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Radioembolization for primary and metastatic liver cancer

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Abstract

The incidence of hepatocellular carcinoma is increasing. Most patients present beyond potentially curative options and are usually affected by underlying cirrhosis. In this scenario, trans-arterial therapies, such as radioembolization, are rapidly gaining acceptance as a potential therapy for hepatocellular carcinoma and liver metastases. Radioembolization is a catheter-based liver-directed therapy that involves injection of micron-sized embolic particles loaded with a radioisotope by use of percutaneous transarterial techniques. Cancer cells are preferentially supplied by arterial blood and normal hepatocytes by portal venous blood; radioembolization therefore specifically targets tumor cells with a high dose of lethal radiation and spares healthy hepatocytes.

The antitumor effect mostly comes from radiation rather than embolization. The most commonly used radioisotope is Yttrium-90. The commercially available devices are TheraSphere® (glass-based) and SIR-Sphere® (resin-based). The procedure is performed on outpatient basis. The incidence of complications is generally less than other locoregional therapies and may include nausea, fatigue, abdominal pain, hepatic dysfunction, biliary injury, fibrosis, radiation pneumonitis, gastrointestinal ulcers and vascular injury. However, these can be avoided by meticulous pretreatment assessment, careful patient selection and adequate dosimetry. This article focuses on both the technical and clinical aspects of radioembolization with emphasis on patient selection, uses and complications.

2. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and the third most common cause of cancer-related mortality ^{1,2}. The incidence of HCC has tripled in the USA from 1975-2005 ³. Metastatic disease to the liver is the most common form of hepatic malignancy ⁴. Common tumors that metastasize to liver include colorectal carcinoma, breast carcinoma and neuroendocrine tumors. Surgical interventions (resection/

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liver transplantation) provide curative options for selected patients, but many patients are precluded from these treatment ^{5,6}.

Given this background, novel liver-directed loco-regional therapies have been investigated for the treatment of primary and metastatic liver cancers. Among these are image-guided endovascular therapies including chemoembolization and radioembolization.

Radioembolization is defined as the injection of micron-sized embolic particles loaded with a radioisotope by use of percutaneous transarterial techniques in order to deliver high focal doses of radiation to cancers. In HCC, chemoembolization and radioembolization can be used to delay disease progression, downstage or bridge HCC in order to permit liver transplantation ⁷, or as palliative therapies. Chemoembolization is considered as a standard of care in HCC; radioembolization with Yttrium-90 has regulatory approval for HCC. Randomized controlled trials comparing chemoembolization and radioembolization are underway. Recently, a comparative effectiveness study of radioembolization versus chemoembolization in a cohort of 123 patients (without portal venous thrombosis and/or extrahepatic metastases at baseline) treated with radioembolization and 122 with chemoembolization was published ⁸. The investigators concluded that radioembolization leads to longer time-to-progression and reduced toxicity with similar survival outcomes when compared with chemoembolization.

Herein, we discuss radioembolization as a potential therapy for hepatocellular carcinoma and liver metastases. Our discussion incorporates both clinical and technical aspects of this therapy with emphasis on appropriate patient selection, indications, clinical efficacy and complications.

3. Radioembolization: Technical Aspects

3.1 Vascular anatomy of the Liver

Given that radioembolization is hepatic arterial directed therapy, special attention to vascular anatomy, reviewed here, is required. The liver has a dual blood supply (portal vein and hepatic artery). The portal vein, which carries venous blood from the gastrointestinal tract to the liver is the predominant source of vascular supply for hepatocytes. The hepatic artery proper is a branch of the common hepatic artery which itself arises from the celiac trunk. This branch divides into the right and left which supply their corresponding hepatic lobes. The right hepatic artery also gives off the cystic artery supplying the gall bladder. Interestingly, normal hepatocytes are primarily supplied by portal blood whereas cancer cells are supplied primarily by the hepatic artery ⁹⁻¹². This variable blood supply is exploited by intra-arterial therapies and forms the basis for prioritizing the delivery of cytotoxic therapy to the capillary bed of tumor cells via the hepatic arterial route while limiting the exposure to normal hepatocytes. Given this fact, very high doses of radiation can be selectively administered to hepatic tumors, with little dose to the surrounding liver.¹³

3.2 Available Radioisotopes

3.2.1 Yttrium-90—⁹⁰Y is the most commonly used radioisotope used for radioembolization. It is a pure beta emitter with a half-life of 64.2 hours. It decays into the stable element Zirconium-90. The range of tissue penetration of the emissions is 2.5 to 11 mm. It is the most commonly used radionuclide for the treatment of both primary and secondary liver malignancies. There are two forms available (TheraSphere and SIR-Spheres).

TheraSphere® (MDS Nordion, Ottawa, Canada) consists of nonbiodegradable glass microspheres that have a diameter between 20 and 30 microns. It was approved by the FDA in 1999 as a bridge to transplantation ¹⁴ and recently has been approved for use in HCC

patients with PVT. Six activity vials are available differing from each other only in the number of spheres per vial e.g. 1.2 million microspheres are present in a vial with an activity of 3 Gigabecquerel (GBq). Each microsphere has an activity of 2500 Becquerel at the time of calibration. The activity of the vial varies inversely with the time elapsed after calibration.

SIR-Spheres® (Sirtex, Lane Cove, Australia) consist of biodegradable resin microspheres. The spheres are slightly larger and less dense than TheraSphere® and hence associated with more embolic effect. One vial of SIR-Spheres® of 3 GBq is available and contains 40-80 million microspheres ranging from 20 to 60 microns. SIR-Spheres® was approved by the FDA for metastatic colorectal cancer to the liver. Each microsphere has a specific activity of 50 Bq at the time of calibration.

3.2.2 Iodine-131 Labeled Iodized Oil (I-131 Lipiodol)—I-131 is a beta and gamma emitter. The iodine moiety of lipiodol can be substituted for the radionuclide, ^{131}I . It is used exclusively for the treatment of HCC. It has a half-life of 8 days. The thyroid gland, due to its use of iodine to make thyroid hormones, is susceptible to the toxicity of ^{131}I . Therefore, the thyroid gland is blocked before and after the treatment to minimize toxicity. The radionuclide is excreted in urine and thus the patient has to be hospitalized for approximately six days after treatment as a radioactivity safety measure. Patients are told to refrain from possible conception until six months after treatment. The use of ^{131}I -Lipiodol has been studied in a prospective randomized trial in 142 patients where it was compared to chemoembolization. Overall survival rates at 6 months, 1, 2, 3, and 4 years were 69%, 38%, 22%, 14%, and 10%, and 66%, 42%, 22%, 3%, and 0% in the I-131 labeled Lipiodol and chemoembolization groups, respectively. Complete response in 1 and 0 patients and partial response in 15 and 16 patients were noted in the I-131 labeled Lipiodol and chemoembolization groups, respectively. The incidence of adverse effects was low in I-131 group versus chemoembolization group (3 severe side effects vs. 29, $P < 0.001$; 1 arterial thrombosis vs. 10, $P < 0.01$)¹⁵.

3.2.3 Rhenium-188 HDD Labeled Iodized Oil—Transarterial radionuclide therapy (TART) with Rhenium-188 (^{188}Re) 4-hexadecyl-1, 2, 9, 9-tetramethyl-4, 7-diaza-1, 10-decanethiol (HDD)-labeled iodized oil has been recently studied for use in inoperable HCC. ^{188}Re has a shorter half-life (16.9 hours), high beta energy (maximum: 2.1 MeV) and low gamma energy (155 keV) emissions, and is available through a Tungsten-188 (^{188}W - ^{188}Re) generator¹⁶. The quantity of ^{188}Re HDD iodized oil (lipiodol) administered is based on the radiation absorbed dose (RAD) to critical organs, which is calculated after administration of test dose of the radioconjugate, transarterially¹⁶. The incidence of serious adverse events is low.

3.2.4 Milican/Holmium-166 Microspheres (HoMS)—Holmium-166 is used in a complex with Chitosan, which is a unique substance derived from chitin. It has the ability to liquefy in an acidic environment and form a gel in basic environments. The gel has embolic effects. Holmium-166 has a half-life of 26.8 hours and emits both a beta particle for therapy and a gamma that can be used for imaging. The use of Holmium/chitosan complex (Milican, Dong Wha Pharmaceutical Co., Seoul, Korea) has been shown to be effective in treating small HCCs in a novel study based on 40 patients with single HCC <3cm in size from Korea¹⁷ with satisfactory response rates and survival rates of 87.2%, 71.8%, and 65.3% at 1, 2 and 3 years respectively. Two patients had transient bone marrow depression requiring hospitalization.

Since ^{90}Y is the most commonly used radioisotope, it will be the topic of discussion for the remaining portion of this manuscript.

3.3 Pretreatment Evaluation

All patients undergo pretreatment assessment consisting of history, laboratory and imaging work-up. Pretreatment cross sectional imaging is essential for treatment planning and post treatment response assessment. All patients undergo the following essential pretreatment evaluation procedures approximately 1 week before the planned first treatment. They are not usually repeated for any subsequent treatments.

3.3.1 Pretreatment Angiography—Given the high propensity for arterial variants and hepatic tumors to exhibit arteriovenous shunting, all patients being evaluated for ^{90}Y must undergo pretreatment mesenteric angiography^{10-12,14}. This permits tailoring of the treatment plan according to each patient's individual anatomy and helps assess for the possibility of any inadvertent spread of the microspheres to non-target organs¹⁸. This can be mitigated by prophylactic embolization of aberrant vessels to non-hepatic targets.

An aortogram is necessary to assess the tortuosity and the presence of atherosclerosis in the aorta; it also permits optimal base catheter selection. The superior mesenteric and celiac trunk angiograms permit the interventional radiologists an opportunity to study the hepatic vascular anatomy. The patency of the portal vein and the presence of arterio-portal shunting are also assessed. Prophylactic embolization of the gastroduodenal artery and right gastric artery is recommended as a safe and efficacious mode of minimizing the risks of hepatoduodenal flow since this can lead to inadvertent deposition of microspheres in the gastrointestinal tract causing severe ulcers that are highly symptomatic and difficult to manage^{10,19,20}. Other vessels that need to be interrogated and potentially embolized are the falciform, inferior esophageal, left inferior phrenic, accessory left gastric, supraduodenal and retroduodenal arteries.

Diagnostic angiography is essential to ensure that the blood supply to the tumor(s) has been adequately identified as incomplete identification of the blood supply to the tumor may lead to incomplete targeting and treatment. This facilitates accurate calculations of target volumes²¹.

3.3.2 Pulmonary Shunting and Technetium-99m labeled macroaggregated albumin ($^{99\text{m}}\text{Tc-MAA}$) scan—In contrast to metastatic tumours, one of the angiographic features of HCC is the direct arteriovenous shunting bypassing the capillary bed to the liver²²; shunting of ^{90}Y microspheres to lungs therefore becomes a concern as this could result in radiation pneumonitis²³. Because the size of $^{99\text{m}}\text{Tc-MAA}$ particle closely mimics ^{90}Y , it is assumed that the distribution of the two will be identical; this concept is utilized in assessing splanchnic and pulmonary shunting. It is important to correlate the findings of angiography to the findings of the $^{99\text{m}}\text{Tc-MAA}$ scan as the proximity of some portions of the gastrointestinal tract to the liver may confuse the findings of nuclear medicine scans. Lung shunt fraction (LSF) is used to calculate the dose delivered to the lungs and appropriate adjustment for this parameter minimizes the risk of radiation pneumonitis. If LSF is deemed to be high, appropriate reduction is made in the overall dose administered.

3.4 Dose Calculation

3.4.1 Dose Calculation for TheraSphere®—The volume of the liver to be infused in cubic centimeters is calculated using 3-dimensional reconstruction through commercially available software. This value is used to calculate the mass of infused liver tissue in grams by multiplying it by a factor of 1.03 mg/cc. The activity administered to the target volume of the liver (A) in GBq, assuming uniform distribution of microspheres, is calculated using the following formula:

$$A = D \times m / 50$$

Where D is the dose administered in Gray (Gy) and m is the mass in kilograms (kg).

Dose delivered to the treated mass also depends on the percent residual activity (R) in the vial after treatment and the LSF which is calculated beforehand using the ^{99m}Tc -MAA scan. These factors are accounted for in the following formula,

$$D = A \times 50 \times (1 - \text{LSF}) \times (1 - R) / m$$

3.4.2 Dose Calculation for SIR-Spheres®—The dosimetry model for SIR-Spheres® is based on whole liver infusion. The calculated activity in GBq of the whole liver is multiplied by the ratio of the target volume to the whole liver volume. Three methods for dosimetry of SIR-Spheres® are recommended by the manufacturers. The partition method is seldom used as it is applicable only in special circumstances. The simple empiric method is based on percent tumor involvement of liver and recommends doses of 2 GBq for ≤25% involvement, 2.5 GBq for 25-50% involvement and 3 GBq for >50% involvement.

The most widely used body surface area (BSA) method is calculated as follows,

$$A = \text{BSA} - 0.2 + (\% \text{ tumor burden} / 100)$$

Where A is the activity in GBq, BSA is the body surface area in meters squared (m^2), and % tumor burden is the percentage of the liver that is involved by tumor. There is often a 20% dose reduction factor that is applied in order to reduce the incidence of radiation pneumonitis. The issue of LSF is not commonly associated with metastatic disease and hence dose reduction is usually applied only for HCC. Moreover, the dose calculation is independent of tumor burden.

4. Radioembolization: Clinical Aspects

4.1 Patient Selection

All patients undergo clinical evaluation which includes history, physical examination, laboratory profile including liver function and detailed radiological imaging to establish the extent of disease. A multidisciplinary team consisting of professionals from interventional radiology, hepatology, medical, surgical and radiation oncology, transplant surgery and nuclear medicine is involved in selecting suitable patients for radioembolization. Patients are selected according to following criteria:

4.1.1 Inclusion criteria—(a) confirmed diagnosis of surgically unresectable HCC or intrahepatic cholangiocarcinoma (ICC) or metastatic disease, (b) age >18 years, (c) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, (d) adequate pulmonary function test findings, (e) adequate hematologic parameters (granulocyte count $>1.5 \times 10^9/\text{L}$, platelet count $>50 \times 10^9/\text{L}$), renal function (serum creatinine level $<2.0 \text{ mg/dL}$) and liver function (serum bilirubin level $<3.0 \text{ mg/dL}$) and, (f) ability to undergo angiography and selective visceral catheterization ^{24,25}. Most commonly, patients with Child-Pugh score ≤ 7 are eligible for radioembolization; however, Child-Pugh score > 7 is not an absolute contraindication.

4.1.2 Exclusion criteria (Contraindications)—(a) any other liver therapy planned for cancer treatment, (b) uncorrectable flow to the gastrointestinal tract, (c) estimated radiation doses to the lungs greater than 30 Gy in a single administration or 50 Gy in multiple administrations, and (d) significant extrahepatic disease representing imminent life-threatening outcome.

4.2 ⁹⁰Y Radioembolization Procedure

The procedure is carried out according to previously published guidelines^{21,26}. The administering device for the administration of ⁹⁰Y is designed to minimize radiation exposure to persons involved in the procedure. The tumor is approached under fluoroscopic guidance; the activity vial is injected into the vessel feeding the tumor. Tumor distribution guides for the selectivity of the treatment i.e. to one or more lobes/segments as required. A physicist is present throughout the case to ensure that proper protocols are followed to minimize accidental radiation exposure. Radioembolization is performed as an outpatient procedure and patients are discharged 4-6 hours after treatment¹⁴. Due to the possibility of GI ulcers, prophylactic proton pump inhibitors are advised for a period of 14 days.

4.3 Post-treatment Assessment

Clinical, laboratory and radiological follow-up is essential to monitor response to treatment and identify any toxicity. Regular laboratory follow-up includes the hepatic panel and tumor markers. Cross sectional imaging is performed one month post-treatment and then every three months to assess response to treatment or progression of disease.

4.4 Response Assessment Following Radioembolization

4.4.1 Imaging Following Radioembolization—Changes in tumor size using World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, and amount of enhancing tissue by European Association for the Study of the Liver (EASL) guidelines are used to assess tumor response to therapy following radioembolization²⁷⁻²⁹.

In a recent series of 245 patients treated with locoregional therapies, Riaz *et al* investigated the concept of the Index lesion and inter-method agreement between RECIST, WHO and EASL guidelines. They concluded that there is high agreement between RECIST and WHO guidelines but low between each of these and EASL. Moreover, the primary index lesion (the dominant lesion) can be used to measure response to therapy by applying the above mentioned guidelines³⁰. In another series of 35 patients who underwent radioembolization, Riaz *et al* correlated post-treatment radiologic findings to pathologic data³¹. They concluded that changes in amount of enhancing tissue and size of a tumor following therapy are predictors of complete pathologic necrosis. In a recent study, investigators compared various combinations of WHO, EASL and RECIST guidelines and devised various scoring systems based on the combinations of these guidelines. They concluded that EASL×WHO scoring system provides a simple and clinically acceptable method of response assessment and radiological-pathological correlation³².

Rhee *et al* concluded that HCC tumor response using diffusion-weighted imaging changes after Yttrium-90 radioembolization (⁹⁰Y) preceded anatomic size changes. Conventional anatomic imaging studies are not able to assess tumor response until six weeks have elapsed after treatment and functional MRI may have a role in earlier detection of tumor response³³.

In addition to conventional cross-sectional imaging such as CT and MRI, positron emission tomography (PET) has a role in assessing response to treatment for secondary liver tumors.

4.4.2 Using Tumor Markers as Biomarkers—Riaz *et al* investigated the use of AFP in locoregional therapies; they concluded that AFP response seen after transarterial locoregional therapy could be used as an ancillary method of assessing tumor response and potential surrogate for survival³⁴. Although utilized clinically, the benefit of other tumor markers such as carcinoembryonic agent and CA 19-9 in assessing response following radioembolization of secondary liver tumors have not been studied.

4.5 Indications for Radioembolization

4.5.1 Hepatocellular carcinoma (HCC)—The use of radioembolization has been shown to limit progression of the disease in HCC. This helps in bridging the patient to transplant as it allows the patient more time to wait for donor organs³⁵. Lewandowski *et al* compared chemoembolization to radioembolization in their retrospective analysis in patients with HCC beyond Milan criteria³⁶. Radioembolization was shown to be a better tool than chemoembolization for downstaging the disease to within transplant criteria. In a recent study analyzing the long-term outcomes of patients treated with ⁹⁰Y for HCC, investigators concluded that patients with Child-Pugh A class disease, with or without PVT, benefited most from the treatment, and patients with Child-Pugh B class disease who had PVT had poor outcomes. Time-to-progression was higher for Child-Pugh A and B patients without PVT (15.5 and 13 months respectively) than those with PVT (5.6 and 5.9 months respectively). Overall survival for patients with Child-Pugh A and B disease was: CP-A, 17.2 months; CP-B, 7.7 months; $P = .002$) Time-to-progression and overall survival varied by patient stage at baseline³⁷.

Malignant vascular invasion in patients with advanced HCC is an exclusion criterion for transplantation. Embolic therapies are also relatively contraindicated as they may lead to further deterioration of blood supply to already compromised liver parenchyma. However, patient with vascular invasion have shown a survival benefit with ⁹⁰Y as it is not a macro-embolic procedure³⁸.

Kooby *et al* have compared radioembolization to chemoembolization in a series of retrospectively studied patients and conclude that radioembolization and chemoembolization have similar effectiveness and safety profiles³⁹. In a similar analysis, Carr *et al* performed a retrospective study of North American patients who had unresectable HCC⁴⁰. They concluded that radioembolization and chemoembolization are equivalent locoregional therapies for patients with unresectable and non-metastatic HCC.

In a recent comprehensive comparison analysis, Salem *et al* compared 123 patients treated with radioembolization and 122 patients with chemoembolization. They concluded that radioembolization leads to longer time-to-progression and less toxicity than chemoembolization with similar survival times⁸.

4.5.2. Intrahepatic Cholangiocarcinoma (ICC)—A pilot study analyzing the use of ⁹⁰Y in 24 patients with biopsy proven ICC has shown a favorable response to treatment and survival outcomes⁴¹. Patients with better performance status according to the Eastern Cooperation Oncology Group (ECOG) criteria had a significantly better survival in this study. In a recent series of 25 patients with unresectable intrahepatic cholangiocarcinoma, Saxena *et al* studied the safety and efficacy of ⁹⁰Y radioembolization. They concluded that ⁹⁰Y may be a safe and efficacious treatment for unresectable ICC with a median survival of 9.3 months and low incidence of grade 3 toxicities. Further investigations are underway⁴².

4.5.3 Secondary liver tumors

Colorectal Carcinoma (CRC): Radioembolization is employed to treat patients with unresectable hepatic CRC metastases. In a phase III randomized trial of 74 patients with CRC liver confined metastases, systemic chemotherapy alone was compared to the combination of radioembolization and systemic chemotherapy; the combination was shown to have significantly better tumor response (44% vs. 17.6%, $P = 0.01$), a longer time to progression (15.9 vs. 9.7, $P = 0.001$), similar survival outcome (72%, 39%, 17% and 3.5%, compared to 68%, 29%, 6.5% and 0% and 1,2,3 and 5 years respectively) and an acceptable safety profile⁴³. Studies have shown a better response with increasing doses; a study showed that doses >95 Gy (median) reduced mortality by 50% and were associated with odds of tumor response of 3.1 times greater than the odds of tumor response for doses ≤ 95 Gy.⁴⁴

In a series of 72 patients with unresectable hepatic colorectal metastases, Mulcahy et al investigated the safety and efficacy of ^{90}Y radioembolization. They observed that grade III and IV bilirubin toxicities were seen in 12.6% of patients. The CT response rate was 40.3%; PET response rate was 77%, and the median response duration and time to hepatic progression was 15 and 15.4 months respectively. Overall survival was 14.5 months from first treatment date. They concluded that ^{90}Y is a safe and efficacious therapy for colorectal metastases⁴⁵.

In a recent multi-center phase II trial, Cosimelli *et al* found that radioembolization produced meaningful responses and disease stabilization in patients with advanced, unresectable and chemorefractory metastatic CRC. By RECIST criteria, complete response, partial response, stable disease and progressive disease were noted in 22%, 24%, 44% and 8% patients respectively. Median overall survival was 12.6 months.⁴⁶

Sharma *et al* performed a phase I study analyzing the combination of radioembolization with modified FOLFOX4 systemic chemotherapy in patients with unresectable CRC metastases in the liver in a series of 20 patients with the primary endpoint of toxicity⁴⁷. Five patients experienced grade 3 abdominal pain (two of whom had microsphere-induced gastric ulcers); grade 3 or 4 neutropenia was recorded in 12 patients; one episode of transient grade 3 hepatotoxicity was noted. Partial responses were demonstrated in 18 patients and stable disease in two patients. Median progression-free survival was 9.3 months, and median time-to-progression in the liver was 12.3 months. They concluded that this chemo-radiation regimen merits investigation in a phase II-III trial.

In a recent multicenter phase III randomized trial of 46 patients with unresectable liver-limited metastatic colorectal cancer, Hendlisz et al compared intravenous fluorouracil alone (arm A) with combination of radioembolization and intravenous fluorouracil (arm B). Median overall survival was 7.3 and 10.0 months in arms A and B respectively ($P = 0.80$). Median time to tumor progression (TTP) was 2.1 and 4.5 months, respectively ($P = 0.03$). Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after radioembolization plus FU treatment ($P = 0.10$). They concluded that combination therapy is well tolerated and significantly improves time-to-progression compared with fluorouracil alone, and that this procedure is a valid therapeutic option for chemotherapy-refractory liver metastases from CRC⁴⁸. Due to low accrual and follow up longer than planned, the trial was closed earlier with 46 patients included in the study instead of the anticipated 58 patients required to obtain estimated 90% power.

Neuroendocrine Tumors: Patients with unresectable metastatic neuroendocrine tumors have also been treated with radioembolization, with limited toxicity and prolonged responses noted. A 148 patient analysis by Kennedy reported response rates of 63.2% with

survival of 70 months⁴⁹. In a multicenter phase II study with 42 patients of hepatic neuroendocrine tumor metastases, Rhee et al investigated the efficacy and safety of ⁹⁰Y radioembolization. They observed that 92% and 94% of patients treated with glass and resin microspheres respectively showed either partial response or stable disease at 6 months and median survival was 22 and 28 months respectively. Complete response was not observed in any patient. Grade 3 toxicities were recorded in 6 patients and included bilirubin toxicity (n=1), ALT toxicity (n=1), AST toxicity (n=1) and ALP toxicity (n=3). They concluded that ⁹⁰Y is a viable therapy with acceptable toxicity for hepatic metastases of neuroendocrine tumors⁵⁰.

Other Metastases: ⁹⁰Y has been used to treat patients with other primary cancers metastatic to liver with variable results. Since not established in these tumor types, we recommend that it be limited to use in patients unsuitable for standard systemic therapies or those who have become chemorefractory⁵¹.

Breast cancer has a tendency to metastasize to the liver. However, a survival benefit from this treatment in this patient population has not been established. Bangash et al investigated ⁹⁰Y radioembolization in 27 patients with progressing liver metastases of breast cancer on standard polychemotherapy. The response rate was 39.1%; stable and progressive disease was seen in 52.1% and 8.8% respectively; response on PET was noted in 63%. Median survival was 6.8 and 2.6 months in patients with ECOG 0 vs. 1, 2 and 3. 11% of patients showed grade III bilirubin toxicity. They concluded that ⁹⁰Y may be a viable option for treating patients with breast cancer metastases to liver who have progressed on standard polychemotherapy⁵². Coldwell et al investigated the use of ⁹⁰Y microspheres in the treatment of unresectable chemorefractory liver metastases from breast cancer in 44 patients in a multi-institutional study. No treatment-related procedure deaths or liver toxicity was seen. Computed tomographic imaging partial response was 47% and positron emission tomographic response 95%. Patients without PET or CT response had a median survival of 3.6 months. Survival was longer for responders and patients with slowly progressing disease; however, median survival was not reached with a follow up of 14 months.⁵³.

4.6 Complications and Toxicities

The post-radioembolization syndrome (PRS) consists of the following clinical symptoms: fatigue, nausea, vomiting, anorexia, fever, abdominal discomfort, and cachexia. However, it occurs less commonly after radioembolization due to the small particle size and microembolic effect⁵⁴⁻⁵⁶. Serious adverse events related to radioembolization are explained below:

4.6.1 Hepatobiliary dysfunction—Radiation induced liver disease (RILD) usually occurs between four to eight weeks after radioembolization; its incidence varies from 0%-4%. Classic and non-classic RILD may be seen following radioembolization. Ascites and jaundice are associated with an increased risk of ultimate liver failure⁵⁷. The presence of factors such as abnormal hepatic functions at baseline, increased age and activity delivered may influence the risk of patients to RILD. It has been shown that liver radiation dose to a maximum of 150 Gy for a single administration is associated with increased risk of liver toxicities. The biochemical toxicity rates following radioembolization have ranged between 15-20%^{57,58}.

The incidence of biliary sequelae after radioembolization is reported to be <10%. According to Atassi *et al*, less than 2% of patients required intervention for the biliary toxicity induced by radioembolization³³. These included drainage of three bilomas, one abscess and two cholecystectomies. Radiation-induced cholangitis has also been reported³³.

In the long-term, radioembolization has been shown to cause liver fibrosis, resulting in the contraction of the hepatic parenchyma and portal hypertension radiologically. Despite the imaging findings indicative of portal hypertension, the clinically significant occurrence of portal hypertension is low,⁵⁹ as clinically relevant manifestations such as reduced platelet counts (<100,000/dL) or variceal bleeding are rarely seen. It is recommended to observe for radiologic and clinical evidence of portal hypertension routinely, as this is not an acute process^{60, 61}. This finding is more commonly seen with bilobar treatment and its incidence is increased in patients who have chemotherapy associated steatohepatitis. The presence of preexisting cirrhosis leading to portal hypertension in most HCC patients makes them more susceptible to the aggravation of this complication.

4.6.2 Radiation Pneumonitis—The incidence of radiation pneumonitis is less than 1% if standard dosimetry protocols are followed⁶². Caution has to be taken when the LSF is >13% and resin microspheres are used⁶³. A restrictive pulmonary dysfunction may be seen after radioembolization in a few cases with a predisposing high LSF. The LSF is used to calculate the dose that will be administered to the lung; patients with elevated LSF resulting in a delivery of >30 Gy in a single session or >50 Gy cumulatively over multiple sessions are contraindicated from receiving radioembolization⁶⁴.

4.6.3 Gastrointestinal Complications—Gastrointestinal complications after radioembolization have been reported; the incidence is <5% when proper techniques are used i.e. slow and controlled injection of microspheres and prophylactic coil embolization of vessels to prevent deposition of microspheres in the GI tract.⁶⁵ The inadvertent deposition of microspheres to the gastrointestinal tract may result in ulceration^{65,66}. The pathophysiology behind this complication is the ectopic distribution of radioembolic microspheres into the lining of the gastrointestinal tract. Severe epigastric pain after treatment should be aggressively managed; early intervention may prevent serious complications. As opposed to a normal ulcer that develops at the mucosal surface, ⁹⁰Y-induced ulcers originate from the serosal surface.

4.6.4 Vascular Injury—Radioembolization is an invasive procedure. The incidence of vascular injury is very low and is mostly seen in patients previously exposed to systemic chemotherapy⁶⁷. This might cause increased fragility of the vessel wall leading to a susceptibility to injury (spasm, dissection). These adverse effects occur in <1% of patients and are related to technique/previous chemotherapy rather than the dose of microspheres.

5. Conclusion

Radioembolization is a novel trans-arterial locoregional therapy that is gaining recognition as a treatment option for primary and metastatic liver cancers. The incidence of complications is low and can be further reduced by rigorous pretreatment assessment and careful patient selection i.e. patients with preserved liver function without ascites or encephalopathy, Child-Pugh score ≤7, hypervascular tumors and low lung shunt fraction. Randomized comparative studies with other therapies are lacking; however a comparative effectiveness study with chemoembolization has been recently published, suggesting longer time-to-progression and reduced toxicities for patients treated with radioembolization (Table)⁸. Additional studies will be required to evaluate the combination of radioembolization with other locoregional and systemic therapies in order to enhance the treatment options for patient with liver cancer further.

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Table 1

Summary of few landmark studies

	Salem et al	Hilgard et al	Salem et al	Kennedy et al	Hendlish et al
Purpose	To assess clinical outcomes of HCC patients treated with ⁹⁰ Y	To assess clinical outcomes of HCC patients treated with ⁹⁰ Y in Europe	To compare the effectiveness of ⁹⁰ Y vs. TACE in HCC patients	To assess ⁹⁰ Y as a salvage therapy for unresectable colorectal liver metastases	Prospective randomized phase III trial comparing FU alone (arm A) with ⁹⁰ Y + FU (arm B) for unresectable CRC metastases
Disease	HCC	HCC	HCC	CRC metastases	CRC metastases
Patients	291	108	⁹⁰ Y: 123 TACE: 122	208	Arm A: 23 Arm B: 21
Response rate	WHO: 42% EASL: 57%	EASL: 40%	⁹⁰ Y: 49% TACE: 36%	CT: 35% PET: 91% CAE: 70%	-
TTP (months)	7.9	10	⁹⁰ Y: 13.3 TACE: 8.4	-	Arm A: 2.1 Arm B: 4.5
Survival (months)	Child-Pugh A: 17.2 Child-Pugh B: 7.7	16.4	⁹⁰ Y: 20.5 TACE: 17.4	Responders: 10.5 Nonresponders: 4.5	Arm A: 7.3 Arm B: 10