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TOPIC HIGHLIGHT

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Radioembolization for the treatment of unresectable hepatocellular carcinoma: A clinical review

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Abstract

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world. The majority of patients with HCC present with unresectable disease. These patients have historically had limited treatment options secondary to HCC demonstrating chemoresistance to the currently available systemic therapies. Additionally, normal liver parenchyma has shown intolerance to tumoricidal radiation doses, limiting the use of external beam radiation. Because of these limitations, novel percutaneous liver-directed therapies have emerged. The targeted infusion of radioactive microspheres (radioembolization) represents one such therapy. Radioembolization is a minimally invasive transcatheter therapy through which radioactive microspheres are infused into the hepatic arteries that supply tumor. Once infused, these microspheres traverse the hepatic vascular plexus and selectively implant within the tumor arterioles. Embedded within the arterioles, the ^{90}Y impregnated microspheres emit high energy and low penetrating radiation doses selectively to the tumor. Radioembolization has recently shown promise for the treatment of patients with unresectable HCC. The objective of this review article is to highlight two currently available radioembolic devices (^{90}Y, ^{188}Rh) and provide the reader with a recent review of the literature.

Key words: Radioembolization; Brachytherapy; Hepatocellular carcinoma; Yttrium-90; Rhenium-188

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INTRODUCTION

Hepatocellular carcinoma (HCC) claims half a million lives across the globe each year[1]. It is the sixth most common cancer in the world and is the third most common cause of cancer-related mortality[2]. Various etiologic factors have been implicated in the transformation of benign hepatic parenchyma to malignancy, however, no one factor has been shown to cause cancer in all cases. Although several postulates for tumorigenesis have been proposed, the exact underlying mechanism for neoplastic change remains unknown[1,3].

The incidence of HCC varies considerably across geographic regions with some areas reporting cases as high as 20/100 000 per annum[3]. Various studies have shown that advanced age and male sex portends a higher likelihood of developing HCC. Several important risk factors have been identified which substantially increase the possibility of developing disease. Among these, the most common risk factor recognized worldwide is the hepatitis B carrier state. Others inciting factors include chronic hepatitis C infection, cirrhosis, environmental toxins such as aflatoxin and contaminated drinking water, alcohol abuse, diabetes mellitus, and hereditary hemochromatosis.

In patients diagnosed with this lethal malignancy, less than 15% are candidates for surgical procedures. A survival

benefit has been observed in patients that meet the rigorous criteria for curative resection or transplantation[4]. For the remaining majority, various treatments options have become available without universal agreement on which treatment option offers the greatest survival benefit with the least toxicity.

The use of external beam irradiation has historically played a limited role in the treatment of HCC due to the radiosensitive nature of normal hepatic tissue[5]. Investigators have shown that liver exposure to radiation doses greater than 40 Gy may result in a clinical syndrome characterized by ascites, anicteric hepatomegaly, and elevated liver enzymes weeks to months following therapy[5,6]. Additionally, a condition recognized as veno-occlusive disease, marked by central venous congestion and atrophy of adjacent hepatocytes, may develop. Together, the clinical and pathologic spectrum described above has been referred to as radiation induced liver disease (RILD) or radiation hepatitis. This is the most prominent treatment related complication in patients undergoing hepatic irradiation from external sources[7].

Given this limitation and the need for higher doses to inflict lethal injury to malignant tissue[8-10], minimally invasive intra-arterial devices have emerged. These devices, loaded with radioactive Yttrium-90 microspheres or Rhenium-188, can deliver very high tumoricidal doses without the development of RILD[11]. Using segmental infusion techniques, doses as high as 4993 Gy to liver tissue have been reported[12]. Although the use of these devices dates back to the early 1960's, only recently has the therapeutic safety and efficacy associated with its use been realized[13,14]. For the purpose of this review, we aim to highlight the use of intra-arterial radiotherapy for the treatment of inoperable HCC and update the reader on recent clinical and research advancements.

DEVICE AND DOSIMETRY CONSIDERATIONS

Yttrium-90 intra-arterial radiotherapy, also known as radioembolization, is a minimally invasive catheter-based therapy that delivers internal radiation via the arterial vessels that feed tumors. "Radio" refers to the radiation that is imparted to tissue; "embolization" refers to the microembolic effect[15]. This technology takes advantage of the dual blood supply to the liver. Normal hepatic tissue derives greater than 70% of its blood supply by way of the portal system whereas malignant tissue is preferentially supplied by the arterial system. There are currently two commercially available Yttrium-90 microsphere devices. TheraSphere® (MDS Nordion, Ottawa, Ontario, Canada) is made of glass and SIR-Spheres® (Sirtex Medical, Sydney, Australia) is made of resin. These two devices are different in a number of important respects[16]. TheraSphere® is a minimally embolic device consisting of 20-30 micron particles with higher specific activity (2500 Bq) and lower number of spheres (1.2 million microspheres/3 GBq). Conversely, SIR-Spheres® are moderately embolic, consisting of 20-60 micron particles, with lower specific activity (50 Bq), and greater number of spheres (approximately 40-80 million spheres/3 GBq). A third agent, available in certain countries, uses a Rhenium-188 based radioconjugate delivered in a trans-arterial manner analogous to the Yttrium-90 based devices[14].

^{90}Y Glass microspheres

^{90}Y microspheres (TheraSphere®, MDS Nordion, Ottawa, Canada) are composed of nonbiodegradable glass microspheres ranging from 20 to 30 μm in diameter, in which ^{90}Y is an integral constituent of the glass. ^{90}Y is a pure β-emitter with a physical half-life of 64.2 h, after which ^{90}Y decays into stable zirconium. The average energy of β-emission is 0.9367 MeV, mean tissue penetration of 2.5 mm and a maximum penetration of 10 mm. One gigabecquerel (27 mCi) of ^{90}Y per kilogram of tissue provides a dose of 50 Gy. The microspheres are supplied in 0.5 mL of sterile, pyrogen-free water contained in a 0.3-mL V-bottom vial secured within a 12-mm clear acrylic shield. The specific activity is 2500 Bq at the time of calibration.

The typical method of calculating the required activity level (in GBq) to be injected and the actual dose delivered to the liver and lung has been previously published. CT or MR imaging is used to determine the targeted liver volume to be treated with ^{90}Y microspheres[17-19]. The targeted liver volume is that portion of liver tissue that will be perfused once the catheter is in the desired location. A conversion factor of 1.03 g/cm^3 is used to calculate the corresponding targeted liver mass from the targeted liver volume. The required activity is calculated from the following formula:

Activity (GBq) = [target dose (Gy) × target liver mass (kg)]/50

When lung shunt fraction (LSF) and percentage of residual activity (R) in the vial after treatment are taken into account, the actual dose delivered to the target mass is calculated by rearranging the previous equation as follows:

Dose (Gy) = [Infused activity (GBq) × 50 × (1- LSF) × (1-R)]/liver mass (kg)

Cumulative liver dose is defined as the accumulated dose to that specific volume that was treated multiple times. By targeting delivery to a hepatic segment or lobe, ^{90}Y therapy results in high radiation doses to the tumor while sparing liver parenchyma. These tumoricidal doses have proven effective in the ability of ^{90}Y microspheres to reduce tumor viability, demonstrating an increasing therapeutic effect with radiation dose[11].

^{90}Y Resin microspheres

SIR-Spheres® consist of biodegradable resin-based microspheres containing ^{90}Y. The average size of a sphere is 35 microns in diameter. Upon *in vivo* administration, the spheres are permanently implanted. Each vial contains 3 GBq of ^{90}Y in a 5 mL vial. Each vial contains 40-80 million spheres. The activity per microsphere is 50 Bq at the time of calibration.

The radioactivity to the liver can be calculated by one of two methods:

(1) The first method allows the calculation be based on body surface area to determine an approximate tumor burden:

Activity (GBq) = body surface area (m^2) - 0.2 + (% tumor burden/100)

(2) Based on a broad estimate of tumor burden which then requires the user to increase the recommended activity by 0.5 GBq per 25% increase in tumor burden.

Activity for tumor involvement < 25%, 25%-50% and > 50% are 2.0 GBq, 2.5 GBq and 3.0 GBq, respectively.

Using either dosimetry model, activity administered is decreased depending on the extent of identified lung shunt. Also, recent clinical practices have shown that an additional 25%-30% activity reduction is usually necessary for SIR-Spheres®[20]. The dosimetry model for SIR-Spheres® is based on whole liver infusion. If a lobar administration is intended, the activity to be administered should be calculated using whole liver volume and then corrected for the target volume anticipated for treatment. As an example, if a right lobe infusion is anticipated, the calculated GBq should be multiplied by the percentage of right lobe as a proportion to the entire liver. Dosimetric issues and technical considerations have been described in detail previously[16,20,21].

Rhenium-188 radioconjugate

This is available through the use of a Rhenium-188 generator. The half-life of Rhenium-188 is 16.9 h. The isotope delivers high-energy beta (2.1 MeV max) and a low energy gamma (155 keV) emissions, permitting imaging. Usually, this radioconjugate is in the form of Rhenium-188 4-hexadecyl 1, 2, 9, 9-tetramethyl-4, 7diaza-1, 10-decaethaniol labeled with iodized oil. Dosimetry is based on the safe and tolerable dose to organs at risk including the liver, lungs and bone. A small scout dose of the radioconjugate (3.7 MBq) is administered on the day prior to treatment. Subsequently, transmission scans with a Rhenium-188 flood source are performed to determine the attenuation correction factors for lung and liver to be used in the dosimetric calculations the following day. Anterior and posterior images are obtained to calculate geometric mean counts. After correcting for scatter, regions of interest are placed around the whole liver, tumor and lungs. Using medical internal radiation dosimetry and by adjusting for the difference in total body and organ masses between the patient and the anthropomorphic model, the proper activity required is calculated using the following dose limitations: 12 Gy to the lungs, 30 Gy to the normal liver, 1.5 Gy to the bone marrow.

Absolute and relative contraindications

Two absolute contraindications exist for the use of ^{90}Y microsphere treatment in any patient. The first includes a pretreatment ^{99m}Tc macro-aggregated albumin (MAA) scan demonstrating significant hepatopulmonary shunting that would result in > 30 Gy being delivered to the lungs with a single infusion or as much as 50 Gy for multiple infusions. The second includes the inability to prevent deposition of microspheres to the gastrointestinal tract with modern catheter techniques. A number of relative contraindications exist including non-compromised pulmonary function, adequate liver reserve, serum creatinine < 2.0 mg/dL, and a platelet count > 75×10^9/L. For relative contraindications, clinical judgment should be exercised when determining whether a patient is appropriate to undergo this procedure.

Observed toxicities

The most common clinical toxicity observed with the use of ^{90}Y is a mild post-embolic syndrome. This syndrome, unlike that observed with other embolic treatments such as transarterial chemoembolization (TACE), includes fatigue, vague abdominal discomfort, pain, and fever[11,22,23]. Other avoidable toxicities that occur as a result of non-target radiation include: cholecystitis, gastric ulceration, gastroduodenitis, pancreatitis, radiation pneumonitis, and RILD[16,24-27]. With meticulous planning, careful selection, and proper technique, the majority of these toxicities can be mitigated. Finally, hematologic toxicities seen in the immediate post-procedural period include lymphopenia. This is not an unexpected finding given the sensitivity of lymphocytes to radiation. Despite this, no infectious complications have been documented[16,21,28].

LITERATURE REVIEW

A comprehensive literature review was completed in 2006 describing the entire clinical and scientific evidence for ^{90}Y in detail[13]. Since then, additional evidence has been generated[16]. A consensus panel report from the radioembolization brachytherapy oncology consortium concluded that there is sufficient evidence to support the safe and effective use of this loco-regional therapy in HCC patients[20]. The authors further suggested the need to investigate the benefits of ^{90}Y in combination with other traditional therapies. The results from phase I and II studies in combining ^{90}Y with targeted therapies (Raf-kinase, EGFR) for HCC are underway and should provide valuable insight into the toxicity and efficacy of such regimens.

Sangro *et al* reported on 24 HCC patients with Child-Pugh A disease who underwent radioembolization with resin microspheres[29]. The median activity delivered was 2.2 GBq. The investigators reported a reduction in size of target lesions in 19 patients. Using RECIST criteria, 88% of the cohort had either partial response or stable disease. The authors did not observe any post-embolization syndrome and all patients were discharged within 24 h of treatment. Two patients became jaundiced at 1 mo and 3 mo after the procedure from uncertain causes. Two treatment-related deaths were recorded. At median follow-up of 12.5 mo none of the treated patients progressed. Given the tumor response and minimal toxicity profile, the investigators concluded that radioembolization is a viable therapy for patients with portal vein thrombosis and preserved liver function and that this therapy needs to be considered in patients who are awaiting transplant in order to prevent extension of disease beyond the Milan criteria.

Rivera *et al* presented a case report of a 42 years old hepatitis C cirrhotic male with tumor recurrence 22 mo post-transplantation[30]. The investigators in the study then treated the patient with ^{90}Y resin microspheres. The author noted no change in liver function post-procedurally and follow-up MRI demonstrated the absence of arterial enhancement and tumor necrosis. The authors concluded the use of ^{90}Y for post-transplant recurrence may help prolong patient and graft survival in patients that develop recurrence.

Gulec *et al* retrospectively analyzed the data from a heterogeneous cohort of 40 patients with primary and

metastatic liver malignancies who underwent single whole liver treatments using ^{90}Y resin microspheres[31]. The average administered activity was 1.2 GBq and tumor absorbed doses ranged from 40.1 to 494.8 Gy. Sixty-seven percent of the treated cohort responded to therapy with favorable responses reported in those with higher tumor flow ratios. The authors concluded that doses up to 100 Gy to the uninvolved liver were tolerated by this procedure without the development of veno-occlusive disease or liver failure. The authors further noted that lowest tumor dose necessary to generate a detectable response was 40 Gy.

Kamel *et al* reported on 13 patients prospectively treated with ^{90}Y glass microspheres. MR imaging was compared 24 h pre-treatment to an average follow-up of 55 d post-therapy[32]. Targeted tumors demonstrated a mean decrease in arterial enhancement of 22%, a mean decrease in venous enhancement of 25% and unchanged tumor size in both targeted and non-targeted tumors. The authors reported a median survival of 12 mo from time of diagnosis and emphasized the need for surrogate imaging measures such as diffusion-weighted MR in order to assess response.

Keppke *et al* reported on the imaging findings and median survival of 42 patients using ^{90}Y glass microspheres[33]. The response rates according to WHO, RECIST, necrosis and combined criteria (RECIST and necrosis) were 26%, 23%, 57% and 59%, respectively. The median survival for Okuda I patients was 660 d. The authors concluded that the imaging findings, using a combined criteria (size and necrosis), resulted in a more accurate assessment of tumor response after ^{90}Y radiotherapy when compared to size criteria alone.

In an attempt to address the question of retreatment using this therapy, Young *et al* recently reported on the relationship between cumulative radiation dose and the development of liver toxicities in 41 patients stratified to Okuda I and Ⅱ[34]. The authors observed a statistically significant mean cumulative radiation dose of 390 Gy and 196 Gy tolerated by Okuda I and Okuda Ⅱ patients, respectively, before the occurrences of toxicity. This suggests that some patients can tolerate multiple treatments prior to the development of liver toxicities. Median survival from date of first treatment for Okuda I and Okuda Ⅱ were 660 d and 431 d, respectively ($P = 0.44$).

More recently, Kulik *et al* reported on 21 patients from a large database of 251 patients who had undergone ^{90}Y glass microsphere therapy and subsequently bridged to transplantation[35]. Target tumor dose administered was 120 Gy with toxicities including fatigue in the majority of patients (42%). The authors reported a mean reduction in alpha fetoprotein (AFP) of 33% from pre-treatment levels. The investigators noted complete necrosis by pathologic exam in 14 of 21 patients (66%). Four of 21 patients had disease recurrence with a mean time to recurrence of 250 d, a finding not uncommon following transplantation[36-38]. The authors concluded that treatment with ^{90}Y achieves complete necrosis in the majority of targeted lesions in patients bridged to transplantation, but that recurrence was a possibility despite the radiographic findings of complete necrosis.

Additionally, Kulik *et al* reported on the safety of ^{90}Y in a 108 patient cohort treated with glass microspheres, with subset analysis comparing patients with and without portal vein thrombosis[39]. Thirty-seven of 108 patients presented with imaging proven portal vein thrombosis (PVT). Patients were stratified by Okuda, Child Pugh, baseline bilirubin, ECOG, presence of cirrhosis and location of PVT (none, branch, and main). The cumulative dose administered to those with and without PVT were 139.7 Gy and 131.9 Gy, respectively. Liver related adverse events reported included elevation of bilirubin in 40%, ascites in 18%, and hepatic encephalopathy in 4% of the patients with cirrhosis and main PVT. In the patients without cirrhosis, elevated bilirubin occurred in 4%, ascites in 4% and no cases of encephalopathy. Tumor response using WHO criteria and EASL recommendations were 42.2 and 70%, respectively[40]. Median survival from the date of first treatment for patients without PVT and cirrhosis was 813 d. In patients with branch PVT, survival was 304 d from time of treatment (cirrhotics: 261 d, non-cirrhotics: 427 d). The authors concluded that the microembolic effect of ^{90}Y microspheres did not increase the risk of liver adverse events in patients with proven PVT. Glass microspheres did not result in a microembolic effect that is seen with other loco-regional therapies using larger diameter particles.

Investigators also studied the use of Rhenium-188 for patients with inoperable HCC[14]. A multicenter clinical trial was completed looking at Rhenium-188 (Rh-188) lipiodol delivered in a transarterial manner. After complete clinical evaluation (including serum alpha-fetoprotein (AFP), tumor burden, patency of portal vein, Child-Pugh and Okuda classification), radiation absorbed dose (rad) to various organs, including tumor, was calculated after injecting 185 MBq of Rh-188 iodized oil *via* the hepatic artery. From this value, the maximum tolerable activity, defined as the amount of radioactivity delivering no more than 12 Gy of rad to lungs, 30 Gy to normal liver, or 1.5 Gy to bone marrow, was calculated and injected. Ninety-three patients were successfully treated with a mean age of 53 years (80 men and 13 women). Mean cumulative dose was 7.8 GBq. Sixty-eight percent of patients had serologic evidence of hepatitis B and/or C; 40% had clinical/radiologic evidence of cirrhosis. Mean tumor diameter was 10.3 ± 4.4 cm, with 40% of patients having more than three lesions; in 50% of patients, tumor was either unilateral, occupying 50% or more of the liver, or bilateral. AFP was elevated in 68% of patients and serum levels exceeding 300 ng/mL was observed in 44% of these patients. There was portal vein thrombosis in 38% of patients, Child-Pugh B disease in 37% of patients, and Okuda stage Ⅱ or Ⅲ disease in 50% of patients. Mean first administered activity was 5.3 GBq ± 1.6, which delivered 88 Gy to the tumor. Treatment was tolerated well. Five patients had complete tumor response, while 17 had a partial response (> 50% tumor reduction) for an overall objective response rate of 33%. Thirty-five percent of patients had stable disease. Only dose to the tumor was found to be significantly ($P = 0.001$) associated with tumor and/or AFP response. Median survival for the entire cohort was 356 d and varied accordingly with baseline characteristics. Responders by imaging survived longer than those that did not exhibit a response and interestingly was correlated with dose administered to tumor. The

authors concluded that this was a safe, effective, and promising therapy in patients with HCC with favorable cost-benefit profile.

CONCLUSION

Clinical investigations into the use of ^{90}Y radioembolization for the palliative treatment of unresectable hepatocellular carcinoma appear promising. This therapy potentially offers survival benefit with a low toxicity profile, making it an attractive tool in the battle against a uniformly fatal disease. Unlike external beam therapy, radioembolization can deliver high cumulative radiation doses to targeted hepatic segments without the clinical manifestation of RILD. Additionally, investigators have shown favorable survival outcomes in patients with limited hepatic reserve and portal vein thrombosis. These patients were previously excluded from most therapeutic options. Furthermore, this therapy has successfully been used to bridge and downstage patients to resection, ablation or transplantation[29,41-44]. Although phase Ⅱ paradigms have provided useful data, there is a need to carry out randomized controlled trials comparing ^{90}Y therapy to those accepted as standard of care for this patient population. These studies will then establish the role of radioembolization within the framework of other universally accepted first line therapies for inoperable disease. Finally, the development of targeted therapies at the molecular level represents the beginning of a new era in the treatment of HCC[45]. Clinical investigations into combining the cytotoxic effect of ^{90}Y with the cytostatic mechanism of targeted therapies are currently in progress and will provide valuable safety and toxicity data that may translate into improved clinical outcome and overall survival.

REFERENCES

1 **El-Serag HB**. Hepatocellular carcinoma: an epidemiologic view. *J Clin Gastroenterol* 2002; **35**: S72-S78
2 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108
3 **El-Serag HB**, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; **132**: 2557-2576
4 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699
5 **Ingold JA**, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. *Am J Roentgenol Radium Ther Nucl Med* 1965; **93**: 200-208
6 **Lawrence TS**, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys* 1995; **31**: 1237-1248
7 **Cheng JC**, Wu JK, Huang CM, Huang DY, Cheng SH, Lin YM, Jian JJ, Yang PS, Chuang VP, Huang AT. Radiation-induced liver disease after radiotherapy for hepatocellular carcinoma: clinical manifestation and dosimetric description. *Radiother Oncol* 2002; **63**: 41-45
8 **Kennedy AS**, Nutting C, Coldwell D, Gaiser J, Drachenberg C. Pathologic response and microdosimetry of (90)Y microspheres in man: review of four explanted whole livers. *Int J Radiat Oncol Biol Phys* 2004; **60**: 1552-1563
9 **Yorke ED**, Jackson A, Fox RA, Wessels BW, Gray BN. Can current models explain the lack of liver complications in Y-90 microsphere therapy? *Clin Cancer Res* 1999; **5**: 3024s-3030s
10 **Dawson LA**, McGinn CJ, Normolle D, Ten Haken RK, Walker S, Ensminger W, Lawrence TS. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. *J Clin Oncol* 2000; **18**: 2210-2218
11 **Salem R**, Lewandowski RJ, Atassi B, Gordon SC, Gates VL, Barakat O, Sergie Z, Wong CY, Thurston KG. Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (TheraSphere): safety, tumor response, and survival. *J Vasc Interv Radiol* 2005; **16**: 1627-1639
12 **Lewandowski R**, Salem R, Thurston K, Goin J, Mulachy M, Gates V, Sato KT, Courtney A. Radiation Segmentectomy of Unresectable of Liver Carcinoma Using Selective Infusion of Intraarterial Yttrium-90 TheraSphere. Radiological Society of North America; 2004 Nov 28-Dec 3; Chicago, 2004
13 **Salem R**, Thurston KG. Radioembolization with yttrium-90 microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies: part 3: comprehensive literature review and future direction. *J Vasc Interv Radiol* 2006; **17**: 1571-1593
14 **Kumar A**, Srivastava DN, Chau TT, Long HD, Bal C, Chandra P, Chien le T, Hoa NV, Thulkar S, Sharma S, Tam le H, Xuan TQ, Canh NX, Pant GS, Bandopadhyaya GP. Inoperable hepatocellular carcinoma: transarterial 188Re HDD-labeled iodized oil for treatment--prospective multicenter clinical trial. *Radiology* 2007; **243**: 509-519
15 **Sato K**, Lewandowski RJ, Bui JT, Omary R, Hunter RD, Kulik L, Mulcahy M, Liu D, Chrisman H, Resnick S, Nemcek AA Jr, Vogelzang R, Salem R. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere): assessment of hepatic arterial embolization. *Cardiovasc Intervent Radiol* 2006; **29**: 522-529
16 **Salem R**, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. *J Vasc Interv Radiol* 2006; **17**: 1251-1278
17 **Salem R**, Thurston KG, Carr BI, Goin JE, Geschwind JF. Yttrium-90 microspheres: radiation therapy for unresectable liver cancer. *J Vasc Interv Radiol* 2002; **13**: S223-S229
18 **Dancey JE**, Shepherd FA, Paul K, Sniderman KW, Houle S, Gabrys J, Hendler AL, Goin JE. Treatment of nonresectable hepatocellular carcinoma with intrahepatic 90Y-microspheres. *J Nucl Med* 2000; **41**: 1673-1681
19 **Russell JL Jr**, Carden JL, Herron HL. Dosimetry calculations for yttrium-90 used in the treatment of liver cancer. *Endocurietherapy/Hyperthermia Oncology* 1988; **4**: 171-186
20 **Kennedy A**, Nag S, Salem R, Murthy R, McEwan AJ, Nutting C, Benson A 3rd, Espat J, Bilbao JI, Sharma RA, Thomas JP, Coldwell D. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. *Int J Radiat Oncol Biol Phys* 2007; **68**: 13-23
21 **Salem R**, Thurston KG. Radioembolization with 90yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 2: special topics. *J Vasc Interv Radiol* 2006; **17**: 1425-1439
22 **Kennedy AS**, Coldwell D, Nutting C, Murthy R, Wertman DE Jr, Loehr SP, Overton C, Meranze S, Niedzwiecki J, Sailer S. Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. *Int J Radiat Oncol Biol Phys* 2006; **65**: 412-425
23 **Murthy R**, Xiong H, Nunez R, Cohen AC, Barron B, Szklaruk J, Madoff DC, Gupta S, Wallace MJ, Ahrar K, Hicks ME. Yttrium 90 resin microspheres for the treatment of unresectable colorectal hepatic metastases after failure of multiple chemotherapy regimens: preliminary results. *J Vasc Interv Radiol* 2005; **16**: 937-945
24 **Murthy R**, Nunez R, Szklaruk J, Erwin W, Madoff DC, Gupta S, Ahrar K, Wallace MJ, Cohen A, Coldwell DM, Kennedy AS, Hicks ME. Yttrium-90 microsphere therapy for hepatic malignancy: devices, indications, technical considerations, and potential complications. *Radiographics* 2005; **25** Suppl 1: S41-S55
25 **Murthy R**, Brown DB, Salem R, Meranze SG, Coldwell DM,

Krishnan S, Nunez R, Habbu A, Liu D, Ross W, Cohen AM, Censullo M. Gastrointestinal complications associated with hepatic arterial Yttrium-90 microsphere therapy. *J Vasc Interv Radiol* 2007; **18**: 553-561; quiz 562

26 **Lewandowski R**, Salem R. Incidence of radiation cholecystitis in patients receiving Y-90 treatment for unresectable liver malignancies. *J Vasc Interv Radiol* 2004; **15**: S162

27 **Carretero C**, Munoz-Navas M, Betes M, Angos R, Subtil JC, Fernandez-Urien I, De la Riva S, Sola J, Bilbao JI, de Luis E, Sangro B. Gastroduodenal injury after radioembolization of hepatic tumors. *Am J Gastroenterol* 2007; **102**: 1216-1220

28 **Carr BI**. Hepatic arterial 90Yttrium glass microspheres (Therasphere) for unresectable hepatocellular carcinoma: interim safety and survival data on 65 patients. *Liver Transpl* 2004; **10**: S107-S110

29 **Sangro B**, Bilbao JI, Boan J, Martinez-Cuesta A, Benito A, Rodriguez J, Panizo A, Gil B, Inarrairaegui M, Herrero I, Quiroga J, Prieto J. Radioembolization using 90Y-resin microspheres for patients with advanced hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2006; **66**: 792-800

30 **Rivera L**, Giap H, Miller W, Fisher J, Hillebrand DJ, Marsh C, Schaffer RL. Hepatic intra-arterial infusion of yttrium-90 microspheres in the treatment of recurrent hepatocellular carcinoma after liver transplantation: a case report. *World J Gastroenterol* 2006; **12**: 5729-5732

31 **Gulec SA**, Mesoloras G, Dezarn WA, McNeillie P, Kennedy AS. Safety and efficacy of Y-90 microsphere treatment in patients with primary and metastatic liver cancer: The tumor selectivity of the treatment as a function of tumor to liver flow ratio. *J Transl Med* 2007; **5**: 15

32 **Kamel IR**, Reyes DK, Liapi E, Bluemke DA, Geschwind JF. Functional MR imaging assessment of tumor response after 90Y microsphere treatment in patients with unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2007; **18**: 49-56

33 **Keppke AL**, Salem R, Reddy D, Huang J, Jin J, Larson AC, Miller FH. Imaging of hepatocellular carcinoma after treatment with yttrium-90 microspheres. *AJR Am J Roentgenol* 2007; **188**: 768-775

34 **Young JY**, Rhee TK, Atassi B, Gates VL, Kulik L, Mulcahy MF, Larson AC, Ryu RK, Sato KT, Lewandowski RJ, Omary RA, Salem R. Radiation dose limits and liver toxicities resulting from multiple yttrium-90 radioembolization treatments for hepatocellular carcinoma. *J Vasc Interv Radiol* 2007; **18**: 1375-1382

35 **Kulik LM**, Atassi B, van Holsbeeck L, Souman T, Lewandowski RJ, Mulcahy MF, Hunter RD, Nemcek AA Jr, Abecassis MM, Haines KG 3rd, Salem R. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. *J Surg Oncol* 2006; **94**: 572-586

36 **Lo CM**, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; **35**: 1164-1171

37 **Llovet JM**, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, Bru C, Rodes J, Bruix J. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999; **29**: 62-67

38 **Noguchi Y**, Murakami T, Kim T, Hori M, Osuga K, Kawata S, Kumano S, Okada A, Sugiura T, Nakamura H. Detection of hepatocellular carcinoma: comparison of dynamic MR imaging with dynamic double arterial phase helical CT. *AJR Am J Roentgenol* 2003; **180**: 455-460

39 **Kulik LM**, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, Sato KT, Benson A 3rd, Nemcek AA Jr, Gates VL, Abecassis M, Omary RA, Salem R. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008; **47**: 71-81

40 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodes J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430

41 **Kulik LM**, Mulcahy MF, Hunter RD, Nemcek AA Jr, Abecassis MM, Salem R. Use of yttrium-90 microspheres (TheraSphere) in a patient with unresectable hepatocellular carcinoma leading to liver transplantation: a case report. *Liver Transpl* 2005; **11**: 1127-1131

42 **Kulik LM**, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, Sato KT, Benson A 3rd, Nemcek AA Jr, Gates VL, Abecassis M, Omary RA, Salem R. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008; **47**: 71-81

43 **Goin JE**, Salem R, Carr BI, Dancey JE, Soulen MC, Geschwind JF, Goin K, Van Buskirk M, Thurston K. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: factors associated with liver toxicities. *J Vasc Interv Radiol* 2005; **16**: 205-213

44 **Goin JE**, Salem R, Carr BI, Dancey JE, Soulen MC, Geschwind JF, Goin K, Van Buskirk M, Thurston K. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: a risk-stratification analysis. *J Vasc Interv Radiol* 2005; **16**: 195-203

45 **Llovet J**, Ricci S, Mazzafero V, Hilgard P, Raoul J, Zeuzem S, Poulin-Costello M, Moscovici M, Voliotis D, Bruix J. Sorafenib improves survival in advanced Hepatocellular Carcinoma (HCC): Results of a Phase III randomized placebo-controlled trial (SHARP). 2007 American Society of Clinical Oncology (ASCO) Annual Meeting; 2007 Proceedings Part I; Chicago, 2007: **15**: 18S

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