

Yttrium-90 Microspheres (TheraSphere[®] and SIR-Spheres[®]) for the Treatment of Unresectable Hepatocellular Carcinoma

Summary

- ✓ **Microspheres containing radioactive yttrium-90 (⁹⁰Y) are infused into the hepatic artery. These deliver high doses of ionizing radiation to inoperable hepatocellular carcinoma, the most common type of primary liver cancer.**
- ✓ **Limited evidence from several case series indicates that palliative therapy with ⁹⁰Y microspheres may reduce tumour size and increase survival time.**
- ✓ **In some patients, ⁹⁰Y treatment may result in enough tumour reduction to permit liver resection or transplantation.**
- ✓ **While ⁹⁰Y microsphere therapy is generally well tolerated, major complications and several treatment-related deaths have occurred. Improved patient selection criteria and technical changes to microsphere delivery have reduced the risks of complications and death.**
- ✓ **Patient selection and the technical aspects of ⁹⁰Y microsphere treatment are complex and require the coordinated expertise of a multidisciplinary team.**

Background

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. It usually develops in individuals with chronic liver disease, particularly those with viral hepatitis.¹ HCC is an aggressive disease, especially when chronic liver disease and cirrhosis are present.² It is often at an advanced stage when diagnosed.^{1,3} The median survival time from diagnosis is approximately six to 20 months.²

The Technology

Intrahepatic (in the liver) administration of microspheres that contain radioactive yttrium-90 (⁹⁰Y) is an emerging palliative treatment for some patients with inoperable primary liver cancer.

The microspheres are delivered using a catheter that is inserted through an incision in the groin and guided to the

artery that supplies blood to the liver. The microspheres can be directed to the entire liver or to subregions, where they lodge in the hepatic arterioles (branches of the artery) and embolize (occlude) the blood vessels feeding the tumour. The microspheres also exert a radiotherapeutic effect by emitting beta radiation that destroys local tumour tissue with little damage to surrounding normal tissue. ⁹⁰Y has a half-life of 64.2 hours and an average tissue penetration of 2.5 mm. After they decay to stable zirconium 90, the inert, non-biodegradable microspheres remain in the liver.³

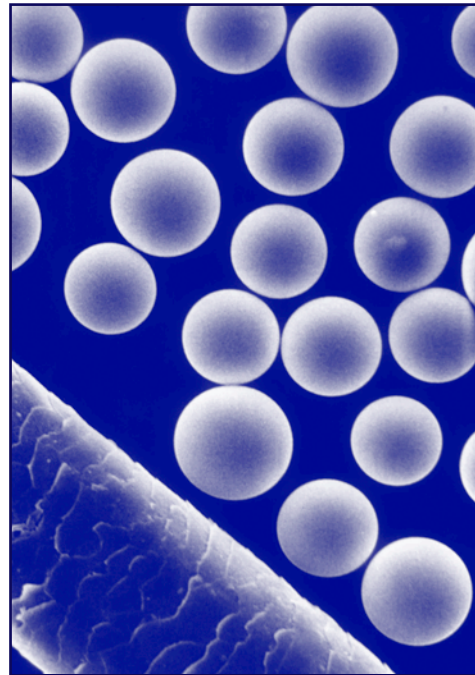


Image courtesy of MDS Nordion Inc.

Microscopic view of yttrium-90 microspheres beside a strand of hair.

The use of ⁹⁰Y microspheres in the treatment of liver metastases from colorectal and neuroendocrine cancers is not assessed in this bulletin.

Regulatory Status

Two ⁹⁰Y microsphere products are commercially available: TheraSphere[®] (MDS Nordion, Ottawa) and SIR-Spheres[®] (Sirtex Medical Limited, Lane Cove, Australia). Only TheraSphere is currently licensed in Canada.

TheraSphere was licensed in February 2005 as a Class III medical device for the treatment of hepatic neoplasia in patients who have appropriately positioned hepatic arterial catheters (Sarah Chandler, Medical Devices Bureau, Health Canada, Ottawa: personal communication, 2007 Jul 25). Prior to this, TheraSphere was licensed in Canada as a drug.⁴

TheraSphere received a Humanitarian Device Exemption from the US Food and Drug Administration (FDA) in 1999, for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately positioned hepatic arterial catheters.⁵ TheraSphere was cleared for marketing in the European Union in 1998.⁵

SIR-Spheres is not licensed for use in Canada. The US FDA gave SIR-Spheres pre-marketing approval in 2002, to be used with intrahepatic floxuridine for the treatment of colorectal metastases to the liver.⁶ The use of SIR-Spheres for the treatment of HCC in the US is an off-label (unapproved) indication. SIR-Spheres received regulatory approval in Australia in 1998 and in the European Union in 2002, for the treatment of patients with advanced inoperable liver cancer (Heather Winslade, Sirtex Medical Ltd., Lane Cove, Australia: personal communication, 2007 May 6).

Patient Group

In 2003, there were 820 new cases of primary liver cancer reported in Canada and 460 deaths due to the disease. Males are affected about three times more often than females.⁷ Although HCC is relatively rare in North America, its incidence has risen with the increase in hepatitis C and hepatitis B infections.⁸

Current Practice

There are four established treatments for HCC: resection, transplantation, ablation, and embolization. The treatment options are determined by tumour stage and the degree of liver impairment.⁹ Surgical resection of the tumour or liver transplantation offer a high rate of complete response and a potential for cure.³ Only about 20% of patients with HCC are surgical candidates because of the presence of extensive disease or poor liver function.^{3,10} The availability of organs for transplantation is also a limitation.³

Percutaneous ablation with ethanol injection and radiofrequency ablation are treatment options for early stage, unresectable HCC.³ More widespread disease is treated with transarterial embolization (TAE), which deprives the tumour of its blood supply by blocking or embolizing the hepatic artery. When TAE is combined with the injection of chemotherapeutic agents that are usually mixed with lipiodol (a contrast agent), the procedure is called “transarterial chemoembolization” (TACE). TACE has been shown to modestly increase survival in selected patients^{3,9,11,12} and has become the standard treatment for unresectable HCC.¹¹

The Radioembolization Brachytherapy Oncology Consortium recently developed clinical guidelines for the use of ⁹⁰Y microspheres in the treatment of liver cancer. The guidelines, which were supported by unrestricted industry educational grants, describe the ideal candidate for ⁹⁰Y microsphere therapy as a patient with unresectable primary liver disease, liver-dominant tumour burden, and a life expectancy greater than three months.¹³

The Evidence

There have been no direct comparisons of the efficacy of the two ⁹⁰Y microsphere products.¹³ No randomized controlled trials (RCTs) have compared TheraSphere or SIR-Spheres therapy with other treatment options for HCC. Information from the largest case series is summarized in Table 1. None of these case series reported on post-treatment quality of life.

One cohort study reported modestly improved functional well-being and health-related quality of life scores at three months in 14 patients treated with TheraSphere compared with 14 patients treated with a hepatic artery infusion of cisplatin ($p < 0.001$). At six months, the overall health-related quality of life was no longer significantly different between the two treatment groups nor was there a difference in survival rates.¹⁴

Adverse Effects

⁹⁰Y microsphere therapy seems to be relatively well tolerated. A mild postembolization syndrome, consisting of fatigue, nausea, and abdominal pain, is common for up to three days after treatment.¹³ Abdominal pain does not usually occur with TheraSphere because of its smaller embolic load.¹¹ Transient fatigue is the most commonly reported adverse effect.^{15,16} Other adverse effects include diarrhea, low-grade fever, shaking, chills, lymphopenia, thrombocytopenia, transient decrease in hemoglobin, and abnormal liver function tests.¹⁵⁻¹⁷ Radiation-induced liver disease may occur 30 to 90 days after treatment, with the development of fibrosis or cirrhosis, ascites, portal hypertension, varices, and permanently elevated liver function tests.¹³ This is more likely to occur in patients with more extensive liver disease and tumour burden.

Major complications have occurred because of the inadvertent flow (shunting) of microspheres from the liver into the lung, gastrointestinal tract, or pancreas. This may result in gastrointestinal ulceration, pancreatitis, cholecystitis, radiation pneumonitis, and radiation hepatitis.^{15,18,19} Several deaths, possibly treatment-related, were reported during the early use of ⁹⁰Y microsphere therapy.^{6,20,21} The incidence of non-target radiation is minimized if meticulous angiographic and dosimetry techniques are used.¹³

Table 1: Selected Case Series Results of TheraSphere or SIR-Spheres for Hepatocellular Carcinoma

Case Series	Number of Patients (n)	Median Survival	Response
TheraSphere			
Dancey <i>et al.</i> , 2000 ²¹	22 Okuda* stage I patients (n=9) Okuda stage II patients (n=11)	54 weeks	Three patients had a >50% reduction in tumour size. One patient had a complete response, with the disappearance of all clinical and radiological evidence of tumour. Three deaths occurred, possibly related to treatment. These were attributed to radiation pneumonitis, liver failure, and hepatitis.
Carr, 2004 ²²	65 Okuda stage I patients (n=42) Okuda stage II patients (n=23)	Okuda* stage I patients (n=42): 649 days (historical comparison† 244 days) Okuda stage II patients (n=23): 302 days (historical comparison 64 days)	A substantial decrease in tumour vascularity was reported in 42 patients. Two patients developed acute cholecystitis, requiring gall bladder removal. Eight patients had worsening ascites (excess fluid in the abdomen). There were 42 deaths: 21 due to liver failure, six from HCC progression, and three from metastases. Of these, one death was related to treatment, two were probably related, and one was possibly related.
Geschwind <i>et al.</i> , 2004 ²⁰	80 (low risk patients selected from a database of 108 patients) Okuda stage I patients (n=54) Okuda stage II patients (n=26)	Okuda stage I patients (n=54): 628 days Okuda stage II patients (n=26): 384 days (p=0.02)‡	Four patients underwent liver transplantation following treatment. One patient died of liver failure possibly related to treatment. Two patients developed acute cholecystitis, requiring gall bladder removal.
Salem <i>et al.</i> , 2005 ²³	43 Okuda stage I patients (n=21) Okuda stage II patients (n=22)	Okuda stage I patients (n=21): 24.4 months Okuda stage II patients (n=22): 12.5 months (p<0.0001)	Twenty patients had a >50% reduction in tumour size. Six patients developed grade 3 bilirubin-related toxicity and three patients developed grade 3 ascites.
Goin <i>et al.</i> , 2005 ⁶	121 Low risk group (n=88) High risk group (n=33)	466 days in low risk group (n=88) versus 108 days in high risk group (n=33) (hazard ratio 6.0; 95% CI 3.6 to 10.1, p<0.0001)	Among 121 patients, 22 died within three months of treatment; of these, 12 patients in the high risk group died possibly as a result of a treatment-related complication.
Kulik <i>et al.</i> , 2006 ²⁴	35 (a selected subset of 150 patients who were treated with the specific intent to downstage to liver transplantation, surgical resection, or radiofrequency ablation)	800 days Survival at one, two, and three years was reported as 84%, 54%, and 27%, respectively.	A >50% reduction in tumour size was reported in 17 patients. Nineteen patients initially staged as being ineligible for transplant were deemed eligible for transplant following TheraSphere treatment. Eight patients subsequently received liver transplants and one patient underwent tumour resection. One patient had grade 3 bilirubin toxicity.
SIR-Spheres			
Lau <i>et al.</i> , 1994 ²⁵	18	30.6 weeks (for all patients who received SIR-Spheres)	Different radiation doses were used; patients who received doses >120 Gy had a median survival of 55.9 weeks compared with 26.2 weeks for patients receiving <120 Gy (p=0.005). Two patients, both with extrahepatic tumour spread, died two and four months after SIR-Spheres treatment.
Lau <i>et al.</i> , 1998 ²⁶	71	9.4 months (range 1.8 to 46.4 months)	A 50% reduction in tumour volume was reported in 19 patients. Four patients underwent residual surgical resection as a result of downstaging from the therapy; two of these patients showed a complete remission. 50 patients died: 32 of residual or recurrent hepatic disease, four of bone metastases, four of lung metastases, three of hepatic failure, four of bleeding esophageal varices, and one of an unrelated cause. Sepsis from acute cholecystitis caused one death that was possibly treatment-related. One patient died after resection to remove residual tumour.
Sangro <i>et al.</i> 2006 ²⁷	24	7 months	Targeted tumours were reduced in 19 patients, usually by 30%. New liver tumours appeared in nine patients at a median time of three months. Three patients died; two due to treatment-related liver injury and one of choledocholithiasis that may have been treatment-related.

* Okuda is a classification system used for staging liver cancer.

† A historical comparison was used in place of a control group to compare survival in individuals treated in the past who did not receive ⁹⁰Y microspheres therapy.

‡ For comparison between Okuda stage I and stage II patients.

Administration and Cost

While TheraSphere and SIR-Spheres are both ^{90}Y -emitting radiotherapeutic devices, they differ in their physical attributes, mechanism of action, and administration.

TheraSphere

TheraSphere consists of glass microspheres, with ^{90}Y as an integral constituent. Each glass sphere has a mean diameter of 25 microns (μm) and contains approximately 2,500 becquerel (Bq), which is a measure of radiation emission. The recommended radiation dose to the liver is between 80 Gy and 150 Gy (the absorbed dose) and is based on the mass of the target liver tissue and the presence and degree of cirrhosis. The dose must be adjusted for vascular shunting to the lung.¹⁵ One million to eight million microspheres are delivered per treatment. This is insufficient to cause significant blockage in the main hepatic artery.¹³

TheraSphere is supplied in 0.6 mL of sterile water, in a vial with an outer acrylic shield. TheraSphere is available in six dose sizes, ranging from 3 GBq to 20 GBq, and is ordered and delivered so that vial contents decay to the required treatment activity for a planned administration date. A pre-assembled single-use TheraSphere Administration Set and needle guide set are provided with each dose. User sites are supplied with a TheraSphere Administration Accessory Kit, which includes re-usable items such as a shielding acrylic box, support stand, handling tools, and radiation dosimeters.

SIR-Spheres

SIR-Spheres are resin-based ^{90}Y microspheres. Each sphere has a diameter of 20 μm to 60 μm and contains approximately 50 Bq. Vials are protected by a lead pot and contain between 40 million to 80 million ^{90}Y microspheres in 5 mL of sterile water. The vial is calibrated to deliver 3 GBq of ^{90}Y on the planned treatment date; however, the activity of the vial must be verified with a dose calibrator and may be adjusted and customized in a nuclear pharmacy by diluting with sterile water.^{11,18} An administration set is provided with each dose.

The dosimetry for SIR-Spheres is based on tumour burden,¹⁸ or a body surface area method,¹³ and is adjusted for patients who have shunting of blood to the lungs that could result in radiation pneumonitis. An average treatment delivers 40 million to 60 million spheres, which can cause arterial embolization.¹³

a) Pre-treatment investigation and work-up

- A pre-treatment angiogram is required to assess the blood supply to the liver and to verify the delivery route.^{18,28}
- A nuclear scan with a radioactive tracer (technetium-99-labelled macroaggregated albumin) is performed before each treatment to measure the percentage of potential shunting

(leakage) of ^{90}Y microsphere from the liver to the lung and gastrointestinal (GI) tract. SIR-Spheres treatment requires dose reduction for lung shunting $>10\%$ and is contraindicated if lung shunting is $>20\%$.¹⁸ TheraSphere is contraindicated if more than 30 Gy of radiation would be delivered to the lung per treatment session.¹⁹ If shunting to the GI tract is present, blood vessels are occluded with coils or gel foam to minimize the potential for radiation gastritis and ulceration caused by microsphere leakage. TheraSphere and SIR-Spheres are contraindicated if GI shunting cannot be corrected.^{15,17}

- A computed tomography (CT) or magnetic resonance imaging (MRI) scan of the liver is essential to calculate the required dose. This is based on the liver volume for TheraSphere and tumour burden for SIR-Spheres.¹⁵ Positron emission tomography (PET) may be used to clarify MRI or CT findings.¹³
- Pre-treatment blood work is performed to evaluate liver function and measure tumour markers.¹³

TheraSphere and SIR-Spheres are contraindicated in patients who have disseminated extra-hepatic malignant disease, severe liver dysfunction, or portal vein occlusion.^{18,19} TheraSphere is also contraindicated in patients with ascites, pulmonary insufficiency, or those who cannot undergo hepatic artery catheterization.¹⁹ SIR-Spheres treatment is contraindicated in patients who have received previous beam radiation therapy to the liver or capecitabine chemotherapy two months before, or at any time after, SIR-Spheres treatment.¹⁸

b) Treatment procedure

If disease is present in both liver lobes, a single liver infusion or sequential unilobar liver treatments are used.¹³ The ^{90}Y microspheres are delivered to the liver using a catheter that is threaded into the femoral artery through a small incision in the groin and guided to the hepatic artery by fluoroscopy (x-ray imaging). Patients are sedated during the outpatient procedure, which is performed in a hospital radiology department.^{28,29} After SIR-Spheres delivery, a single-photon emission computerized tomography (SPECT) scan is performed to confirm placement in the liver.¹⁸ Patients are typically discharged from hospital on the same day, because beta radiation from the ^{90}Y microspheres does not require medical confinement for radiation safety.¹⁵

c) Follow-up

Patients are followed up with laboratory tests and imaging at 30 days to assess the degree of tumour shrinkage. A second treatment for additional lobes is scheduled if a positive response is achieved.¹⁵ Further follow-up occurs at three-month intervals.¹¹

d) Cost

The cost of TheraSphere in the US market is US\$13,000. A Canadian price can be obtained by contacting MDS Nordion directly (Tamra Benjamin, MDS Nordion, Ottawa, ON: personal communication, 2007 Jul 19). Each SIR-Spheres treatment costs US\$14,000 (Heather Winslade: personal communication, 2007 May 6). These prices do not include costs associated with treatment administration and follow-up.

Concurrent Developments

Hormonal manipulation, gene therapy, immunotherapy, new noncytotoxic drugs, and specific inhibition of angiogenesis and growth factors are new treatment options for HCC that are under investigation.¹² Drug-eluting microspheres are also being investigated.³⁰ Phase III trials are underway with sorafenib, an oral multikinase inhibitor with potentially broad-spectrum anti-tumour activity against HCC.³¹

⁹⁰Y microsphere therapy is being investigated for the treatment of breast and neuroendocrine tumours that have metastasized to the liver.³⁰ Other potential applications of ⁹⁰Y microsphere treatment include a combined use with other liver-directed therapies, such as radiofrequency ablation and TACE.³⁰

Rate of Technology Diffusion

Since 2003, MDS Nordion has supplied TheraSphere to treat more than 60 patients with liver cancer in Canada (Tamra Benjamin, MDS Nordion, Ottawa, ON: personal communication, 2007 Jul 19).

⁹⁰Y resin microspheres (SIR-Spheres) have mainly been used with intrahepatic floxuridine to treat metastatic liver disease, particularly from colorectal cancer. TheraSphere has been used in the treatment of colorectal cancer that has metastasized to the liver.

The incidence and mortality of HCC are expected to increase in Canada over the next several years because of the increasing prevalence of people infected with hepatitis B and hepatitis C. Hepatitis prevention strategies such as hepatitis B vaccination and hepatitis C awareness campaigns are expected to eventually reduce the incidence of HCC.^{8,32}

Implementation Issues

Treatment planning, dosimetry calculation, and the technical aspects of ⁹⁰Y microsphere administration are complex and require the coordinated expertise of an experienced multidisciplinary team comprising radiation oncologists, nuclear medicine specialists, medical oncologists, hepatologists, and interventional radiologists.^{11,15}

Microsphere manufacturers provide education, on-site training, and support.^{28,29} Device distribution is limited to institutions that are licensed to handle radioactive materials, including the ⁹⁰Y isotope.^{19,29}

Limited evidence from several case series indicates that treatment with ⁹⁰Y microspheres is a palliative option that may reduce tumour size, with a potential for increased survival. A small number of patients may experience sufficient tumour reduction to become eligible for liver resection or transplantation.

Risks versus benefits must be considered for each patient because of the potential for ⁹⁰Y microsphere-related liver failure and other potentially life-threatening events.

Early data suggest that there are fewer adverse effects and survival is similar with ⁹⁰Y microsphere treatment compared with transarterial chemoembolization therapy.²⁰ Head-to-head controlled trials are needed to compare ⁹⁰Y microsphere therapy with existing therapies for hepatocellular carcinoma.

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Conflict of Interest: The centre where Dr. Valenti practises uses TheraSphere®.

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