

⁹⁰Yttrium Microsphere Radioembolization for Liver Malignancies: A Technical Overview

Sandeep T Laroia

ABSTRACT

The incidence of the liver tumors is increasing worldwide; concurrently liver directed therapies are also evolving rapidly. Management of these complex disease processes involves a multidisciplinary approach, hence it is imperative to understand the underlying management principles thoroughly. This overview is intended to provide an easy, step by step approach to transcatheter brachytherapy, also known as radioembolization (RE). A brief overview of the anatomical issues, transcatheter technique and intraarterial RE will be provided.

Keywords: Liver malignancy, Transarterial brachytherapy, Radioembolization, ⁹⁰Yttrium, Liver directed therapy.

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INTRODUCTION

Liver malignancies have been and continue to be a scourge of mankind. Hepatocellular carcinoma (HCC) is one of the most common forms of cancers. Overall incidence is more than a million cases every year. The worrisome thing is that incidence is increasing over the last decade.¹ The increasing incidence of hepatitis C, alcoholic and nonalcoholic liver disease all probably are contributing to the increasing incidence of this particular tumor. Liver involvement from secondary malignancies especially from gastrointestinal tract, breast cancer is also on the rise both in the developing and developed countries. In colorectal carcinoma, more than 60% of the patients will have liver dominant secondaries in the course of the disease. Similarly neuroendocrine tumors with hepatic secondaries have significant morbidity and mortality. HCC traditionally had few treatment choices, hence was one of areas of intense research for the alternate treatments. The curative options for HCC include surgical resection and liver transplantation. Unfortunately only a minority of patients (10-15%) are candidates for surgery.^{2,4} For metastatic disease systemic chemotherapy is the standard of treatment. However, if standard first- and second-line treatments have failed, which happens in many patients, other therapies need to be considered. Presently, a whole gamut of these options is available.³ The most common ones are enlisted below:

- Transcatheter arterial chemoembolization (TACE)
- Radiofrequency ablation (RFA)
- ⁹⁰Yttrium radioembolization (90YRE)
- Drug eluting microspheres (DEM), etc.

In this article, we will focus on radioembolization with particular emphasis on technical and clinical considerations.

Pathological and diagnostic considerations: Before we embark on the ⁹⁰YRE, it is important to briefly review the pertinent pathology and diagnostic characteristics of the liver malignancies:

HCC: These patients usually have cirrhosis of viral, alcoholic, nonalcoholic or uncertain cause. So in patients with cirrhosis, any hepatic mass should be considered a HCC unless proven otherwise. In appropriate clinical reference there is no need to biopsy these lesions,⁵ as biopsy may lead to the seeding of the tract.⁵ Alpha fetoprotein level of 400 nanogram/ml has aided the diagnosis. Based on the institutional expertise and facilities available, triple-phase computed tomography (CT) or magnetic resonance imaging (MRI) are the imaging modalities of choice.⁶⁻⁸ Ultrasound, because of already altered echotexture of the liver may not be reliable. As many of these tumors are hypervascular, special attention is paid to the arterial phase and subsequent washout on both CT and MRI. Recently, liver imaging-reporting and data system (LI-RADS) of describing liver lesions has been advocated. This should be incorporated in the reporting systems to encourage standardization of the reporting of the liver masses. Another unique feature of HCC is arteriovenous shunting. If the disease is multifocal different masses may show different levels of arteriovenous shunting. This pathological feature has important implications as therapeutic particles can get shunted to the lungs and cause undesirable effects.²² Portal vein thrombosis is another feature of the HCC. The thrombosis can be tumor or bland.

It is also relevant to briefly introduce the staging systems for the liver malignancies. Various systems have been proposed with Child-Pugh, MELD, Okuda, Cancer of Italian Liver Program, Barcelona Clinic Liver Program, etc.⁹ Underlying principle is that as the liver involvement by the tumor becomes extensive, liver's synthetic and excretory functions get affected to a larger extent which gets reflected in various lab and clinical parameters.¹⁰ In short bilirubin levels, ascites, presence of encephalopathy, etc. are taken into account. As the liver is responsible for synthesis of albumin and procoagulant proteins, their levels also are taken into consideration.

Patient's performance status and Karnofsky score are also taken into account. For ⁹⁰YRE, ideal patient will have following parameters:

- Tumor load less than 50%

- Normal bilirubin level
- Albumin level 3 gm/dl or greater
- No ascites
- Good functional status.

In clinical practice, patients may not be presenting early enough to fulfill all or any of these criteria. In such cases, different approaches can still be used which will be discussed in special situations section.

Metastatic Disease

Patients with metastatic disease have different pathological characteristics than HCC. They usually have better laboratory parameters; bilirubin may not be as deranged as in HCC, they are most likely to have completed first or second-line chemotherapy. So in these patients performance status is an important determinant of the suitability for liver directed therapy, other than liver dominant disease.¹¹ Also unlike HCC, whenever a liver mass is discovered in a patient with some primary tumor, it needs pathological confirmation. Positron emission tomography (PET) provides an excellent modality both for initial staging and post therapy follow-up in these cases. For ⁹⁰YRE, an ideal patient with liver metastasis will have following parameters:²⁰

- ECOG performance status of 0 to 2.
- Karnofsky score of above 60%
- Liver dominant metastatic disease
- Hypervascular tumor.

Laboratory Evaluation

Many other laboratory tests having a role in liver directed therapy either for diagnostic, prognostic or follow-up purposes are:¹²

- INR
- Alpha fetoprotein
- Carcinoembryonic antigen
- Cancer antigen 19-9
- Serotonin/Chromogranin A
- Liver function profile including AST and ALT
- Complete blood count with differential
- LDH
- C-reactive protein.

Anatomical and Technical Considerations

It is imperative that a detailed and meticulous vascular anatomy examination be performed prior to actual delivery of ⁹⁰Y.¹³ The following vessels should be checked invariably before therapy:

- Celiac axis
- Common hepatic artery
- Lobar hepatic arteries
- Gastroduodenal artery
- Superior mesenteric artery (SMA).

Aortogram may be added to this protocol to look for any other variant anatomy or additional supply to the liver.

The angiographic goal is to get the following information:

- To outline the normal and variant anatomy of the liver vascular bed.
- To do prophylactic embolization of nontarget vascular beds to prevent inadvertent delivery of the radiopharmaceutical to these areas.
- To plan whether lobar or segmental delivery is possible.
- To estimate the number of treatments based on the vascular.

Normal and common variants of the hepatic vascular supply:

The arterial supply to the liver broadly can follow one of these anatomies:

- Common hepatic artery from the celiac axis and dividing into right and left hepatic arteries.
- Common hepatic artery from the celiac axis and dividing into right left and middle hepatic arteries.
- Replaced common hepatic artery arising from SMA and following any of the above two branching pattern.
- Accessory hepatic artery arising from SMA.
- Left hepatic artery arising from the left gastric artery.

Things to remember are:

Accessory hepatic artery usually supplies segment 6 and 7.

Segment 4 can have either right or left or middle hepatic arteries supplying it.

Right hepatic artery in the presence of accessory hepatic artery usually supplies segment 5 and 8.

This vascular information gleaned from the angiogram is then correlated with the extent of disease seen on cross-sectional imaging.

Prophylactic Embolization

This concept is based on the fact that the ⁹⁰Y particles will cause irreversible damage to the gastrointestinal tract if it gets injected inadvertently to the gastrointestinal blood supply.

Resin spheres are more embolic compared to glass spheres, so resin spheres cause more pronounced slowing of normal antegrade blood flow to the liver. Hence, theoretically chances of reflux to nontarget visceral vessels is higher when resin sphere-based therapy is used, compared to the glass spheres during therapy. The threshold for embolizing GDA, right gastric artery, supraduodenal, retroduodenal, and accessory left gastric artery should be low, especially when the vehicle to deliver ⁹⁰Y is resin spheres. The clinical sequelae of prophylactic embolization of these vessels are insignificant in the carefully studied patient population. Recent development of flow directing devices, to protect nontarget vessels is also being studied; however cumulative experience in the use of these devices is not much.

Some groups have also advocated altering hepatic vascular anatomy to optimize treatment delivery, e.g. embolizing a small middle hepatic artery to increase blood flow to the diseased right or left lobes, however in the majority of cases, this is not warranted.

The basic principal of ⁹⁰YRE is to treat target vascular bed at 30 to 60 days interval. So in more common dichotomous branching of the common hepatic artery (into right and left hepatic arteries) this goal can be achieved in two treatment sessions. For each additional vascular bed an additional session is generally required.

Issues related to Pulmonary Shunting

After arterial anatomy is established, the next step is to calculate the pulmonary shunt fraction. This is done with the help of ^{99m}Tc macroaggregated albumin (MAA).¹⁴ The logic is that, as the size of MAA closely mimics that of ⁹⁰Y spheres, so the distribution of MAA will closely mimic the distribution of the spheres.¹⁵ The dose injected is usually 4 to 5 mCi. The imaging can be done with planar or SPECT gamma camera systems. The imaging should quickly follow the injection of MAA. Gastric mucosa and the salivary gland uptake should be looked carefully. Isolated gastric mucosa uptake indicates true gastrointestinal shunting.

As discussed earlier liver tumor, HCC in particular has varying degrees of arteriovenous shunting. In metastatic tumors, significant shunting is rare. There is important implication of this difference:

- In HCC, if the disease is multilobar, then each lobe must be injected with MAA, prior to the treatment session. So the lobar or segmental branch needs to be cannulated and lung shunt fraction is calculated. This increases the number of angiographic sessions. However observational studies have demonstrated this to be of little clinical importance and many institutions do only one MAA injection at the beginning. If significant shunting (more than 10%) is found in that study, then lobar administration of MAA is undertaken.
- In metastatic disease, the proper hepatic artery may be injected once to calculate the shunt fraction and ⁹⁰Y administration can follow in a sequential manner for each lobe involved.
- In cases of variant anatomy like accessory hepatic artery arising from SMA or left hepatic artery arising from left gastric artery, etc. fractionated injection of MAA is done.

The MAA injection also provides adjunctive information like extrahepatic gastrointestinal uptake. One should look carefully for this on the nuclear scan.

Types of ⁹⁰Y: ⁹⁰Y is available as either glass or resin spheres.^{16,17} There are important differences among them which a practitioner needs to know.

- Glass bead particle size is little smaller than the resin spheres: 20 to 30 micron vs 20 to 60 microns.
- Glass beads are less in number per vial than resin spheres: 1.2 to 8.0 million vs 40 to 80 million.
- Glass beads have more activity per sphere: 2500 Bq vs 50 Bq for resin spheres.
- Resin spheres are more embolic.

- Body excretion through urine is more of a concern with resin spheres.
- Both have half-life of 64.2 hours.
- Near complete decay (3% residual activity) is also the same, 13 days each.

Dose calculation: Glass bead dose is dependent upon the volume of the liver being infused; resin spheres dose depends on the percentage of the tumor load.

The lung dose is also calculated with the help of lung shunt fraction. Lungs tolerate ³⁰Gy in a single session and ⁵⁰Gy cumulative doses.

Treatment process: The patient should have undergone a planning diagnostic and prophylactic embolization as already discussed. The room needs to be prepared with suitable disposable flooring coverings in the event of inadvertent spill of ⁹⁰Y microspheres. Dose calibrator is used to measure the activity before and after the procedure and also to check for activity due to any spillover or leakage. The patient is prepared in the usual way and an initial angiogram obtained to select the spot where ⁹⁰Y will be injected. A 3 Fr system catheter is preferred for the delivery as 5 Fr system increases the chances of reflux; also the chances of vessel injury may be higher with deep placement of these catheters. Smaller catheter systems like 0.018 inch have too much resistance for adequate delivery. Infusion set is now carefully prepared as there are many connections. As resin spheres are more embolic than glass spheres, so chances of reflux are higher. The rate of infusion should be matched to the rate of arterial flow in the hepatic artery being injected. The estimation of dose administered at any particular point can be easily measured with the help of ionization chamber (minimum detection 1 mrem/h). In HCC patients who are usually cirrhotic and significantly hypervascular, a segmental approach is recommended.

Safety concerns: Once the dose administration is completed, all the catheters and tubings must be carefully disposed off. Special care should be taken for any backflow of blood through the catheters as it can cause the reflux of ⁹⁰Y. ⁹⁰Y is a beta-emitter so the main concern is exposure to the eyes, hands and skin. Hence, all personnel involved in the procedure must be checked for any contamination at the end of the procedure. Technically both the glass and the resin microspheres are sealed sources. However, since both are delivered in a liquid medium, all precautions for handling radiopharmaceuticals should be undertaken. The post administration exposure from the patient is within 4 to 12 mrem/h, which is within the acceptable range, so no special precautions are necessary. However, since resin spheres are excreted in the urine so during first 24 hours precautions are needed for urine disposal.²¹

Post-treatment care and follow-up: Major concerns are reflux of the microspheres through unrecognized

gastrointestinal channels.¹⁸ As mucosa of the stomach and proximal duodenum are primarily involved, nonhealing ulcers can cause major morbidity and even mortality, we start antiulcer medications right after the procedure. Some authorities recommend use of steroids for postembolization fatigue. Noninfective fever usually responds to acetaminophen. Nausea, vomiting can happen which responds to conservative measures.¹⁹

The patient is seen within the next 2 to 3 weeks, mainly for the assessment of the functional status. Post-treatment liver function is checked at this time. A transient increase in liver enzymes and tumor markers may be seen at this time; however massive increase in the liver enzymes should be investigated further.

Further treatments: If the disease is confined to one lobe of the liver, above-mentioned protocol is followed. As the disease may be bilobar or the patient may have aberrant vascular anatomy, then more than one session of therapy may be required. Typically the second session is done 30 days after the first one. Before undertaking the second session, imaging of the liver tumor either with MR or PET must be undertaken.²⁰ For HCC, this scan may show shrinkage and necrosis of the tumor. For metastatic tumors, this scan is important as it may show either failure or progression of the disease. For this reason functional imaging like PET is important as it may show the spread of extrahepatic disease, thereby precluding any further liver treatments. A complete blood count may also be obtained at 30 days to look for any radiation-related cytopenias. On the other hand, any progression in the nontreated lobe of the liver is actually an indication for the treatment. Repeated treatment in the previously treated lobe or segment of the liver should be undertaken for definitely hypervascular tumors. In cases where multiple sessions of therapy are required, cumulative radiation dose to the lungs may become a limiting factor. A scrupulous log of radiation dose received by the patient should be maintained in all cases of radioembolization.

REFERENCES

1. American Cancer Society, Cancer Facts and Figures 2004. Atlanta: American Cancer Society 2004.
2. Llovet JM. Treatment of hepatocellular carcinoma. *Curr Treat Options Gastroenterol* 2004;7:431-41.
3. Messersmith W, Laheru D, Hidalgo M. Recent advances in the pharmacological treatment of colorectal cancer. *Expert Opin Investig Drugs* 2003;12:423-34.
4. Sasson AR, Sigurdson ER. Surgical treatment of liver metastases. *Semin Oncol* 2002;29:107-18.
5. Llovet JM, Vilana R, Bru C, et al. Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. *Hepatology* 2001;33:1124-29.
6. Kim TK, Jang HJ, Wilson SR. Imaging diagnosis of hepatocellular carcinoma with differentiation from other pathology. *Clin Liver Dis* 2005;9:253-79.

7. Lim JH, Choi D, Kim SH, et al. Detection of hepatocellular carcinoma: Value of adding delayed phase imaging to dual-phase helical CT. *AJR Am J Roentgenol* 2002;179:67-73.
8. Cortez-Pinto H, Camilo ME. Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH): Diagnosis and clinical course. *Best Pract Res Clin Gastroenterol* 2004;18:1089-104.
9. Toyoda H, Kumada T, Kiriyama S, et al. Comparison of the usefulness of three staging systems for hepatocellular carcinoma (CLIP, BCLC and JIS) in Japan. *Am J Gastroenterol* 2005;100:1764-71.
10. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment: Study of 850 patients. *Cancer* 1985;56:918-28.
11. Yu AS, Keeffe EB. Management of hepatocellular carcinoma. *Rev Gastroenterol Disord* 2003;3:8-24.
12. Hashimoto K, Ikeda Y, Korenaga D, et al. The impact of preoperative serum C-reactive protein on the prognosis of patients with hepatocellular carcinoma. *Cancer* 2005;103:1856-64.
13. Liu DM, Salem R, Bui JT, et al. Angiographic considerations in patients undergoing liver-directed therapy. *J Vasc Interv Radiol* 2005;16:911-35.
14. Mounajjed T, Salem R, Rhee TK, et al. Multi-institutional comparison of 99mTc-MAA lung shunt fraction for transcatheter Y-90 radioembolization. New Orleans, LA: Presented at the Annual Meeting of the Society of Interventional Radiology, 2005.
15. Hung JC, Redfern MG, Mahoney DW, et al. Evaluation of macroaggregated albumin particle sizes for use in pulmonary shunt patient studies. *J Am Pharm Assoc (Wash)* 2000;40:46-51.
16. Murthy R, Nunez R, Szklaruk J, et al. Yttrium-90 microsphere therapy for hepatic malignancy: Devices, indications, technical considerations and potential complications. *Radiographics* 2005;25 (suppl 1):S41-S55.
17. Sato K, Lewandowski RJ, Bui JT, et al. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere): Assessment of hepatic arterial embolization. *Cardiovasc Intervent Radiol* 2006;9:522-29.
18. Yip D, Allen R, Ashton C, et al. Radiation-induced ulceration of the stomach secondary to hepatic embolization with radioactive yttrium microspheres in the treatment of metastatic colon cancer. *J Gastroenterol Hepatol* 2004;19:347-49.
19. Goin JE, Dancy JE, Roberts CA, et al. Comparison of post-embolization syndrome in the treatment of patients with unresectable hepatocellular carcinoma: Trans-catheter arterial chemo-embolization versus yttrium-90 glass microspheres. *World J Nucl Med* 2004;3:49-56.
20. Kosmider S, Tan TH, Yip D, Dowling R, Lichtenstein M, Gibbs P. Radioembolization in combination with systemic chemotherapy as first-line therapy for liver metastases from colorectal cancer. *J Vasc Interv Radiol* 2011 Jun;22(6):780-86.
21. Gaba RC, Riaz A, Lewandowski RJ, Ibrahim SM, Ryu RK, Sato KT, et al. Safety of yttrium-90 microsphere radioembolization in patients with biliary obstruction. *J Vasc Interv Radiol* 2010 Aug;21(8):1213-18.
22. Chen JH, Chai JW, Huang CL, et al. Proximal arterio portal shunting associated with hepatocellular carcinoma: Features revealed by dynamic helical CT. *AJR* 1999;172:403-07.

ABOUT THE AUTHOR

Sandeep T Laroia

Assistant Professor, Department of Radiology, University of Iowa Hospitals and Clinic, Iowa, USA, e-mail: sandeep-laroia@uiowa.edu