MRI. In comparison with ^{90}Y-microspheres the half-life of ^{166}Ho-microspheres is shorter, 27 hours versus 64 hours, thus to achieve the same absorbed dose more activity is needed.
The first human trial, Holmium Embolization Particles for Arterial Radiotherapy (HEPAR I trial), in 2011, was performed in patients with unresectable, chemorefractory liver metastases who were treated with ^{166}Ho-microspheres. This trial concluded that ^{166}Ho-microspheres radioembolization was safe and feasible with an aimed whole liver absorbed dose of 60 Gy (6). This study was followed by the HEPAR II trial, a phase II study examining the efficacy of ^{166}Ho-microspheres radioembolization in salvage patients with liver metastases. It demonstrated that radioembolization with ^{166}Ho-microspheres induced a tumor response with an acceptable toxicity profile (7).

Table 1. Radioembolization microspheres characteristics.

Characteristics	SIR-Spheres®	TheraSphere®	QuiremSpheres®
Material	Resin	Glass	Poly-L-lactic acid
Particle size and range (μm)	30 (20–60)	25 (20–30)	30 (15–60)
Embolic effect	Moderate	Mild	Moderate
Activity per sphere (Bq)	40–70	4534 *	200–400
Specific gravity (g/dL)	1.6	3.7	1.4
Activity available (GBq)	3 #	3–20 ^ "	"
Handling for dispensing	Required	Not required	Not required
Multiple dosing from one vial	Possible	Not possible	Not possible

Note. From " EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds" by Weber, M., Lam, M., Chiesa, C. et al. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. Eur J Nucl Med Mol Imaging 49, 1682-99 (2022). https://doi.org/10.1007/s00259-021-05600-z

Direct measure by Pasciak et al. (8) at calibration, the IFU provide a value of 2500 Bq. The value is variable according to physical decay depending on the day and time of treatment.
Prescribed activity should be withdrawn on site. The FLEXdose option allows injection 3 days before calibration, when the vial activity is 10 GBq at higher specific activities.
^ Vials of 3-20 GBq in steps of 0.5 GBq, calibrated at noon on the Sunday before treatment with a shelf-life of 12 days.
" Patient-specific activity is calibrated at the day and time of treatment.

Radioembolization technique

Overall, ^{90}Y-microspheres radioembolization and ^{166}Ho-microspheres radioembolization are comparable in many aspects.
A standard radioembolization procedure of unresectable liver tumors, can be summarized in four steps.

Step 1. Patient selection
It is strongly recommended that patients referred for radioembolization are discussed in a multidisciplinary tumor board. All locoregional (e.g. resection, ablation, radioembolization, chemoembolization, radiotherapy) or systemic options (e.g. chemotherapy, immunotherapy) should preferably be available. The indication for radioembolization can vary from salvage treatment in advanced stage disease (typically lobar or whole liver treatment), bridging for transplantation (selective treatment) or in a neoadjuvant setting for resection (typically radiation lobectomy or radiation segmentectomy). The inclusion criteria vary depending on the treatment intent. In broad terms, patients should at least have liver-only or liver dominant disease; a life expectancy of at least 3 months; accessible liver vasculature; adequate liver functional reserve; and a favorable scout dose distribution to receive radioembolization. For an overview of indications and contraindications for radioembolization with ^{166}Ho-microspheres and ^{90}Y-microspheres, see table 2.

Step 2. Work-up procedure
Pre-operative CTA is advised to assess the hepatic arterial vasculature and possible anatomical variations. The work-up procedure consists of catheterization of the liver vasculature under angiography and selecting the injection position(s) for the scout dose. The goal of this procedure is to 1) detect any unintended gastrointestinal deposition of activity, 2) calculate the lung shunt fraction, 3) predict the intrahepatic distribution of the microspheres (tumor and non-tumor absorbed doses), and 4) allow for treatment planning (calculate the required activity for treatment). Performing C-arm CT during the work-up procedure is essential. A C-arm CT with transcatheter contrast injection should at the very minimum be performed at every intended injection position. This helps to timely recognize non-target vessels causing extrahepatic deposition, select the tumor feeding arteries and recognize

Table 2. Recommendations and contraindications for radioembolization.

Indications	Contraindications
1. Unresectable primary or metastatic hepatic disease with liver-only or liver dominant tumor burden 2. Life expectancy > 3 months 3. An eastern cooperative oncology group (ECOG) status ≤ 2 4. In case of (suspected) cirrhosis; Child–Pugh score ≤ B7 5. Preoperative radioembolization for: (a) Downstaging (b) Bridge to transplant (c) Hypertrophy induction	1. Pretreatment scan demonstrating (a) The potential of > 30 Gy radiation exposure to the lung (b) Flow to the gastrointestinal tract that cannot be corrected by catheter techniques 2. Limited hepatic reserve (a) Irreversibly elevated bilirubin levels (> 2.0 mg/dl) (b) Reduced albumin (< 3 g/dl) 3. Prior external beam radiation therapy involving the liver in the treatment field of view. Systemic radionuclide treatments are allowed (e.g., [^{177}Lu]Lu-dotatate) 4. Severe contrast allergy, not manageable or responsive to prophylaxis

Note. From "Holmium-166 Radioembolization: Current Status and Future Prospective" by Stella et al. Cardiovascular Interventional Radiology 2022 Nov;45(11):1634-45. doi: 10.1007/s00270-022-03187-y.

potential parasitic tumor feeders. In general, a scout dose of technetium-99m macroaggregated albumin ([^{99m}Tc]Tc-MAA) is used. It acts as a surrogate particle and emits gamma radiation (with minimal radiation exposure to the patient), which can be visualized on planar imaging and SPECT/CT.
Alternatively, a scout dose of ^{166}Ho-microspheres (QuiremscoutTM, Terumo) can be used instead of [^{99m}Tc]Tc-MAA. The ^{166}Ho-microspheres scout dose consists of the exact same microspheres as used for ^{166}Ho-microspheres therapy. Only the number of microspheres and specific activity per microsphere is lower. [^{99m}Tc]Tc -MAA differs greatly in shape, size and density from ^{90}Y- or ^{166}Ho-microspheres. By using a ^{166}Ho-microspheres scout dose, the possible discrepancy between planning and treatment is greatly reduced in comparison to [^{99m}Tc]Tc -MAA. Disadvantages of ^{166}Ho-microspheres scout include that it is more costly, takes more time to administer (same administration system as for the treatment procedure itself) and comes with a low amount of beta radiation. However, data from the first trials have shown that the absorbed dose of encountered extrahepatic depositions are insufficient to cause any complications (6,9,10). Furthermore, ^{166}Ho-microspheres scout has been proven to be superior in its predictive value for intrahepatic distribution and in assessing possible lung dose in comparison with [^{99m}Tc]Tc-MAA (11,12). Development of a ^{90}Y-microspheres scout is underway with the first prospective single-arm clinical trial, utilizing 0.56 GBq resin scout ^{90}Y-microspheres, reporting superior results in biodistribution in comparison with [^{99m}Tc]Tc-MAA for non-segmental therapies (13).

Step 3. Treatment planning
Treatment planning is the most important step of the entire treatment. Data from the work-up procedure and scout dose SPECT-CT are used to determine a plan, including the number of injection positions, activity per injection position, time frame for treatment (instance e.g. whole liver treatment in one session or sequential treatment). Calculating the required amount of activity should be dosimetry based. Dosimetry can roughly be divided into three models: Single compartment model, a multi-compartment model or a voxel-based model. In the single compartment model, there is no distinction between the tumor and the normal liver parenchyma, and a mean dose is calculated for the entire perfused volume. In the multi-compartment model (also known as partition model), doses are evaluated separately for the tumor and the normal perfused liver. In voxel-based dosimetry, dosimetry is evaluated for each reconstructed voxel with predefined volumes of interest. Recent guidelines by the European Association of Nuclear Medicine recommend using multi-compartment dosimetry, whenever tumor segmentation is feasible. Clinical data support tumoricidal doses and maximum tolerated doses for each product used (14). When multi-compartment dosimetry is not possible, single compartment dosimetry can be used as an alternative.

Step 4. Treatment procedure
One to two weeks after the scout dose ([^{99m}Tc]Tc -MAA or ^{166}Ho scout) the radioembolization is performed based on the scout procedure. Depending

on the treatment plan (whole liver, unilobar or segmental) the catheter is placed at the same position(s) as in the scout dose.
Since all currently used microspheres emit beta radiation, they are delivered in a vial that is positioned centrally in a Perspex administration box for radiation shielding. The vial is connected to the intra-arterially placed catheter through the tubing of the administration system. Administration of glass ^{90}Y-microspheres is performed by semi-continuous infusion controlled by a single syringe. This differs from resin ^{90}Y-microspheres and ^{166}Ho-microspheres for which the administration is performed intermittently to check for stasis and possible backflow. Finally, to quantify delivery after radioembolization, either SPECT or MRI can be used for ^{166}Ho-microspheres and either PET or Bremsstrahlung-SPECT can be used for ^{90}Y-microspheres. Radioembolization can be performed as an outpatient treatment depending on the local radiation safety regulations. In many centers, patients stay in the hospital for one night (15,16).

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy, accounting for 80-90% of all primary hepatic malignancies. HCC has a 5-year survival rate of approximately 70% with early-stage HCC, which decreases to a median overall survival of 1-1.5 years for symptomatic advanced-stage cases treated with systemic therapies (17,18).
Several trials examining ^{90}Y-microspheres radioembolization in HCC have been published over the last few years. There have been three major trials that have compared ^{90}Y-microspheres radioembolization with sorafenib (multikinase inhibitor approved for treatment of HCC) in locally advanced HCC: SARAH trial, SIRveNIB trial and SORAMIC trial. Although radioembolization was proven to be safe, there was no significant difference in overall survival

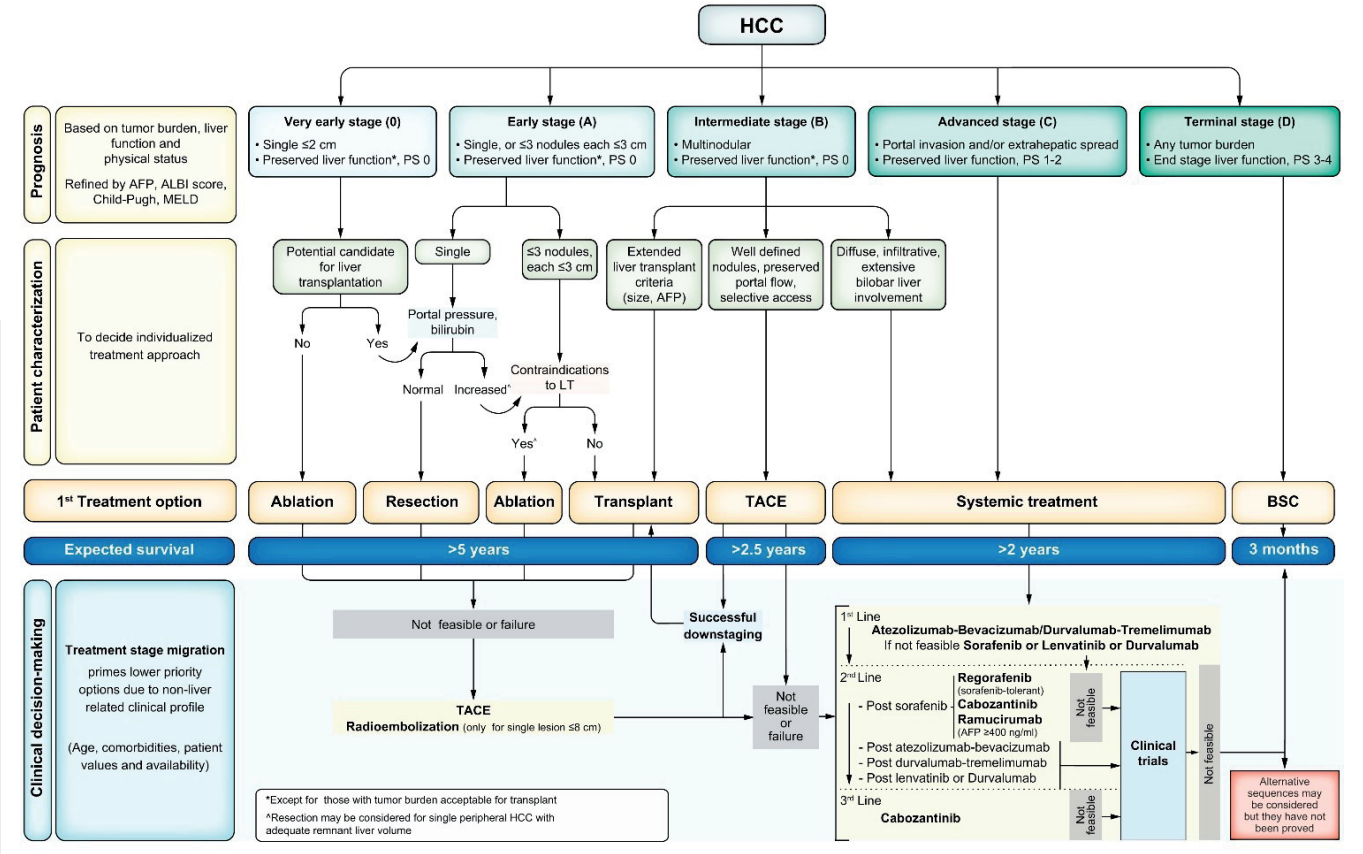

Figure 1. BCLC staging and treatment strategy in 2022.
Note. From "BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update" by Reig et al. J Hepatol 2022 Mar;76 (3):681-693.

either when performed in addition to sorafenib or in comparison with sorafenib (19-21). However, since the publication of the IMbrave trial, sorafenib is rarely implemented anymore. The IMbrave trial compared a combination of atezolizumab (anti-programmed death-ligand 1 (PD-L1) antibody) and bevacizumab (VEGF-A-targeting monoclonal antibody) with sorafenib in patients with unresectable HCC. This combination resulted in a significantly improved overall survival and progression-free survival (PFS) compared to sorafenib (22). Since then, the combination of atezolizumab and bevacizumab, as well as several other immunotherapeutics, are incorporated in the Barcelona Clinic Liver Cancer (BCLC) staging system (see figure 1).
In the same period, the first data on ^{166}Ho-microspheres radioembolization for HCC were reported. This HEPAR Primary study demonstrated in 31 patients with liver-dominant HCC that ^{166}Ho-microspheres radioembolization is a safe treatment with unacceptable toxicity occurring in 10% of patients (23). There was complete or partial response for 84% of the target liver lesions at 6 months follow-up and median overall survival was 14.9 months.

Above mentioned prospective studies all provided valuable information on safety and efficacy of radioembolization in HCC, however it was the retrospective LEGACY study that made the largest impact in terms of guideline adjustments. The LEGACY study was a single-arm, retrospective study that included all eligible, consecutive patients with HCC treated with radioembolization with eligibility criteria that included solitary HCC ≤ 8 cm, Child-Pugh A cirrhosis and ECOG performance 0-1.
A total of 162 patients were included and median tumor size was 2.7 cm (range 1-8 cm).
Median follow-up time was 29.9 months by reverse Kaplan-Meier.
ORR (best response) was 88.3% (CI: 82.4-92.4), with 62.2% (CI: 54.1-69.8) exhibiting a duration of response ≥ 6 months. Three-year overall survival was 86.6% in all patients. For patients with neoadjuvant therapy with resected or transplanted liver overall survival was 92.8% (24).
Based on these results, radioembolization was included as a treatment option in the updated 2022 BCLC strategy. Based on this updated version, radioembolization could be considered in patients with single nodules up to 8 cm in very early stage (BCLC 0) ,early stage (BCLC A) and intermediate stage (BCLC B) if not suitable for resection or ablation (see figure 1) (25). The aforementioned 8 cm limit is somewhat remarkable as there were no tumors included in the LEGACY study above 8 cm and the large majority were much smaller than 8 cm with a median of 2.7 cm (range 1.0 - 8.0). Furthermore, there is no scientific data indicating that radioembolization would not be efficacious in tumors larger than 8 cm.

Another landmark study was the Dosisphere-01 trial which was a randomized, multicenter, open-label phase II trial. In this trial the usage of multi-compartment dosimetry in comparison with single compartment dosimetry significantly improved the ORR in patients with locally advanced HCC (p=0.01).
Furthermore, there was no increase in the toxicity profile and an improvement in overall survival was observed with a median OS of 26.6 months vs. 10.7 months in the single compartment dosimetry group (26).
These results made it clear that multi-compartment dosimetry should become the standard-of-care method for radioembolization treatment planning.
Moreover, these results confirm that the absence of multi-compartment dosimetry limits the value of study results, as confirmed by the SARAH post-hoc analysis (27).

Metastatic colorectal cancer

Metastatic colorectal carcinoma (mCRC) is the most prevalent type of hepatic metastases, accounting for 35% of patients with hepatic metastases (28). Radioembolization is an established treatment option for mCRC patients in a salvage setting. This was in part due to an RCT published in 2010 that demonstrated that radioembolization with resin ^{90}Y-microspheres in patients with liver-limited metastases failing the available chemotherapeutic options prolonged time to tumor progression and time to liver progression (29). Positive results were also reported in the MORE study, a retrospective analysis of 606 patients with unresectable colorectal liver metastases treated with radioembolization using resin ^{90}Y-microspheres. Authors concluded that resin ^{90}Y-microspheres radioembolization offers favorable survival benefits for patients with unresectable metastatic colorectal cancer, even among patients who received three or more prior lines of chemotherapy with a median OS of 10.0 months (95% CI: 9.2-11.8 months) (30).
In first line however, data were less favorable. A combined analysis of three multicenter, randomized, phase III trials (Sirflox, Foxfire, FoxFire Global) failed to show benefit in overall survival when first-line FOLFOX chemotherapy was supplemented with radioembolization in comparison with FOLFOX alone (31). However, data from the Sirflox trial suggested that radioembolization may be most beneficial in liver-limited or liver predominant disease. In this trial radioembolization with resin ^{90}Y-microspheres gave significantly better 'liver-specific-PFS' but failed to show an overall PFS benefit, with 45% of patients having their primary tumor in place and 40% with extrahepatic disease (32). One potential subgroup

with a distinct benefit consisted of patients with right-sided primary tumors (33).

In second line, a recent large phase III (EPOCH) trial comparing second-line chemotherapy alone with second-line chemotherapy plus glass ^{90}Y-microspheres radioembolization in 428 patients with liver-dominant or liver-only disease was recently published (2021). In this trial a significant improvement in PFS was reported with an ORR of 34% with second-line chemotherapy augmented with ^{90}Y-microspheres radioembolization compared to 21.1% in only second-line chemotherapy. Further subgroup analysis identified possible factors that might improve PFS benefit, patients with fewer than three lesions, resected primary tumor, lower tumor burden, left primary tumor location (PTL) and a KRAS mutation (34).
^{166}Ho-microspheres radioembolization for chemorefractory mCRC patients has been studied in the HEPAR I, II and SIM trials, which confirmed safety and efficacy with a reported median OS of 14.5 months in the HEPAR II trial (35).

Based on these performed trials, radioembolization as a first-line treatment in patients with mCRC was not recommended. Current radioembolization should be considered in patients with mCRC when available chemotherapeutic agents fail (36). However, data on radioembolization in mCRC is limited by the absence of prospective multi-compartment dosimetry studies (37).

Neuroendocrine liver metastasis

Neuroendocrine neoplasms (NEN) are a rare (2% of all malignancies) and very heterogenous group of tumors (38,39). A well-established negative prognostic factor for NEN patients is the presence of neuroendocrine liver metastases (NELM) with one quarter of NEN patients having distant metastases at presentation with the liver being the most affected (40,41). Since the majority (60-70%) of NELM patients have diffuse liver disease, which does not allow for surgical resection, there is a clinical need for liver-directed treatments in light of the limited systemic options for NENs. The large majority of data regarding radioembolization come from retrospective studies with heterogenous study populations and primarily in a salvage setting. These studies confirmed safety and efficacy of radioembolization of NELM in a salvage setting with reported median OS of 28.5-39 months (42). Only one retrospective study specifically investigated radioembolization in a second-line setting. In this study a median hepatic PFS of 18.6 months and median global PFS of 18.8 months was reported. These results are slightly better than the results obtained in a salvage setting. Furthermore, median OS was prolonged compared to the salvage setting group, 44.8 vs. 30.6 months respectively (43), however biased by subsequent treatments.

In order to boost the benefit for patients suffering from high intrahepatic tumor burden, several studies have examined the possible synergy between radioembolization and systemic treatments. To date, three small studies have been performed, the first by Soulen et al. in which resin ^{90}Y-microspheres radioembolization was combined with systemic chemotherapy capecitabin plus temozolomide (CAPTEM) in patients with NELM of different origins who were primarily treated in a second-line setting. In this study high response rates and long survival were reported suggesting a synergistic effect (44). Only one patient of 21 in total developed hepatic failure due to radioembolization-induced liver disease (REILD). Kim et al. examined the combination of everolimus and pasitreotide augmented with ^{90}Y-microspheres radioembolization in a phase 1b study, where everolimus dosage was escalated whilst pasitreotide and radioembolization were standardized. This treatment was safe and no additional hepatotoxicity was identified (45). The first combination study with ^{166}Ho-microspheres radioembolization came with the HEPAR plus trial. In this trial peptide receptor radionuclide therapy (PRRT) was combined with ^{166}Ho-microspheres radioembolization, by adding radioembolization within 20 weeks after the fourth cycle of PRRT (46). The combination treatment was proven to be safe and effective with only one case of REILD.
Above mentioned studies further confirm the added value of radioembolization as a local treatment option in NELM. Furthermore, in the European Neuroendocrine Tumor Society (ENETS) guideline from 2016 and the European Society for Medical Oncology (ESMO) guideline from 2020 the role of radioembolization has been extended, including early application as a tumor debulking treatment or as a salvage treatment in selected cases, after the failure of systemic treatments (47,48).
However, like with mCRC, data on radioembolization in NELM is limited by the absence of prospective multi-compartment dosimetry-based studies. Especially since clear dose-response and dose-survival relationships have been reported in NELM (42).

Future Directions

As mentioned earlier one of the great limitations of the published studies was the lack of multi-compartment dosimetry. As demonstrated in the Dosisphere-01 trial, multi-compartment dosimetry is superior to single compartment dosimetry. Multi-compartment dosimetry requires a reliable scout particle for predicting microsphere distribution

and it requires understanding of dose-response relationships. ^{166}Ho-microspheres scout has proven to be a more reliable predictor than [^{99m}Tc]Tc -MAA. Dose-response relationships are now studied for the different types of microspheres and for different tumor types, which will help us develop more patient tailored treatments with better outcome and less toxicity. Moving forward, there will be more attention to dosimetry, not only in clinical trials but also in clinical practice.

Another shift in the treatment paradigm will be the choice of type of radioembolization or treatment strategy. Instead of whole liver radioembolization for all, the emphasis will be put more on (super) selective radioembolization or radiation lobectomy in preparation for surgical liver resection. The main benefits of these approaches are the reduced healthy liver toxicity, improved disease control and the potential for curation, either directly or after surgery (49). Immunotherapy has had a huge impact on how HCC patients are being treated today. In the coming years, the position of radioembolization relative to immunotherapies must be established. Since radioembolization significantly enhances intra-tumor immune infiltrates, combining immunotherapy with radioembolization may have a synergistic effect (37).

Lastly, ^{166}Ho-microspheres are gradually gaining a foothold in the radioembolization landscape. Data on ^{166}Ho-microspheres radioembolization is still scarce compared to ^{90}Y-microspheres radioembolization but there are many clinical studies ongoing or in preparation. The first randomized clinical trial on ^{166}Ho-microspheres radioembolization recently started in the Netherlands: CAIRO7 (NCT05092880). This study will investigate if ^{166}Ho-microspheres radioembolization is an effective alternative, better tolerated and more cost-effective treatment option in elderly or frail patients compared to chronic systemic treatment with comparable progression-free survival.

Conclusion

Hepatic radioembolization is a safe and effective treatment in primary and secondary hepatic malignancies. The position of radioembolization for these indications has changed due to new evidence and alternative treatment options like immunotherapy. The field of radioembolization is evolving, driven amongst other things by multi-compartment dosimetry, more reliable scout particles and combination treatments.

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