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^{90}Y Radioembolization

Success in Colorectal Cancer Liver Metastases

Colorectal cancer does not discriminate; it is the third leading type of cancer among men and women in the United States.[1] While the disease is largely preventable through early detection, the Centers for Disease Control and Prevention (CDC) reports that more than 20 million adults in this country have not had the recommended screening for colorectal cancer.[2] Early detection is essential because often when a patient becomes aware of symptoms, the disease has spread to other organs, resulting in a diagnosis of metastatic colorectal cancer (mCRC). In fact, of the nearly 140,000 Americans diagnosed with colorectal cancer every year, at least 60 percent will see their cancer spread to the liver and will die of the disease.[3,4] While surgical resection of liver tumors is the preferred treatment, factors such as size, distribution, and accessibility of tumors often preclude a patient from this treatment path.

An Alternative Treatment Option

More than 30 years ago, selective internal radiation therapy (SIRT) or radioembolization via microsphere therapy began to gain momentum as an option to target challenging liver tumors. With the development of a ^{90}Y bound microsphere that could be carried easily in the bloodstream to the capillary bed of the liver tumor, targeted internal liver radiation was achieved. In 2002 SIR-Spheres® microspheres received pre-market approval by the U.S. Food and Drug Administration (FDA) for colorectal cancer that has metastasized to the liver;[5] currently, they are the only microspheres approved for this indication. Today, the therapy continues to gain acceptance through ongoing trial results supporting the survival, tumor response, safety, and quality of life among patients who were challenged in finding an effective treatment option after heavy pre-treatment, including multiple lines of systemic chemotherapy and biological agents.

SIR-Spheres microspheres and SIRT are considered a safe and effective method of using radiation to treat colorectal liver metastases and are often used concurrently with chemotherapy or as monotherapy.

How SIRT Works

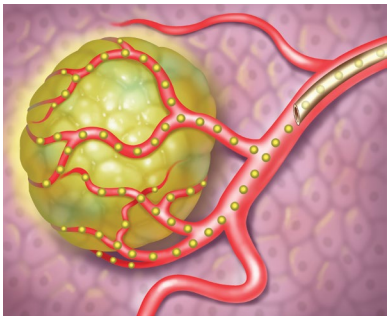
The microspheres are microscopic polymer beads that contain the radioactive isotope ^{90}Y and emit beta radiation to kill cancer cells. Due to their small size—the average size is approximately 32.5 microns—the microspheres travel easily through the bloodstream directly to the tumor. The microspheres become lodged in the tumor vasculature and kill the cancer cells by emitting beta radiation to the tumors, while the surrounding healthy liver tissue remains unaffected. SIR-Spheres microspheres and SIRT are considered a safe and effective method of using radiation to treat colorectal liver metastases and are often used concurrently with chemotherapy or as monotherapy.

SIRT is performed as an outpatient procedure by a team that includes an interventional radiologist who places a transfemoral microcatheter into the hepatic arteries. Other team members include radiation oncology, nuclear medicine, and medical oncology. Using the liver's unique vascular supply, millions of tiny resin microspheres charged with ^{90}Y are released into the hepatic artery leading to multiple tumors. The radioactive microspheres selectively implant in the microvascular supply of the tumor where they become trapped and emit beta radiation for a period of about two weeks. Concurrent chemotherapy has been safely given via the typical agents proven to be effective in colorectal cancers.

SIRT treatment normally takes about 60 to 90 minutes. After careful monitoring, most patients return home four to six hours after the procedure. The reported side effects are few; most patients experience only mild temporary abdominal pain, minimal nausea, and fatigue, (Grade 3 toxicity is <10 percent, CTCAE [Common Terminology Criteria for Adverse Events] 3.0) for a period of one to three weeks.

In prospective clinical studies of mCRC patients who were heavily pre-treated with multi-agent chemotherapy, SIRT with ^{90}Y resin microspheres delivered as monotherapy or combined with modern chemotherapy has been proven to:

- Decrease the tumor burden in the liver [6-13]
- Increase time-to-disease progression[7-8]
- Increase survival time[14]
- Potentially downsize tumors to liver resection or ablation[7,9,12-13]
- Provide palliation of symptoms.



Tumor with microspheres. Here yttrium-90 kills tumor cells while preserving healthy liver tissue.

The MORE Study

The **M**etastatic colorectal cancer liver metastases **O**utcomes after **R**adio **E**mbolization (**MORE**) retrospective study (clinicaltrials.gov identifier: NCT01815879) was designed to evaluate the safety and overall survival associated with ^{90}Y therapy in patients with mCRC, based on the collective experience of SIRT centers of excellence in the United States. The multi-center retrospective review includes eight years of clinical and radiographic outcomes after ^{90}Y resin microsphere radioembolization treatment (SIR-Spheres microspheres) in patients with metastatic colorectal liver metastases. Below are highlights of the MORE's study safety and efficacy findings.

Safety and Efficacy: Overview. Patients in the MORE study had a history of heavy pre-treatment, including multiple lines of systemic chemotherapy and biological agents, and were challenged in finding an effective treatment option. The primary purpose of the study was to further define the role of SIRT in treating mCRC

The key finding of this study—with SIRT, patients have an opportunity to live longer and live well.

patients. This retrospective study provided "real world" patient experience to confirm results from initial prospective studies used to gain regulatory approval of the microsphere therapy, initially granted in 2002. It is well accepted that the highest response rate and tumor control indices are accomplished when the intervention is applied earliest in the course of therapy. Despite the fact that most patients presenting for SIRT received more than one year of multi-agent chemotherapy and biologic agents, liver-directed radiotherapy was shown to be both safe and well tolerated, and for some patients likely improved survival with no negative impact on quality of life.

Safety and Efficacy: Methods. A total of 606 patients were included in the overarching MORE study that lasted from July 2002 to December 2011 and included 11 U.S. institutions.[15] Centers invited to participate included those that had more than 50 cases of mCRC patients treated with SIR-Spheres microspheres. The investigator-initiated study was a retrospective analysis that involved the collection of data by independent clinical researchers who compiled all the data from the source documents and submitted them to a central data bank. Original pre- and post-treatment CT, MRI, and PET scans were included in this data collection process and were sent to commercial clinical research organizations (CROs) outside the U.S. specializing in liver-directed radiology reviews. A stringent reading protocol was instituted for all the data to ensure that the retrospective data was handled as close to the manner in which prospective study data would be handled. Finally, independent groups completed audits of data. This method helped to provide the truest picture of SIR-Spheres microspheres/mCRC outcomes in the U.S.

In order to ensure efficient assessment of the data and the ability to identify trends, the principal investigator partnered with an independent medical statistics company to develop a specially-designed database for this project. The CROs at each center used source data and a toxicity grade assigned to ensure consistent reporting. Pre- and post-treatment (CT, MRI, PET) imaging data were sent via CD or DVD to an independent central radiology review center outside the U.S. that is experienced in radioembolization. RECIST and WHO criteria were used for objective grading of response at 12 weeks, and for later time points if scans were available for a large number of patients. All data were analyzed by the independent medical statistics company, which has significant experience in clinical oncology trials, specifically in radioembolization protocols.

Key Findings from the MORE Study

The MORE study's design yielded a great amount of data, and the findings may be considered as valuable or more valuable than prospective study results. Further, the results validate every previous study conducted on microspheres over the past 20 years—in many cases within a percentage point. As time progresses, researchers continue to dissect the data from the MORE study. The areas to be discussed here include the following:

- Overall safety and efficacy findings from a multi-institutional U.S. study
- An independent imaging study confirming the efficacy of SIRT
- Safety and efficacy in patients over the age of 70
- Pre-^{90}Y hepatic radiotherapy; diagnostic values help to predict overall survival in mCRC patients.

A Safety and Efficacy Study. One study of the safety and efficacy of resin ^{90}Y-microspheres examined the outcomes in 548 patients with metastatic colorectal cancer treated with microspheres therapy.[17] All patients in this subset of data had received prior chemotherapy, with more than 30 percent having also received prior liver surgery or ablation. Survivals of 13.0, 9.0, and 8.1 months, respectively, were reported in patients who had received 1, 2, or 3+ prior lines of chemotherapy. There were no significant differences in the adverse event profiles between the three groups. Most patients (97.8 percent) spent less than 24 hours in the hospital with the most common grade 3 side effects being abdominal pain (7 percent) and fatigue (6 percent). Data indicated that SIRT with microspheres appears to have a favorable risk/benefit ratio in patients with metastatic colorectal cancer who failed chemotherapy. These data show a clinically relevant survival benefit in patients not responding to chemotherapy, including those who have been heavily pre-treated.

While SIRT treatment is not a silver bullet, it does offer a potential gift of time for patients to spend with loved ones while maintaining a good quality of life. The key finding of this study—with SIRT, patients have an opportunity to live longer and live well. Specifically, recent studies in chemo-refractory patients with colorectal liver metastases reported a median survival range of 10.5 to 13 months compared to 3.5 months for untreated patients.[6,14,16]

An Independent Imaging Study. The response to SIRT therapy from an imaging perspective was assessed using further results from the MORE study.[17] Findings from the independent central review by a board-certified radiologist evaluated 195 patients with metastatic colorectal cancer that were treated with microspheres therapy and had measureable lesions at baseline and follow-up imaging. Patients who showed a partial response using

RECIST 1.0 and 1.1 criteria—with tumors shrinking at least 30 percent—had triple the survival rate compared to the expected historical rate in chemo-refractory disease studies. The patients who showed stable disease actually demonstrated doubled survival rate. Even in patients with progressive disease, SIRT therapy offered additional time, coupled with the improved quality of life that all patients were afforded.

Overall, the results show that hepatic radiological response to SIRT appears to predict longer-term prognosis. It is important to note that response to SIRT by RECIST 1.0 and 1.1 criteria at three months must be interpreted with caution due to the significant proportions of peri-tumoral edema and necrosis encountered. Imaging findings may lead to either the underestimation of partial response/stable disease or the overestimation of progressive disease, respectively.

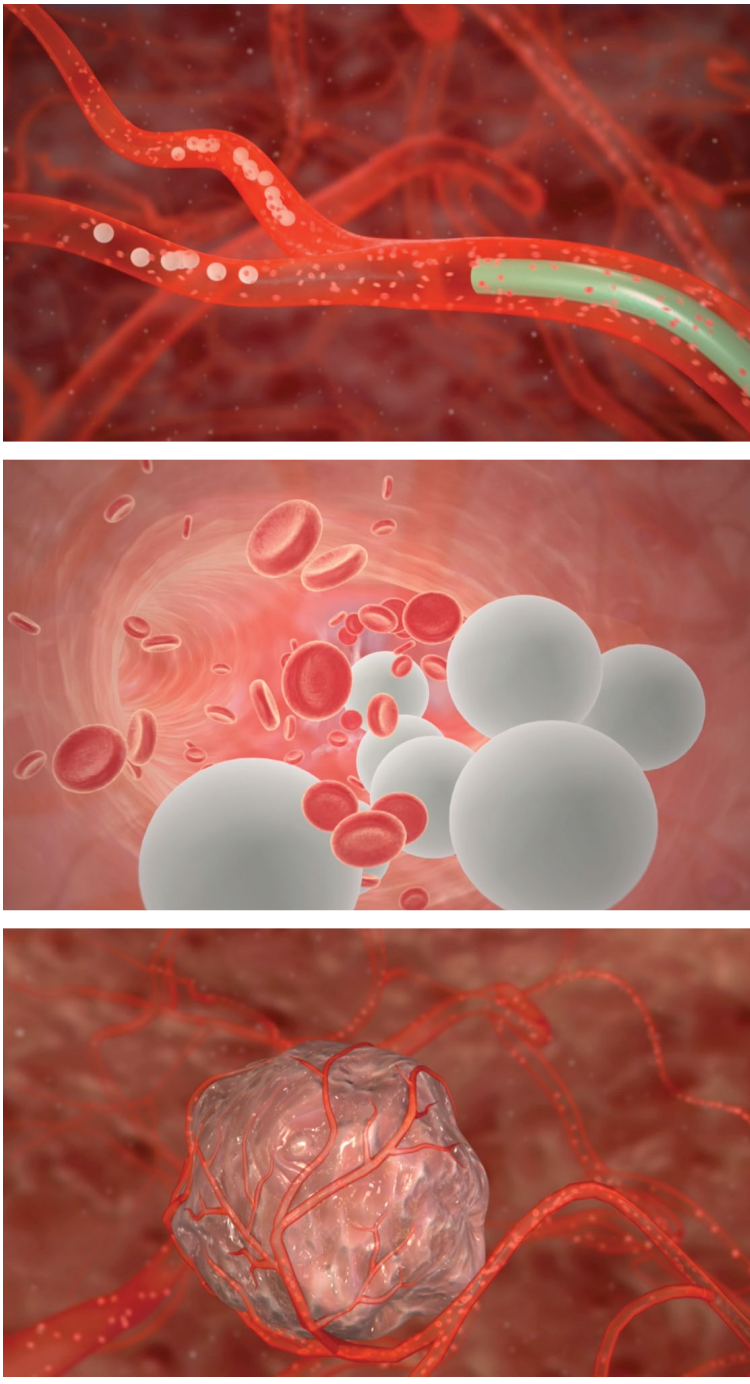
Safety and Efficacy of ^{90}Y Resin Microspheres in the Elderly. Many standard chemotherapy regimens are either not offered to elderly patients (≥ 70 years of age) or are given at lower, potentially less effective, levels due to the perception or existence of data indicating that elderly patients cannot tolerate these drugs. As a result, this population of patients has been left without effective treatment options. Due to the minimally invasive nature of ^{90}Y microsphere therapy, researchers hypothesized that SIRT may provide an effective treatment option for older patients without the concerns of side effects often seen with chemotherapy.

One retrospective analysis, which also was part of the MORE study, evaluated clinical outcomes among 160 elderly (≥70 years) and 446 younger (<70 years) patients with unresectable mCRC consecutively treated using resin ^{90}Y microspheres.[18] Regardless of age, patients were similar in terms of sex, race, performance status, and other characteristics.

Outcomes between both cohorts were similar following treatment with resin ^{90}Y microspheres. Median overall survival in elderly patients was 9.3 months compared to 9.7 in the younger group. The treatment was equally well-tolerated in both age groups, with no significant increase in grade 3+ adverse events in elderly patients. The most common grade 3+ adverse events were abdominal pain and fatigue. Investigators also noted that a sub-analysis of the oldest patients in the study (98 patients ≥75 years) compared to younger patients also confirmed equivalent outcomes for survival and toxicity.

These outcomes are significant since the oncology community has long struggled to understand the best approach for treating older patients with inoperable liver tumors. The main contribution of this particular subset analysis is important, namely SIRT is equally as effective in all patient ages. Too many times clinicians undertreat this patient population or these patients often choose to forgo treatment due to concerns about quality of life.

Images, top to bottom:
Mode of Action 1. SIR-Spheres microspheres are released into the arterial blood supply. **Mode of Action 2.** SIR-Spheres microspheres being carried through the hepatic arteries to the tumor. **Mode of Action 3.** Tumors can be selectively irradiated leaving normal tissue unaffected.



Pre-^{90}Y Hepatic Radiotherapy Hemoglobin and Liver Functions Help Predict Overall Survival in mCRC Patients.[19] The MORE study findings continue to unveil additional insights of importance to SIRT therapy for mCRC patients. New trends and opportunities to improve patient outcomes using SIR-Spheres microspheres cannot be overlooked. For example, researchers have learned that diagnostic results reflecting organ function are valuable predictors of the patient's survival after resin ^{90}Y microsphere radioembolization. Among the data collected in retrospective review 10 days prior to treatment: hemoglobin, albumin, alkaline phosphatase, AST, ALT, total bilirubin, and creatinine. A CTCAE v3.0 Grade was assigned to each parameter and analyzed for impact on survival by line of chemotherapy. Where applicable, consensus guidelines[20] were used to establish the abnormal limits of these parameters prior to radioembolization. While some parameters might be challenging to improve prior to radioembolization, hemoglobin <10 g/dL, which is a well-known negative factor in radiation response in external beam therapy, can be easily corrected before the procedure. These data suggest hemoglobin correction prior to radioembolization will enable maximal tumor response.

This retrospective MORE study analysis to establish predictive survival results evaluated clinical data values, including medical histories and pre-treatment laboratory values, obtained from 606 mCRC patients.[19] The patients (370 male; 236 female) were studied with a median follow-up of 8.5 months after radioembolization. Fewer than 11 percent of patients were treated outside recommended guidelines, with grade 2 albumin (<3–2.0 g/dL) being the most common (10.5 percent) at time of radioembolization. Abnormal parameters (grade >0) were associated with statistically significantly decreased median survivals ($p<0.05$) and this was consistent across most lines of prior chemotherapy. Compared to patients with grade 0, those with grade 2 albumin decreased median survival by 67 percent; for grade 2, total bilirubin by 63 percent; and grade 1, hemoglobin by 66 percent.

The team concluded that review of pre-radioembolization laboratory parameters may aid in improving median survival if correctable grade >0 values are addressed prior to radiation delivery. These efforts are important in optimizing treatment response to liver radiotherapy.

MORE Study Conclusions

The MORE study findings and other research studies to date have helped to improve understanding and acceptance of SIRT using SIR-Spheres microspheres and the results have further validated the treatment's safety and efficacy. Researchers look to continue the study of SIR-Spheres microspheres in various patient populations, with the goal of adding this treatment to conventional chemotherapy even earlier in the treatment algorithm. Separately, the SIRFLOX study, which completed enrollment in 2013, will test this hypothesis with the hope that controlling liver tumors will allow patients to live longer and experience an improved quality of life. Researchers look forward to those results.

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As scientific developments continue to enhance treatment options for patients, it is the role of the medical provider to understand the various treatment avenues to identify the proper fit for a patient based on his or her comprehensive medical history and needs. With any procedure there are risks. In the case of SIRT, those risks have been presented earlier. Additionally, radiation damage (radioembolization-induced liver disease, REILD) to normal liver reserve is always a concern and guides careful ^{90}Y activity selection and catheter placement. Fortunately, the incidence of REILD in the MORE study is the lowest of any study of mCRC patients to date (all grades 1.7 percent; grade ≥3, 0.5 percent), compared with 2 to 10.3 percent in key series.[14,17,20,21]

Going Forward

These insights show that even among patients who were heavily pre-treated, ^{90}Y-radioembolization appears to have a favorable risk/benefit profile. A clinically meaningful survival benefit was evident, even among patients who had received three or more prior chemotherapy regimens.

Going forward, the cancer research community continues to uncover new technologies and advancements in treatment. Researchers have said a lot about the MORE study and have even alluded to alternate treatment modalities. So what is next for delivery of SIRT for mCRC patients?

Further analysis of results shows promise to expand and improve treatment outcomes by identifying potentially correctable pre-radiation abnormalities prior to delivery of radioembolization. A new method is being proposed to enable complex modeling of the hepatic arterial route, and the tumor microvascular bed in which the radioactive particles will become permanently embedded to enhance treatment delivery.[25] I have begun to explore, with another talented team of physicians, predictive modeling in order to understand a patient's personal anatomy and the microspheres' final position in a tumor end arteriole.[25]

In January 2014 the findings surrounding research into the predictive modeling of the hepatic arterial tree and tumor microvasculature were announced. These findings, like earlier data discussed, were aimed at further advancing the SIRT treatment approach. Fractal methods were used to develop a software tool

that can represent the microvasculature of the human liver and different organs and can account for disease states, such as liver tumors. Normal liver and tumor artery trees were created, with malignant vessels employing a random generator at each node resulting in corkscrew, bifurcation, and/or trifurcation daughter-vessel pattern.

The team concluded that predictive modeling may now be possible for radioactive or non-radioactive microspheres exiting from a catheter into the hepatic artery to its final position in a tumor end arteriole, or for systemic therapies. In a nutshell, researchers learned that having access to predictive modeling software in the individualized pre-treatment mapping process will help to more accurately outline the final stop for radioactive particles in the tumor end arteriole, thereby helping to improve success rates.

It Takes a Multidisciplinary Team

With all of the data at the hands of treating physicians and patients, it is important for the oncology team to focus on each patient's individual medical history. Tumor board discussions play an essential role in encouraging dialogue among specialists to identify the best treatment course of action for a patient. It is during these valuable discussions that clinicians essentially put their heads together and discuss the patient's previous treatments. The interventional radiologist's seat at the table is relatively new in the area of oncology, but a valuable one. Many of the treatments offered through interventional radiology or interventional oncology actually help to enhance the body's acceptance of later treatments.

All treatment options, including newer agents such as aflibercept and regorafenib, must be considered, and the pros and cons for each patient should be weighed on balance.

There is a great deal of engaging work underway that is making great strides to improve patient outcomes in the area of SIRT delivery for mCRC patients. The MORE study research adds to the growing body of scientific data further supporting the role of SIRT in treating metastatic colorectal cancer. In this specific patient population, the results compare favorably to many recently-approved chemotherapy and biologic agents, and provide another option to patients who may have stopped responding to systemic therapy.

At the end of the day, the best action clinicians can take for their patients is to collaborate; through dialogue, clinicians are able to arrive at the best possible treatment path for a patient. Many cancer programs are enhancing their multidisciplinary approach to care, which is good news for patients. Tumor board discussions are another valuable strategy for cancer programs wishing to enhance their holistic approach to cancer care.

OTHER TREATMENT OPTIONS

Two other treatments are now being used with mCRC patients:

1. Regorafenib, a newly-approved oral multikinase inhibitor used in mCRC patients previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with an anti-VEGF therapy, and, if *KRAS* wild type, with an anti-EGFR therapy.
2. Aflibercept, a dual vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF) inhibitor approved to treat mCRC when given in combination with the FOLFIRI (leucovorin calcium, fluorouracil, irinotecan hydrochloride) chemotherapy regimen.

Based on results from the recently published pivotal CORRECT trial,[22] the acute and delayed toxicities of regorafenib appear to be higher than ^{90}Y- radioembolization. Comparison of all toxicity grades, regorafenib vs. ^{90}Y-radioembolization revealed:

- Fatigue, 63 percent vs. 54 percent
- Anorexia, 47 percent vs. 8 percent
- Weight loss, 32 percent vs. 0 percent
- Fever, 28 percent vs. 8 percent
- Rash, 29 percent vs. <1 percent
- Hypertension, 30 percent vs. <1 percent
- Hand-foot syndrome, 47 percent vs. 0 percent
- Equal rates of hyperbilirubinemia, 20 percent respectively.

That said, caution should always be exercised in direct comparisons of data from prospective vs. retrospective studies.

SIRT studies have shown a median survival range of 10.5 to 13 months, which compares well to similar second-line patients receiving aflibercept (median 13.5 months)[23] and bevacizumab beyond progression (median 11.2 months).[24] The median survival of 9.0 and 8.1 months following ^{90}Y-radioembolization in patients with 2 or ≥3 prior lines of chemotherapy, respectively, in this study compares favorably with patients treated in a similar setting using regorafenib or placebo (median 6.4 vs. 5.0 months).[23]

The findings detailed here are important as researchers continue to identify trends and opportunities to improve patient outcomes using SIR-Spheres microspheres. Further, if clinicians work collaboratively to improve a patient's less than favorable results prior to undergoing a SIRT procedure, researchers believe they may be able to enhance outcomes. OI

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