Advances in Radioembolization - Embolics and Isotopes

Joshua Burrill¹, Urs Hafeli³ and David M Liu¹*##

¹Department of Radiology, St Pauls Hospital, Vancouver, British Columbia, Canada
²Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada
³Department of Radiology, Vancouver General Hospital|University of British Columbia, Vancouver, BC, Canada
⁴Angio/interventional Section, UCLA Department of Radiological Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA

Abstract

Selective internal radiation therapy (SIRT), otherwise known as radio embolization is now becoming a common procedure performed for those patients with primary hepatic neoplasia [such as hepatocellular carcinoma], and liver dominant metastatic disease [such as in near endocrine disease, and colorectal carcinoma]. The current technology platforms incorporate the use of yttrium 90, a pure beta emitter loaded on either a resin microsphere, or ceramic microsphere.

Although clinical outcomes have been encouraging with both technology platforms, second-generation radioembolic devices [utilizing either new processes of microsphere synthesis, or different radioactive isotopes] are currently under development, or clinical study. The purpose of this manuscript is to provide the reader with some perspectives regarding the next generation of radioembolic devices, and discussing the advantages and disadvantages of both current, and future platforms.

Introduction

It is estimated that more than 1 million people are diagnosed with primary or secondary liver malignancy each year [1]. Secondary hepatic metastases (including those from the gastrointestinal tract, breast, and neuroendocrine tumours) are common; with 60% of patients with colorectal carcinoma develop liver metastases [2]. Primary liver cancer including hepatocellular carcinoma (HCC) and cholangiocarcinoma, is the sixth most common cancer worldwide with an abysmal five year survival of 3-5% [1].

Radiation therapy using direct external beam irradiation has been used to treat both HCC and liver metastases, with limited results. Partial response with symptomatic improvement in the treatment of HCC was demonstrated back in the 1970s [3], limited by the inability to provide whole liver irradiation in an effective manner, with documented radiation induced liver disease (presenting in a fashion similar to venoocclusive disease), so termed RILD developing at exposure levels as low as 30 – 35 Gy (RILD) [4]. This dose, resulting in a 5% incidence of RILD, is well short of the exposure required to elicit tumoricidal effect.

Intra-arterial radiotherapy of liver cancer is not a new concept having been first attempted in the 1960s with yttrium-90 microspheres with encouraging response within the neuroendocrine population [5]. Selective internal radiation therapy (SIRT), taking advantage of the preferential hepatic arterial supply of liver neoplasms experienced technical limitations, predominantly due to challenges of dosimetry, non-selective injection of microspheres (injected at the level of the celiac artery), and leaching, that has not been described in reference to current commercialized products [2].

The evolution of more advanced dosimetric techniques, supra-selective hepatic arterial catheterization, awareness of the importance of hepatic-gastric and pancreatic anastomoses, measurement of hepatopulmonary shunting, and stable embolic platforms with minimal leaching have acted to improve the ratio of tumour to liver/rest of the body dose.

Radioisotopes

Radioembolization uses an active radioisotope combined with an embolic delivery platform. Various radioisotopes have been used including yttrium-90 (Y-90), iodine-131 (I-131), rhenium-188 (Re-188), and holmium-166 (Ho-166). These are all β emitters, with γ emission from Re-188, Ho-166, and I-131.

The tissue penetration of β particles (electrons) is from a few millimetres up to 1 cm which reduces the dose to the normal liver when combined with the appropriate embolic. As current methods in yttrium 90 microparticle manufacture require access to facilities they can perform neutron bombardment, the logistics involved in not only the manufacturing, but also the rapid transportation due to its relatively short half-life provide significant challenges in both the manufacture, and transportation of the radial embolic material. As a result of the geographic distribution of manufacturing facilities, and clinical sites, high variation in the specific activity per particle may occur as a result of decay kinetics at the time of transportation, or variations in the dose calibration techniques.

Other radioisotopes, including phosphorus-32, copper-64, zirconium-89, fluorine-18, and yttrium-86, have all been investigated as possible sources for either SIRT or dosimetry, including yttrium-99m however have encountered challenges. For example decayed SIR-Spheres have been loaded with F-18 produce in a cyclotron. Problems occurred due to substantial in-vivo leaching in a rat model [7].

Ideal Radioisotope

Half-life of hours

Easily synthesized; can be loaded with radioactivity close to the

*Corresponding author: David Liu, Department of Radiology, Vancouver General Hospital|University of British Columbia, 855 W 12th Ave, JP Pavilion G873, Vancouver, British Columbia, Canada, V5Z 1M9, E-mail: dave.liu@vch.ca

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facility in which implantation is to occur
High energy particle with low mean free path e.g. β
Detectable percentage of γ, or positron emission for imaging
Safe decay product: Biocompatible and bioabsorbable
Cheap local manufacture
No leaching, and carrier free suspension, minimizing hematogenous and systemic exposure

**Embolics**

It has been well established that tumor vascularity within the hepatic circulation is a complex anatomical structure, consisting of the vascular plexus of abnormal blood vessels ranging in size from 25 to 75µm. These abnormal blood vessels have been targeted through various embolic methods, including starch particles, albumin, polyvinyl alcohol, gelatin, ethiodol, glass and resin. Recent literature utilizing super paramagnetic iron oxide (SPION) loaded particles demonstrate improved penetration into tumor vascular plexus with smaller size particles (as small as 100µm) [8], however particles smaller than 40µm had demonstrated significant pulmonary shunt tumor perfusion [9]. This is abnormal bypassing of the liver and tumor, with non-targeted embolization of the lungs. Commercial radioembolic products currently are produced in the 30 to 70µm range, with a variance in the particles size to allow for deposition and distribution into various tumor vessel sizes, permitting a more even distribution.

**Ideal embolic platform**

Isodense with blood
Stable embolic/radioisotope ligand with no leaching
Ease of production
Consistent size
Can be utilized with a pure γ emitter for dosimetry and estimation of hepatopulmonary shunt fraction
Particle or material utilized for mesenteric angiography, and pollination perfusion determination should behave in a similar fashion to the therapeutic radionuclosphere
Bioabsorbable polymer or substrate with a half life at least 7x longer that the radioisotope

**Radioembolic Platforms**

**Yttrium-90 (commercially available)**

β emitter: average 933.7 KeV, max 2.28 MeV
Half life: 64.2 hours
Average tissue penetration: 2.5 mm
X90°: 5.2 mm (radius of the sphere in which 90% of the energy emitted from a point source is absorbed.)
Method of manufacture: Neutron activation of stable Y-89 in a nuclear reactor.

| Type of microsphere | SIR-Spheres | Theraspheres |
|---------------------|-------------|--------------|
| Diameter (µm)       | 32 ± 10     | 25 ± 10      |
| Specific gravity +   | 1.6         | 3.7          |
| Specific activity (Bq/MS) | 40         | 2467^       |

Mean no spheres / dose 20 x 10^8 4 x 10^8
Patient dose (GBq) 0.5 - 3 3 - 20
^ at time of manufacture
+ Specific gravity of Blood: 1.05 [10]

**SIR-SPHERES (Sirtex Medical Inc, Sydney, Australia)**

In a cohort study looking at 110 patients with liver metastases from various primaries treated with SIR-Spheres SIRT the average survival was 323 days (10.6 months). 350 day survival was 55% for colorectal metastases and 39% for breast carcinoma metastases [11]. Complications included three cases of cholecystitis, six of gastritis and one hepatic failure. Post-embolization syndrome occurred in approximately two-thirds of patients. A phase III randomized trial comparing fluorouracil chemotherapy with and without SIRT in 44 patients with colorectal metastases showed a significantly better time to tumor progression (TTP) with SIRT. Survival was also better but not significantly, however there was substantial crossover with 10 of 23 fluorouracil patients receiving SIRT [12]. Similar findings have been seen in other studies [13,14].

SIR-Spheres have been used to treat 71 patients with unresectable HCC [15]. Median survival was 9.4 months, and in two cases there was complete histological response suggesting this can be curative. 16% had post-embolization syndrome, but no cases of radiation pneumonitis or hepatitis were recorded. A similar survival has been seen elsewhere [16]. SIR-Spheres have been used to treat HCC with portal vein thrombosis, with no significant liver toxicity and a median survival of 10.1 months [17]. Data collected on a cohort of 515 patients treated with SIR-Spheres for unresectable liver tumors showed that 5% (28 patients) died from RILD. Out of the 680 treatments, 79 were for HCC and thee HCC patients died of RILD [18].

**Advantages**

- Lower specific activity allows for more uniform distribution of radioactivity within tumor.
- Dose arrives as a parent dose, allowing for multiple fractionated doses to be drawn per patient.
- Delivery device allows for intermittent administration of contrast to assess blood flow.
- Lower specific gravity may allow for more uniform, flow directed deposition of microspheres.
- Pure Y-90 radioactive species without mutant radioactive species.
- 'carrier free' suspension, resulting in minimal systemic exposure.
- Extensively published clinical outcome literature in the context of metastatic colorectal carcinoma, neuroendocrine disease, hepatocellular carcinoma.

**Disadvantages**

- Standardized body surface area [BSA] dose activity model may result in under demonstration of targeted dose in situations of large bulky tumors.
- Dose administration Kit is designed primarily for safety, however can be somewhat cumbersome during administration.
- Lower specific activity of particles may result in stasis, or sluggish antegrade flow prior to full dose administration.

**Theraspheres (MDS Nordion, Ottawa, Ontario, Canada)**

Theraspheres have been used in a number of studies looking at the treatment of HCC with and without portal vein thrombosis (PVT). One study of 118 patients showed a median survival of 15.3 months.
for patients without PVT and 4.4 months with main PVT [19], which is better than seen with I-131-Lipiodol [20]. There were few complications with no cases of radiation pneumonitis or gastrointestinal ulceration. In a retrospective review of patients with HCC treated with Therasphere SIRT or mitomycin-cisplatin-adrinamycin-lipiodol chemoembolization there was a longer TTP and less toxicity with SIRT [21]. A survival benefit was not demonstrated. Similar toxicity and TTP findings were seen with another cohort study from Germany looking at 159 cases [22]. This study suggested that the median survival after SIRT of 16.4 months was better than in the SHARP trial for sorafenib (10.7 months). Theraspheres have also been used to downstage HCC prior to transplantation or resection, with a significant improvement in the percentage downstaged from T3 to T2 when compared to chemoembolization (58% versus 31%). A study has looked at using extended-shelf-life Theraspheres to increase the number of particles used and therefore increase the distribution and reduce the risk of a severe response from non targeted embolization [23].

**Advantages**

- High specific activity allows for complete administration of partition modeled dose activity.
- Lower risk of non-targeted embolization due to high specific activity and high specific gravity per microsphere.
- Pre administration and calibration of dose activity prior to administration is a single step process.
- Extensive published literature demonstrating positive outcome for use in hepatocellular carcinoma.
- Current dose administration kit intuitive, and easy to use.

**Disadvantages**

- Dose must be delivered at a specific day and time.
- Precalibrated vials contain radioactivity that cannot be divided or fractionated.
- May result in under distribution of microspheres in larger tumors resulting in ‘swiss cheese’ response, and non-uniform microdosimetry.
- High specific gravity may cause settling or migration of microspheres.
- Due to higher specific activity, non-targeted embolization may result in more severe response (e.g. radiation cholecystitis)
- Unable to check for reflux or stasis during administration (this is especially relevant in extended decay strategies such as Therasphere EX)
- Inherent non-intended radioactive species present in matrix (e.g. Y-88 half-life 107 days, Europium-154 half-life 8.8 γ)

**Iodine-131**

β emitter: mean 192 KeV, max 610 KeV
γ emitter: 364 KeV
Half life: 8.04 days
Average tissue penetration: 0.4 mm

X90: 0.7 mm (radius of the sphere in which 90% of the energy emitted from a point source is absorbed.)

Method of manufacture: Isotope exchange after formation in a nuclear reactor.

**Patient dose: 0.9 – 2.4 GBq**

Iodine-131 had been used to label lipiodol, a mixture of iodized esters of poppyseed oil fatty acids. It forms an emulsion of fat droplets with a diameter of 20 - 200µm. I-131-lipiodol has been used for the treatment of HCC in cases with and without portal vein thrombosis, and for the treatment of liver metastases. The procedure involves a selective hepatic artery injection of 2 to 3 ml of I-131-lipiodol with an activity of 0.9 to 2.4 GBq [24,25]. Biodistribution studies using low dose 1-131-lipiodol showed that it is almost exclusively retained by the liver and the lungs with a greater liver to liver+/liver ratio for HCC (mean 76%) than for liver metastases (mean 86.2%). However the tumor to non-tumor ratio was higher in the HCC group (4.3 ± 2.6) than for the liver metastases group (2.4 ± 0.7) [26]. This high lung uptake may explain lung fibrosis which occurs in around 2% of patients and is fatal in about half of those. It is the most serious complication of treatment with I-131-lipiodol [20].

In a randomized study looking at the treatment of HCC and portal vein thrombosis with I-131-lipiodol versus best supportive care there was a 71% versus 10% 3 month survival, despite a uniformly poor long term survival of 7% and 0% at 9 months respectively [27]. Another randomized study compared HCC chemoembolization and SIRT with I-131-lipiodol. There was a similar overall survival at 1 and 2 years (38.5% and 22% for chemoembolization, and 42% and 22% for I-131, respectively), but with significantly less side effects in the SIRT group [28]. As a post-surgical adjuvant after potential curative resection for HCC, I-131-lipiodol has been shown to significantly improve overall and disease-free survival for more than 5 years after surgery (overall survival at 5 years 66.7% versus 36.4%) [29]. I-131-lipiodol has been used to treat colorectal carcinoma metastases combined with chemotherapy resulting in an objective response in two out of three of the patients [1]. No significant reduction in the size of liver metastases was seen in one small study although there was a clear reduction in abdominal pain which was thought to be tumour-related [25].

**Advantages**

- Easy administration.
- Gamma emission enables post-procedural imaging.
- High tumor to non-tumor uptake by HCC.
- Gamma emission enables post-procedural imaging.

**Disadvantages**

- Short β range.
- Lung fibrosis resulting in death in approximately 1% of cases.
- No significant tumor reduction seen in the treatment of liver metastases.
- May require multiple sessions to achieve maximum response.

**Rhenium-188**

β emitter: mean 764 KeV, max 2.1 MeV
γ emitter: 155 KeV
Half life: 16.9 hours
Average tissue penetration: 3.8 mm

X90: 1.9 mm (radius of the sphere in which 90% of the energy emitted from a point source is absorbed.)

Method of manufacture: W-188 / Re-188 generator possible on site.

| Diameter (µm) | Re-188-HSAM | Re-188-PLA |
|--------------|-------------|-------------|
| 25 (14 - 40) | 30±1        |             |
Average tissue penetration: 2.2 mm

Half life: 26.8 hours

γ emitter: 80.6 KeV

β emitter: mean 670 KeV, max 1.85 MeV

**Holmium-166**

Disadvantages

- Produced on site using a low-cost Tungsten-188 / Re-188 generator.
- β and γ emission allow post-procedural dosimetry.

Advantages

- Chemistry and studies are ongoing looking at the in-vivo performance of the microspheres.
- The mean size of the microspheres has been determined to be sized within less than +/- 5%. Re-188 and Tc-99m have a similar biodistribution.
- Re-188-PLA and 78% of patients who were suitable for resection unlike most other Y-90 studies.
- Partial response or stable disease was seen in 89% by RECIST criteria.
- An unpublished phase 2 clinical trial had 22 patients. At 3 months either progression free survival of 34 months and a one year overall survival of approximately 88%.
- There was significant toxicity with transient RILD in 26% of patients and two fatalities due to infection and hepatoma rupture.
- Transient hematological abnormalities occurred in up to 28% of patients.

**Re-188-Lipiodol**

Re-188 has been conjugated with lipiodol using 4-hexadecyl-1,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol (HDD) and used to treat HCC. Re-188 has obvious advantages over I-131 due to less γ emission, greater β penetration, and reduced cost. One and two year survival is similar to I-131-Lipiodol, 46% and 23% respectively [31]. Disadvantages of Re-188-lipiodol include urinary excretion of metabolites resulting in a loss of 44.1% (mean) of the administered activity, a low radiochemical yield, and lung fibrosis, also seen with I-131-lipiodol [32].

**Re-188-HSAM**

Re-188 has been added to HSAM using a W-188/Re-188 generator with 10% leaching after 30 hours incubation [33]. Re-188-HSAM has been used to treat HCC and colorectal liver metastases in 10 patients [34]. Tc-99m-HSAM was used to determine the treated volume of the liver and work out applied activity. In this limited study it was only possible to treat the entire tumor mass in two of the 10 patients as selective angiographic administration was used. Despite this, 1 year survival was 40% and either partial remission or stable disease was seen in 70%. A mean urinary excretion rate of 8.9% of the injected activity was measured within 72 hours. There was no RILD-related fatality despite a single patient with grade three liver toxicity. A further unpublished phase 2 clinical trial had 22 patients. At 3 months either partial response or stable disease was seen in 89% by RECIST criteria, and 78% clinically [35].

**Re-188-PLA**

Tc-99m labeled PLA microspheres have been manufactured and used to perform lung perfusion imaging as a proof of concept study prior to labeling with Re-188 [36]. These microspheres are manufactured with a high degree of accuracy allowing the diameter to be sized within less than +/- 5%. Re-188 and Tc-99m have a similar chemistry and studies are ongoing looking at the in-vivo performance of Re-188-PLA. Currently under active investigation, however this technology platform has not been attempted in humans.

Advantages

- β and γ emission allow post-procedural dosimetry.
- Produced on site using a low-cost Tungsten-188 / Re-188 generator.

Disadvantages

- Greater patient dose required due to its shorter half-life.

**Holmium-166**

β emitter: mean 670 KeV, max 1.85 MeV

γ emitter: 80.6 KeV

Half life: 26.8 hours

Average tissue penetration: 2.2 mm

X0: 2.1 mm (radius of the sphere in which 90% of the energy emitted from a point source is absorbed.)

Method of manufacture: Neutron activation in a nuclear reactor.

| Ho-166-PLA | Diameter (µm) | 30±5 |
| Ho-166-PLA | Specific gravity | 1.4 |
| Ho-166-PLA | Specific activity (Bq / MS)-up to 450 |
| Mean no spheres / dose | 50 x 10⁶ |

Holmium-166 has been combined with a PLA embolic platform and chitosan embolic platform. It has a lower energy and shorter half life than Y-90 and therefore a lower absorbed dose requiring three times more radioactivity than Y-90 [2].

**Ho-166-PLA**

No human studies have been performed using Ho-166-PLA, however animal studies have been performed to assess biodistribution of the microspheres using pigs with no postembolization syndrome [37]. A study with VX2 carcinoma implanted rabbits with Ho-166-PLA injected into the hepatic artery showed an arrest in tumour growth [2]. Low leaching occurs with a cumulative release in vitro 0.7% in a phosphate buffer after 52 weeks. The HEPAR phase 1 clinical trial is ongoing [38].

**Ho-166-Chitosan**

Ho-166-Chitosan dissolves in water under acidic conditions but forms a solid under neutral or basic conditions. A study has looked at treating single HCC in 54 patients [39]. Serum alkalinization was necessary to reduce the amount of leaching into the systemic circulation. Partial or complete response occurred in 78% of patients, with a median progression free survival of 34 months and a one year overall survival of approximately 88%. There was significant toxicity with transient RILD in 26% of patients and two fatalities due to infection and hepatoma rupture. Transient hematological abnormalities occurred in up to 28% of patients. It is important to note that this study was performed on patients who were suitable for resection unlike most other Y-90 studies.

Advantages

- High x-ray attenuation and well imaged with fluoroscopy.
- Paramagnetic and therefore visualized by MRI.
- Low leaching as PLA microspheres.
- Biodegradability of both PLA and chitosan.

Disadvantages (Ho-166-Chitosan)

- Supraselective catheterization required.
- Serum alkalinization needed to avoid leaching.
- Difficult determination of microdosimetry.
- Low therapeutic index.

**Radioembolization Protocol**

Standard SIRT is a two stage process. The first stage involves an angiogram to map out and embolize the branches of the hepatic artery supplying non-hepatic tissue. An injection of, usually, technetium-99 microaggregated albumin (Tc-99m-MAA) is used to calculate the proportion of hepatopulmonary shunting and to optimize and exclude significant gastrointestinal uptake. The target dose can be calculated a number of ways but depends on the degree of shunting, which can also be a contraindication to the procedure. The aim is to keep the dose to the lungs below 30 Gy while delivering a dose of 120 ± 20 Gy to the tumour if utilizing a partition model, or alternatively body surface area [BSA formulation] [20].
Conclusions

Over 20,000 radioembolization therapies have been performed to date, utilizing the above technology platforms. In general objective imaging-based response has been excellent, with lower side effect profiles, when administered correctly, as compared to bland embolization and chemoembolization. Each of the discussed platforms possesses unique benefits and limitations. Despite these challenges, several Phase III randomized control trials, predominantly with resin Y-90 microspheres, have been established, e.g., SIRFLOX, FOXFIRE, SORAMIC. These have been specifically powered to determine if incorporation of radioembolization offers overall survival benefit and/or progression free survival benefit in the HCC and metastatic colorectal carcinoma populations. Preliminary results are expected within the next 2-3 years.

Despite the unequivocal success of the therapy, many aspects of radioembolization remain challenging. These include determination of embolic distribution, microdosimetry, optimization of specific activity, active loading of specific activity per sphere and post implantation dosimetry. All aspects of current clinical and pipeline therapeutics serve to address some if not all of these challenges. This paves the way for second generation technologies, allowing for a more predictable administration and reliable response.

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