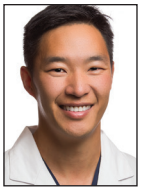
Perspectives on Current Trends in Selective Internal Radiation Therapy With Yttrium-90 Microspheres

An interview with David Liu, MD, FRCPC, FSIR, in which this expert on radioembolic oncology discusses everything from room prep to clinical decision-making and optimal follow-up.



What are some of the most important lessons or key tips you have learned in how to best prepare the room for a selective internal radiation therapy (SIRT) procedure?

Dr. Liu: The introduction of a SIRT program requires the coordinated efforts of three basic teams: the clinical team (to identify patients and to navigate them through their therapy), the nuclear medicine/radiation oncology team (to ensure safe, proper handling of the radioactive dose), and the interventional radiology team (to ensure safe and successful vascular optimization and administration of therapy). ALARA (as low as reasonably acceptable) principles should be observed in all aspects of treatment, from the dosimetry to the dose draw and administration. Constant communication is key. Depending on the center, medical oncologists, surgical oncologists, radiation oncologists, or interventional radiologists may take the lead role in driving the program, but one must keep in mind that all three teams must be competent and on board in order for the program to succeed. Developing a SIRT program is truly a team sport.

At our hospital, we use both glass and resin radioactive microspheres. The dose is prepared and calibrated in the nuclear medicine lab. The microspheres typically arrive in the case of resin microspheres the previous day and are calibrated for the day of procedure, with the dose drawn just prior to administration. Glass microspheres may arrive several days before the procedure in sealed vials and be left to decay to a certain level of activity to be delivered on a specific day at a specific time. The administration of the dose, whether it is glass or resin, only takes a few minutes, and despite many misconceptions, the radiation exposure is the same for both the operator and team as long as ALARA principles are applied. We adhere to a very stringent protocol right from the dose calibration/draw to the postadministration management of the room and patient.

How do you determine the ideal dosing to administer in each individual patient?

Dr. Liu: The concept of dosimetry continues to be mired in controversy. Common misconceptions such as the concept of "hotter is better" and underdosing a tumor due to reaching "stasis" are commonly held beliefs that add to the confusion. Furthermore, dosimetry methods for glass and resin are fundamentally different due to the radioactivity per particle, specific density per particle, and microdistribution/penetration of the particles themselves.

As a result, comparing dosimetry methods between glass (medical internal radiation dose [MIRD] model) and resin microspheres (body surface area) is like comparing apples to oranges. In brief, in the MIRD model, the basic assumption is that there is uniform distribu-

tion within the liver parenchyma and within the tumor itself, which we know to be fundamentally incorrect. This model has been reasonably effective in mitigating complications and should be thought of as a model to ensure safety, but not necessarily optimized treatment. For instance, the MIRD model does not take into account how much tumor is actually present within the targeted tissue nor the distribution of particles within the tumor or adjacent liver. This means that if there is a small tumor burden, a substantial amount of radiation will go into the liver parenchyma, and if there is a large tumor burden, suboptimal distribution of particles may exist within the tumor itself.

The body surface area model has been validated in phase 3 clinical trials in colorectal carcinoma and correlates the patient's theoretical liver volume with body surface area, taking into account the amount of tumor within the targeted area of administration. However, this methodology represents an arithmetic derivation of biological systems. As a result, limitations may exist in cases such as hepatomegaly due to tumor infiltration.

At its core, *dosimetry* is defined as the amount of absorbed radiation within target tissue, and the main objectives when performing SIRT are to (1) provide accurate and uniform distribution of lethal radiation within the tumor and (2) minimize the potential of nontargeted radiation damaging the liver and/or lung parenchyma. When I look at dosimetric methodology in general, I apply a three-step "minus, minus, plus" model regardless of whether I use resin or glass microspheres. For example:

1. (Start) Apply the recommended activity model to establish a baseline estimate of radiation.

2. (Minus) Establish an upper threshold of lung exposure extrapolated from the baseline value, lung parenchyma, and lung shunt fraction. This value is the high-water mark that is not to be exceeded. If the shunt fraction is too high, the tumor may not receive enough radiation before reaching a toxic lung dose.

3. (Minus) Reduce the dose if there is a concern regarding compromised liver parenchyma (eg, as a result of cirrhosis, chemotherapy, or other alterations in hepatic reserve, such as liver resection).

4. (Plus) Make corrections based on optimization of particulate distribution, such as in the case of large hypervascular tumors. For glass microspheres, consider the extended shelf life (EX) method, allowing the yttrium-90 (Y-90) to decay, thus increasing the embolic load, and for resin microspheres, consider an increase in overall activity to increase the number of microspheres to provide even, uniform distribution.

Intraprocedurally, what may cause you to deviate from your initial plan and administer more or fewer spheres?

Dr. Liu: Before the actual administration of SIRT, we learn as much as we can about the patient's disease state and vascular anatomy as possible. We use a dedicated high-resolution CT scan in the arterial phase to premap the anatomy, catheterize all potential vessels in which we intend on administering SIRT, and review the postmapping information in great detail to ensure that we minimize the potential for deviation from our intended plan.

Inevitable situations of catheter-associated iatrogenic vascular injury can occur, and in some instances (such as in the case of arterial dissection), we simply have to postpone the therapy, place the patient on antiplatelet therapy, and observe for re-establishment of flow.

Changes in the vascular anatomy may also occur as a result of redistribution/collateralization of vessels, leading to alterations of our dose plan. This situation may occur when new collaterals develop due to coil or particle embolization (such as in the instance of enlargement/creation of new pancreaticoduodenal branches arising from the common hepatic artery after gastroduodenal artery coil embolization) or tumor angiogenesis, resulting in newly established dual vascular supply (particularly in segment 4 or subcapsular lesions adjacent to the diaphragm).

We use techniques such as split dosing (in the case of resin microspheres), proximal protection devices, superselection, and "free float" to work around any newly established collaterals that we cannot embolize with coils or gelfoam. In the past, with resin microspheres, we had encountered issues of sluggish antegrade flow before the desired activity was injected, but recent data have revealed that the use of sterile water leading to vasospasm was the likely culprit. With the new techniques of using 5% dextrose in water (D5W) instead of sterile water and administration under fluoroscopy guidance with contrast, we have been able to deliver the intended activity in almost every case, with much higher efficiency.

When I use glass microspheres, I sometimes encounter the rare situation of devascularization or alterations of the tumor vasculature that may result in unintended reflux (especially in the situation of the EX technique). Due to the high specific density of the glass microspheres, particles have to be bolused under pressure, and there is no capacity to administer a half dose or check for stasis. As a result, in these situations, a proximal protection device or abandonment of the procedure may be

necessary. If I cannot use a proximal protection method, I would much rather regroup and postpone the administration rather than "push and pray" a dose into the wrong place.

What is the most critical lesson you have learned about patient selection for SIRT?

Dr. Liu: SIRT is a team sport that requires a multidisciplinary group to evaluate and refer patients to therapy. I am fortunate that at our institution, we are very excited about adding SIRT to our armamentarium, with an understanding that we should be performing SIRT based on the published peer-reviewed evidence (with respect to disease process, timing of intervention, and dosimetry) for guidance.

How do you decide whether a patient should undergo SIRT in combination with chemotherapy versus SIRT alone?

Dr. Liu: When we're discussing the compatibility of chemotherapy along with radioembolization, the overwhelming majority of data relate to tolerance of coadministration of SIRT with chemotherapy in the setting of colorectal carcinoma. Resin microspheres have demonstrated safety, with minimum toxicity along all lines of therapy in colorectal carcinoma. An article by Sharma et al demonstrated tolerability as the first-line treatment with contemporary chemotherapeutic administration in a phase 2a trial,[1] complementing the earlier phase 3 pivotal trials that were performed in an older era of chemotherapy.[2] Chemo refractory/chemo salvage safety has been established by Hendlisz et al in their phase 3 randomized controlled trial.[3] Large population retrospective analyses were outlined most recently in the MORE (Metastatic Colorectal Cancer Liver Metastases Outcomes After Radioembolization) study consisting of 606 patients undergoing radioembolization along multiple lines of therapy (including those in the chemo salvage situation) and concluded that a favorable risk/benefit profile was noted.[4] Glass microspheres have also demonstrated an acceptable short-term toxicity profile, mostly in single-institution or small retrospective cohorts, as well as in the chemorefractory palliative setting in smaller cohorts.

Does the nature of radioembolic material limit the amount of creativity or unplanned variation an operator might otherwise attempt during a procedure?

Dr. Liu: Of commercially available devices, there are advantages and challenges to each product and its method of administration. Glass microspheres arrive in a sealed vial several days before administration. The sealed vial cannot be divided or split and is intended for the exact area or point of administration that was planned at the time of ordering. Advantages of this system include minimal handling and preparation by the nuclear medicine department, as well as a system designed for a relatively easy method of delivering multiple vials in a single session. However, given the nature of the sealed vial, there is very little flexibility to change or adapt the dose plan. In addition, the specific gravity (weight) of the particle is much more dense and, as a result, requires a pressurized bolus injection to deliver the microspheres.

The resin microsphere protocols allow for more flexibility on the day of administration. As the actual amount of activity (the number of particles) is drawn out from a parent vial on the day of administration, the advantage is that multiple doses can be drawn and potentially changed up to the time of administration. Because the specific density of the resin microsphere is close to plasma, the microspheres are administered through small injections of D5W that allow the particles to infuse into the target vascular bed in a more physiologic nature. This feature also allows for intermittent or simultaneous injection of contrast to better define the changes in blood flow.

What is your standard follow-up regimen for patients who are treated with SIRT? In what ways might postprocedural expectations and SIRT follow-up differ from other embolotherapy methods?

Dr. Liu: Many think of radioembolization as similar to other types of liver-directed embolic therapy, but there are key differences in the mechanism of action that may warrant consideration with respect to response, toxicities, and complications. The term *radioembolization* is somewhat of a misnomer. All forms of radioembolization, regardless of whether glass or resin microspheres are used, act primarily through radiation and not by the embolic effect. Thus, complications are a direct result of the radiation and not the embolization. This means that complications and toxicities typically require a week or two before presenting.

Immediate routine postprocedure management includes the use of proton pump inhibitors, which may be started several days to a week before treatment and typically extends for approximately 1 month afterward. A low-dose steroid is used to reduce fatigue and mild nausea/flu-like symptoms that can be associated with treatment. The indications for the use of antibiotics are unclear; some institutions use antibiotics in cases when there is a history of biliary surgery or intervention.

I will typically follow with liver function tests at 1 week and 1 month looking for trends to correction of the transient transaminitis that is common with this therapy. Follow-up imaging with magnetic resonance imaging or CT is performed at least 3 months after completion of treatment to ensure that a misinterpretation of either tumor markers or imaging does not occur; early multiphasic imaging may not reflect the response and might in fact be misinterpreted as progression of disease due to the early inflammatory phase. If I see some indication of response (devascularization, decrease in size, or correction of tumor markers), I will continue follow-up imaging at 3-month intervals, as the maximum response may take as long as 6 to 9 months.

Symptomatic nontargeted embolization into the mesenteric vessels may present as early as 1 week or as late as 3 weeks following administration. Radioembolization-induced liver disease (REILD) may occur weeks to months following treatment and should always remain in consideration should there be evidence of liver compensation.

What side effects or complications specific to SIRT should operators keep in mind? Is inadvertent embolization of nontarget vessels and organs managed differently than with other embolic options?

Dr. Liu: It is important to note that the side effect profile of radioembolization is minimal, and the procedure is typically performed on an outpatient basis (and in some cases, the entire liver is treated during single-session administration). Most of the acute symptoms that constitute postembolization syndrome in liver-directed embolic therapy have to do with either the profound ischemia or the systemic release of chemotherapy and its associated systemic toxicity, and this simply does not occur with SIRT. Patients undergoing radioembolization will typically present with mild flu-like symptoms and fatigue 48 to 72 hours following administration, which may last for 1 to 2 weeks. Low-dose steroids help control the symptoms.

Complications can be severe; however, they are very rare and, for the most part, avoidable with a meticulous and disciplined approach to treatment. Nontargeted radiation sources may be identified immediately through new positron emission tomographic (PET) CT imaging techniques; however, they typically present symptomatically 1 to 2 weeks following administration. If there is a concern regarding gastric ulceration or mucosal irritation, sucralfate, Pepto-Bismol, and higher doses of proton pump inhibitors may be utilized. If symptoms do not resolve at 6 to 8 weeks following onset, endoscopy may confirm the diagnosis through biopsy and visualization, with a possibility of surgical consultation if there is evidence to suggest full thickness or impending ulcer rupture.

If REILD is suspected, radiation protectants such as ursodeoxycholic acid, pentoxifylline, and high-dose steroids may be considered. If there is a suspicion of veno-occlusive disease, anticoagulation may also be warranted. Management of radiation-induced pneumonitis is typically symptomatic, with high-dose steroids and bronchodilators in cases of dyspnea.

What have been the most important technological advances in microsphere technology in recent years? What limitations did these overcome?

Dr. Liu: The technology associated with radioembolization (ie, the particles themselves) has not changed since gaining regulatory approval more than 10 years ago. What has changed is our fundamental understanding of how to optimize the delivery of these particles through different techniques, as well as an understanding of where local regional liver therapies fit within the disease spectrum, particularly within metastatic colorectal carcinoma and hepatocellular carcinoma. From a technical standpoint, administration methods have drastically improved as a result of the advancements in the angiography suite that include the common use of cone-beam CT, improved equipment (microwire, microcoil, and microcatheter technologies), and the introduction of proximal protection devices.

Our understanding of the process of neovascularization, as well as the establishment of collateral flow, has also drastically improved, contributing to an improvement in safety and increased reliability of the preprocedural planning. Dosimetry remains a challenge, but the more recent advancements in Tc-99m MAA SPECT CT (utilizing Monte Carlo iterative reconstruction algorithms), as well as postimplantation three-dimensional time-of-flight PET CT, continue to improve our understanding of tumoral heterogeneity and perfusion.

What else can you tell us about current delivery methods and the progress observed there?

Dr. Liu: We're beginning to understand that the nontargeted regions of exposure to radioembolization may potentially be beneficial due to elicitation of hypertrophy and growth factors in the unexposed areas. The concept of radiation segmentectomy (administration of extremely large amounts of radioactivity to obliterate a surgical segment) and radiation lobectomy (administration of extremely large amounts of radioactivity

to obliterate an anatomical lobe) have received much interest. It is important to note that both of these techniques operate on the basis of intentional nontargeted distribution of activity into normal liver parenchyma; in essence, we are intentionally damaging normal liver parenchyma. Although this is exciting in principle, the techniques should be considered with caution (especially in the circumstances of deliberate radiation lobectomy for contralateral hypertrophy as a substitute to portal vein embolization) and only by experienced users, for implementing this technique may result in transient or permanent liver failure.

In the glass microsphere arena, the development of the second-generation administration kit has improved safety and efficiency. The implementation of the EX concept introduced the importance of adequate particulate distribution in heterogeneous tumor vascularity into the mainstream. Improvements in shipping customized vials of radiation have improved efficiencies during the day of administration.

In the resin microsphere arena, the most substantial development in recent times has been the acceptance of the use of D5W as compared to sterile water for administration. It is now recognized that the sterile water had likely led to premature angiographic endpoints due to vasospasm, and now it appears that the use of D5W in the administration has drastically improved both the ability to deliver targeted activity and to speed up the actual administration. Furthermore, with the introduction of delivery of the parent vial the day before the procedure, further manipulation and customization of the radioactivity can be performed, allowing for even better scheduling and workflow.

What are the biggest remaining hurdles or opportunities for technological advancement? In other words, what do you want from the next generation of SIRT technologies?

Dr. Liu: Designing a microsphere is relatively easy, and from our experiences with the first generation of radioembolic materials, much has been learned about the additional specifications and requirements for the second generation. Ultimately, the ideal microsphere will be isodense to blood (to allow for the particle infusion instead of bolus), inherently (and ideally, transiently) radiopaque to minimize contrast load and confirm postimplantation distribution, bioabsorbable (after the radiation has been delivered, the particle dissolves), and finally, from a logistic standpoint, be delivered cold and loaded with radiation (to varying degrees of intensity) in the hospital before administration to maximize the availability and flexibility of delivery.

If we can reach this point, all aspects of radioembolization will become much easier. The logistical challenges of shipment and delivery, in addition to the difficulty in confirming dosimetry, are issues that must be resolved before this therapy becomes commonplace. Active research is being conducted in all aforementioned technologies, and given the growing body of evidence for the support of radioembolization, the excitement continues to build for the second-generation devices.

Do you think more technologies or manufacturers will enter the market?

Dr. Liu: We are reaching a point in this technology where we know that the platform works. Although it is difficult to say whether there are any direct competitors that are going to enter into the clinical space, there certainly are areas where new technology such as improved delivery systems, purpose-designed microsphere manufacture, and techniques and optimizations are possible.

Barriers to entry from the business standpoint are substantial, as this is a very technical and specialized field from the sales, clinical, manufacturing, regulatory, and distribution perspectives. I think a lot of manufacturers and interested parties are waiting for the next series of reported results in order to hone the business model and determine whether it is worth entering.

Both products have been on the market for close to 10 years without competitors, and it is the natural course of the innovation curve to look at methods of improvement and models of efficiency that will overcome the identified challenges and limitations that are inherent to what may be considered legacy processes.

What other future opportunities might exist outside of application in colorectal liver metastases?

Dr. Liu: Currently, there are only two manufacturers that provide commercialized forms of SIRT. Both manufacturers are actively looking toward clinical trials and possible indications for other oncologic disease processes that lead to liver metastases that are life-limiting. Cholangiocarcinoma, neuroendocrine disease, uveal melanoma, prostate cancer, and breast cancer are just a few of the disease processes that can result in liver-dominant, life-limiting disease, and all are under active investigation. In addition, other organ systems have been targeted as well, including the kidneys, lungs, and even brain.

Is Y-90 the only isotope that is suitable for radioembolization?

Dr. Liu: In fact, the answer is no. There are a number of other radioisotopes that have great potential, includ-

ing iodine-131, holmium-166, and rhenium-188. All of these isotopes have been used in embolic therapies in the past, with varying degrees of success. The benefit of holmium and rhenium is their relatively similar energy profiles to Y-90, with the ability to provide gamma particle emissions that allow for more accurate postimplantation determination of particle distribution, as well as dosimetry.[5]

Is Authorized User status really necessary for operators performing Y-90 radioembolization, or should a different standard be adopted?

Dr. Liu: As SIRT becomes more of a mainstream treatment supported not only by the available clinical data but also the vast amounts of clinical experience that are being gained each day, the need for Authorized User status is an interesting question. Of course, we want to make sure that physicians performing SIRT do so in a safe and effective manner, and as such, an understanding of not only the technical procedure associated with the dose administration but also the anatomy and the many variants thereof involved in the mapping are key.

Although I agree that a thorough understanding of the safe handling of the Y-90 is of importance, training programs are adding SIRT to the myriad procedures that new physicians are exposed to, and many of the issues regarding safe handling of Y-90 are addressed in these programs. Optimally, it would be great to see us move to a place where the technology and techniques have matured to a point where new physicians coming out of training feel competent and comfortable performing the procedure without proctoring or direct supervision.

Which data are you most looking forward to, and which trials or areas of study are needed to gain further understanding of SIRT?

Dr. Liu: Despite all of the advancements in the technology and techniques in the world of oncology, safety, compatibility, and improvement in overall survival must be balanced with an improvement in quality of life for each and every disease process. This situation has been an uphill battle in the device and surgical world with respect to medical oncology. I'm happy and excited to say that in the next 2 to 3 years, there will be a substantial body of evidence to either support or refute the use of radioembolization in disease-specific states.

Within metastatic colorectal carcinoma, four major clinical studies are underway. By the time this issue is published, data from SIRFLOX will have been reported, which is a phase III trial studying first-line use of Y-90 resin microspheres in the setting of unresectable colorectal carcinoma with a primary outcome of overall progression-free survival that has recruited more than 500 patients. This study has been designed to piggyback onto other first-line metastatic colorectal trials such as FOXFIRE and FOXFIRE Global to report on progression-free survival and overall survival, with results due in 2017. With these studies combined, the patient population will represent the largest clinical trial in the device world relating to medical oncology. The current glass microsphere phase III clinical trial, entitled EPOCH, is designed as a sandwich therapy between first- and second-line regimens, with the primary outcome of progression-free survival. Although recruitment in this trial has been somewhat challenging and limited, the enthusiasm still remains, and I have no doubt that the trial will be completed; however, at this time, there is no definitive date or projection made for completion.

Within hepatocellular carcinoma, a number of trials are actively recruiting or are close to completion. Within the resin microsphere arena, the French-led SARAH trial, pitting sorafenib against SIRT, has almost completed recruitment, with anticipated reporting in late 2016 or 2017. The SIRveNIB randomized controlled trial is being conducted in the Asia-Pacific region and is a similar format of study comparing sorafenib to SIRT. The multinational European trial SORAMIC possesses a treatment arm that compares SIRT versus SIRT + sorafenib and is also close to completion.

Two phase III glass microsphere trials are currently being conducted as well. A global trial, entitled STOP-HCC, will evaluate glass microspheres introduced before the administration of sorafenib versus sorafenib alone, and YES-PVT will compare SIRT to sorafenib in the presence of branch portal vein tumor thrombus.

What do you think the potential impact of the SIRFLOX and FOXFIRE/FOXFIRE Global studies will be?

Dr. Liu: All of these studies will help us to better understand how Y-90 resin microspheres combine with standard first-line chemotherapies to affect treatment. It has been shown in previous similar studies that the earlier SIR-Spheres (Sirtex) are introduced into the treatment algorithm, the better outcomes we tend to see. These studies will definitively determine not only if patients might benefit by adding SIR-Spheres to their first-line treatment (and specifically in how it might impact liver-only/liver-dominant disease), but also how it might assist the physician community in establishing treatment algorithms based on large, prospective, randomized, multicenter level 1 data. ■

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RECOMMENDED READING

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