Objectives: To discuss the basic concepts involved in the development of yttrium 90 (Y-90) microsphere selective internal radiation treatment and review the clinical data pertaining to its application in hepatic colorectal cancer metastases.

Data Sources: Published studies and scientific paper presentations.

Study Selection: Randomized clinical studies and retrospective reviews.

Conclusions: Selective internal radiation treatment is a promising new modality in the treatment of patients with hepatic colorectal cancer metastases as part of a multimodality approach. A chemo–selective internal radiation treatment neoadjuvant approach has a potential to improve therapeutic outcomes. Clinical studies in neoadjuvant and salvage settings are needed for more concrete outcome data and design of optimal multimodality treatment strategies.

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Selective internal radiation treatment (SIRT) is the delivery of radiation treatment via intrahepatic arterial administration of yttrium 90 (Y-90) microspheres. Selective internal radiation treatment is emerging as a mainstream treatment modality in the management of patients with primary and metastatic liver cancer. Yttrium 90 is a high-energy beta particle–emitting radioisotope. It is incorporated in biocompatible microspheres measuring 30 to 40 µm. The intellectual basis of Y-90 microsphere treatment is the preferential distribution of microspheres, which, when injected in the hepatic artery, yield in the tumor compartment in high concentration. The technique involves the administration of Y-90 microspheres into the hepatic artery accessed via the transfemoral route. Hepatic arterial infusion pump access can be used but is not preferred.

Selectivity of the procedure is due to the unique pattern of hepatic inflow. The overwhelming majority of the tumor blood supply is derived from the hepatic artery, whereas hepatic parenchymal flow largely comes from the portal vein. Intrahepatic arterially administered Y-90 microspheres are entrapped within the microvasculature and release β-radiation with a maximum energy of 2.27 MeV and a mean range of 2.5 mm in the liver tissue. Because of the 2.67 days' half-life of Y-90, 94% of the radiation dose is delivered during 11 days following the administration of the treatment. The high tumor concentration of Y-90 microspheres results in an effective tumoricidal radiation-absorbed dose while limiting the radiation injury to the normal liver parenchyma (Figure 1).

Selective internal radiation treatment is frequently referred to as radioembolization because of its technical similarities with chemoembolization. In reality, however, both the theory and practice of SIRT are different than chemoembolization. Contrary to chemoembolization, optimal perfusion and blood flow are required to enhance the free radical–dependent cell death in SIRT. Radiation combined with embolization-induced hypoxia is therefore undesirable. The biologic response is optimized by preservation of flow to the target area and, hence, oxygenation.

DEVELOPMENT OF THE SIRT CONCEPT

The first report of Y-90 microsphere treatment in patients with colorectal cancer liver metastases (C.RCLM) was published in 1964 by Ariel, a New York surgeon who was among the first to use radioisotopic techniques in clinical diagnostics and therapy. Ceramic or resin Y-90 microspheres were injected in the aorta at the level of the celiac axis using transfemoral catheter access or in the hepatic artery via retrograde catheterization of the gastroepiploic artery using di-
rect surgical access. Selective internal radiation treatment given with concomitant chemotherapy resulted in better objective and subjective response rates than either treatment alone. The Ariel group later published 2 subsequent studies reporting combined use of SIRT with 5-fluorouracil (5-FU) in symptomatic and asymptomatic patients with CRCLM. The mean administered activity in these studies was 3.7 GBq, which was well tolerated by the liver. Chemo-SIRT tripled the life span of patients with asymptomatic metastases to an average of 28 months compared with the historic controls.2,3

The second stage in the development of Y-90 microsphere technology involves systematic experimental studies designed by Gray et al4 exploring the intrahepatic and intratumoral distribution kinetics of different sizes and concentrations of microspheres. Animal studies demonstrated that the concentration of arterially administered microspheres with diameters of 15 to 35 µm in tumor tissue was 3 times that of the ambient normal liver tissue. In contrast, microspheres with a diameter of 50 µm or larger had lower concentrations in tumor tissue than in normal liver tissue. Homogeneity of distribution, on the other hand, improved with larger diameters.5 The optimal therapeutic microsphere size based on these observations was determined to be approximately 30 to 35 µm. Microspheres of this size distribute more homogeneously within the vascular bed, yet provide a higher concentration in the tumor tissue. Further animal experimentation demonstrated that to achieve maximum homogeneity in distribution, 4000 microspheres per gram of liver tissue was required.6 Gray et al4 also studied the radiation dose delivered to tumor and liver parenchyma using an intraoperative solid-state radiation detection probe in patients who were treated with Y-90 microspheres. Radiobiologic effects were evaluated by liver function tests and by histologic changes in liver biopsy specimens. The results confirmed that radiation doses of 80 Gy delivered by Y-90 microspheres could be tolerated by the human liver.

There are currently 2 commercially available Y-90 microsphere products: glass microspheres (TheraSphere; MDS Nordion, Ottawa, Ontario, Canada) and resin microspheres (SIR-Spheres; Sirtex Medical, Sydney, Australia). Both microspheres have relatively consistent sizes ranging from 20 to 40 µm, and neither is metabolized or excreted but remain in the liver permanently. The main differences are in the density (grams per cubic centimeter) and specific activity (activity per sphere). The glass microspheres are 3 times heavier per volume and carry 50 times more activity per sphere than resin microspheres. The resin microspheres are approved for the treatment of CRCLM. The glass microspheres have “humanitarian device exemption” for the treatment of hepatocellular carcinoma.

CLINICAL TRIALS WITH SIRT

To date, there have been 4 structured clinical trials with SIRT using Y-90 resin microspheres: a randomized phase 3 study using hepatic artery chemotherapy (HAC) with flouxuridine, a randomized phase 2 trial comparing systemic chemotherapy with 5-FU/leucovorin (LV) with or without SIR-Spheres, a phase 1/2 dose-escalation study with oxaliplatin, and a phase 1/2 dose-escalation study with irinotecan hydrochloride.7-10

The Randomized HAC Study

The first randomized phase 3 trial in 74 patients with CRCLM compared SIRT (2-3 GBq of Y-90 activity) plus HAC with 0.3 mg/kg of flouxuridine per day for 12 days and repeated every 4 weeks for 18 months vs HAC alone (0.3 mg/kg of flouxuridine per day for 12 days and repeated every 4 weeks for 18 months). Toxicity data showed no difference in any of the grade 3 or 4 toxicity between the 2 treatment arms. There was a significant increase in the complete and partial response rate (17.6% vs 4%; P=.01) and prolongation of time to disease progression (9.7 months vs 15.9 months; P=.001) in the liver for patients receiving the combination treatment. Although the trial design was not of sufficient statistical power to detect a survival difference, a trend was observed toward improved survival for the combination treatment arm7 (Figure 2A).
The Randomized 5-FU/LV Study

The second study, combining SIRT with systemic chemotherapy, was designed as a randomized phase 2/3 trial in which SIRT was used in combination with 5-FU and LV. This trial accrued 21 patients and closed prematurely because of the paradigm shift in the systemic therapy of metastatic colorectal cancer, which involved new-generation chemotherapy agents. Although the toxic effects were higher in patients receiving the combination treatment, a dose modification in SIRT decreased the toxic effects to an acceptable level. The objective response rate in this small phase 2 trial was significant. Progression-free survival in the combination therapy arm was 18.6 months compared with 3.4 months in the chemotherapy alone arm (P<.001). Overall median survival was 29.4 months in the combination therapy arm, compared with 12.8 months in the chemotherapy alone arm (P=.02) (Figure 2B).

The Oxaliplatin Dose-Escalation Study

A phase 1 dose-escalation trial of systemic chemotherapy using FOLFOX4 plus SIRT was conducted in Australia and the United Kingdom.2 Twenty patients with non-resectable liver-dominant metastatic disease who had not previously been treated with chemotherapy were entered in this trial. The trial was successfully escalated up to the standard oxaliplatin dose (85 mg/m^2) and demonstrated a safety profile very similar to that observed in other phase 3 trials of FOLFOX4 alone (Figure 3A). Twenty patients were enrolled in the study. Five patients experienced National Cancer Institute grade 3 abdominal pain, 2 of whom had microsphere-induced gastric ulcers. The dose-limiting toxicity was grade 3 or 4 neutropenia, which was recorded in 12 patients. One episode of transient grade 3 hepatotoxicity was recorded. Mean splenic volume increased by 92% following 6 months of protocol therapy. Partial responses were demonstrated in 18 patients and stable disease, in 2 patients.

Two patients underwent partial hepatic resection following protocol therapy. Median progression-free survival was 9.3 months, and median time to progression in the liver was 12.3 months.

The Dose-Escalation Study With Irinotecan

A second phase 1 dose-escalation trial of systemic chemotherapy using irinotecan plus SIRT was also performed by the Van Hazel group.10 Twenty-five patients who had failed previous chemotherapy but were irinotecan-naive were entered into the study. Irinotecan was given weekly twice every 3 weeks, starting the day before SIRT, for a maximum of 9 cycles. The irinotecan hydrochloride dose was escalated from 50 to 100 mg/m^2. The combined treatment was well tolerated (Figure 3B). Partial responses were seen in 9 of 17 patients, median time to progression in the liver was 7.5 months, and median survival was 12 months.

Retrospective Data From New Zealand

Stubbs et al11 published the New Zealand experience with SIRT in patients with CRCLM. Stubbs et al adapted the SIRT technique to involve administration of 2 to 3 GBq of Y-90 microspheres into the hepatic artery via a subcutaneous port, followed, at 4-week intervals, by regional chemotherapy with 5-FU. An early report on 50 patients with advanced, non-resectable CRCLM who were treated with SIRT between February 1997 and June 1999 demonstrated that SIRT was well tolerated with no treatment-related mortality. However, morbidity, including duodenal ulceration, was noted in 12 of 50 patients (24%). Responses to SIRT were assessed by serial carcinoembryonic antigen (CEA) measurements and computed tomographic (CT) scans. Median CEA values 1 and 2 months after SIRT (expressed as a percentage of initial CEA measurement) were 19 and 13, respectively. Median survival for patients who developed extrahepatic dis-

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Figure 2. Survival curves of 2 randomized studies. A, In the floxuridine (FUDR) vs the FUDR plus selective internal radiation treatment (SIRT) phase 3 randomized study, survival at 1 year was 68% in the FUDR group vs 72% in the FUDR + SIRT group; at year 2, 29% vs 39%; at year 3, 6% vs 17%; and at year 5, 0% vs 3.5%. The difference is most significant in years 2 and 3. The 5-year survival difference is not significant largely because of the progression of extrahepatic disease. B, In the 5-fluorouracil (5-FU)/leucovorin (LV) vs 5-FU/LV + SIRT phase 2 randomized study, the median survival was 12.8 months in the 5-FU/LV group vs 29.4 months in the 5-FU/LV + SIRT group. The difference is significant in year 3.
ease within 6 months of SIRT (n = 26) was 6.9 months (range, 1.3-18.8 months). In those who did not develop extrahepatic disease (n = 24), the median survival was 17.5 months (range, 1.0-30.3 months).11

The US Experience

Clinical trials of resin microspheres for colorectal cancer have been conducted in Australia in chemotherapy-naive patients. However, the US experience has been only in salvage patients until most recently. Cumulative data analyzed by Kennedy et al12 on 208 patients who were treated from April 2002 to April 2005 at 7 institutions with a median follow-up of 13 months (range, 1-42 months) indicated a median survival of 10.5 months for responders and 4.5 months for nonresponders. No treatment-related procedure deaths or radiation-related liver failure were encountered. Response rates as defined by CT, CEA, and positron emission tomography (PET) with fludeoxyglucose F 18 (FDG) were 35%, 70%, and 91%, respectively, respectively.12

A phase 2 clinical trial investigating the efficacy and safety of Y-90 microsphere SIRT combined with modern chemotherapy (chemo-SIRT) as a frontline treatment is under way at the Center for Cancer Care, Goshen, Indiana.13 The interim analysis of this trial demonstrated that functional tumor volume and total glycolytic index measurements showed a substantial decrease in all patients receiving combined treatment. The mean decrease in both parameters was significantly higher with combined treatment than chemotherapy alone.13

PRE-SIRT PATIENT EVALUATION

Evaluation of Liver Function/Reserve

Liver reserve might be (and often is) affected by neoplastic replacement and prior hepatotoxic treatments. Alanine aminotransferase/aspartate aminotransferase and alkaline phosphatase/gamma-glutamyl transpeptidase levels are the markers for acute and subacute hepatocellular and bilio-canaliculare injury, respectively. More difficult to evaluate is the actual “functional volume” in the anatomic intact—appearing liver region(s). Bilirubin level is a composite marker of liver reserve and has been widely used in many classification systems as a predictive measure. A bilirubin level higher than 2 mg/dL in the absence of correctable obstructive etiology is considered a contraindication.

Multiphase Liver Scan

Currently, the optimal imaging protocol for Y-90 microsphere workup is PET/CT. The new comprehensive protocol starts with an FDG-PET/CT dual-image set, where the noncontrast images are used for attenuation correction and for coregistration with PET images; FDG serves as a “metabolic contrast.” A conventional 3-phase (arterial, portal, and equilibrium phases) liver scan is preceded by FDG-PET imaging, completing the protocol with a total of 4 image sets (4-phase liver scan). Also, PET/CT interface with radiation treatment planning software allows image quantitation with tumor and liver volume determinations.

Angiography

Angiography has a paramount importance in the planning and administration of SIRT. All patients undergo a standard mesenteric angiography that involves an abdominal aortogram, a superior mesenteric angiogram, and a celiac angiogram followed by a common hepatic angiogram. This initial step allows assessment of first- and second-order anatomy and variations (Figure 4). The second step of angiography involves selective catheterization of the left and right hepatic branches. The assessment of segmental blood flow and third-order vascular anatomy is then performed with identification of smaller gastrointestinal branches, such as the falciform, phrenic, right, or accessory gastric arteries and the supraduodenal, retroduodenal, retroportal, and cystic arteries. An aggressive prophylactic embolization of the gastroduodenal and right gastric arteries as well as other vessels in the hepatofugal direction is recommended by most investigators. A flux of Y-90 microspheres into unrecognized collateral vessels may result in gastrointestinal tract

Figure 3. Liver toxicity data of 2 dose-escalation studies. A, In the FOLFOX4 plus selective internal radiation treatment (SIRT) phase 1 study, the enzyme changes noted are at the grade 1 to 2 level. No changes in bilirubin levels reach grade 1 toxicity. B, In the irinotecan hydrochloride plus SIRT phase 1 study, the enzyme and bilirubin level changes noted are at the grade 1 level. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; alk phos, alkaline phosphatase.
toxicities including gastroduodenal ulceration and, rarely, pancreatitis, cholecystitis, and esophagitis.

**Technetium 99m–Macroaggregate Albumin Hepatic Scintigraphy**

Macroaggregate albumin (MAA) is a particulate form of albumin with an average size of 20 to 40 µm and a density that is close to that of resin microspheres. Labeled with technetium Tc 99m (99mTc), MAA constitutes a reasonable surrogate diagnostic radiopharmaceutical to simulate Y-90 microsphere distribution when injected in the hepatic artery. A 99mTc-MAA hepatic scintigraphy is routinely performed at the completion of the visceral angiography. There are 3 objectives of 99mTc-MAA study. First and foremost is the detection and quantitation of pulmonary shunting, which could potentially cause radiation pneumonitis (Figure 5A). Fortunately, the incidence and degree of shunting is not clinically significant in the majority of patients. The second objective of 99mTc-MAA imaging is the identification of extrahepatic gastrointestinal uptake, which might be caused by an unrecognized hepatofugal vascular runoff. This finding, depending on its size, might preclude further treatment with Y-90 microspheres unless a safe interventional plan for prevention of extrahepatic flux can be made (Figure 5B). The third use of 99mTc-MAA hepatic scintigraphy is the determination of the blood flow ratio between the tumor and the liver compartments, which is the major determinant of the degree of "selectivity" of SIRT, also a prerequisite for radiation-absorbed dose calculations (Figure 5C).

**ADMINISTRATION OF SIRT**

The administration of the Y-90 microspheres is performed in an angiography suite. The catheter is situated in a position determined by the choice of the treatment mode (whole liver, lobar, or segmental). The technique of microsphere administration is different for resin microspheres than glass microspheres. Yttrium 90 resin microspheres are administered in a manually controlled manner using a dedicated apparatus with angiofluoroscopic guidance. Sequential angiographic assessments are recommended during the administration of the resin microspheres. Flow stasis and reflux could complicate the administration of a high number of microspheres. Reflux is a sign of increased risk for hepatofugal flux and is considered an indication to discontinue the administration. A different apparatus is used for administration of glass microspheres. Because the number of microspheres is much less, administration can be performed without monitoring flow stasis. Strict adherence to radiation safety guidelines is critically important in patient and personnel safety.

The determination of the Y-90 microsphere treatment activity (gigabecquerels) is either based on body surface area and estimated tumor burden or individualized prescriptions could be prepared by using the Medical Internal Radiation Dosimetry method. Furthermore, tumor, liver, and lung radiation dose (gray) calculations could be performed with the dosimetric approach.

Yttrium 90 microsphere treatment is an outpatient procedure. Patients who experience moderate postembolic syndrome could be admitted for less than 24 hours. Symptomatic treatment might be indicated for pain or nausea. Routine prophylactic use of antibiotics is not indicated. The role of proton pump inhibitors in the prevention of gastroduodenal ulceration and the role of steroids in minimizing chronic liver injury are not well established at present. Patients are provided with radiation safety instructions on hospital discharge.

**COMPLICATIONS OF SIRT**

In approximately one-third of patients, administration of SIRT causes immediate short-term abdominal pain requiring narcotic analgesia. This adverse effect is more common as the number of microspheres administered is increased. Some patients develop a mild fever for several days following SIRT administration. Lethargy and mild nausea are common symptoms after SIRT, can last up to 10 days, and may require symptomatic treatment.

The most serious complications are gastric or duodenal ulcers resulting from reflux of Y-90 microspheres into the gastrointestinal vascular bed and radiation hepatitis resulting from a radiation dose higher than the tolerable level. The incidence rate of gastrointestinal complications can be reduced by experience and using a meticulous administration technique. Radiation injury to the liver can be kept at a minimum using dosimetric guidance in the determination of administered activity and making a reduction in the administered activity when there is an increased risk of causing radiation damage, such as in preexisting liver disease.

Radiation pneumonitis has been reported to occur at an estimated lung dose level of 30 Gy, associated with severe pulmonary shunting. Presence of substantial...
shunting, as demonstrated by MAA scan, is a contraindication for Y-90 microsphere treatment.

Distant organs are not subjected to β-radiation because of the short range of beta particles. Radiation doses to the gonads are unlikely, given the distance to the liver and very short range of Y-90 beta particles. Similarly, radiation doses to the bone marrow are unlikely, and data have not demonstrated myelosuppression with Y-90 microsphere treatment.

SIRT-ASSOCIATED HEPATIC INJURY

The pathogenesis of radiation damage to the liver from conventional external beam irradiation is dominated by vascular injury in the central vein region. Early alterations in the central vein caused by external beam irradiation are an intimal damage that leads to an eccentric wall thickening. This process, when diffuse and progressive, results in clinical veno-occlusive disease characterized by the development of portal hypertension, ascites, and a deterioration in liver function test results. Selective internal radiation treatment–associated radiation injury has a different pattern. Radiation from microspheres is deposited primarily in the region of the portal triad and away from the central vein, thus minimizing damage to healthy liver parenchyma that is distant to the microspheres administered. The clinicopathological picture is determined by the degree of portal triad injury; varying degrees of cholangiopathy and a subclinical increase in portal resistance are not uncommon. Clinical veno-occlusive disease is not typical with SIRT.

THE POTENTIAL ROLE OF SIRT IN THE CONTEMPORARY MANAGEMENT OF CRCLM

The natural course of untreated metastatic liver disease is poor. Data from the 1960s and 1970s show that the median survival of patients receiving no treatment ranges between 3 to 12 months, with an overall median survival of 7 months. Liver resection provides the most favorable outcomes in appropriately selected patients. With the advancements in surgical, anesthetic, and perioperative care and in medical imaging, which allow better patient selection and surgical planning, liver resections have become accepted as standard therapy. Increasingly, aggressive resections are being performed with an operative mortality less than 5%. At many centers, more than two-thirds of resections now consist of major hepatectomies. While the liver resection has been accepted to be the only treatment with a chance of long-term survival in patients with CRCLM, the resectability rate of metastases at the time of diagnosis has been low, accounting for the low proportion of patients who may benefit from a surgical approach. Until recently, patients initially considered as having unresectable disease were treated with palliative chemotherapy, with poor response rates and obviously little chance of 5-year survival. Chemotherapy as a first-line treatment of metastatic colorectal cancer has greatly changed within the last decade. Oxaliplatin- and irinotecan-based combination regimens have improved the efficacy of systemic treatment. The new combination regimens not only allow increased patient survival in a palliative setting but also offer the possibility of cure to patients with previously unresectable disease with liver surgery after tumor downsizing. By reconsidering the initial unresectability for patients who strongly respond to chemotherapy, Adam et al have shown that survival could be achieved by liver resection in a significant proportion of patients otherwise destined to a poor outcome. This group analyzed a consecutive series of 1439 patients with CRCLM managed in a single institution during an 11-year period (1988-1999). Metastatic disease was determined to be resectable in 335 (23%) of the patients at initial presentation. The remaining 1104 (77%) were treated by chemotherapy, involving new-generation protocols. Among 1104 patients with unresectable disease, 138 (12.5%) underwent secondary hepatic resection after an average of 10 courses of chemotherapy. Seventy-five percent of procedures were major hepatectomies. Portal embolization and ablative treatments were liberally used as adjunct mo-
also prolong survival. Although a controversy still exists regarding the long-term outcomes of cytoreduction in the management of patients with cancer, the concept is supported by several clinical trials and basic scientific principles. Cytoreduction often improves function and quality of life by control of the symptoms. The volume reduction also diminishes the metabolic demands made on the host by the tumor. Chronomodulation of cytoreductive interventions with systemic chemotherapy might be the best weapon against repopulation kinetics of the tumor. Reducing the initial tumor volume increases the likelihood that repeated cycles of chemotherapy would further reduce the number of viable tumor cells toward the desired end point of undetectability. Reducing the total tumor volume to be treated also substantially diminishes the chances of cancer cells developing drug resistance, an event that increases directly with the number of cancer cells and the time it takes to complete treatment. Over the years, a number of cytoreduction methods have been developed that are available to assist the surgeon and oncologist in the quest to reduce tumor burden. Although surgical resection is the most effective technique for cytoreduction, when it cannot be safely performed, other techniques assume the primary role in cytoreduction. Cryoablation, radiofrequency ablation, and, more recently, microwave ablation techniques have been successfully used for this purpose. Selective internal radiation treatment could achieve an effective cytoreduction encompassing the whole liver or a lobar volume. Segmental administration of Y-90 microspheres could accomplish a complete radioablation in the target segment(s). Selective internal radiation treatment, even in a salvage setting, appears to be a reasonable cytoreductive technique with a relatively wide margin of safety.

CONCLUSIONS

Selective internal radiation treatment is a promising new modality in the management of patients with CRCLM.

Figure 6. Positron emission tomography (PET) with fludeoxyglucose F 18 (FDG) images before and after treatment. A, Pretreatment image of a patient treated with first-line chemo–selective internal radiation treatment (FOLFOX6) showing multiple bilobar liver metastases. B, Posttreatment image of the patient showing complete FDG-PET metabolic response in the liver. Note the subhepatic nodal activity (arrow) indicating progression of extrahepatic disease not exposed to yttrium 90 activity.
This article reviews the potential role of SIRT as part of a multimodality treatment of patients with unresectable CRCLM. Clinical studies in neoadjuvant and salvage settings are needed for more concrete outcome data and design of optimal multimodality treatment strategies. A chemo-SIRT neoadjuvant approach has the potential to improve therapeutic outcomes in hepatic metastatic disease in patients with colorectal cancer.

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REFERENCES