The Emerging Synergy between Radioembolization, Systemic Chemotherapy, and Liver Surgery in Metastatic Colorectal Cancer

a report by

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Colorectal cancer is one of the most common malignancies and a leading cause of death. It is estimated that during 2006 there were 412,900 new cases of colorectal carcinoma diagnosed in Europe and 207,500 deaths.¹ The five-year survival of patients with metastatic disease is less than 7%. Hepatic metastases are present in 15–25% of patients at the time of diagnosis of colorectal cancer, and another 15–20% will develop metachronous liver metastases within five years following resection of the primary tumor.² Progression of liver disease also leads to significant clinical morbidity, which is frequently correlated with overall survival.¹ The earlier identification of liver metastases should improve the management and survival of patients with colorectal cancer.¹

Unfortunately, only a small proportion—between 10 and 15%—of patients with liver metastases only are primary candidates for potentially curative liver resection, since surgery is limited to those with a good performance status, and those who fall within ‘limited disease criteria’ (generally four or fewer tumors in one lobe of <4cm each, not involving major vascular structures). Of those who do have a complete surgical resection undertaken with curative intent, the five-year survival rate is 30–40%, with at least two-thirds of patients developing recurrent liver metastases within two years after surgery.⁴ The majority of patients with liver metastases are initially not candidates for liver resection and are managed with systemic chemotherapy; there have been major palliative advances in this field over the last 10 years.

Until the mid-1990s the only available drug—which had limited activity in metastatic colorectal cancer—was fluorouracil (5FU). The last decade has seen a rapid evolution of systemic chemotherapies for metastatic colorectal cancer with the development of new cytotoxic agents such as

oxaliplatin and irinotecan; oral analogs (Capecitabine; Xeloda® and UFT-tegafur); and targeted biologicals such as bevacizumab (a monoclonal antibody against vascular endothelial growth factor) and cetuximab and panitumumab (monoclonal antibodies against the epidermal growth factor receptor type-1).

Combined with 5FU plus leucovorin (LV), irinotecan-based (FOLFIRI) and oxaliplatin-based (FOLFOX) regimens have evolved as standard first- and second-line treatments for metastatic colorectal cancer (see *Table 1*). More recently, phase II/III clinical trials have shown that the addition of bevacizumab increases the activity of 5FU/LV, irinotecan combinations,⁵ and oxaliplatin-based (FOLFOX) regimens.⁶ Recent trials (XELOXA/NO16966 and CRYSTAL) have suggested that biologicals may not provide the level of added benefit that was originally hoped for.⁷

These important new advances in biologic and cytotoxic agents have resulted in a significant prolonging of median survival time from approximately six months with 5FU-containing chemotherapy regimens⁸ to an excess of 20 months in some studies.^{5,9,10} Yet, despite these valuable gains, metastatic colorectal cancer is almost always fatal, with up to 90% of patients dying of liver failure caused by local effects of hepatic tumors. In high-risk patients with non-resectable and chemo-refractive liver tumors, therapies should be considered palliative, with the primary aim of treatment being to achieve a maximum reduction in tumor cell burden and improvements in progression-free survival and quality of life, as well as improving overall survival.

External-beam radiation therapy (EBRT) is a cornerstone of curative and palliative therapy in nearly all malignancies, but has not been applied with much success to hepatic disease due to the low tolerance of the organ to radiation compared with tumor. Significant technological advances in radiation treatment planning and delivery—which may benefit an increasing number of patients with liver metastases—have led to improved tumor-directed radiotherapy approaches, such as:

- 3-D radiotherapy;
- intensity-modulated radiotherapy; and
- stereotactic radiotherapy.

However, the key limitation of this treatment is the tolerance of normal liver parenchyma to radiation. The maximum acceptable dose to the whole liver is 35Gy, which is far below the required dose to destroy adenocarcinoma metastases, estimated at 70Gy or above (for monotherapy) or at 50Gy or above when concurrent chemotherapy is given. An alternative approach is the implantation of radiation sources into the tumor (brachytherapy).

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One form of brachytherapy is radioembolization, or selective internal radiation therapy (SIRT), which has been successfully utilized for the treatment of liver metastases and primary liver tumors. This procedure delivers radiation particles intravascularly, and takes advantage of the differential blood supply to tumors and normal parenchyma in order to ensure tumor-directed therapy. Eighty percent of the blood supply to the liver is via the portal vein, whereas almost all of the blood supply to the tumors is via the hepatic artery. By using the hepatic artery to inject embolic particles, multiple sites of disease within the liver can be selectively irradiated in a single procedure. The radiation is delivered by SIR-Spheres® (Sirtex Medical, Australia), which are biocompatible microspheres containing the pure beta-emitter radionuclide yttrium-90, which decays to stable zirconium-90 with an average half-life of 2.67 days (64.2 hours). The microspheres, with a mean diameter of 32µm, lodge within malignant microvasculature where they deliver high localized doses of ionizing radiation (100–3,000Gy) to tumors and the neovascular supply of the tumor while delivering safe levels to the normal tissue (mean penetration of radiation into tissues is 2.4mm).¹¹ Notably, the size of the microspheres means that they cannot pass into the capillary bed.

This loco-regional approach has been used for many years to deliver chemoembolization to hepatic malignancies, but such treatments have not provided any evidence of survival benefits in metastatic colorectal cancer (mCRC). In contrast, there is a growing body of evidence demonstrating the efficacy of radioembolization using SIR-Spheres in improving the treatment-related response, time to disease progression, and survival either in combination with systemic chemotherapy compared with chemotherapy alone^{12,13} or as a monotherapy.¹⁴ The evidence shows that responders appreciate a longer survival with little, if any, detrimental impact of treatment on quality of life.

The Clinical Evidence for Radioembolization with SIR-Spheres

In parallel with the evolution of systemic chemotherapy, a series of randomized, controlled trials has been conducted combining SIR-Spheres initially with hepatic artery chemotherapy then systemic chemotherapy, as well as in single-arm dose-escalation studies. A summary of the results from these trials is outlined in *Table 2*.

In one of the early trials, SIR-Spheres were evaluated as a first-line treatment in patients with non-resectable liver-only colon cancer metastases.¹² Combined with hepatic artery chemotherapy with floxuridine, patients treated with SIR-Spheres showed a significant reduction in tumor volume ($p=0.03$) and increase in time to progression (15.9 versus 9.7 months; $p=0.001$) compared with those receiving hepatic artery chemotherapy alone (see *Table 2*). The one-, two-, three-, and five-year survival for patients receiving SIR-Spheres was 72%, 39%, 17%, and 3.5%, respectively, compared with 68%, 29%, 6.5%, and 0%, respectively, for hepatic artery chemoembolization alone. However, the study was halted prematurely and not powered adequately to show survival advantage.¹² Nevertheless, the study was important in demonstrating the efficacy and tolerability of SIR-Spheres, and cox regression analysis suggested a benefit for patients treated with SIR-Spheres surviving beyond 15 months ($p=0.06$). Moreover, the addition of SIR-Spheres microspheres to hepatic artery chemotherapy was found to have no major adverse impact on quality of life, with both treatment groups demonstrating some improvement in quality of life.

It is apparent from clinical reports that one of the principle determinants of

Table 1: Investigational First-line Treatments for Metastatic Colorectal Cancer

FOLFOX	Oxaliplatin + fluorouracil + leucovorin
XELOX	Oxaliplatin + capecitabine
FOLFIRI	Irinotecan + fluorouracil + leucovorin
FOLFOXIRI	Oxaliplatin + irinotecan + fluorouracil + leucovorin
Bevacizumab + fluorouracil/leucovorin	Bevacizumab + fluorouracil + leucovorin
Bevacizumab + FOLFIRI	Bevacizumab + irinotecan + fluorouracil + leucovorin
Bevacizumab + FOLFOX	Bevacizumab + oxaliplatin + fluorouracil + leucovorin

Figure 1: Kaplan-Meier Survival Curve Following First-line Treatment SIR-Spheres plus 5FU/LV or 5FU/LV Alone in 21 Patients with Metastatic Colorectal Cancer¹²

Figure 2: Kaplan-Meier Survival Curve from Day of Treatment to Censure or Death in 208 Patients with Chemotherapy-refractory Disease Treated with SIR-Spheres

survival after radioembolization is the presence or subsequent development of clinically relevant extrahepatic disease. The experience of investigators indicates that median survival times are reduced in patients who either have significant extrahepatic disease prior to treatment or who develop such disease within six months of radioembolization compared with those who did not (8.3 versus 12.6 months; $p<0.001$).¹⁴ These results suggest that localized treatment with SIR-Spheres should be combined with systemic chemotherapy in order to achieve the maximum survival benefit.

Table 2: Overview of Clinical Study Results

Reference	No.	Treatment Regimen	Clinical Response		
			Overall Response Rate	Time to Progression/ Progression-free Survival	Overall Survival
First-line					
Gray et al. ¹²	74	SIR-Spheres + HAC floxuridine	44%***	15.9 months***	39% at 2 years*
		HAC floxuridine	18%	9.7 months	29% at 2 years
Van Hazel et al. ¹³	21	SIR-Spheres + 5FU/LV	91%***	18.6 months***	29.4 months**
		5FU/LV	0%	3.6 months	12.8 months
Sharma et al. ¹⁶	20	SIR-Spheres + FOLFOX4	90%	9.2 months/ 14.2 months ^a	Not reported
de Gramont et al. ²¹		FOLFOX4	27–59%	7.6–9.2 months	16.2–20.7 months
Kalofonos et al.					
Second-line					
Van Hazel et al. ¹⁸	25	SIR-Spheres + irinotecan	48%	6 months	12.2 months
Van Cutsem et al. ²²		Irinotecan	5–13%	2.7–4.2 months	6.4–9.4 months
Schoemaker et al. ²⁴					
Van Cutsem et al. ²³					
Salvage therapy					
Kennedy et al. ³⁰	208	SIR-Spheres			
		Responders	90%	7.2 months	10.5 months****
		Non-responders/controls	0%	Not applicable	4.5 months

SIR-Spheres for the first- and second-line treatment or salvage therapy of metastatic colorectal cancer.

* $p = 0.06$; ** $p \leq 0.05$; *** $p \leq 0.001$; **** $p = 0.0001$ SIR-Spheres versus active control.

^a Patients with liver-only disease; HAC = hepatic artery infusion; 5FU = fluorouracil; LV = leucovorin.

12.2 months (range 2.8–42.3 months).¹⁹ Again, these results compare favorably with studies on irinotecan alone in second-line therapy.^{22–24}

Radioembolization in the Continuum of Care

In summary, the evidence indicates a clear synergy between radioembolization with SIR-Spheres and systemic chemotherapy, extending survival and progression-free survival and improving response rates as a first- and second-line therapy, or as a salvage monotherapy in patients with chemorefractory disease. Furthermore, radioembolization with SIR-Spheres appears to be well tolerated and maintains quality of life in patients with unresectable tumors.¹² The relative ease of administration means that treatment can be delivered on an outpatient basis, or involving one night's hospitalization in the majority of patients.

SIR-Spheres used in conjunction with modern systemic chemotherapies are appropriate both to avoid extrahepatic progression and to prolong the local effects of radioembolization. While the evidence supports the potential of radioembolization using SIR-Spheres to provide substantial clinical benefit for patients with liver-predominant colorectal metastases at various points in the continuum of care—from first-line setting through to salvage therapy—the benefits in reducing tumor burden appear to be greatest early on when the liver vasculature is also less compromised. Moreover, because the liver is the major initial site of metastases,²⁵ improved early responses at this site may improve overall survival. With the availability of more effective systemic chemotherapies, strategies are now being developed to resect what in the near past was regarded as 'unresectable' disease. The evidence indicates that this may well be a realistic goal in up to 25% of patients with metastases confined to the liver who are treated with chemotherapy alone. For these patients, the curative potential of treatment compared with classical palliative end-points of response or progression-free survival becomes a real

Figure 5: Comparison of the Median Overall Survival from Reported Studies of Chemotherapy Regimens either with or without Biological Agents, or with or without Radioembolisation Using SIR-Spheres^{4,11,12,15,42–44}

possibility. In a retrospective analysis of published studies, Folprecht and colleagues²⁶ found a significant correlation between response rates and the resection rate in studies with patients with isolated liver metastases ($p=0.002$). It is increasingly likely that radioembolization will be adopted to

augment the regional response of systemic chemotherapies in the liver and increase the number of patients who are candidates for colorectal liver metastases resection. Application of an innovative multidisciplinary approach that integrates advanced surgical techniques with new drug treatments and therapeutic approaches (such as radioembolization and local ablative therapy) will allow the benefits of curative hepatic resection to be extended to a broader group of patients. However, the optimal management of patients with colorectal liver metastases can be provided only by close co-operation with various specialists (comprising a liver surgeon, oncologist, hepatologist, interventional radiologist, nuclear medicine physician, and histopathologist) who have an in-depth understanding of the latest diagnostic and therapeutic options.

Radioembolization 'Comes of Age'

An international clinical program is now ongoing evaluating radioembolization using SIR-Spheres in phase I/III studies in combination with the newest and most effective chemotherapy agents for colorectal cancer (such as FOLFOX) in the SIRFLOX study and biologicals such as bevacizumab (concurrently administered with either FOLFOX6 or FOLFIRI) in the FAST study, and cetuximab combined with irinotecan in another phase I/III study. Finally, there is increasing evidence that the role of radioembolization is not limited to colorectal liver metastases, since significant clinical benefits have also been reported in liver metastases from breast cancer,²⁷ neuroendocrine tumors,²⁸⁻³⁰ and other cancers,³¹⁻³⁴ as well as in primary liver cancers such as hepatocellular carcinoma³⁵⁻³⁹ and nodular cholangiocarcinoma.⁴⁰ Research into these other indications is also ongoing. ■

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