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Review

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Radioembolization for the treatment of hepatocellular carcinoma

Hyo-Cheol Kim

Department of Radiology, Seoul National University Hospital, Seoul, Korea

Transarterial radioembolization (TARE) with yttrium 90 (^{90}Y), an intra-arterial procedure performed by interventional radiologists, has begun being utilized in managing hepatocellular carcinoma (HCC) in Korea. There are two available TARE products: glass and resin microspheres with different physical characteristics. All patients undergoing TARE must be assessed with clinical examination and laboratory tests as well as a thorough angiographic evaluation. TARE is safe and effective in the treatment of unresectable HCC, as it has longer time-to-progression, greater ability to downsize tumors for liver transplantation, less post-embolization syndrome, and shorter hospitalization compared with chemoembolization. TARE can also serve as an alternative to ablation, surgical resection, portal vein embolization, and sorafenib. The utility of TARE continues to expand with new insights in interventional oncology. **(Clin Mol Hepatol 2017;23:109-114)**

Keywords: Hepatocellular carcinoma; Radioembolization; Transarterial radioembolization (TARE); Yttrium-90 (^{90}Y)

INTRODUCTION

Radioembolization is a transcatheter intra-arterial therapy using radioisotope yttrium 90 (^{90}Y), and is also called as transarterial radioembolization (TARE), selective internal radiation therapy (SIRT), and ^{90}Y therapy. Microspheres impregnated with ^{90}Y are delivered through the hepatic artery to the tumors with preferential blood flow. Whereas transarterial chemoembolization (TACE) is the standard treatment option for patients with intermediate stage of hepatocellular carcinoma (HCC), TARE is not included in the Barcelona Clinic Liver Cancer (BCLC) staging system guidelines. However, TARE is acquiring popularity in Western countries and expanding its indication. Current ongoing randomized clinical trials are expected to establish the role of TARE in the management of HCC in the near future. Until now, overall survival appears comparable between TACE and TARE, but TARE has longer time-to-progression, higher quality of life, and shorter hospitalization compared with TACE.[1-4] This review discusses the essential features of TARE, with emphasis on the interventional radiology perspective for the treatment of HCC.

MICROSPHERES

Currently, two ^{90}Y products are commercially available: TheraSphere® glass microspheres (BTG, London, United Kingdom) and SIR-Spheres resin microspheres (Sirtex Medical, North Sydney, Australia). Although both microspheres are approved by the US

Abbreviations:

BCLC, Barcelona Clinic Liver Cancer; CBCT, Cone-beam computed tomography; FDA, US Food and Drug Administration; FLR, future liver remnant; HCC, hepatocellular carcinoma; PVE, portal vein embolization; RFA, Radiofrequency ablation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TTP, time to progression; ^{90}Y, yttrium-90

Corresponding author : Hyo-Cheol Kim
Department of Radiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Tel: +82-2-2072-2584, Fax: +82-2-743-6385
E-mail: angiointervention@gmail.com
http://orcid.org/0000-0002-6016-247X

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Table 1. Comparison between glass microsphere and resin microsphere

	TheraSphere	SIR-Spheres
Half-life	64.2 hours	64.2 hours
Material	Glass	Resin
Size	20-30 μm	20-60 μm
Distribution of ^{90}Y	Mixed with glass matrix	Surface of resin sphere
Activity per sphere	2500 Bq*	50 Bq†
Available vial	3, 5, 7, 10, 15, 20 GBq*	3 GBq†
Limitation of total activity per treatment	No	3 GBq
Limitation of Lung shunting	Lung dose > 30 Gy	20%
Specific gravity	3.6 g/mL	1.6 g/mL
Number of sphere	1.2-8 milion	40-80 milion
Handling for dispensing	Not required	Required
Splitting one vial for two or more patients	Not possible	Possible
Embolic effect	Minimal	Moderate
Indication approved by FDA‡	Hepatocellular carcinoma	Colorectal metastases

*Activity is measured at calibration. Custom doses (3.5-19.5 GBq, 0.5 GBq increment) are also available.
†Activity is measured at administration.
‡FDA = Food and Drug Administration.

Food and Drug Administration (FDA) for the intra-arterial delivery of ^{90}Y, they are different with regard to microsphere composition, size, degree of embolic effect, and specific activity per sphere (Table 1). There are no randomized studies comparing the two microspheres, but current literature has shown similar clinical outcomes.[5-9] One recent article showed lower toxicity and improved overall survival with glass microspheres in the treatment of HCC with portal vein invasion.[10]

TheraSphere® has minimal embolic effect and can be infused without concern for blood flow stasis.[11] Glass microspheres have specific activity of 2500 Bq at calibration and variable specific activity (150-1000 Bq) at administration, depending on the treatment schedule. Specific activity of TheraSphere® would be about 250 Bq at week 2 (Tuesday treatment), which is preferred by the author. Custom doses between 3 GBq and 20 GBq with increments of 0.5 GBq are available, but usage of custom doses may sometimes delay the treatment schedule by 1 week. Six regular doses (3, 5, 7, 10, 15, and 20 GBq) may not be enough for fine dose adjustment, although this adjustment would not be critical in most cases. Several vials can be ordered for 1 treatment; thus, the maximal activity at administration is not limited, which can be an advantage over SIR-Spheres for large tumors. For large tumors, the week 2 treatment schedule is preferred for a more uniform tumor absorbed dose. Due to high activity of the microspheres, tumor absorbed dose is greater with TheraSphere® than with SIR-Spheres.

SIR-Spheres are a moderately embolic device consisting of slightly larger particles with a specific activity of 50 Bq at administration. One vial of 3 GBq is delivered to the hospital and should be dispensed by the nuclear medicine technician. Fine dose adjustment of each aliquot is possible. A higher number of microspheres are required to deliver an effective dose and angiographic stasis can be reached during the procedure.[12] Due to a higher number of microspheres, SIR-Spheres show more uniform tumor absorbed dose, particularly in large tumors. However, maximal activity of SIR-Sphere is 3 GBq, which may not be enough for a large tumor. Because SIR-Spheres are usually delivered to the hospital one day before the treatment, if SIR-Sphere is administered just after delivery, maximal activity could be as high as 3.7 GBq.

PATIENT EVALUATION

Patient selection for TARE is similar with that of TACE and includes an assessment of disease burden, biochemical profile, and performance status. In Korea, since radioactive microspheres are not currently reimbursed by the national health insurance system, economic status and private health insurance are important factors. Patients with an ECOG score >2 are excluded. Patients should have a serum bilirubin <2 mg/dL. Patients with excessive tumor burden (more than 70% of liver volume) are also excluded. Ideal candi-

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dates have HCC confined to the liver, although combination therapy of TARE and sorafenib can be used for patients with metastases.

ANGIOGRAPHIC CONSIDERATION

TARE requires pretreatment simulation test including hepatic angiography and ^{99m}Tc-MAA nuclear scan. Angiographic evaluation should examine celiac trunk and hepatic artery anatomy, non-hepatic artery from the hepatic artery, possible extrahepatic collateral arteries, portal vein patency, and the presence of arterioportal shunting. HCC may parasitize blood flow from extrahepatic collateral arteries, and failure to recognize a vessel feeding the tumor may lead to incomplete treatment. If radioactive microspheres are injected into non-hepatic arteries such as the cystic artery and gastric artery, serious complications can occur. Although coil embolization of the gastroduodenal artery is no longer routinely recommended, accessory left gastric arteries, right gastric arteries, hepatic falciform arteries and esophageal branches from the replaced left hepatic artery are commonly embolized before treatment if present. Cone-beam computed tomography has become an indispensable tool for angiographic evaluation and is particularly useful to visualize small non-hepatic arteries.

^{99m}Tc-MAA is injected into the hepatic artery to assess pulmonary shunting and distribution of microspheres. For TheraSphere®, a lung dose >30 Gy per treatment or cumulative lung dose of 50 Gy is the recommended limit. For SIR-Spheres, 20% of lung shunting is a suggested limit, and reduced activity is recommended for patients with 10-20% of lung shunting. Although single photon emission computed tomography (SPECT)/CT is not essential in dosimetry, SPECT/CT can show exact distribution of ^{99m}Tc-MAA on axial image, which may be useful to predict tumor response and elaborate dosimetry of partition model.

SPECIAL SITUATIONS

High lung shunt

In patients with high lung shunt fraction, common in huge tumor or hepatic vein invasion, several measurements can be suggested to prevent radiation pneumonitis. The most definite method is turning to an alternative treatment such as TACE or sorafenib. If hepatic vein tumor thrombus is the cause of high lung shunt, external radiation therapy to the hepatic venous thrombus can induce regression of the tumor thrombus and decrease lung shunt. Sorafenib may reduce lung shunting, and reassessment of lung shunting may be tried 1 or 2 months after sorafenib administration. Conventional TACE followed by TARE may be an option, even though conventional TACE may cause hepatic arterial attenuation, resulting in interfering the effect of subsequent TARE. If lung shunting is not excessive, a reduced dose of TARE (50-80 Gy to the target volume) is first tried, reassessment of lung shunting is performed 2 - 4 weeks later, and a subsequent regular dose of TARE is administered.

Radiation segmentectomy

Radiofrequency ablation (RFA) is an established treatment option for small tumors less than 3 cm, showing comparable clinical outcomes to surgical resection.[13] Superselective intensified radioembolization (termed *radiation segmentectomy*) is a feasible alternative to ablation or surgical resection.[14] Ablative radiation dose up to 1,000 Gy can be safely administered into one segment and induce complete necrosis of target tissue. Tumors meeting the following criteria are best for radiation segmentectomy: a small or medium size tumor, peripheral location, no extrahepatic collateral blood supply, apart from watershed zone, apart from gallbladder bed, and apart from falciform ligament.

Boosted SIRT

The concept of TARE is to deliver a radiation dose enough to kill all tumor cells while sparing healthy liver tissue. Boosted SIRT consists of increasing dosage over 200 Gy to the tumor and sparing normal liver tissue, which can maintain a patient's life. Boosted SIRT may result in a better response for aggressive tumors with portal vein invasion or large tumors >5 cm.[15] To prevent liver failure after boosted SIRT, it is most important to save normal liver tissue to at least 2 corresponding segments.

Radiation lobectomy

Some patients are unable to undergo surgical resection of HCC due to inadequate future liver remnant (FLR). Currently, portal vein embolization (PVE) is the established method to increase the FLR volume over 40% prior to resection, which is an accepted target for patient with cirrhosis. Unfortunately, PVE must delay surgical resection 1 or 2 months, and this may result in progression of the untreated tumor.

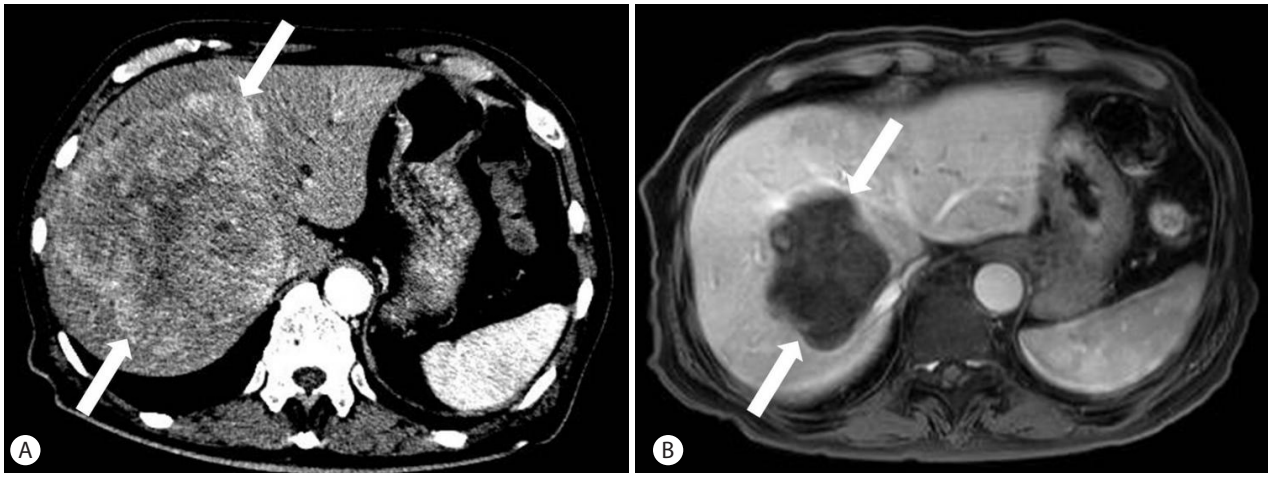

Figure 1. A 78-year-old man has 13 cm sized tumor in liver S4/8. Viral markers were negative, and Child-Pugh class was A5. Alpha fetoprotein was 769 ng/mL and PIVKA was 75,000 mAU/mL. (A) CT scan shows 13cm sized well-demarcated hypervascular tumor (arrows) in liver S4/8. (B) MR image 1 month after two sessions of TARE shows no enhancement of tumor (arrows). Note shrinkage of tumor to 7cm and hypertrophy of S2/3.

Radiation lobectomy, lobar infusion of ^{90}Y, has been shown to induce volumetric changes comparable to PVE and can control the tumor during the time to hypertrophy.[16] One disadvantage of radiation lobectomy is that it needs longer time to hypertrophy than PVE.[17] However, radiation lobectomy can control ipsilateral tumors and test tumor nature, making it a more suitable modality for some patients.

Recurrent or residual tumor after TARE

There is no guideline for the treatment of recurrent or residual tumor after TARE. Repeated TARE is technically and clinically possible in most patients, although many patients can not afford TARE due to its high cost. However, radiologists have to be cautious about making a decision to perform repeated TARE. If repeated TARE covers all liver parenchyme, radiation-induced liver disease may occur. Thus, if repeated TARE targets to the previously treated area and at least two segments of normal liver can be saved, repeated TARE can be safely performed (Fig. 1). If not, TACE would be chosen for preservation of liver function.

Previous TACE

Previous TACE itself is not a contraindication to TARE. But, the hepatic artery is severely attenuated by previous TACE, the effect of TARE could be significantly reduced. Since tumors unresponsive to TACE can be easily controlled by TARE, however, clinician should consider TARE in patients with HCC refractory to TACE, particularly in localized disease. Radiologists should confirm the integrity of the hepatic artery as well as possible extrahepatic collateral artery during the simulation test in patients with previous TACE.

OVERVIEW OF CLINICAL DATA

Many published articles regarding TARE in HCC has shown consistent outcomes in overall survival, ranging from 15.4 months to 17.2 months in BCLC B stage.[5-9] These results are similar to previously reported overall survival after TACE in BCLC B disease. Recent prospective randomized control trials also showed no statistical difference in overall survival between the two therapies.[18] Although many studies have not shown differences in overall survival, several studies have demonstrated that TARE had a longer time to progression (TTP) than TACE, thus TARE may have better role in a bridge to transplantation at centers with a long wait time. In addition, TARE was more effective in downstaging patients from United Network for Organ Sharing (UNOS) T3 to T2 than TACE.[19]

TARE can be performed on an outpatient base because of minimal incidence of post-embolization syndrome, while TACE typically needs brief hospitalization for symptom management. Many studies demonstrated that TARE results in shorter hospitalization times, fewer necessitated treatment sessions, and fewer visits to hospital than TACE. Thus, in terms of quality of life, TARE is superior to TACE.[20,21]

Oral sorafenib is considered the standard of care for BCLC C

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disease such as portal vein invasion. But, in Korea, sorafenib is not commonly chosen by hepatologists as a primary treatment option in HCC with portal vein invasion due to its low response rate. TACE followed by external radiation therapy showed better outcome than TACE alone or sorafenib.[22,23] Some studies have suggested that TARE is more advantageous than sorafenib in portal vein thrombosis.[24] Thus, further comparative study between TARE vs sorafenib vs TACE followed by external radiation vs other combination therapy is needed.

COMPLICATION

The mild postembolization syndrome and outpatient-based treatment are attractive advantages for TARE over conventional TACE. However, non-target radiation may cause serious complications, which should be managed by surgical treatment. Most of these complications are preventable by comprehensive angiographic evaluation.

The origin of the cystic artery is quite variable, including the segmental hepatic artery, even though the cystic arteries commonly from main trunk of the right hepatic artery. Although the incidence of radiation cholecystitis requiring surgical cholecystectomy is quite low, imaging findings of gallbladder injury are relatively common, including enhancing gallbladder wall, gallbladder edema, and mural disruption.

Nontarget administration of microspheres into the accessory left gastric artery, the right gastric artery, and the gastroduodenal artery may cause gastrointestinal ulcer by radiation. Radiation ulcer is commonly refractory to medical treatment and needs surgical resection. For angiographic technique to prevent gastrointestinal ulcer refer to the current literature.

Radiation pneumonitis is quite uncommon, provided proper lung shunting studies and dosimetry are obtained. When the right inferior phrenic artery, the most common extrahepatic collateral artery, supplies the tumor, special caution is needed to prevent radiation pneumonitis, because the right inferior phrenic artery commonly accompanies pulmonary shunting.

The classical manifestation of radiation-induced liver disease includes anicteric ascites, increased alkaline phosphatase levels, and thrombocytopenia. The exact tolerable dose to the liver by TARE is not known, and true absorbed dose to the normal liver tissue can be hardly assessed. Thus, the easiest and definite way to prevent radiation-induced liver disease is to avoid whole liver irradiation in single treatment or sequential treatment.

CONCLUSION

TARE is an attractive intra-arterial treatment modality with powerful anti-tumor effect and minimal post-embolization syndrome. Although patients who can afford TARE are limited due to its high cost in Korea, doctors should inform all HCC patients of TARE as a possible treatment option. In BCLC A, radiation segmentectomy may eliminate the pain after surgical resection. In the early stages of BCLC B, TARE may have better tumor control and higher chance to liver transplantation than TACE. In late stage of BCLC B or BCLC C, TARE may offer better quality of life and fewer visits to the hospital than TACE. TARE has specific roles in inducing contralateral lobe hypertrophy and in downstaging to liver transplantation and can be used as an alternative to TACE, ablation, surgical resection, and sorafenib. The utility of TARE continues to expand with new insights in interventional oncology.

Conflicts of Interest

The authors have no conflicts to disclose.

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