SMGroup

Radioembolization for Primary or Metastatic Hepatic Tumors

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Radioembolization is the method of the selective, trans-catheter, and intra-arterial injection of micrometer-sized spheres loaded with Yttrium-90 (Y^{90}). Y^{90} is a pure beta emitter radioisotope with 64.2 hours half-life and 2.5-11 mm tissue penetration. In the market there are two different types of spheres, glass microspheres range in size 20-30 μm (TheraSphere, BTG, London, UK) and resin microspheres range in size 20- 60 μm (SIR-Spheres, Sirtex Medical, LaneCove, Australia). While normal liver parenchyma receives most of its blood supply from the portal venous system, hepatic malignancies receive most of their blood supply from the hepatic arteries [1,2]. Because of that difference preferential deposition of particles within tumor as opposed to normal liver tissue. Intra-arterial injection of the radioactive microspheres results in greater deposition of the microspheres in the arterially perfused tumors compared to liver parenchyma. Hereby, radioembolization allows for safe administration of high and therapeutic doses of radiation, whereas the radiosensitive nature of normal liver tissue.

Table 1: Properties of microspheres in the market.

Properties	Glass Microsphere	Resin Microsphere
Trade Name	ThereSphere	SIR-Sphere
Diameter (μm)	20-30	20-60
Specific activity (Bq/sphere)	2500	50
Number of spheres	$1.2x10^6$	$40\text{-}80x10^6$

PATIENT SELECTION

A multidisciplinary team approach is usually necessary when selecting patients for radioembolization. A consensus panel consisting of experts from medical oncology, surgical oncology, nuclear medicine, interventional radiology and radiation oncology has outlined patient selection criteria for radioembolization [3]. Patients who are not resection candidates and who have a life expectancy longer than 3 months should be considered.

During pretreatment evaluation of patients for eligibility for transarterial radioembolization the patient's burden of disease, biochemical parameters, and performance status are taken into consideration. Patients with Eastern Cooperative Group Score 0-2 and liver-only or liver-dominant disease with tumor burden less than 60% of liver are ideal candidates for radioembolization. Hepatic reserve is evaluated by serum bilirubin level (<2mg/dL), albumin (>3g/dL) and normal international normalized ratio measurements. Although the presence of Portal Vein Thrombosis **(PVT)** has been traditionally considered a contraindication to hepatic arterial embolization procedures, radioembolization has been shown to be safe and effective in the setting of PVT [4,5]. After the first evaluation, an initial mapping angiography is performed at which time a radioisotope hepatic artery perfusion scintigraphy was performed to calculate the lung shunt fraction.

The administration of microspheres smaller than these shunts could therefore result indirect shunting of the radioactive microspheres to the lungs, which can cause radiation pneumonitis at sufficient doses [6]. Because Technetium-99^m (Tc^{99m}) Macroaggregated Albumin **(MAA)** is of similar size to the ^{Y90} microspheres, it is expected to similar distribution. Planar scintigraphic images of thorax and abdomen planar gamma camera images, with or without concomitant Single Photon Emission CT **(SPECT)** gamma camera images, were obtained after administration of 75-150MBq (2-4mCi) of Tc^{99m}-MAA via to the hepatic artery. Lung shunt fraxion was calculated by using planar images and additionally, the distribution of the Tc^{99m}-MAA could be evaluated by using tomographic images (Figure 1 and 2). A shunt equal or more than 20% associated with the development of radiation pneumonitis [7].

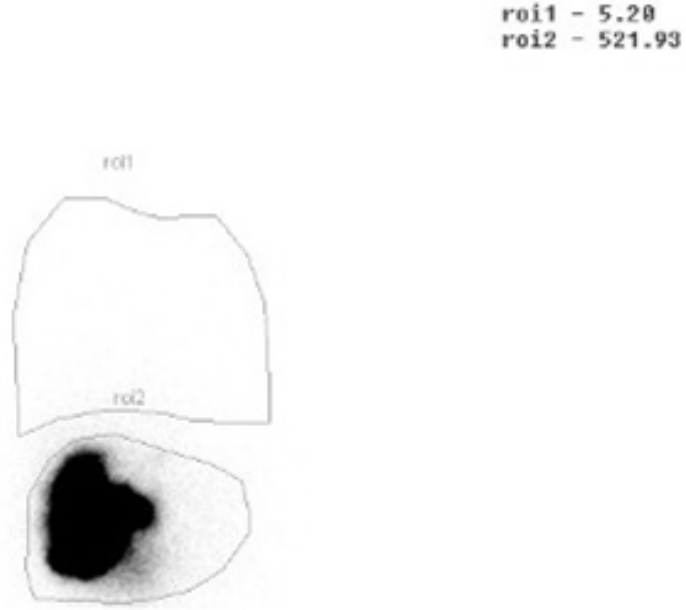

Figure 1: Planar hepatic artery perfusion scintigraphy images without any significant lung shunt.

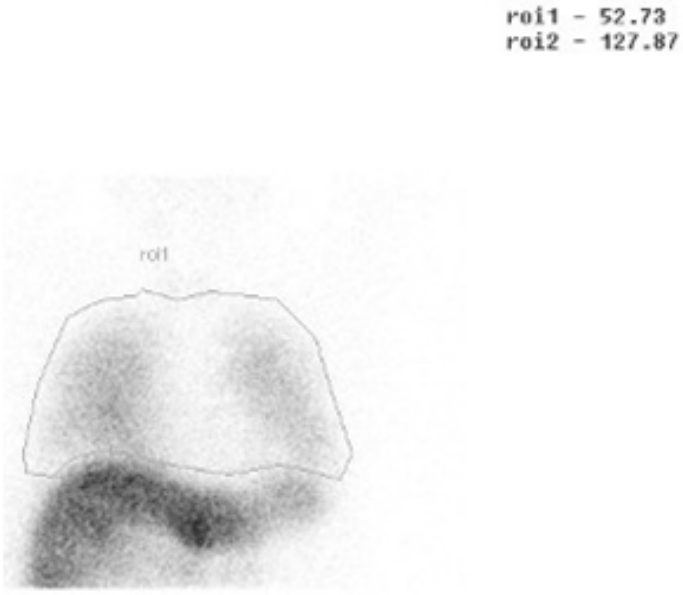

Figure 2: Planar hepatic artery perfusion scintigraphy images of patient with 44% LCF.

DOSIMETRY

Resin microsphere dosimetry can be calculated by using Body Surface Area **(BSA)** and estimates of tumor burden according to the formula:

$$A(GBq) = BSA - 0.2 + \frac{\%tumor\ involvement}{100}$$

Activity is decreased depending on the degree of Lung Shunt Fraxion **(LSF)** [8].

10-15% LSF—20%reduction;

15-20% LSF—40% reduction;

> 20% LSF—contraindication for treatment.

Glass microspheres are available in vials with different activities. Depending on the underlying liver disease, the recommended activity to be administered to a tumor containing hepatic lobe should correspond to a dose between 80 and 150Gy.

$$A(GBq) = \frac{DxM}{50x\left(1-\frac{\%LSF}{100}\right)x(1-\frac{\%R}{100})}$$

D: absorbed dose (Gy), M (kg): target liver mass

Liver volume (mL) is calculated from computed CT images. Lung-shunt fraction (%LSF) is calculated from hepatic artery perfusion scintigrapy images [8]. During pretreatment evaluations, absorbed doses to tumor and normal tissues should be considered to achieve tumor response as well as to protect normal tissues from radiation damage. For resin microspheres, mean absorbed dose thresholds are 120Gy for tumor, 50Gy to non-tumorous whole liver and, 20Gy to the lung [9]. The threshold for HCC complete response dose–volume histogram analysis of posttreatment Y^{90} PET/CT identified to be D70. 100Gy using resin microspheres, where D70 is the minimum absorbed dose delivered to 70% tumor volume [10]. Lam et al found responders to have a mean tumor absorbed dose of 82.7 6 23.9Gy, whereas non-responders had 31±10.9Gy, for colorectal liver metastasis treated with resin microspheres [11]. The mean absorbed dose threshold for non-tumorous whole liver recommended to be 50–70 Gy for colorectal liver metastasis, depending on liver reserve and prior systemic therapy [9]. For glass microspheres, HCC thresholds found to be 205Gy for tumor response, 120Gy to healthy liver and, 30Gy to the lung [10]. There is currently no data on glass microspheres tumour absorbed dose thresholds for colorectal liver metastasis. In the case of repeated radioembolization to the same arterial territory, the cumulative absorbed dose to healthy tissue and time interval between radioembolizations are important safety considerations.

Side Effects

A postradioembolization syndrome including fatigue, weakness, nausea, anorexia has been described that can last up to 3 weeks after the procedure and is usually self-limited

[12]. Rare complications are biliary necrosis (3.9%), biloma formation (1%), biliary stricture (2.4%), gallbladder wall enhancement (1.8%), and gallbladder wall disruption (0.9%) [13]. Gastrointestinal ulceration may be seen after inadvert administration of radioactive microspheres to the gastrointestinal tract. Meticulous angiographic technique and identification of extrahepatic arterial flow are absolutely essential to avoid biliary and gastrointestinal complications. All intrahepatic arteries such as gastroduodenal, cystic or falciform arteries that supply extrahepatic organs originating distal to the point of Y^{90} microspheres release should be prophylactically embolized [14] In addition, there is some consensus on the use of premedications to help prevent complications, such as proton pump inhibitors (starting one week before treatment and continuing for one month after the procedure), corticosteroids (for approximately 5 days from the interventions to reduce the incidence of PRS), antiemetics and analgesics before the interventions and as needed [15]. Pretreatment absorbed dose estimations are well performed otherwise radiation induced liver disease and radiation pneumonitis could develop.

Post-treatment Follow up

Treatment response to radioembolization could be evaluated radiologically and metabolically. From the radiological aspect, contrast enhanced Computed Tomography **(ceCT)** or Magnetic Resonance Imaging **(MRI)** can be used. Radiological size criteria (Response Evaluation Criteria in Solid Tumors **(RECIST)**) have limitations to evaluate response to radioembolization [16]. Indeed, tumors that responded to radioembolization may show an initial transient increase in size. Necrosis and ring enhancement are associated with radiological response findings [17] (Figure 3). In HCCs necrosis criteria has shown to be superior to predict pathological response [18]. Similarly necrosis following radioembolization demonstrated to correlate with survival in intrahepatic cholangiocarcinoma patients [19]. Secondary to radioembolization, ascites, pleural effusion, perihepatic fluid, hepatic fibrosis could be observed. Diffusion-weighted MRI has shown some promise in early detection of response in HCC, and could be considered. However, post-radioembolization diagnostics still remain an open issue, especially in patients with partial response or stable disease -which represent the majority of cases. The optimal time for the evaluation of treatment response is also debated. Although the first dimensional changes may already be observed after 1 mo, it is widely accepted that at least 3 to 4 mo are necessary to reliably estimate the actual response and therefore evaluate whether re-treatment may be considered. Metabolic response evaluation may be performed with 18F-FDG PET/CT and it is especially beneficial in colorectal cancer liver metastases. Advantage of metabolic imaging is the possibility to response prediction within 6-8 weeks when radiological changes do not occur yet [20].

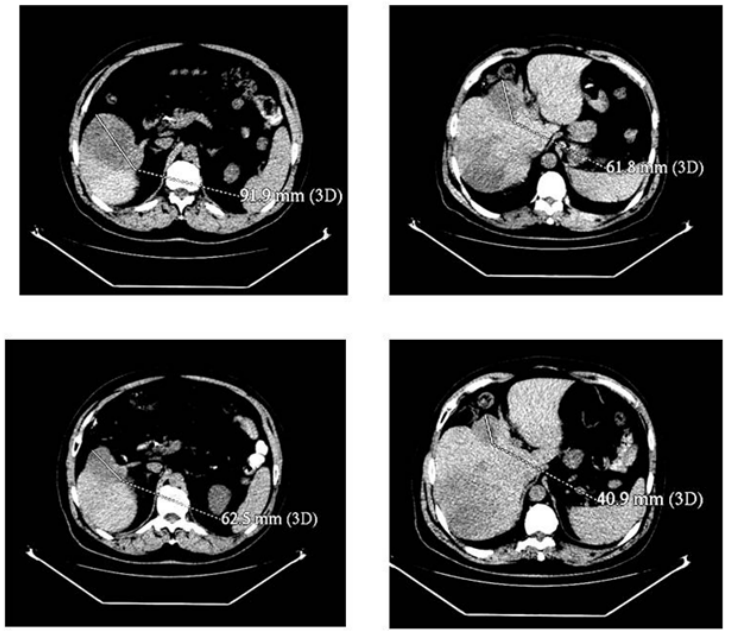

Figure 3: Pre and posttreatment axial CT images of patients who received 1.6 GBq Y^{90} microspheres treatment for neuroendocrine tumor liver metastases revealed partial response.

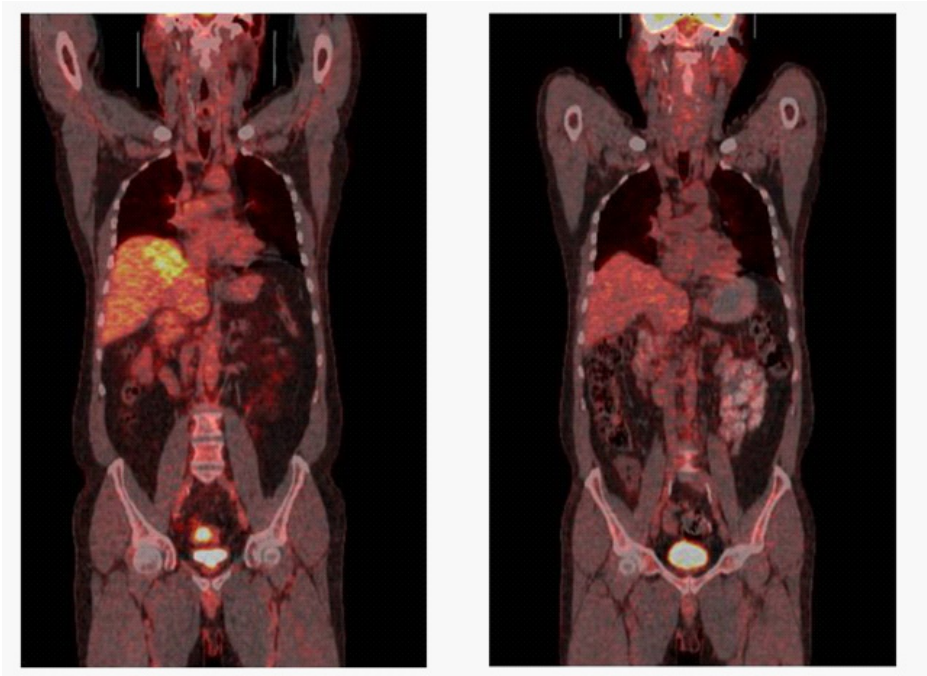

Figure 4: Pre and postreatment fused F^{18} FDG PET/CT images of patients who received 1.8 GBq Y^{90} microspheres treatment for CRC liver metastases demonstrated complete metabolic response.

Clinical Indications and Outcome

Hepatocellular Carcinoma (HCC)

Optimal treatment for early-stage (BCLC-A) HCC patients are the curative treatments such as liver transplant. Therefore, a group of patients has no chance for transplantation due to absence of living donors and to long waiting list for cadaver donors. During this waiting period, radioembolization as well as other locoregional threapies might have a role in order to limit the risk of local progression [21].

Patients with intermediate-stage (BCLC-B) HCC represent a very heterogeneous population [22,23]. TACE is usually the treatment of choice in this setting, additionally alternative loco-regional and sorafenib treatment are the other options. In the contraindication or failure of TACE, radioembolization might be an effective therapeutic option. Salem et al compared radioembolization and TACE on the basis of overall survival and median time to progression. They found that time to progression is longer after radioembolization (13.3 months vs 8.4 months, P = 0.046), and it was also associated with a more favorable safety profile [24]. Other data in the literature is similar [25-28]. Additionally another advantage of radioembolizastion is the lower incidence of adverse effects and need for hospitalization [28]. In the first sight, radioembolization might be seen more complex and expensive than TACE, however indirect cost could be lower in the consideration of its more rare repeated treatment sessions and associated with more favorable safety profile. A retrospective analysis has also suggested that both radioembolization and sorafenib are effective in patients with intermediate-stage HCC, and are associated with a similar survival [29].

However major indication for Sorafenib treatment includes advanced stage (BCLC-C) HCC patients. Overall survival with Sorafenib has reported about 11 months [30-33]. In the advance stage group, in this setting radioembolization could be an alternative to sorafenib with 6 to 10 months overall survival times [34,35]. The preliminary results of the SORAMIC trial, have shown that radioembolization followed by sorafenib appears to be as well tolerated as sorafenib alone [36]. In intermediate-stage HCC patients, downsizing may convert the disease to operable or may have a chance for liver transplantation [37]. Radioembolization seems to have higher tumor shrinkage percentage rate in the comparison to TACE (58% vs 31%, P = 0.023) [38]. In another problem for liver surgery in large extent patients is the insufficiency of the remnant liver tissue. In this patients Portal Vein Embolization **(PVE)** could be applied to induce hypertrophy of contralateral lobe. Radioembolization may induce a hypotrophy of the treated hepatic lobe and related with a hypertrophy of the contralateral lobe [39]. For this reason, radioembolization has been an alternative to PVE in HCC patients. Moreover, radioembolization have a treatment effect the in applied lobe and it reduces tumor progression risk [40].

Colorectal Carcinoma (CRC) Liver Metastasis

Radioembolization could be given in different settings for CRC liver metastases. Different randomized studies have been established to analyze the outcome of radioembolization versus or plus different chemotherapy regiments [41-45]. The first study has compared hepatic artery chemotherapy (HAC with FUDR 0.3 mg/kg/day for 12 days and repeated every 4 weeks for 18 months) vs HAC plus radioembolization. This study revealed a significant improvement of outcome was observed in the addition of radioembolization without any increase of toxicity. There was a significant increase in the complete and partial response rates (17.6% and 44%, P= 0.01) and prolongation of time to progression (9.7 months vs 15.9 months, p= 0.001) for patients receiving the combination treatment [41]. Van Hazel G et al have compared the outcome of radioembolization in the combination with 5FU and Leucovorin. Toxicity rate was higher in the combination group; however it decreased by modifying applied Y-90 microsphere activities. Progression free (18.6 vs 3.4 months, P<0.0005) and overall (29.4 vs 12.8, p=0.02) survival times was longer in the combination-therapy [42]. Same group also studied FOLFOX 4 oxaliplatin dose escalation in liver dominant metastatic chemotherapy naïve CRC patients. They demonstrated that FOLFOX 4 oxaliplatin dose could be successfully escalated to the standard level (85 mg/m^2). 90% of patients were responder accordinmg to RECIST criteria and rest of the patients had stable disease [43]. In an in vivo double-arm-controlled phase II trial, Gulec et al. compared the treatment responses of treated and untreated lobed after radioembolization in the combination with FOLFOX-6 of FOLFIRI. They used metabolic and anatomic response evaluations together. A decrease in Functional Tumor Volume **(FTV)** on F^{18} FDG-PET/CT imaging was seen in all except one patient. A significant difference between the change of FTVs in the tumors receiving chemotherapy plus radioembolization and chemotherapy only were 80.47% ± 25.67% and 41.32% ± 58.46% (P<0.01), 90.67% - 17.01% and 46.67% - 60.59 % (P <0.01), and 82.22% ± 38.85% and 56.00% ± 28.93% (P<0.08) at 4 weeks, 2-4 months, and 6-8 months after the treatment, respectively [45]. SIRFLOX study was designed to compare efficacy of mFOLFOX6 ± bevacuzimab (Arm A) vs mFOLFOX6 + radioembolization ± bevacuzimab (Arm B). The median overall PFS was 10.2 vs 10.7 months in arms A vs B, respectively (P=0.428) by Kaplan-Meier analysis; the median PFS in the liver was 12.6 vs 20.5 months in arm A vs B (P= 0.002) by competing risk analysis. Overall response rate (PR and CR) was 68.0% vs 76.4% in arm A vs B, respectively (P=0.113); hepatic response rate was 68.8% vs 78.7% in arm A vs B (P=0.042), including CR rate 1.9% vs 6.0% (P=0.02); the liver resection rate was 13.7% vs 14.2% in arm A vs B (P= 0.857) [46,47].

In chemorefractory patients, it may be administered in the salvage protocol. In this case, response to treatment has been reported as 35.5% by CT and 85% by F^{18} FGD PET/CT. Moreover response to radioembolization has been found highly correlated with median survival times (10.5 vs 4.5 months, p<0.0001) [48]. In another multicenter phase II trial, 50 chemorefractory (oxaliplatin and irinotecan based regiments) patients have been evaluated and response rates after single administration of Y^{90} microspheres was reported as 24% (range: 12.2%-35.8%).

Additionally 2 patients had a chance for surgical resection due to marked downsizing of their tumors. Similarly former study, the treatment response was associated with prolonged survival times (16 vs 8 months, p<0.0006) [49]. In another indication for radioembolization in CRC liver metastases is to induce hypertrophy in contralateral lobe during treatment of ipsilateral liver lobe in patients with insufficient liver remnant tissue. Thus; the remnant liver tissue of a group of patient could get sufficient to let surgical procedure.

OTHER TUMORS

Even in a salvage setting, radioembolization appears to be a reasonable technique with a relative wide safety margin. The use of radioembolization against to other primary liver tumors (cholangiocellular carcinoma.etc) and liver metastases from different primary cancers is also expanding. Such examples would include metastases from breast, uveal melanoma, neuroendocrine tumors, sarcoma, esophageal, endometrial, lung, ovarian and squamous cell carcinoma of the anus [50-54]. Because of limited number of patients, most of the data on radioembolization for other tumors are based on retrospective and small studies. Regardless primary origin of tumor, patient's life expectancy and performance status, vascularity of liver metastases, extrahepatic tumor load should be considered during pretreatment evaluation for radioembolization.

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