Yttrium-90 Radioembolization

Recent advances in hepatic embolotherapy.

BY DAVID M. LIU, MD, FRCP(C); DAVID N. CADE, MD; JESSE KNIGHT, MD; RODNEY RAABE, MD; STEPHEN KEE, MD; ANDREW KENNEDY, MD, FACRO; AND RIAD SALEM, MD, FSIR, MBA

The concept of endovascular therapy for both primary and secondary neoplasia within the liver has been rooted in basic mechanisms of locoregional anatomy and the biologic processes that occur as a result of malignant transformation and metastatic deposition.

To date, more than 2,600 articles have been published regarding hepatic arterial embolic therapy, revealing a distinct evolution from particulate embolization (bland embolization), nonparticulate oily based embolic therapy (so-called chemoembolization), to the third-generation of terminally embolic therapeutics (yttrium-90 [Y90] microspheres and drug-eluting spheres). The technique involving the injection of Y90-labeled radiomicrospheres has been referenced as selective internal radiation therapy (SIRT), Y90 radioembolization, as well as intra-arterial brachytherapy. For the purposes of this article (and to reflect both the embolic and radiotherapeutic effect of therapy), the procedure will be hitherto described as radioembolization (RE).

The purpose of this article is to provide the reader with the rationale and context of RE in the clinical setting using an evidence-based approach. The article will cover histology and pathology, physical properties/advantages of RE, anatomic consideration/administration protocol, and indications/clinical results.

HISTOLOGY AND PATHOLOGY

Key characteristics of hepatic histology and pathology provide an ideal environment for concentrated locoregional therapeutics in the treatment of neoplasia. As established in the early literature, liver perfusion is unique in that vascular inflow is established through both an arterial supply, as well as portal inflow.[1] Under normal physiologic conditions, approximately two thirds of the hepatic inflow blood is provided by the portal vein, and the hepatic artery supplies one-third. Angioneogenesis serves as the quintessential starting

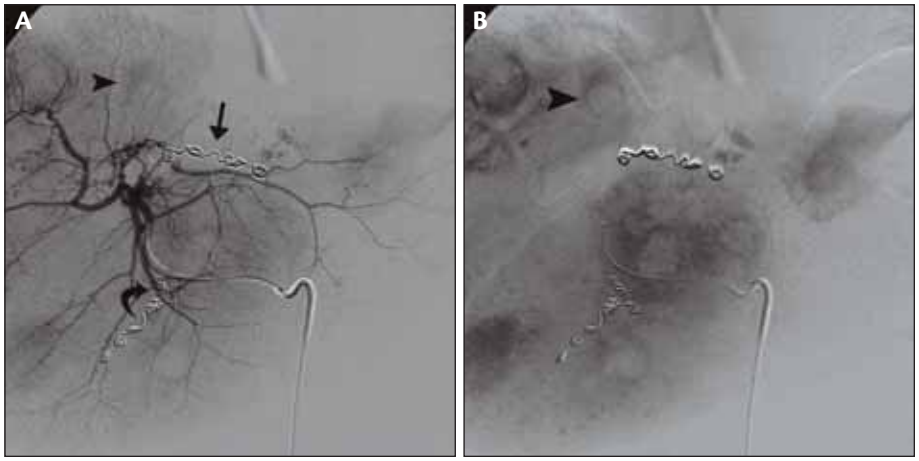
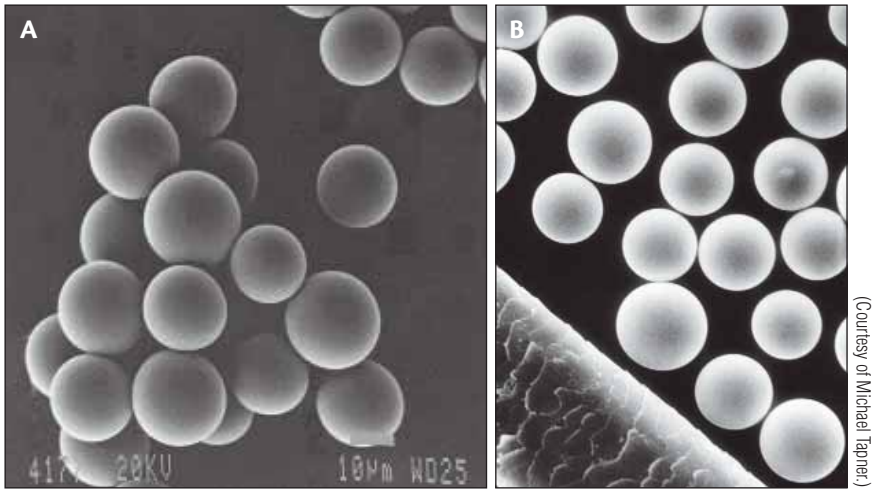


Figure 1. Mesenteric arteriogram of lesions through catheter-based injection from the right hepatic artery (colorectal carcinoma). Early arterial phase angiogram demonstrates coil embolization of accessory left gastric artery (straight arrow) and gastroduodenal artery (curved arrow) and well-defined hypervascular lesions (arrowhead) (A). Late arterial phase demonstrates hypervascularity in the periphery of the tumor burden, corresponding to aberrant vascular plexus of tumor (arrowhead) (B).

point for tumor seeding and propagation. As with any tissue, malignant cells require proximity to vascular flow to sustain cellular respiration and metabolic function. Thus, if vascular supply of the liver (or tumor) is stripped, cells will resultantly undergo stress, hypoxia, and may ultimately result in apoptosis.[2] This concept is clearly demonstrated in tumors that experience central necrosis as a result of outstripping of their own vascular supplies.

Although the pathway to the proliferation of a tumor cell population is fundamentally different between primary neoplasia and metastatic disease (usually through embolic seeding from the portal venous inflow), the end mechanism of angioneogenesis is dependent on highly vasoactive substances (such as vascular endothelial growth factor) that result in recruitment arterial blood supply.[3] Angioneogenesis (in its chemotherapy-naïve iteration) is derived almost exclusively from the hepatic artery, proven through silicone cast injections conducted in the 1950s by Breedis and Young, demonstrating 80% to 95% arterial contribution.[4] Through this inherent differential flow, a natural perfusional shunt ratio results in administration of the targeted therapy to tumoral blood supply while decreasing the relative exposure to the normal hepatic parenchyma (Figure 1). Although the ratio varies between tumor lines (described as the tumor to normal liver parenchyma ratio), the inherent nature of the tumors is such that the most aggressive and vascular portions of the tumors demonstrate a well-established vascular plexus around the periphery (Figure 2), with vessel diameter ranging in size from 25 µm to 75 µm in tumors larger than 3 mm.[5] Variations in tumor vascularity resulting from abnormal fistulae, intercapillary distance, and loss of normal hierarchy have also been established.[6]



(Courtesy of Michael Tapner.)

Figure 2. Photomicrographs. Ceramic Y90 microsphere relative to a single strand of human hair (A). Cluster of resin Y90 microspheres (B).

PHYSICAL PROPERTIES OF Y90

Y90 is an emitter of virtually pure beta radiation (99.7%), with an atomic half-life of 64.2 hours, resulting in decay to stable zirconium-90. With an effective mean free path in tissue of 2.5 mm, beta particle emission is ideally suited as a locoregional brachytherapeutic. Tagging of this radioisotope onto targeted antibodies has been successfully implemented in the treatment of lymphoma with ibritumomab tiuxetan, a Y90-labeled antibody,[7] as well as in somatostatin receptor analogues,[8] for the treatment of neuroendocrine disease.

Two current manifestations of Y90 radioembolic microspheres are currently FDA approved. One product consists of a ceramic sphere, with the radioisotope impregnated into the matrix (TheraSphere, MDS Nordion, Ottawa, Canada), and another consists of an inert microsphere coated with a resin that is bound to Y90 (SirSpheres, SirTex Medical, Wilmington, MA) (Figure 2). The current size range of both microsphere products varies from 20 µm to 70 µm and has been specifically designed to imbed within the aberrant peripheral vascular plexus.[9] Current approved indications will be discussed subsequently.

The inherent differences in physical properties of the two products result in variations in the specific gravity, number of spheres per unit of radioactivity administered, as well as the methods of administration,[10] and ultimately indications for treatment; the determination of which product to use lies beyond the scope of this discussion.

Standard dosimetric methodology is divided into three categories: (1) standardized MIRD (medical internal radiation dose) modeling and body surface area, (2) partition modeling (looking at specific volume treated and calculated dose), and (3) empiric method (the least sophisticated of the methodologies and most prone to under/overadministration and/or nontargeted administration).

All models are based on safety profiles, with corrections made in the case of potentially large pulmonary shunt (that may result in radiation pneumontitis), and other factors that may require adjustments in dose.

These factors include overall hepatic exposure, tumor bulk and vascular capacitance (ie, how many beads may be embolized in the tumor vascularity), previous chemotherapy, and operator experience. The authors refer to Salem and Thurston for a review of the methods and controversies of contemporary dosimetry.[11]

ADVANTAGES OF Y90 THERAPY

All brachytherapy requires an oxygenated environment to promote free-radical generation, and thus, preservation of arterial and portal inflow are desirable, as opposed to chemoembolization, in which the complete cessation of flow via embolization of low-order vessels has been associated with longer dwell times of the oily substrate in which the chemotherapy is suspended.[12]

It is important to note that although the embolic effect contributes to the overall dose-response characteristic of the therapy, the fundamental principle of the locoregional radiotherapeutic effect is dependent on the universally accepted principle of free-radical generation, and in particular, oxygen-free radicals.[2,13] Thus, true complete embolization/dearterialization is not desirable, and, in fact, a well-oxygenated environment results in increased radical generation, translating into increased radiotherapeutic effect.

Furthermore, specific tumor lines are more sensitive to the radiation than others. For example, it has been demonstrated that the prolonged secretion of serotonin in APUD (amine precursor uptake and decarboxylation) cell lines exposed to radiation increases tissue radiosensitivity, further potentiating the radionecrotic effects.[14] With this in mind, the theoretical utility of Y90 microspheres to develop a mild embolic effect while preferentially irradiating radiosensitive tumor lines, in addition to increasing the radiosensitivity of the tumor itself during the therapeutic window has the potential to evoke synergistic insults to tumor lines while preserving vascular inflow.

Postembolization syndrome has been documented to be less severe with RE versus oily based chemoembolization, perhaps due to the lack of high concentration chemotherapy, or due to the decreased embolic load. In a comparative study analysis, analyzing the severity of postembolization syndrome comparing ethiodol-based chemoembolization versus RE demonstrated postembolization syndrome in 20 of 29 (69%) with traditional chemoembolization as opposed to six of 34 (18%) in the RE population, with a much less severe form of postembolization syndrome in the RE cohort.[15] In a comprehensive review of the literature and with exhaustive experience with Y90 microspheres, Salem and Thurston concluded that other than fatigue and flu-like symptoms for approximately 2 weeks after treatment, there are virtually no clinical toxicities.[16] Steel et al, through standard quality-of-life questionnaire/models have also illustrated the increased quality of life postprocedurally in the RE population as opposed to traditional chemoembolization.[17]

In brief, some benefits of Y90 over the chemoembolization and bland embolization techniques are:

- Outpatient-based staged procedure; no hospital stay required.
- Significantly lower incidence and severity of postembolization syndrome.[18]
- No damage to hepatic arterial architecture.
- No embolic therapy; microvasculature still preserved.
- Safe as an adjunct to most systemic chemotherapies used in metastatic colorectal carcinoma.[19]
- Subclinical transaminitis only; rare cases of liver failure[20] (in patients with

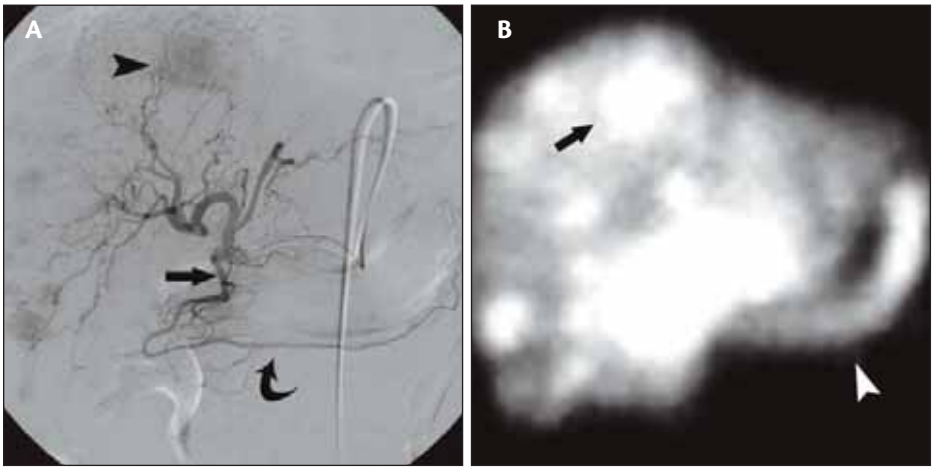


Figure 3. Scintigraphic and angiographic evidence of gastroepiploic reflux via gastroduodenal artery (carcinoid metastasis). Injection arteriogram performed via microcatheter placed in the common hepatic artery illustrates hypervascular tumors within the liver parenchyma (arrowhead) as well as reflux of contrast into the gastroduodenal artery (straight arrow) and gastroepiploic (curved arrow) (A). Coronal reconstruction SPECT scan after Tc-99 MAA injection demonstrates similar distribution of radiopharmaceutical in the tumor (arrowhead) gastroduodenal/gastroepiploic region (straight arrow) (B).

TABLE 1. CURRENT ACTIVE Y90 STUDIES

Study	Tumor Line	Product	Primary Investigator	Country	Design	Protocol	N	Endpoint	Comments
SIRFLOX	mCRC	Resin	Van Hazel Gibbs	Australia Europe USA	mRCT	mRCT FOLFOX6m ±Y90	35/320	PFS	Phase III
FAST	mCRC	Resin	Nutting Carter	USA	Multi	FOLFOX6m+Avastin+ Y90	2/30	S&T	Phase II
SITILO	mCRC	Resin	Cosimelli	Italy	Multi	Y90 in chemorefractory	52/52	Clinical response	Phase II enrollment
—	mCRC	Resin	Hendlisz Flamen	Belgium	mRCT	mRCT Y90 vs 5-FU HAI in chemorefractory	50/56	TTP	Phase III
Chemo-SIRT	mCRC	Resin	Gulec	USA	SASI	Y90 + FOLFOX	20/25	Radiographic biologic S&T	Phase II
—	mCRC	Resin	Cohen	USA	SASI	Capecitabine + Y90	8/28	S&T	Phase I
—	HCC	Resin	Murthy Gamblin	USA	Multi	Y90 monotherapy	1/40	OS	Phase II
SIRTACE	HCC	Resin	Sangro Kolligs	Europe	mRCT	TACE vs Y90	6/28	QoL	Phase III
SIRSA	HCC	Resin	Chow	Singapore	SASI	Y90 + Sorafenib First Line	0/31	T&S	Phase I/II
—	NET	Resin	Morris	Australia	SASI	Y90 monotherapy	35/35	Radiologic	Phase II
—	Breast	Resin	Calkins	USA	SASI	Chemorefractory	8/50	Tumor response	Phase II
—	All Mets	Ceramic	Benson	USA	Multi Open	All mets	50/150	Radiologic	Phase II

normal hepatic function).

• Surgical, ablative, and chemotherapeutic options remain open.[21]

TREATMENT PROTOCOL

As established in the early literature, complications as a result of RE are primarily due to nontargeted embolization. The incidence of gastric ulceration and gastrointestinal-related complications were as high as 15% when therapy was initiated through surgically placed hepatic arterial infusion pumps without angiographic assessment or optimization.[22] Due to the high variation of locoregional anatomy, great care must be taken in the optimization of vascular flow. Because the physical sphere itself also serves as the radiotherapeutic, the potency of locoregional delivery (as compared to oily based embolization) is significantly greater.

During the vascular optimization session, meticulous selective catheterization and microcatheterization of the hepatic arterial system are required to simulate delivery of the radioembolic. It is important to selectively embolize potential extrahepatic sumps, intestinal collaterals, variant anatomy, parasitizing vessels, or direct shunt to pulmonary capillary beds (Figure 1). The discussion of angiographic technique, identification of normal anatomy, and recognition of variance is beyond the scope of this review; however, the reader is directed to several comprehensive reviews on the principles of anatomy, tumor perfusion, and sump vascularity.[23-25]

Because the particle itself carries the therapeutic without dissipation, the procedure requires a much higher degree of caution and more aggressive selective embolization than oily based embolization or even bland embolization. Complications associated with nontargeted embolization are predominantly due to embolization of gastric and gastrointestinal beds, resulting in ulceration (Figure 3A).[26]

The microspheres themselves are of a nominal size, and in the process of malignant angioneogenesis, aberrant arterioportal and arteriovenous fistulae can form on a microscopic level. Thus, to avoid inadvertent delivery of potentially lethal doses to extrahepatic beds (most commonly the pulmonary capillary beds), a nontherapeutic

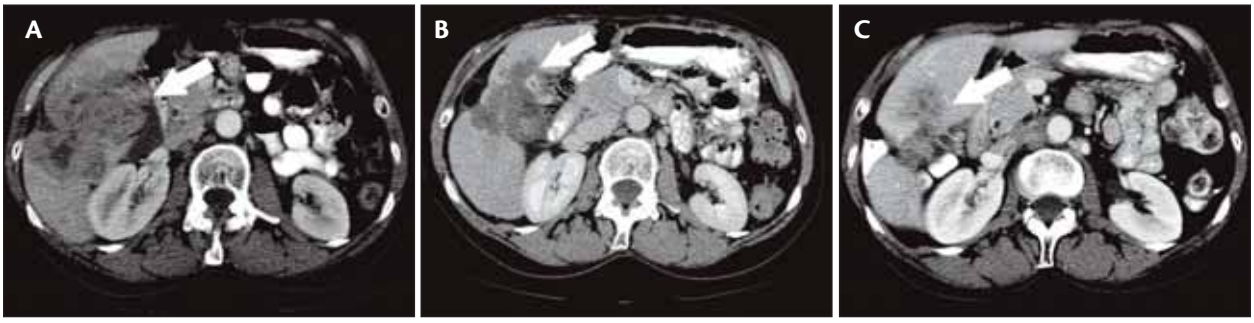


Figure 4. Morphologic response after adjunctive RE (breast metastasis). Chemorefractive metastatic breast carcinoma (straight arrows) pre-RE (A), 5 months after (B), and 18 months after (C) confirming significant tumor response without change of systemic chemotherapy (due to stable axial skeletal metastatic disease).

surrogate for the Y90 spheres (technecium-99 macroaggregated albumin) is injected before the actual radioembolic dose delivery but after macrovascular optimization. After injection of the radiopharmaceutical, gamma camera, single photon emission computed tomography (SPECT), or single photon emission computed tomography-computed tomography (SPECT-CT) scanning is performed to determine pulmonary shunt percentage (to minimize the theoretical risk of radiation pneumonitis) as well as for nontargeted embolization of technecium-99 MAA (Figure 3).

INDICATIONS

Ceramic microspheres (Therasphere) are only FDA approved for Humanitarian Device Exemption (HDE) in cases of unresectable hepatocellular carcinoma. Resin Y90 microspheres (SirSpheres) are FDA approved as adjunctive therapy to floxuridine, with administration during hepatic arterial pump infusion for the treatment of metastatic colorectal carcinoma (however, the vast majority of infusions are performed via off-label endovascular catheter-based infusion).

OFF-LABEL INDICATIONS

A large body of literature supports the adaptation of angiographic catheter-based RE for the resin sphere. In fact, the overwhelming majority of administrations of both ceramic and resin spheres (worldwide) are through catheter- and microcatheter-based super-selective administration. As outlined previously, this has dramatically decreased the complication rate secondary to nontargeted embolization because real-time administration (allowing for assessment of the embolic load and targeted tissue bed) can be performed under fluoroscopic guidance.

Another advantage of RE over conventional chemoembolization and/or bland embolization is the potential synergistic effect with radiosensitizing chemotherapeutics. Phase 1 data demonstrating minimal toxicity when RE is used with modified 5-FU (fluorouracil)–based first-line therapy for metastatic colorectal carcinoma has been established.[19] However, its safety profile with some potent radiosensitizing chemotherapeutics, such as gemcitabine and capecitabine, are under active investigation. The recent advent of first-line biologic therapy (bevacizumab, cetuximab) has changed the approach to metastatic colorectal carcinoma, and active clinical studies are currently enrolling to determine the safety profile of RE in the context of first-line colorectal carcinoma metastatic chemotherapy (Table 1).

Clinically, RE has been used in a number of tumor lines with encouraging results. Published applications in cholangiocarcinoma,[27] hepatocellular carcinoma,[16,17,20,28-30] neuroendocrine disease/carcinoid,[31-34] breast cancer metastases,[19,35-37] and metastatic colorectal carcinoma[30,38,39,42] attest to the versatility of this therapeutic platform as an adjunct to surgery/chemotherapy and also as monotherapy. Anecdotal applications in sarcomatous line tumors, prostate cancer, ovarian metastases, melanoma, renal cell carcinoma, and other hypervascular metastases have been discussed and/or reported. Clinical research is ongoing in many tumor lines through an active worldwide network of collaborators (Table 1).

RESULTS/CLINICAL OUTCOMES

Colorectal Carcinoma

The cornerstone of therapy for the treatment of metastatic colorectal carcinoma remains systemic chemotherapy. Adjunctive administration of Y90 provides a locoregional method for the management of the hepatic component, but this scenario also offers significant challenges because the evolution of systemic chemotherapies is active and ongoing. As clearly demonstrated in the literature, overall survival is dependent upon hepatic function with overall mortality. Hepatic decompensation occurs in upward of 80% of patients due to uncontrollable liver tumor progression (despite systemic chemotherapy).[40]

The pivotal trial by Gray (resulting in FDA approval), examining the use of Y90 microspheres as adjunctive therapy to hepatic arterial infusion pump FUDR (floxuridine) administration demonstrated compelling results in a phase 3 randomized format utilizing 5-FU–based hepatic arterial infusional chemotherapy with and without Y90. Significant RECIST (Response Evaluation Criteria in Solid Tumors)-based criteria response (PR+CR) (44% vs 17.6%; *P*<.01) and carcinoembryonic antigen response (72% vs 47%; *P*<.005) was elucidated. One-, 2-, 3-, and 5-year survival for patients receiving SirSpheres was 72%, 39%, 17%, and 3.5%, compared to 68%, 29%, 6.5%, and 0% for infusional chemotherapy alone, with no significant reported toxicity and a Cox survival analysis in favor of patients receiving Y90.[41]

In a recent phase 2 trial investigating the application of Y90 resin microspheres in the setting of contemporary 5-FU infusion therapy (5-FU/leucovorin) for patients with irrefutable evidence of bilobar nonresectable liver metastasis from colorectal carcinoma, prospective randomization of patients into the conventional chemotherapy (n=10) arm versus chemotherapy plus Y90 (n=11) revealed significant improvement with RE. Time to progression (3.6 vs 18.6 mo; *P*<.0005) and median survival (29.4 vs 12.8 mo; *P*<.02) were heavily in favor of combination therapy, with a trend toward more grade 3 and 4 toxicities, however, with no significant difference in changes in quality of life. Although a small cohort, the compelling results serve as a platform for future study with systemic 5-FU–based therapy.[42]

Studies examining the application of ceramic microspheres have also revealed excellent radiographic response. Lewandowski has demonstrated up to 88% metabolic response (via PET CT scan) in salvage patients (n=27) undergoing ceramic microsphere embolization who have failed at least two lines of chemotherapy, with a median survival of 339 days.[38] These results have been confirmed in similar studies, such as Coldwell et al, who showed a 90% radiographic response in 12-month median survival in patients who failed to respond to third-line therapy chemotherapy (n=84) using resin microspheres.[43]

To reinforce not only the radiographic but also the clinical response, Kennedy et al examined 208 patients who failed third-line chemotherapy, treated with both resin and ceramic microspheres. Expected survival based on historical figures was 4.5 months, with an observed survival of 10.5 months, including a cohort of patients with demonstrated extrahepatic disease. Objective response (FDG-PET) in this series was 91%.[39]

Application of Y90 to current first-line chemotherapy regimens, such as FOLFOX (5-FU, leucovorin, and oxaliplatin) and FOLFIRI (5-FU, leucovorin, and irinotecan), both with and without biologics are under active investigation (Table 1). To date, a published study by Sharma et al has established the base phase 1 data for application of Y90 to FOLFOX regimens. Dose reduction of oxaliplatin (60 mg/m^2 due to statistically increased incidence of leucopenia) has been proposed. The median progression-free survival of 9.3 months (progression occurring in the majority of patients due to lung metastasis) and median time to liver progression of 12.3 months provided a strong basis for further investigation and a segue into phase 2/3 data.[19]

Hepatocellular Carcinoma

Y90 microsphere administration as monotherapy has been extensively investigated. As outlined by key articles by Carr and Salem et al, survival benefit in Okuda I and II patient populations are substantial. In both studies, similar in design, and using ceramic microspheres, significant survival benefit was demonstrated as compared to historical controls. In the study performed by Carr, 65 patients enrolled presented with overall survival of 649 days and 302 days, stratified into Okuda stages I and II, respectively. Salem et al reported a population of 43 patients, stratified according to Okuda stages I and II, and demonstrated overall survival of 617 days and 322 days, respectively. Historical survival corresponded to 244 days (Okuda I) and 64 days (Okuda II), respectively.[20,28]

In 2006, Sangro et al reported on 24 patients diagnosed with hepatocellular carcinoma, as well as cirrhosis. The consecutive patients, receiving resin microspheres as monotherapy on an outpatient basis, were assessed based on Response Evaluation Criteria on Solid Tumors (RECIST), with a demonstrated reduction in reference lesion size in 20 of 21 measurable patients, with minimal toxicity.[44]

Regarding size reduction and its clinical implications, Kulick et al demonstrated the ability of locoregional monotherapy to decrease tumor by upward of 56%, essentially downstaging patients from stage T3 to T2, with 66% of T3 tumors reaching criteria of T2 lesions <3 cm, enabling surgical resection.[21]

With the minimal level of the parenchymal inflammation/damage and arteritis, repeat therapy is easily performed, and minimal postembolization syndrome has translated into overall improved quality of life.[17] Studies involving resin microspheres in the setting of hepatocellular carcinoma have been conducted, with ongoing enrollment and interim analyses demonstrating encouraging results (Table 1).

Breast Cancer

In the case of hepatic metastatic breast cancer, resin microsphere-based RE has shown promising results (Figure 4). In an article published by Coldwell et al, heavily

pretreated patients (chemo resistance and failure on third-line therapy) who were not candidates for locoregional therapies (radiofrequency ablation, transit or chemoembolization, resection, IMRT (intensity-modulated radiation therapy), or stereotactic radiotherapy) were subject to whole liver or sequential lobe RE. Of the 44 women treated in the study, extrahepatic metastases were demonstrated in more than 50%, and thirty-two patients had failed all forms of chemotherapy prior to RE. CT partial response was 47%, and PET scan response was 95%. At a follow-up point of 14 months after RE, 86% of the women were alive although mean survival had not been reached.[36]

In a similar study by Bangash et al, ceramic microspheres were utilized in a sequential lobar administration in an open label phase 2 protocol. Of the 22 women recruited, 30-day response on CT scan showed complete or partial response in 39%, stable disease in 52%, and progressive disease in only 9%. Tumor response on PET scan was noted in 63%. Treatment was well tolerated with a minimal toxicity profile.[37] The results of these two investigations suggest a role for RE in progressive hepatic metastatic breast disease. Studies are ongoing (Table 1).

Neuroendocrine/Carcinoid Disease

Initial studies investigating the application of Y90 microspheres were established by Kennedy et al. Using both ceramic and resin microspheres, retrospective analysis of the 40 patients enrolled showed significant radiographic response (complete and partial response) in 93% (n=34) of patients. Low toxicity was demonstrated, with a subset of patients able to discontinue ongoing palliative somatostatin analogue treatments.[45] The safety of RE in patients who have been heavily pretreated with conventional chemoembolization has been studied by Murthy et al, with five of eight patients undergoing RE expressing partial response or stable disease, without significant postprocedural complication.[32]

In a multicenter retrospective review of patients with metastatic neuroendocrine tumors, both resin (n=22) and ceramic (n=20) microspheres demonstrated equivalent safety and efficacy, with a reported RECIST-based response of 92% in patients treated with ceramic microspheres and a 94% response in the resin microsphere population and with (nonstatistically significant) survival of 22 months and 28 months, respectively.[33]

Recently, the largest reported cohort of patients with neuroendocrine metastatic disease undergoing Y90 microsphere embolization has been reported. Retrospective and multi-institutional in design, 148 patients were treated and followed. A median survival of 70 months was reported. Interestingly, as opposed to the commonly accepted severe toxicity profile of chemoembolization, no statistically significant toxicities were identified in liver synthetic parameters, with only grade 1 to 2 ECOG (Eastern Cooperative Oncology Group) toxicities demonstrated for aspartate aminotransferase and alanine transferase alone. Statistically significant drops in CgA levels were evident in subset analysis, reflecting the tumoricidal effect of therapy.[34]

CONCLUSION

Y90 RE represents a level of complexity that is an order of magnitude above traditional chemoembolization. Y90 RE (ceramic and resin) represents the evolution of locoregional embolic therapy and cancer treatment paradigms. As demonstrated in this review, active research and publication are ongoing within both primary and secondary hepatic neoplasia. Although the principles of embolotherapy and, in particular, radioembolotherapy date back to 1968,[31] recent advances in imaging, angiography, embolics, techniques, technology, and manufacture have developed to achieve the current level of consistency, safety, and response. Understanding of disease process, vascular physiology, anatomy, dosimetry, chemotherapy, and the potential complications are crucial to optimizing response while minimizing morbidity.

This exciting form of therapy has now transitioned from the innovative to early adopter phase, with rapid development of expertise and experience. With this growth come the challenges and responsibilities of optimization of patient care through careful patient selection via a multidisciplinary, multimodality approach. As research and clinical experience increase, the contemporary interventional oncologist will continue to evolve with the technology and will continue to establish the substantial contribution of RE and other forms of locoregional cancer care to quality of life, overall survival, and care. ■

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David M. Liu, MD, FRCP(C), is an interventional oncologist, Interventional Radiology Section, Inland Imaging LLC, in Spokane, Washington. He has disclosed that he is a paid consultant to SirTex Medical. Dr. Liu may be reached at (509) 474-5832 liudave@hotmail.com.

David N. Cade, MD, is Medical Director, SirTex Medical Limited, in Lane Cove, NSW, Australia. He has disclosed that he is salaried by SirTex Medical. Dr. Cade may be reached at (888) 474-7839; dcade@sirtex.com

Jesse Knight, MD, is from the Interventional Radiology Section, Inland Imaging LLC, in Spokane, Washington. She

has disclosed that she holds no financial interest in any product or manufacturer mentioned herein. Dr. Knight may be reached at (509) 474-5842; jknight@inland-imaging.com.

Rodney Raabe, MD, is Section Head, Interventional Radiology Section, Inland Imaging LLC, in Spokane, Washington. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Raabe may be reached at (509) 474-5832; rraabe@inland-imaging.com.

Stephen Kee, MD, is Associate Professor of Radiology, and Chief, Interventional Radiology, UCLA Medical Center, in Los Angeles, California. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Kee may be reached at (310) 206-4277; skee@mednet.ucla.edu.

Andrew Kennedy, MD, FACRO, is Medical Director, Wake Radiology Associates, in Carey, North Carolina. He has disclosed that he has received honoraria for CME lectures in 2008 from SirTex Medical. Dr. Kennedy may be reached at (919) 854-4588; akennedy@wakerad.com.

Riad Salem, MD, FSIR, MBA, is Director, Interventional Oncology Section, Assistant Professor, Northwestern Memorial Hospital, Robert Lurie Cancer Center, in Chicago, Illinois. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Salem may be reached at r-salem@northwestern.edu.

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