

Radioembolization of Yttrium-90 Microspheres for Clinical Treatment of Hepatic Malignancy

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Abstract

Trans hepatic arterial radioembolotherapy using yttrium-90 microspheres represents in situ therapy in hepatocellular cancer, which is the third leading cause of cancer-related deaths in the world. This therapy shows interesting results in the treatment of these patients. This review focuses on clinical application, advantages, side-effects and toxicity, and contradictions of the radioembolization treatment program

Keywords: Liver cancer; Yttrium-90; Radioembolization; Technetium-^{99m}Tc; Macroaggregated; Albumin; ⁹⁰Y PET/CT; ^{99m}Tc-MAA SPECT/CT

(Thera-Sphere; MDS Nordion, Ottawa, Ontario, Canada) and the other with microspheres made of resin (Sir-Spheres; Sirtex Medical, Sydney, Australia) [17].

Introduction

Hepatocellular cancer (HCC) is the third leading cause of cancer-related deaths in the world [1-3]. The incidence of HCC is increasing in the United States due to increasing infections with Hepatitis B and C. Although the definite cure includes surgical intervention and liver transplant, yet, in many patients, general medical contraindications, unfavorable tumour characteristics and complications like portal hypertension leave a vast majority of tumours unresectable or even poor candidates for trans-arterial chemoembolization (TACE) [4-8].

Selective internal radiation therapy (SIRT) is a new developing method using yttrium element [9,10]. The hypothesis behind this treatment is indebted to the unique hepatic blood circulation and its distinguished characteristics in a cancerous liver. While a healthy normal liver receives around 80 percent of its blood supply from the portal vein, this proportion is reversed in case of hepatic carcinoma and its metastases. The affected liver would be supplied 80 percent by hepatic artery and only 20 percent by portal vein [11-13].

⁹⁰Y microsphere is an artificial radioactive isotope of the element yttrium, used in selective beam radiotherapy, SIRT, as a part of a multidisciplinary approach mainly for treating the hepatocellular carcinoma and its metastases [14,15]. The concept of using SIRT first started to be developed by a Surgeon from New York who was a frontier in applying radioisotopes in clinical diagnosis and therapy [16]. ⁹⁰Y is produced by bombardment of yttrium 89 with neutrons in a nuclear reactor. It has a physical half-life of 64.2 hours (2.67 days), and it decays to stable zirconium 90. ⁹⁰Y emits pure high-energy beta rays (energy maximum, 2.27 MeV; mean, 0.9367 MeV) with an average penetration range of 2.5 mm and a maximum range of 11 mm in tissue. One gigabecquerel (27 mCi) of ⁹⁰Y delivers a total absorbed radiation dose of 50 Gy/kg. In therapeutic use in which the isotope decays to infinity, 94% of the radiation is delivered in 11 days. There are currently two commercially available microsphere devices in which ⁹⁰Y is incorporated: one with microspheres made of glass

Clinical Application

^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) is a necessary step before applying the therapy [18]. To minimize the possible spreading of radioisotope to the intact hepatic tissue as well as the nearby organs, the possible arterial shunts should be embolized prior to applying ⁹⁰Y. No need to say that the bigger tumour is, the more extensive the collateral arterial supplies are. Therefore, mapping the blood supply with ^{99m}Tc-MAA is routinely performed before applying the therapy. Although the embolization of Gastro-duodenal artery (GDA) is greatly performed to reduce the spreading of radioisotope to unnecessary locations, still in some cases, despite coiling of GDA, there would be some spreading into other parts of gastrointestinal organs. However, in some cases as if a retrograde flow exists, keeping the GDA patent during the procedure seems to have a minimum or no role in increasing the related mortality [18-20].

After two injections of ^{99m}Tc-MAA are done via the hepatic catheter, SPECT images of the liver and the whole body scan are acquired to analyze the existence of extra-hepatic shunt via calculation of count ratio of the lungs/(liver+lungs) (Figure 1). The imaging will evaluate abnormal lung uptake when there is an extra-hepatic shunt. ^{99m}Tc-MAA scintigraphy scan is routinely performed for lung perfusion imaging and for the assessment of in vivo distribution of ⁹⁰Y- SIRSpheeres prior to selective internal radiation treatment for hepatocellular carcinoma. Positron emission tomography (PET) imaging is superior to gamma scintigraphy in terms of sensitivity, spatial resolution and accuracy of quantification. A recent study reported that ¹⁸F-labeled macroaggregated albumin (¹⁸F-MAA) is an ideal PET imaging surrogate for ^{99m}Tc-MAA in rats [19]. Starting from commercial MAA kit, an efficient preparation of ¹⁸F-MAA was successfully established. Highly correlated, almost parallel, regional distribution of ¹⁸F-MAA and ^{99m}Tc-MAA in both normal rats and hepatoma-bearing rats was observed.

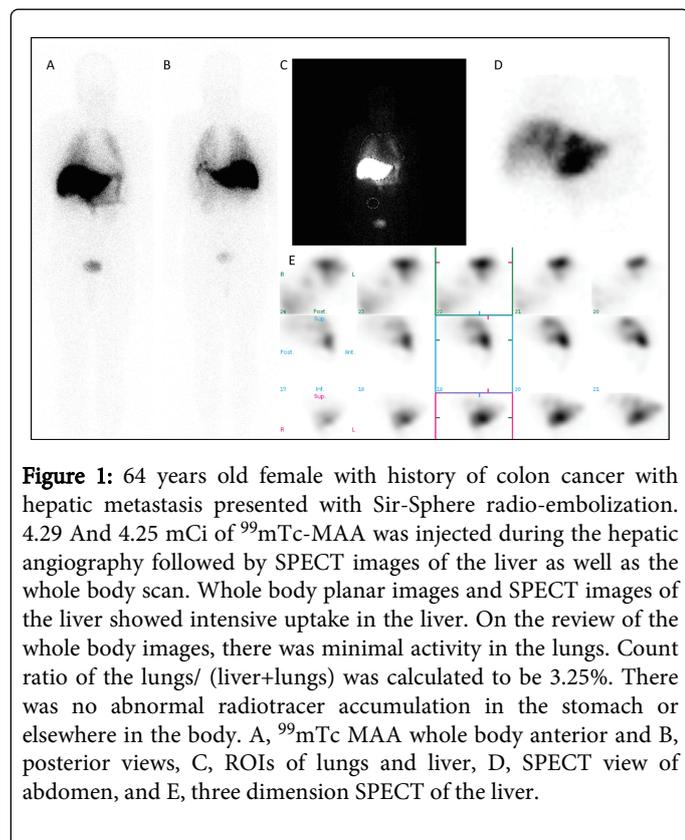


Figure 1: 64 years old female with history of colon cancer with hepatic metastasis presented with Sir-Sphere radio-embolization. 4.29 And 4.25 mCi of ^{99m}Tc-MAA was injected during the hepatic angiography followed by SPECT images of the liver as well as the whole body scan. Whole body planar images and SPECT images of the liver showed intensive uptake in the liver. On the review of the whole body images, there was minimal activity in the lungs. Count ratio of the lungs/ (liver+lungs) was calculated to be 3.25%. There was no abnormal radiotracer accumulation in the stomach or elsewhere in the body. A, ^{99m}Tc MAA whole body anterior and B, posterior views, C, ROIs of lungs and liver, D, SPECT view of abdomen, and E, three dimension SPECT of the liver.

cholangiocarcinoma [32-34], metastatic neuroendocrine tumours [35], and breast cancer liver metastasis [36].

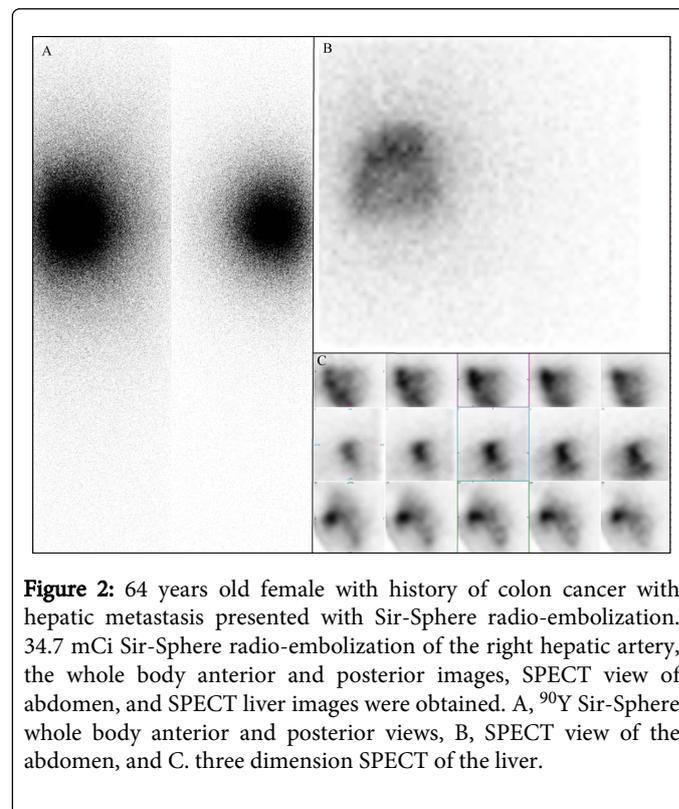


Figure 2: 64 years old female with history of colon cancer with hepatic metastasis presented with Sir-Sphere radio-embolization. 34.7 mCi Sir-Sphere radio-embolization of the right hepatic artery, the whole body anterior and posterior images, SPECT view of abdomen, and SPECT liver images were obtained. A, ⁹⁰Y Sir-Sphere whole body anterior and posterior views, B, SPECT view of the abdomen, and C. three dimension SPECT of the liver.

After extra-hepatic shunts are ruled out, patients will be then treated with ⁹⁰Y microspheres. 24-48 hours later after the administration of ⁹⁰Y microspheres via arterial catheter, anterior and posterior whole body bremsstrahlung scans are acquired, followed by SPECT tomographic imaging of the liver region (Figure 2). These images assist referring physicians to determine whether or not ⁹⁰Y microspheres is within the liver lobes of radioactive targeted tumour and to find any evidence for pulmonary or gastric shunts. The modalities of SPECT or SPECT/CT images are currently replaced by ⁹⁰Y microspheres PET/CT in our hospital (Figure 3). In general, the advantage of PET/CT imaging is high resolution on PET and definite anatomic structure on CT in tumour imaging (Figure 3).

The way to determine the suitable dosage to give the drug is either consistent with body mass index (BMI) or applying partition model dosimetry. In a study done by Kao, et al. [21], partition model dosimetry is more useful in applying ⁹⁰Y due to limitation of body surface area (BSA) method in over or under treatment in some patients. They put their comparison in two tables to show advantages and disadvantages of both methods [21-23].

Series of clinical trials demonstrate that the utility of ⁹⁰Y microsphere radioembolization therapy is safe and it exhibits antitumoural response and survival benefit in select patients with primary and secondary liver cancers [24-27]. Results are most pronounced in patients with solitary tumours, for whom conversion to curative resection is possible. The clinical usage of ⁹⁰Y microsphere radioembolization focuses on treating the unresectable hepatic cancer either primary or the metastases like colorectal tumours [28-30], testicular liver metastasis [31], and unresectable intrahepatic

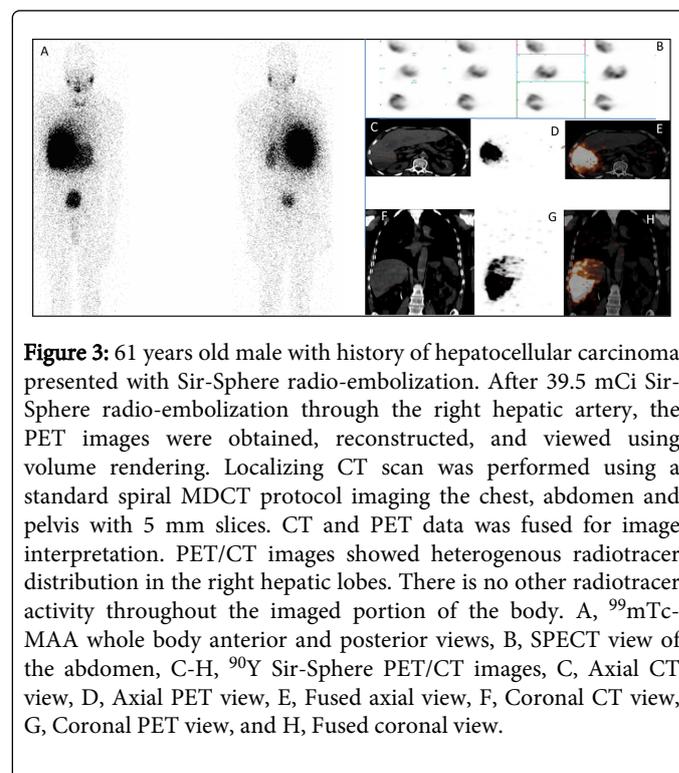


Figure 3: 61 years old male with history of hepatocellular carcinoma presented with Sir-Sphere radio-embolization. After 39.5 mCi Sir-Sphere radio-embolization through the right hepatic artery, the PET images were obtained, reconstructed, and viewed using volume rendering. Localizing CT scan was performed using a standard spiral MDCT protocol imaging the chest, abdomen and pelvis with 5 mm slices. CT and PET data was fused for image interpretation. PET/CT images showed heterogenous radiotracer distribution in the right hepatic lobes. There is no other radiotracer activity throughout the imaged portion of the body. A, ^{99m}Tc-MAA whole body anterior and posterior views, B, SPECT view of the abdomen, C-H, ⁹⁰Y Sir-Sphere PET/CT images, C, Axial CT view, D, Axial PET view, E, Fused axial view, F, Coronal CT view, G, Coronal PET view, and H, Fused coronal view.

Accumulating clinical data would provide fundamental guidance for clinical and therapeutic efforts for disease types for which clinical trials are not feasible due to their low incidence or for the vast majority of those afflicted who do not meet eligibility criteria.

108 consecutive patients with advanced HCC and liver cirrhosis were treated with ⁹⁰Y microspheres administered over the right or left branch of the hepatic artery. 159 treatment sessions were performed ranging between one to three treatments per patient. The mean radiation dose per treatment was 120 (618) Gy. According to the European Association for the Study of the Liver (EASL) criteria, complete responses were determined in 3% of patients, partial responses in 37%, stable disease 53%, and primary progression in 6% of patients. Time to progression (TTP) was 10.0 months, whereas the median overall survival was 16.4 months. No lung or visceral toxicity was observed. This clinical study demonstrated that radioembolization with ⁹⁰Y glass microspheres for patients with advanced HCC was a safe and effective treatment which could be utilized even in patients with compromised liver function [37]. In comparison to chemoembolization, another clinical study showed that radioembolization had less systemic toxicity and could be performed as an outpatient procedure, which makes it more attractive to both patients and physicians. The radioembolization procedure is considered as a promising first-line treatment in unresectable liver cancer [38]. ⁹⁰Y radioembolization in patients with HCC who have received sorafenib demonstrate acceptable toxicity and rates of radiographic response. However, the overall survival is lower than that reported in the literature on radioembolization alone or sorafenib alone. This may be due in part to more patients in this study having advanced disease compared to these other study populations. Larger prospective studies are needed to determine whether the combination of radioembolization and sorafenib is superior to either therapy alone [39]. Hypertrophy of the contralateral liver lobe after treatment with ⁹⁰Y microspheres has recently been reported. This study quantified left liver lobe hypertrophy after right-sided radioembolization for HCC and identified pre-treatment predictive factors of hypertrophy in an Asian population. Administration of unilobar SIRT to the right liver lobe in patients with HCC resulted in a significant degree of contralateral left lobe hypertrophy. Patients with hepatitis B experienced a greater degree of hypertrophy compared to patients with hepatitis C or alcoholic liver cirrhosis [40].

The majority of patients with advanced colorectal cancer die from hepatic metastases caused by disease progression; radioembolization was a technique for administering radiotherapy internally to unresectable secondary hepatic malignancies in a single procedure. Several reports suggested that radioembolization was associated with significant downsizing of liver metastases to permit subsequent surgical resection. Clinical data from trials of radioembolization with concomitant systemic treatment also emphasized the appropriateness of primary end points in large-scale trials and the practical aspects of surgical resection in patients whose tumours were successfully downsized by this chemo radiation approach [28,29]. 41 patients affected by colorectal cancers from a cohort of selective internal radiation therapy patients with disease progression by an abdominal CT, a body PET, and a hepatic angiography were underwent for treatment of ⁹⁰Y radio-embolism. Side effects by Common Terminology Criteria on Adverse Events were represented by one grade 4 hepatic failure, two grades 2 gastritis, and one grade 2 cholecystitis. The median survival and the progression-free survival calculated by Kaplan-Meier analysis were 354 and 279 days, respectively. This clinical study demonstrated that ⁹⁰Y SIR-Spheres

radioembolization is a feasible and safe method to treat colorectal cancers liver metastases, with an acceptable level of complications and a good response rate [31].

Recent clinical study showed a total of 214 patients with colorectal cancers liver metastases were treated with ⁹⁰Y radioembolization. Survival was significantly longer in patients who received ≤ 2 cytotoxic drugs and who received no biologic agents. Multivariate analyses identified ≤ 2 cytotoxic agents, no exposure to biologics, ECOG 0, tumour burden $<25\%$, lack of extrahepatic disease and albumin >3 g/dL as independent predictors of survival. The data indicated that ⁹⁰Y radioembolization was found to be safe; survival varied by prior therapy [41].

Another recent clinical report showed asystematic review of clinical studies before November 2012 with twenty studies comprising 979 patients. The average reported value of patients with complete radiological response, partial response and stable disease was 0%, 31% and 40.5%, respectively. The median overall survival was 12 months. The overall acute toxicity rate ranged from 11 to 100% (median 40.5%). Most cases of acute toxicity were mild (Grade I or II) (median 39%; range 7-100%) which resolved without intervention. The number of previous lines of chemotherapy (≥ 3), poor radiological response to treatment, extra-hepatic disease and extensive liver disease ($\geq 25\%$) were the factors most commonly associated with poorer overall survival. ⁹⁰Y radioembolization overall is a safe and effective treatment of chemorefractory colorectal cancer liver metastases in the salvage setting and should be more widely utilized [25].

24 patients with unresectable standard-chemorefractory intrahepatic colangiocarcinoma (ICC) treated with ⁹⁰Y were studied for analysis for survival, tumour response and complications. Median survival from the time of diagnosis and first ⁹⁰Y procedure was 752 ± 193 and 345 ± 128 days, respectively. Median survival with Eastern Cooperative Oncology Group (ECOG) performance status and ECOG performance status 2 was 450 ± 190 and 345 ± 227 days, respectively ($p=.214$). Patients with extra hepatic metastasis had a median survival of 404 ± 309 days versus 345 ± 117 days for patients without metastasis ($p=.491$). No mortality was reported within 30 days from first ⁹⁰Y radioembolization. One patient developed grade 3 thrombocytopenia as assessed by NCI CTCAE. Fatigue and transient abdominal pain were observed in 4(21%) and 6(32%) patients, respectively. The study indicated ⁹⁰Y radioembolization is effective for unresectable standard-chemorefractory ICC [33].

The present study expands on the cohort of 24 patients with ICC described in a pilot study, and includes 46 patients treated with (90)Y radioembolization during an 8-year period. Patients were stratified by performance status, tumour distribution (solitary or multifocal), tumour morphology (infiltrative or peripheral), and presence/absence of portal vein thrombosis. Ninety-two treatments were performed, with a mean of two per patient. Fatigue and transient abdominal pain occurred in 25 patients (54%) and 13 patients (28%), respectively. Treatment-related gastroduodenal ulcer developed in one patient (2%). WHO imaging findings included partial response ($n=11$; 25%), stable disease ($n=33$; 73%), and progressive disease ($n=1$; 2%). EASL imaging findings included partial/complete response ($n=33$; 73%) and stable disease ($n=12$; 27%). Survival varied based on presence of multifocal (5.7 mo vs 14.6 mo), infiltrative (6.1 mo vs 15.6 mo), and bilobar disease (10.9 mo vs 11.7 mo). Disease was converted to resectable status in five patients, who successfully underwent curative (i.e., R0) resection. Radioembolization with ⁹⁰Y is safe and demonstrates antitumoural response and survival benefit in select

patients with ICC. Results are most pronounced in patients with solitary tumours, for whom conversion to curative resection is possible [32]. Another study was performed in patients with unresectable, chemorefractory liver-dominant disease. Addition of FDG-PET/CT images showed significantly more extrahepatic diseases and led to a considerable change of management [34].

For patients with biopsy-proven, chemotherapy-resistant testicular cancer, liver metastasis was successfully treated with ⁹⁰Y radioembolism selective internal radiation treatment. The result was marked tumour response by PET/CT as well as significant improvement of the patient's quality of life accompanied by a substantial decrease of his tumour markers [31].

A study was carried out to evaluate the anatomic and physiologic determinants of radiation dose distribution, and the dose response of tumour and liver toxicity in patients with liver malignancies who underwent hepatic arterial ⁹⁰Y resin microsphere treatment [42]. In this clinical report, doses up to 99.5 Gy to uninvolved liver are well tolerated with no clinical venoocclusive disease or liver failure. The lowest tumour dose producing a detectable response is 40.1 Gy. The further utilization of ^{99m}Tc-MAA imaging to determine tumour and liver blood flow for clinical treatment planning and the calculation of administered activity could improve clinical outcomes. However, Radioembolization therapy of ⁹⁰Y-Microspheres of other low incidence liver cancers and liver metastasis of low incidence extrahepatic cancers needs more clinical studies. Accumulating clinical data would provide fundamental guidance for clinical and therapeutic efforts for disease types for which clinical trials are not feasible due to their low incidence or for the vast majority of those afflicted who do not meet eligibility criteria.

Advantages

Perhaps the biggest advantage of ⁹⁰Y is that it targets the cancerous tissue more exclusively than conventional radiation which affects whole liver and since the normal hepatic cells have even lower threshold for radiation than the cancerous ones, the majority of patients develop hepatic dysfunction after conventional radiation [43-45]. Furthermore, in comparison to patients left untreated in TACE, the patients, who underwent SIRT, have a greater chance of up to 1 year survival [43]. Another definite advantage in the field of ⁹⁰Y is its use in patients with HCC and portal vein thrombosis (PVT) which occurs in almost one third of the patients and makes them very poor candidates for TACE due to its fatal complications. According to Alkalbani, et al. [45], the median survival dates with ⁹⁰Y increased from less than 100 days to 469 days in those who received the therapy comparing to those who left untreated with TACE due to PVT [45]. An emerging alternative to ⁹⁰Y radioembolization is drug-eluting beads impregnated with irinotecan (DEBIRI). The unique properties of the beads allow for fixed dosing and the ability to release the chemotherapeutic agent in a sustained and controlled manner. This reduces systemic toxicity and theoretically improves tumour response. Initial evaluations of DEBIRI have demonstrated that it has acceptable toxicity and has promising activity [46,47]. In addition, ⁹⁰Y radioembolization therapy for liver cancers is safe due to beta emission. Patients can be treated as outpatients with relative easy prevention of radiation exposure to public and close family members.

Side Effects and Toxicity

Although selective beam therapy is wildly spreading, literature on the side effects of this procedure has not been thoroughly understood. Some more recognized and incriminated complications include: post radio embolization syndrome (PRS), hepatic dysfunction, biliary complications, **portal hypertension**, **radiation pneumonitis**, gastrointestinal **ulcers**, vascular injury, and **lymphopenia** [21]. Lymphopenia due to leaching of ⁹⁰Y was reported in early phases. Lung injury due to chemical pneumonitis can occur and is considered as a life threatening condition in patients with marked hepatopulmonary shunting [48,49]. PRS includes fatigue, nausea, vomiting, anorexia, fever, abdominal discomfort, and cachexia, occurring in 20-55% of patients. Steroids and antiemetic agents may decrease the incidence of PRS. However, there is no supported evidence of infections with opportunistic agents in treatment with ⁹⁰Y microsphere biliary complications, including cholecystitis and **biliary strictures**.

The radiology literature reports a significantly wide range (3%-24%) of the incidence of GI complications from SIRT [48-50]. According to the study done by Konda, et al. [51], significant GI complications and symptoms could be nausea/vomiting, odynophagia, hematemesis, and melena. Also, radiation ulcers can occur in the gastric antrum, pylorus, and duodenum [51].

Early stasis occurred in approximately 20% of infusions with similar incidences in hyper and hypovascular tumours. Whole-liver therapy reduced the incidence of stasis. However, stasis did not appear to affect initial imaging outcomes [52].

Contraindications

In many classification systems, a bilirubin greater than 2 mg/dl in the absence of a correctable obstructive reason is considered to be a contraindication [21]. Massive hepatopulmonary shunting and reflux into that supply of the gastro duodenal region will put the patient at risk of radiation pneumonitis and gastric ulceration [43,53]. In the retrospective study by Goin, et al. [54], predictive factors of 3 month survival identified as having bigger tumour size that 70 % in those with local tumour, amino transaminases level more than 5 times of upper limit, bilirubin level greater than 2 mg/dl, and albumin less 3 g/dl [54].

Conclusion

Radioembolization represents an effective, repeatable and palliative therapy for patients with primary and secondary liver cancers. The utility of ⁹⁰Y microsphere therapy is being evaluated by performing series of clinical trials. Accumulating clinical data would provide fundamental guidance for clinical and therapeutic efforts for disease types for which clinical trials are not feasible due to their low incidence or for the vast majority of those afflicted who do not meet eligibility criteria.

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