

# Transarterial Radioembolization: A New Selection to Treat Hepatocellular Carcinoma

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## Abstract

With the development of the material science, the clinical application of stable nuclide microspheres has become a hot spot of endovascular treatment of liver cancer in last 10 years. Transarterial radioembolization came to be a new selection to treat hepatocellular carcinoma. The characteristics of the radioactive microsphere determine obvious different between TARE and TACE. For early HCC, TARE as the degradation treatment or transition treatment waiting for liver transplantation. For advanced HCC, TARE as the treatment of unresectable advanced hepatocellular cancer. TARE as the rescue treatment of recurrence after liver resection. TARE as a treatment of HCC with portal vein tumor thrombus. How to make more patients in Asia countries such as China benefit, the optimization of treatment, indications of therapy, radioactive microsphere local production, health economics studies, all needed to further research.

**Keywords:** transarterial radioembolization, hepatocellular carcinoma

## 1. Introduction

1962 Young Songtin etc. treated tumor successfully by local and transarterial injecting colloidal <sup>90</sup>Y, which marked the start of local irradiation of the treatment of tumors (Ariel IM and Pack GT, 1967) (Blanchard RJ, et al, 1964). But due to the limitation of the development of material science, people could only use the radioactive microsphere made of colloid or resin, which is easy to entrance the blood. It can cause bone marrow suppression and severe systemic radiation reactions such as pulmonary fibrosis, which limited the development of local radionuclide irradiation in treatment of tumor. Gray B (Ryan N et al, 2008) reports the application of <sup>90</sup>Y in liver cancer in 1992. Professor Zhi-ping Yan (Yan Z et al, 1993) reported the experiment and clinical application of <sup>90</sup>Y glass microspheres in HCC in details, which was published in Journal of Cancer, which created a new field in the study of radioactive microsphere. With the development of the material science, the clinical application of stable nuclide microspheres has become a hot spot of endovascular treatment of liver cancer in last 10 years.

## 2. The Treatment Principle and Features of the Radioactive Microsphere

<sup>90</sup>Y launch pure beta-ray, with half-life of 64.2 hours (2.67 days), the largest energy is 2.27 MeV (average 0.937 MeV), maximum range is 11mm in soft tissue, average thickness is 2.5 mm. (Rodolfo Sacco et al, 2015, Riaz A et al 2014). Because of the structure and the diameter of the radioactive microsphere characteristics, the major role of the radioactive microsphere in the treatment is the nuclide radiation, rather than the embolization effect. It is different from the traditional conventional embolization application of iodized oil, gelatin sponge, and the new carrier drug microsphere.

There are two kinds of nuclide microspheres' application has been approved nowadays. One of them is the <sup>90</sup>Y glass microspheres produced by Canadian Nordion Company, whose commodity name is Thera Sphere and the microspheres's diameter is from 20 to 300  $\mu$ m, with the isotope in the microspheres. Thera Sphere went public in 1999, whose indication is the palliative care of unresectable HCC approved by FDA.

The other one is the <sup>90</sup>Y resin microspheres produced by Australia Sirtex Medical company, named Sir-Spheres, with the diameter from 20 to 60  $\mu$ m, and the isotope was labeled in the surface of the microspheres. SIR Sphere went public in 2002, with the indications of combining chemotherapy in the treatment of colorectal cancer liver metastases. According to the existing data, the number of Thera Sphere microspheres is 4 million, and the radiation energy is 2500 bq. The number of Sir-Spheres microspheres is 40 million, and the radiation energy is 50 bq. Since the larger quantity of

Sir-Spheres microspheres, it can cover large load or range of the lesions, but the demands of process controlling were higher.

### 3. Curative Effect Evaluation Method and the Treatment Time of TRAE

Similar with TACE, at the beginning of the effective rate study of radioactive microsphere used RECIST criteria for HCC, and the effective rates were 25%-60%. But the effective rates became 80% with the EASL criteria (Bruno et al 2012, Lewandowski et al 2009). Recent studies show that the mRECIST criteria could be more objective.

Although the change of the lesion size could be observed in 1 month after TRAE, but most experts tend to evaluate the fully reflect the effect of lesions in 3-4 months after TRAE, and make the decision of the second TARE treatment after that (Riaz A et al 2014).

### 4. Clinical Effect of TARE

The characteristics of the radioactive microsphere determine obvious different between TARE and TACE. Because the reduction of tumor mass needs a period of time after radiotherapy, the maximum reduction needs 3 to 6 months in generally, and mean time is 6.6 months, so there are differences of radioactive microsphere treatment efficacy. The other reason is that the difference of the actual injection dose of Y90 is associated with the reduction of tumor mass, as the difference of ray absorption depending on the activity of rays, hepatic arterial blood flow mechanics, tumor vascular density and so on (Bruno S et al.2012).

#### 4.1 For Early HCC, TARE

For the early HCC patients who can accept the liver transplantation treatment, due to the limited the source of liver, the effective control during waiting for liver source is one of important factors affecting the prognosis. Lewandowski (Lewandowski et al 2009) reported 43 cases who accepted TARE and 43 cases who accepted TACE as the treatment before liver transplantation and perform a retrospective analysis: the percentage of HCC degradation patients who accepted TARE is 58%, median survival time is 42 months, this is obvious superior to the patients who accepted TACE as the degradation treatment (the percentage of degradation patients is 31%, median survival time is 42 months). More similar studies have shown that using 90Y microspheres treatment can extend the time of waiting for liver transplantation, compared with the patients without transition treatment, and there is no significant difference in the survival rate of the two groups of patients after liver transplantation. As the degradation treatment or transition treatment waiting for liver transplantation.

#### 4.2 For Advanced HCC, TARE as the Treatment of Unresectable Advanced Hepatocellular Cancer

A large number of research results show that interventional therapy plays an important role in the treatment of advanced HCC, and it is the most effective treatment besides surgery, which can effective reduce the tumor load, control or decrease the occurrence of complications, prolong survival and improve the quality of life. TARE, as an emerging interventional treatment, is gradually applied in advanced liver cancer treatment. The related research results suggested that 90Y microspheres TARE is beneficial to the advanced liver cancer. Mazzaferro (Morosi C 2013) reported the second phase of clinical trial results which applied the 90Y microspheres TARE and it shows that the patients' median survival time is 15 months, tumor median progression time is 11 months. Hilgard etc. (Hilgard et al 2010) research results show that for the BCLC B stage patients who accepted the 90Y microspheres TARE, the median survival time is 16.4 months. Salem etc. performed a prospective study about the BCLC B stage liver cancer patients who accepted the 90Y microspheres TARE and it shows that the median survival time is 17.2 months.

#### 4.3 TARE as the Rescue Treatment of Recurrence after Liver Resection

Recurrence after radical resection of liver cancer is one of the important factors affecting the prognosis of liver cancer. Related studies have shown that the recurrence rate within five years is 50%~80%. Lau etc.(Lau WY et al,2011) used 90Y microspheres to cure 51 patients who couldn't accept resection of hepatocellular cancer and 20 patients who were recurrence after resection of hepatocellular cancer. And then they compared the curative effect and prognosis of the two groups, they found the similar curative effect and all patients had no serious adverse reactions. These suggest that TARE can be one of the rescue treatment of recurrent live cancer.

#### 4.4 TARE as a Treatment of HCC with Portal Vein Tumor Thrombus

The latest published papers since 2014 (Ana Maria C et al, 2014, Jordi B, et al, 2014, Hyun Young Woo et al, 2015) are almost focus on the patients with portal vein tumor thrombus, thus we suggest that interventional radiology academics raise great expectations with TARE treatment for portal vein tumor thrombus. Actually, TARE treatment for portal vein tumor thrombus begins with stratification analysis of large sample TARE treatment for HCC. In these studies (Hilgard P et al 2010, Salem R, et al 2010), scholars have found TARE can make the overall survival of HCC with portal vein tumor thrombus reach 10~10.4 months. For the liver function grade A with tumor thrombus of branch of portal vein, the

overall survival can achieve to 16.6 months, however, for the liver function grade B with tumor thrombus of branch of portal vein, the overall survival is just 4.5 months.

### 5. The Side Effect of TRAE

The side effect of radiation embolism is relatively weak, manifested as fatigue, mild abdominal pain or discomfort, with or without cachexia, elevated bilirubin and similar flu-like symptoms, some experts call it post-radioembolization syndrome (Bruno S, et al, 2012). The incidence of PRS reported by literature is 12% to 54% (Hyun Young Woo and Jeong Heo, 2015), and self-relieved within ten hours. Because the main function of drug loading TRAE embolism is the nuclide therapy, so treatment-related side effects is weak. In the European and American countries, TRAE treatment does not need to be hospitalized, only for observation of 1 day in the clinic. In fact, due to the abnormal distribution of radioactive microsphere, the side effects often manifest as radioactive radiation injury, such as liver damage, pneumonia, biliary complications. Although these side effects are rare, but may be more serious, even require surgical intervention. Biek (Bieke Lamber, et al 2011) investigated the urinary excretion of  $^{90}\text{Y}$  following treatment. The urinary excretion was estimated by 12-h urine collections post-injection for analysis in a gamma counter. Concerning the substudy on urinary excretion, only 0.0025% of the administered activity was excreted in the urine within the first 12 h following Thera Sphere. The study encountered four cases of clinically severe adverse events. One patient developed grade 4 hyperbilirubinaemia and ascites and offered a liver transplantation. Another patient died 58 days after treatment due to spontaneous bacterial peritonitis and subsequent liver failure. Two patients presented with a subacute GI bleeding. Lidia Strigari (Lidia S et al. 2010) reported the toxicity related to treatment of hepatocellular carcinoma with  $^{90}\text{Y}$ -SIR spheres. With a median liver dose of 36 Gy (range, 6-78 Gy), the  $\geq$  grade 2 (G2),  $\geq$  grade 3 (G3), and  $\geq$  grade 4 (G4) liver toxicities were observed in 32% (23/73), 21% (15/73), and 11% (8/73) of patients, respectively. This suggests that TRAE treatment still has certain risk. We need to strengthen preoperative assessment, and explore the modality of multi-disciplinary team (MDT), to ensure the safety of the treatment.

### 6. Radioactive Microsphere and TRAE Clinical Studies

The P32 and Y90 microsphere carrier is more commonly used, with an ideal effect for local radiation and embolism functions.

At present, the radioactive microsphere 32 p with  $\beta$ -rays emitted is used in our China. Its half-life is  $14.28 \pm 0.02$  days. The average penetration depth is 3.2 mm, a maximum depth of 8 mm, vary depending on the organizational structure. The latest in research there is  $^{166}\text{Ho}$  and  $^{188}\text{Re}$ , both have therapeutic value, and emit  $\gamma$  rays used for nuclear imaging, to facilitate follow-up study after treatment. Believe that the future has a higher practical value in clinic.

TRAE has been as a latest technology of endovascular treatment of liver cancer. Combine with drug or other therapy methods is one of the main trend (Ana Maria C et al, 2014, Jordi B, et al, 2014, Hyun Young Woo et al, 2015). Currently, a large randomized study PREMIERE (NCT00956930) in United States is being implemented. It compares the value of radioactive microspheres with RFA, TACE or combination therapy for unresectable HCC. The Asia Pacific region SIRveNIB experiments (NCT01135056), to carry out radioactive microspheres and sorafenib head to head research. The European SORAMIC experiments (NCT01126645) will carry out the evaluation of radioactive microspheres combined with sorafenib, and sorafenib alone for advanced HCC, at present has not yet been published results.

### 7. Problems and Research Area of TARE

Overall, both study of radioactive microspheres for treatment of HCC is retrospective non-randomized, the evidence grade II-2 and II-3. TRAE compared with TACE, who is better, there is no high-level evidence studies confirmed. In a retrospective study of a large sample group, the radioactive microspheres therapy of 104 cases of HCC patients, TACE treatment of 100 cases, with a median survival time of two groups: Child-Pugh A group was 22.1 versus 15.6 months,  $P = 0.24$ , Child-Pugh group B is 13.5 versus 12.8,  $P = 0.64$ . TRAE is non-inferior to TACE (Lorenzo et al., 2012). This is actually the disadvantage of TARE evaluation. As lack of high-level evidence based-medicine, TRAE does not appear in the guideline of ASCO (the American Society of Clinical Oncology). Of course, European Society of Medical Oncology and the National Comprehensive Cancer Network (NCCN) recommend TRAE as complementary treatment for liver metastasis in patients with HCC. Thus, randomized controlled multi-center study is urgent needed for further study of TRAE.

Currently, only two companies were approved for radioactive microspheres therapy clinically. The cost of treatment per patient is about 50,000 US dollars, or about 300,000 RMB Yuan. It imposed a heavy burden to the patient or insurance company of developed European countries, although their medical insurance system is better. Therefore, how to make more patients in Asia countries such as China benefit, the optimization of treatment, indications of therapy, radioactive microsphere local production, health economics studies, all needed to further research.

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