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REVIEW

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Radioembolization for the Treatment of Primary and Metastatic Liver Cancers

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Abstract

Radioembolization using ^{90}Y microspheres (glass or resin) has been introduced as an effective intraarterial therapy for unresectable primary and metastatic liver cancers. Although the basic therapeutic effect of chemoembolization results from ischemia, the therapeutic efficacy of radioembolization comes from radiation. Furthermore, compared with surgical resection and local ablation therapy, radioembolization is available with less limitation on the sites or number of liver cancers. The radioisotope ^{90}Y is a β-radiation emitter without γ-radiation, with the emission of secondary bremsstrahlung photons and small numbers of positrons. Administration of ^{90}Y microspheres into the hepatic artery can deliver a high dose of radiation selectively to the target tumor with limited radiation exposure to the surrounding normal parenchyma, and has low systemic toxicity. In general, radioembolization has been considered for patients with unresectable primary or metastatic liver-only or liver-dominant cancers with no ascites or other clinical signs of liver failure, life expectancy of > 12 weeks, and good performance status. Here, we review the current radioactive compounds, pretreatment assessment, and indications for radioembolization in patients with hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and liver metastases from colorectal cancer.

Keywords Radioembolization · Yttrium-90 · Hepatocellular carcinoma · Intrahepatic cholangiocarcinoma · Liver metastasis

Introduction

Primary liver cancer is one of the most commonly diagnosed cancers with high mortality worldwide [1]. Hepatocellular carcinoma (HCC) is the most common primary form and intrahepatic cholangiocarcinoma (ICC) comprises the second most common form [2]. Curative treatment for patients with HCC or ICC is surgical resection. However, unfortunately, many patients are not candidates for this because of the advanced stages of tumors at the time of diagnosis [3, 4]. Colorectal cancer (CRC) is also one of the most common cancers and often metastasizes to the liver via portal venous drainage [5]. Only 10–20% of patients with liver metastases from CRC can be treated using surgical resection [6].

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Radioembolization using yttrium-90 (^{90}Y) microspheres has been introduced as an innovative intraarterial therapy for patients with unresectable primary liver cancers and liver metastases [7]. Although the basic therapeutic effect of chemoembolization results from ischemia, the therapeutic efficacy of radioembolization is from radiation [3, 8]. Furthermore, compared with surgical resection and local ablation with radiofrequency or microwave, radioembolization is available with less limitation on the sites or number of liver cancers.

The radioisotope ^{90}Y is a β-radiation emitter without γ-radiation. However, it emits secondary bremsstrahlung photons and small numbers of positrons, which makes it amenable to scintigraphy and positron emission tomography (PET) imaging [8]. The physical half-life is 2.67 days (approximately 64 h); the maximum and mean decay energies are 2.26 and 0.94 MeV, respectively; and the maximum and mean soft tissue penetrations are 1.1 and 0.4 cm, respectively [9]. Transarterial injection of ^{90}Y microspheres can deliver high doses of radiation selectively to the target tumor, which will cause cellular breakdown and necrosis with limited radiation exposure to the surrounding normal parenchyma and relatively low systemic toxicity. Furthermore, the short range of tissue penetration by β-

radiation of ^{90}Y avoids possible unnecessary radiation exposure to the medical personnel and the patient's family [10].

In general, radioembolization has been considered for patients with unresectable primary or metastatic liver-only or liver-dominant cancer(s) with no ascites or other clinical signs of liver failure, life expectancy of greater than 12 weeks, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) of two or less who are usually tolerant to the treatment, with adequate hepatic arterial flow to the cancer(s) [11, 12]. The aim of this article is to review the current radioactive compounds, pretreatment assessment, and indications for radioembolization in patients with HCC, ICC, or liver metastases from CRC.

Radioactive Compounds

Since the first report of radioembolization for the treatment of unresectable liver cancer in 1965, a number of phase I trials were performed in the late 1980s and early 1990s for the development of glass or resin microspheres delivering localized radiotherapy [13, 14]. Subsequently, several studies on dose adjustment evaluated the safety and efficacy of glass microspheres for treating patients with HCC and resin microspheres for treating those with liver metastases from CRC [15–17]. As a result, in 1999, humanitarian device exemption was received from the United States Food and Drug Administration (U.S. FDA) for the treatment of unresectable HCCs using glass microspheres. Furthermore, in 2002, premarket approval by the U.S. FDA for resin microspheres was given for the treatment of liver metastases from CRCs [18, 19].

Currently, two types of ^{90}Y microspheres have been available for clinical use: glass microspheres (TheraSphere®, BTG International Ltd., London, UK) and resin microspheres (SIR-Spheres®, SirTex Medical, Sydney, NSW, Australia) (Table 1) [8, 20]. The TheraSphere® consists of 20–30-μm-diameter glass microspheres with ^{90}Y embedded in the matrix. SIR-Spheres® are 20–60-μm-diameter (median 33 μm) resin-based microspheres with ^{90}Y bound to the surface [21, 22]. The main difference between glass and resin microspheres is the activity in each: about 2500 Bq/particle for a glass microsphere at the production time and about 50 Bq/particle for a resin microsphere [23]. Thus, for the same given activity, resin microspheres require more to be delivered than do glass microspheres [24]. Theoretically, the delivery of more resin spheres could provide more uniform particle distribution and saturate larger hypervascular tumors with improved biological outcomes [25]. However, in practical terms with a higher number of particles, early stasis of resin microspheres at angiography during infusion is observed in some patients, particularly in those who have been heavily pretreated [26]. In such cases, incomplete dose delivery with the refluxed particles into off-target arteries might be possible. Thus, a small study reported that a higher effective dose of radiation is delivered to the targeted tumor by glass microspheres than resin microspheres [27]. However, the risk of disease progression was not actually increased by stasis [28]. At present, there is no strong evidence of overall differences in survival rates between patients treated with resin or glass microspheres [29, 30].

Pretreatment Assessment

Patients undergo preprocedural angiography of the celiac trunk for mapping the tumor-supplying hepatic artery. Protective coil embolization of the right gastric, gastroduodenal, and cystic arteries that usually arise distally to the origin of the hepatic artery should be performed to prevent extrahepatic depositions of microspheres in the bowel, stomach, or pancreas. Following this, ^{99m}Tc-macroaggregated albumin (MAA) is administered to the hepatic artery using the same catheter selected for the ^{90}Y radioembolization treatment. Because ^{99m}Tc-MAA particles (10–90-μm-diameter) are very similar in size to ^{90}Y microspheres, the distribution of therapeutic

Table 1 Comparison of ^{90}Y microspheres

	TheraSphere®	SIR-Spheres®
Material	Glass	Resin
Particle size (μm)	20–30	20–60
Number of spheres per dose	$1.2–8 \times 10^6$	$40–80 \times 10^6$
Specific gravity	High	Low
Specific activity per sphere (Bq)	2500	50
Embolic effect	Mild	Moderate
Activity available (GBq)	3, 5, 7, 10, 15, 20	3
Hepatopulmonary shut upper limit (%)	10	20
Handling for dispensing	Not required	Required
Solution used for suspension of spheres	Normal saline	Sterile water

microspheres can be simulated using ^{99m}Tc-MAA planar and/or tomographic scintigraphy [11].

All patients present with some degree of blood shunting between the liver and lungs, called a hepatopulmonary shunt fraction, which can be caused by normal collateral vessels, arteriovenous malformation, or hypervascular tumor vessels [31]. The hepatopulmonary shunt fraction is determined after the injection of ^{99m}Tc-MAA according to an equation using total counts in the lungs divided by the sum of total counts in the lungs and liver. Geometric mean total counts were acquired by regions of interest around the lungs and the liver. Excessive radiation exposure (> 25 Gy for resin microspheres and > 30 Gy for glass microspheres) to the lungs by hepatopulmonary shunt (> 20% for resin microspheres and > 10% for glass microspheres) and shunting to the gastrointestinal tract that cannot be corrected by pretreatment embolization are well-known contraindications for radioembolization [20, 32, 33]. High doses of radiation delivered to off-target organs such as the normal liver tissues, the lungs, the gastrointestinal tract, and the pancreas can result in serious complications.

Depending on the tumor response, life expectancy, and condition of the patient, radioembolization can be performed repeatedly [34]. However, repeated radioembolization of the whole liver can increase the risk of radioembolization-induced liver disease [35]. If radioembolization for both liver lobes is scheduled, two-staged sessions with an interval of 4–6 weeks for one lobe at a time are recommended. Repeated ^{99m}Tc-MAA scintigraphy is also mandatory in subsequent treatments to evaluate extrahepatic accumulations of microspheres caused by collateral vessels or by hepatopulmonary shunting, which might have changed in the meantime.

In patients with liver metastases, staging with ^{18}F-fluorodeoxyglucose PET should be considered to evaluate the extent of hepatic disease and to exclude extrahepatic manifestations. Because radioembolization is often used for palliative treatment, a minor extrahepatic spread of cancer is not an absolute contraindication for this management strategy [8].

Radioembolization in the Treatment for HCC

According to the Barcelona Clinic Liver Cancer (BCLC) guidelines, patients with very early (BCLC stage 0; single nodule ≤ 2 cm, preserved liver function, ECOG PS 0) or early (BCLC A; single or up to three nodules ≤ 3 cm, preserved liver function, ECOG PS 0) stage of HCC are eligible for curative therapies such as surgical resection or liver transplantation. Radiofrequency ablation can also be recommended for patients with early stages of HCCs. Transarterial chemoembolization (TACE) or radioembolization is available as alternative treatments to resection or ablation for patients with an intermediate stage (BCLC B; multinodular, preserved liver function, ECOG PS 0). For patients with advanced (BCLC C; portal invasion, extrahepatic spread, preserved liver function, ECOG PS 1–2) or terminal (BCLC D; end-stage liver cirrhosis, ECOG PS 3–4), systemic therapy with sorafenib or best supportive care is considered [36].

Hepatic intraarterial treatment for patients with HCC is based on the arterial hypervascularity of the tumor. While normal liver parenchyma derives more than 80% of its blood supply from the portal vein, HCC lesions receive more than 80% of their blood from the hepatic artery [37, 38]. Thus, highly selective doses of radiation can be delivered to tumors by the administration of radiopharmaceuticals into the hepatic artery [39].

Radioembolization has been investigated in patients with HCC as an alternative to TACE. Since two randomized controlled trials for TACE in the treatment of HCCs were published, patients with multinodular HCCs without vascular invasion and preserved liver function have been recommended as the best candidates for TACE with survival benefits [40, 41]. For radioembolization, patients who have failed TACE in early or intermediate stages of HCCs or patients with diffuse disease (> 4 tumors) or large tumors (> 5 cm) have been suggested as having the best indications [42]. Recently, a phase II prospective randomized study of TACE versus radioembolization for the treatment of HCCs was performed with 179 patients with BCLC stages A or B [43]. In that study, patients in the radioembolization group showed significantly longer median time to progression (> 26 months) than patients in the TACE group (6.8 months) with similar adverse events, which may be considered for bridging to transplantation. However, overall survival was not significantly different between the two groups suggesting that local tumor control was insufficient for improved survival.

HCC with portal vein thrombosis has been contraindicated for TACE for the increased potential of embolization causing hepatic infarction and liver failure [44]. The SorAfenib versus Radioembolization in Advanced Hepatocellular carcinoma (SARAH) and the Selective Internal Radiation Therapy Versus Sorafenib (SIRveNIB) phase III trials were undertaken to compare the efficacy and safety of radioembolization using ^{90}Y-resin microspheres with sorafenib in patients with locally advanced HCCs (Table 2) [45, 46]. In those studies, no significant differences in overall survival were found between the two modalities, but the reduced toxicity profile of radioembolization was regarded as helpful for selecting this treatment considering the patient's quality of life and tolerance.

The 2018 European Association for the Study of the Liver guidelines strongly recommended TACE for patients with BCLC stage B tumors. However, radioembolization was recommended with a moderate level of evidence in patients with BCLC stage A tumors for bridging to surgical transplantation and in patients with BCLC stages B or C when compared with TACE or sorafenib because of the lack of definite benefits for

Table 2 Comparison of radioembolization and sorafenib in patients with locally advanced hepatocellular carcinoma

Trial	No. of patients		Median OS (months)			Grade ≥ 3 AEs		
	RE	Sorafenib	RE	Sorafenib	*p*	RE (%)	Sorafenib (%)	*p*
SARAH (2017)	237	222	8.0	9.9	0.18	77	82	NR
SIRveNIB (2018)	182	178	8.8	10.0	0.36	27.7	50.6	< 0.001

RE radioembolization, *OS* overall survival, *AE* adverse event, *NR* not reported

overall survival despite good local tumor control and safety profile [47]. In addition, the 2019 National Comprehensive Cancer Network (NCCN) guidelines for hepatobiliary cancers still consider locoregional therapies such as ablation and arterially directed therapies (not specifically TACE or radioembolization) as category 2A (lower-level evidence and uniform NCCN consensus) options for patients with unresectable liver cancers [48].

Radioembolization in the Treatment for ICC

The highest curative chance for patients with ICC is offered by surgical resection. However, only 18–70% of patients present resectable cancer with a 20–40% 5-year survival rate even after surgery [49, 50]. For patients with locally advanced unresectable ICC, TACE has been an alternative to systemic chemotherapy [51]. Historically, external beam radiation showed a limited role in the treatment of liver cancers because of the fragility of adjacent normal liver parenchyma to radiation [52]. Scheuermann et al. reported interesting results in a retrospective study on the survival benefits of surgery, TACE, and systemic chemotherapy/best supportive care in patients with ICC [53]. Patients underwent TACE for treating local tumor infiltration of vital structures and tumor multiplicity. In that study, the median survival of patients undergoing surgery with a positive resection margin (11 months) or lymph node metastases (9 months) showed no survival benefit over patients receiving TACE (11 months). However, in the 273 patients, only 32 received TACE compared with 130 patients undergoing surgery and 111 patients receiving chemotherapy/best supportive care.

Because of the uncommon incidence and poor prognosis of ICCs, most reported data for radioembolization in patients with unresectable ICC were derived from small retrospective/prospective cohort studies. One open-label cohort study of 24 patients with unresectable ICC treated by ^{90}Y glass microspheres reported that patients with good performance status, no prior chemotherapy, no portal vein thrombosis, or peripheral rather than infiltrative tumor morphology presented with better survival rates with an acceptable safety profile [54]. Hoffmann et al. evaluated the efficacy and safety of radioembolization using ^{90}Y resin microspheres for the treatment of 33 patients with unresectable ICC with no portal vein thrombosis, no extrahepatic disease, and no response to other previous systemic or local therapies [55]. There were no major acute or delayed complications after radioembolization. The common clinical toxicities were increased bilirubin levels, abdominal pain, and nausea. Patients with an ECOG PS 0, tumor volume/liver volume ratios ≤ 25%, partial responses, or stable disease after radioembolization showed prolonged overall survival and times to progression. Reimer et al. also reported that a tumor burden of ≤ 25% was the only significant prognostic factor for patients with unresectable ICC who underwent radioembolization without prior ICC-related therapy such as resection, local ablation, TACE, or chemotherapy [56].

Radioembolization in the Treatment for Liver Metastases from CRC

Liver metastases may have variable vascularity, from hypovascular (e.g., the colonic, pancreatic, or breast) to hypervascular (e.g., renal, neuroendocrine, or thyroid) metastases. Typically, hypovascular liver metastases do not show enhancement as much as the normal background liver on contrast-enhanced computed tomography scans. However, even in hypovascular metastases, liver metastases demonstrate hypervascular hepatic arterial blood supply on catheter angiograms [57]. By preferential arterial flow to the tumor and selective catheter positioning, specific intraarterial therapy for liver metastases from CRC can be achieved [8].

The efficacy of radioembolization as a salvage treatment among patients with liver metastases from CRC has been evaluated. A phase III trial reported that significantly increased times to liver progression (2.1 vs 5.5 months) and times to tumor progression (2.1 vs 4.5 months) were shown in patients treated with fluorouracil chemotherapy alone and fluorouracil plus radioembolization, respectively [58]. Furthermore, in chemotherapy-refractory patients, radioembolization plus best supportive care demonstrated longer times to progression than best supported care alone (8.3 vs 3.5 months, respectively) [59].

The role of radioembolization as a first-line treatment was also evaluated. First-line radioembolization using ^{90}Y resin microspheres plus fluorouracil/leucovorin chemotherapy showed significantly improved progression-free (18.6 vs

3.6 months) and overall (29.4 vs 14.1 months) survival rates in patients with liver metastases from CRC compared with chemotherapy alone. However, the chemotherapy regimens used in those trials are currently outdated [18, 60].

Recently, radioembolization using ^{90}Y resin microspheres plus oxaliplatin-based chemotherapy (FOLFOX: leucovorin, fluorouracil, and oxaliplatin) as a first-line treatment for patients with unresectable liver-only or liver-dominant metastases from CRC was investigated in three large randomized controlled phase III trials, SIRFLOX (randomized comparative study of selective internal radiation therapy with ^{90}Y resin microspheres plus standard systemic chemotherapy regimen of FOLFOX versus FOLFOX alone as first-line treatment of non-resectable liver metastases from CRC), FOXFIRE (an open-label, randomized, phase III trial of 5-fluorouracil, oxaliplatin, and folinic acid with or without interventional selective internal radiation therapy as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic CRC), and FOXFIRE-Global [61, 62]. SIRFLOX and FOXFIRE trials were originally planned, but the FOXFIRE study took longer than expected to set up and recruit, so FOXFIRE-Global was added as an independent trial. Firstly, the SIRFLOX trial reported that the addition of radioembolization to first-line chemotherapy did not improve progression-free survival at any site (10.2 months for FOLFOX alone vs 10.7 months for FOLFOX plus radioembolization) but significantly delayed progression in the liver (12.6 months for FOLFOX alone vs 20.5 months for FOLFOX plus radioembolization) [63]. Designs and eligibility criteria were similar for the three trials so that they could be combined prospectively for analysis of primary and secondary endpoints [64]. In the combined analysis of these three trials, the cumulative incidence of first radiological progression in the liver was lower in the FOLFOX plus radioembolization group than in the FOLFOX alone group. However, the cumulative incidence of first progression outside the liver or death before radiological progression was higher in the FOLFOX plus radioembolization group than in the FOLFOX alone group. Furthermore, no significantly different overall survival rates (23.3 months for FOLFOX alone vs 22.6 months for FOLFOX plus radioembolization) or safety profile were found between the two groups [65]. Therefore, radioembolization as a first-line treatment in patients with liver metastases from CRC was not recommended.

Conclusion

Radioembolization has shown promising results with acceptable efficacy and safety in carefully selected patients with HCCs, ICCs, or liver metastases from CRC. For patients in whom surgical resection or other locoregional/systemic therapies are not indicated but who are tolerant to the treatment, radioembolization can provide improved survival and quality of life. To define the role and optimal patient population for radioembolization, further investigations and a better understanding of the treatment are necessary.

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Compliance with Ethical Standards

Conflict of Interest Eun Jeong Lee, Hyun Woo Chung, Joon Hyung Jo, and Young So declare that they have no conflicts of interest.

Ethical Statement This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed Consent For this type of study, formal consent is not required and informed consent is not applicable.

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