The Role of Radioembolisation Using SIR-Spheres® in Secondary Liver Metastases of Non-colorectal Cancer Origin – Emerging Clinical Data

a report by

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Whether primary or metastatic in nature, hepatic tumours are a leading cause of cancer morbidity and mortality. Most liver metastases are multiple, involving both lobes in 77% patients; only 10% are solitary. A few tumour types, such as colon cancer, carcinoid tumours and hepatocellular carcinoma (HCC), may present with lesions confined to the liver. Most tumours that metastasise to the liver, such as breast and lung cancers, often spread to other sites at the same time.[1] Indeed, circulating cancer cells can be detected in most cases even if the disease is thought to be early or localised.

The liver provides fertile ground for the formation of metastases, not only because of its dual blood supply but also because of humoral factors that promote cell growth required for constant cell-line function and regeneration. The blood supply of the liver is exceeded only by that of the lung in terms of blood flow per minute.[2] The fenestrations in the sinusoidal endothelium allow circulating tumour cells and/or tumour emboli, arriving via the blood stream, to take a foothold in the space of Disse. These circulating tumour cells are often physically obstructed and destroyed by the Kupffer cells, but if tumour emboli are large, they tend to become lodged in the portal venous branches.

Consequently, the liver is one of the most commonly involved organs for metastatic disease, second only to the lymph nodes. The liver may be the site of metastasis from virtually any primary malignant neoplasm, but the most common primary sites implicated are the eye, colon, stomach, pancreas, breast and lung.[1,3] In children, the most common liver metastases are from a neuroblastoma, a Wilms tumour or leukemia.

For a minority of patients, the number of liver metastases is limited and some form of local ablative treatment such as surgical removal, cryotherapy or radiofrequency ablation (RFA) can offer a chance of long-term survival. However, for most patients with metastatic liver cancer, by the time it is diagnosed the disease has progressed well beyond the point at which any form of ablative therapy can be used. Therefore, the majority of patients with liver metastases are managed with systemic chemotherapy, which has evolved over the past decade with the development of new agents and biologicals. However, these agents usually control the growth of cancer rather than eradicating it. Despite valuable gains with new chemotherapies and biologicals, metastatic cancer is usually fatal, with up to 80% of patients with colorectal cancer and liver metastases dying of liver failure caused by the local effects of hepatic tumours.[4] Depending on the site of the primary tumour, between 30 and 70% of patients have liver metastases when they die.

In high-risk patients with non-resectable and chemo-refractory liver tumours, therapies should be considered palliative with the primary aim of treatment being to achieve a maximum reduction in tumour-cell burden, improvements in progression-free survival and quality of life and improvement of overall survival with acceptable toxicity.

External-beam radiation therapy (EBRT) is a cornerstone of curative and palliative therapy in many malignancies, but has not been applied with much success to the liver due to the low tolerance of this organ to radiation compared with tumour. With significant technological advances in radiation treatment planning and delivery, improved tumour-directed radiotherapy approaches are evolving such as 3D radiotherapy, intensity-modulated radiotherapy and stereotactic radiotherapy, which may benefit an increasing number of patients with liver metastases. The key limitation in this treatment is the tolerance of normal liver parenchyma to radiation. The maximum acceptable dose to the whole liver for EBRT is 35Gy, which is far below the dose required to destroy adenocarcinoma metastases, estimated at 70Gy or above (for monotherapy) or at 50Gy or above when concurrent radio-sensitising chemotherapy is given.[5]

An alternative approach is the implantation of internal radiation sources into the tumour (or brachytherapy). One form of brachytherapy is radioembolisation, or selective internal radiation therapy (SIRT), which has been successfully utilised for the treatment of liver metastases and delivers radiation particles intravascularly. This procedure takes advantage of the differential blood supply to tumours and normal parenchyma in order to ensure tumour-directed therapy.

Eighty per cent of the blood supply to the normal liver is via the portal vein, whereas almost all of the blood supply to the tumours is via the hepatic artery. By using the hepatic artery to inject microspheres, multiple sites of disease within the liver can be selectively irradiated in a single procedure. The radiation is delivered by SIR-Spheres® (yttrium-90-labelled resin microspheres; Sirtex Medical Limited). These biocompatible microspheres (2,030µm in diameter) contain the pure beta-emitter radionuclide yttrium-90, which decays to stable zirconium-90 with an average half-life of 2.67 days (64.1 hours). The microspheres are injected slowly into the hepatic artery via a transfemoral catheter.[6] Once injected, the microspheres travel through the hepatic arteries and become lodged in the tumour capilliary plexus, delivering high doses of beta radiation of 0.93MeV energy with a maximum and mean penetration in tissue of 11 and 2.5mm, respectively.

In an analysis of microdosimetry in four explanted livers from patients previously treated with radioembolisation, Kennedy and

Table 1: Clinical Study Results with SIR-Spheres for First-line, Second-line or Salvage Therapy of Metastatic Colorectal Cancer[5,7–14]

Reference	n	Treatment Regimen	Clinical Response		
			Objective Response Rate	TTP or PFS	Overall Survival
First-line					
Gray et al., 2001[7]	74	SIR-Spheres + HAC floxuridine	44.0%**	15.9 months*** TTP	39.0% at 2 years
		HAC floxuridine	18.0%	9.7 months TTP	29.0% at 2 years
van Hazel et al., 2004[8]	21	SIR-Spheres + 5FU/LV	91.0%***	18.6 months*** TTP	29.4 months *
		5FU/LV	0.0%	3.6 months TTP	12.8 months
Sharma et al., 2007[9]	20	SIR-Spheres + FOLFOX4	90.0%	9.2/14.2[a] months PFS	Not reported
Second-line					
van Hazel et al., 2006[10,11]	25	SIR-Spheres + irinotecan	48.0%	6.0 months TTP	12.2 months
Lim et al., 2005[12]	30	SIR-Spheres + 5FU/LV (in 70%)	33%	5.3 months PFS	Not reported
Salvage Therapy					
Cosimelli et al., 2008[13]	50	SIR-Spheres	24%	4 months PFS	13 months
Jakobs et al., 2008[14]	41	SIR-Spheres	17%	5.9 months TTP	10.5 months
Kennedy et al., 2006[5]	208	SIR-Spheres	35.5%/90%[b]		
		*Responders	Not applicable	7.2 months TTP	10.5 months ****
		*Non-responders/controls	Not applicable	Not applicable	4.5 months

*TTP = time to progression; PFS = progression-free survival; HAC: hepatic artery chemotherapy; 5FU = fluorouracil; LV = leucovorin. Statistical significance: *p=0.05; **p=0.01; ***p=0.001; ****p=0.0001. SIR-Spheres® versus active control. a Patients with liver-only disease; b By positron emission tomography (PET) imaging.*

colleagues noted that high numbers of microspheres were preferentially deposited in the periphery of tumours, resulting in high cumulative doses to the tumour, varying from 100Gy to more than 3,000Gy, but that the normal liver showed little radiation effect away from tumours.[6] It is possible that such high radiation doses to tumour explains why the efficacy of radioembolisation appears to be independent of the primary tissue or cell of origin, with essentially any vascular lesion in which there is a favourable tumour-to-normal ratio of blood flow tending to respond well to this treatment modality. In contrast, other loco-regional therapies such as chemoembolisation have only demonstrated a survival benefit for a highly selected group of patients with primary hepatocellular carcinoma.

Initial work on radioembolisation using SIR-Spheres in colorectal liver metastases (mCRC) produced encouraging results in patients with advanced disease with unresectable liver tumours (see *Table 1*).[5,7–14] The studies found that the addition of systemic chemotherapy was effective in potentiating the efficacy of SIR-Spheres, as well as having an effect on extrahepatic disease, resulting in a significantly improved survival benefit. Based on this evidence, SIR-Spheres are now approved by the US Food and Drug Administration (FDA) for the treatment of inoperable tumours from primary colorectal cancer that have spread to the liver,[15] and in the EU, Australia and an increasing number of countries for the treatment of any inoperable liver tumours.

In recent years, this treatment approach has been embraced with great enthusiasm for the management of patients with both primary and metastatic liver diseases. Adoption of radioembolisation in most clinics, including the Hammersmith Hospital, started conservatively as salvage therapy for the treatment of non-resectable hepatic metastases when extrahepatic disease was minimal or absent.[16,17] Jiao et al. showed a significant effect with SIR-Spheres on liver disease such that only patients with extra-hepatic disease died. Importantly, measures to ensure the proper selection of patients, accurate interpretation of pre-treatment investigations, including angiography and 99mTc-MAA, can significantly reduce the incidence of serious adverse events. Provided that adequate measures are made to prevent extrahepatic leak (by embolisation of gastroduodenal, right gastric and other arteries), the shunting of SIR-Spheres to undesirable destinations can be prevented.[17]

Clinical Evidence in Non-colorectal Liver Metastases

The most attractive use of SIR-Spheres is perhaps in cancer, where conventional hepatic arterial embolisation (HAE or TAE) is a standard of care as SIR-Spheres increase efficacy. The main tumours this applies to are neuroendocrine tumours and hepatocellular carcinoma, but it is incresingly recognised that in other common tumours such as breast cancer liver metastases are a serious cause of morbidity and mortality, often with no current treatment options once chemotherapy options are exhausted.

Metastatic Neuroendocrine Tumours

Neuroendocrine tumours (NETs) are an uncommon, heterogeneous group of typically but not always slow-growing malignancies, including hormone-secreting 'carcinoid' tumours associated with debilitating symptoms, as well as non-functional tumours.[18,19] In these patients, the aim of treatment is to maintain a good quality of life for patients over a long period.[18] In the presence of liver metastases, 'curative' liver resection is possible in <10% of patients.[18] Overall, five-year survival rates are <50% with hepatic artery embolisation or chemoembolisation.[20] However, recent studies have shown that five-year survival can be improved (to >60%) with debulking surgery of the primary tumour or liver metastases in patients with more advanced-stage disease.[21,22] There remains much controversy as to whether current treatments make any difference to the natural history of the disease or its impact on survival. Alternatively, in patients presenting with small metastases, radioembolisation is increasingly being used to debulk the hepatic metastases and palliate the carcinoid syndrome or local pain from liver capsular stretching.[19]

Interim results of phase I/II studies with SIR-Spheres in patients with mNET have showed impressive response and disease control rates and good survival (see *Table 2*).[23–28]

Table 2: Clinical Study Results with SIR-Spheres for the Treatment of Metastatic Neuroendocrine Tumours[23–28]

Reference	n	Treatment Regimen	Clinical Response		
			Objective Response Rate	Time to Progression	Overall Survival
First-line Through Salvage Therapy					
King et al., 2008[23]	34	SIR-Spheres + 5FU	50%	Not reported	59% alive at 35 months
Kennedy et al., 2008[24]	148	SIR-Spheres	63.2%	Not reported	70 months (median)
Meranze et al., 2007[25]	10	SIR-Spheres	40%	Not reported	70% alive at 28 months
Wagner et al., 2008[26]	9	SIR-Spheres	78%	12 months	73% alive at 36 months
Kennedy et al., 2006[27]	18	SIR-Spheres	89%[a]	Not reported	89% alive at 27 months
Salvage Therapy					
Murthy et al., 2008[28]	8	SIR-Spheres	12.5%	Not reported	14 months (median)

5FU = fluorouracil. a By imaging or tumour marker CgA.

Table 3: Clinical Study Results with SIR-Spheres for the Treatment of Metastatic Breast Cancer[34,35]

Reference	n	Treatment Regimen	Clinical Response		
			Objective Response Rate	Time to Progression	Overall Survival
Treatment Hiatus or Salvage Therapy					
Coldwell et al., 2007[34]	44	SIR-Spheres	47%	Not reported	86% alive at 14 months
Salvage therapy					
Jakobs et al., 2008[35]	30	SIR-Spheres	61%	Not reported	11.7 months (median)

In a prospective study in 34 patients with unresectable mNET treated using SIR-Spheres and a seven-day systemic infusion of 5FU, King and colleagues demonstrated a complete response (CR) (by computed tomography [CT] using Response Evaluation Criteria In Solid Tumours [RECIST]) in six patients (18%), a partial response (PR) in 11 (32%) and stable disease (SD) in five (15%).[23] Symptomatic improvement was reported in 55% of patients at three months, and 50% at six months. The mean survival was 27.6 months at a follow-up of 35.2 months. The median survival had not been reached, with 14 patients having died at mean of 14.6 months and 20 patients (59%) remaining alive at a mean of 36.7 months. Twelve patients remained alive without any recurrence of liver metastases at a mean of 33.3 months. All six patients with a CR were alive at 26–46 months post-treatment, and the authors questioned whether any other therapy had previously achieved such useful results in mNET patients with inoperable disease.

Another prospective study of SIR-Spheres in 10 patients found a PR rate of 40% with SD in the remaining 60%.[25] Overall survival was 70% after a follow-up of eight to 35 months, with three patients having succumbed to progressive extra-hepatic disease.

A prolonged median survival of 70 months and high response rates were reported in a retrospective review of 148 patients with mNET who were treated using SIR-Spheres in US and European centres of excellence.[24] Overall, patients in this series had a good performance status (median Eastern Cooperative Oncology Group [ECOG] performance score of 0 [PS 0; range 0–3]) and presented with functional as well as non-functional tumours, which are typically associated with a worse outcome. Objective responses (as measured by CT, magnetic resonance imaging [MRI] or OctreoScan at three months post-treatment) included 2.7% with a CR, 60.5% with a PR, 22.7% with SD and 4.9% with progressive disease. Treatment was well tolerated, with two-thirds of patients (67%) reporting no grade 3 acute or delayed toxicity. The most common grade 3 side effect was fatigue in 6.7% of patients.

Overall, these results compare favourably with other loco-regional therapies such as transcatheter arterial chemoembolisation (TACE), or systemic chemotherapy and radionuclide therapy.[24,29] The same group have also reported on the safety of re-treatment with SIR-Spheres in selected mNET cases, noting acceptable acute and late toxicities without any grade 4 events or radiation-induced liver disease.[27]

Metastatic Breast Cancer

Over recent years, there have been significant gains in the management of patients with advanced breast cancer. The introduction of taxanes and trastuzumab has offered new hope for patients with metastatic breast cancer.[30–32] However, despite these valuable treatment gains, metastatic breast cancer is nearly always fatal, with up to 60% of patients dying of the local effects of hepatic tumours. Treatment is made more difficult because many patients with metastatic disease present with multiple disseminated hepatic lesions.[33]

The experience with SIR-Spheres in unresectable hepatic metastases from breast cancer was recently reported from two studies in patients who had failed chemotherapy (see *Table 3*).[34,35] In the first, retrospective cohort, 44 patients with symptomatic bilateral lesions (including left quadrant pain, hepatomegaly, lethargy and mass effect from the enlarged liver) were included.[34] The majority also had bone (61.5%) or nodal (52.3%) metastases. Nearly three-quarters of patients (72.7%) had failed three lines of chemotherapy, while the remaining quarter (27.2%) had progressive liver metastases following first- or second-line chemotherapy.

Following treatment with SIR-Spheres, 95% of patients demonstrated a response by PET and 94% by CT (47% PR, 47% SD). Treatment was associated with palliation of liver-related symptoms among responders. Median survival had not been reached at a median follow-up of 14 months post-treatment, with 86% of patients alive, including 92% of the treatment-hiatus cohort and 84% of the chemo-refractory group. Deaths were due to

Table 4: Clinical Study Results with SIR-Spheres for Treatment of Non-resectable Chemorefractory Liver Metastases[17,38–49]

Reference	n	Overall Survival (Months)	Imaging Response *				Grade 3/4 Adverse Events
			CR	PR	SD	PD	
Szyszko et al., 2007[17]	14 PET 15 CT	Not reported		12 PET 2 CT	 9 CT	 4 CT	None
Gulec et al., 2007[38]	40	Not reported		27 CT		13 CT	None reported
Gulec et al., 2007[39]	56	Not reported		42 PET		14 PET	None reported
Jakobs et al., 2007[40]	36	10**		31 CT		5 CT	None reported
Yu et al., 2006[41]	49	10 mean		39 PET 14 CT		10 PET 35 CT	None reported
Cianni et al., 2006[42]	29	Not reported		29 PET			None reported
Murthy et al., 2008[43]	6***	2.7 (range: 1–26 months)		1 CT 1 CT mixed	1 CT	3 CT	None reported
Poepperl et al., 2005[44]	13	Not reported	3 PET	7 PET	2 PET	1 PET	None reported
Wong et al., 2005[45]	19	Not reported		15 PET		4 PET	3 hyper-bilirubinemia; 2 post-embolisation syndrome
Lim et al., 2005[46]	43	Not reported		12 CT	12 CT	19 CT	4 GI ulcers; 1 bleeding oesophageal varices; 1 radiation hepatitis
Bailey et al., 2003[47]	27	Not reported	1 CT	7 CT	5 CT	14 CT	1 unspecified
Stuart et al., 2008[48]	30	21.0 (overall) 21.0 (non-mCRC/ non-mBC)		7CT	7CT	16CT	1 GI ulcer
Kennedy, 2009[49]	11	80% at 1 year	1 CT 1 PET	6 CT 6 PET	1 CT 2 PET	1 CT 0 PET	1 GI ulcer

*CR = complete response; PR = partial response; SD = stable disease PD = progressive disease. *Based on imaging by positron emission tomography (PET) or computed tomography (CT) scans; **In non-colorectal cancer (CRC), non-metastatic breast cancer (MBC) and non-hepatocellular carcinoma (HCC) patients; ***Evaluation of liver dominant disease from lung cancer.*

brain metastases (three patients), recurrent hepatic disease (one patient) or both (two patients). All patients reported mild to moderate post-embolisation syndrome, which was treated symptomatically. Grade 3 gastrointestinal toxicity was reported in seven patients with symptoms of nausea or vomiting. No occurrences of veno-occlusive disease or occlusion of the portal vein were reported in this cohort.

In the second, prospective study of 30 chemotherapy-refractory patients reported by Jakobs and colleagues, CT/MR imaging revealed a response rate of 61% in evaluable patients, SD or minor response in 35% and progressive disease in 4%.[35] The median overall survival was 11.5 months, with a significant difference between responders (PR) and non-responders (23.6 versus 5.7 months; p=0.005). There were no life-threatening morbidities or treatment-related deaths within 30 days of treatment. The study found that radioembolisation with SIR-Spheres was an effective treatment option with an acceptable toxicity profile. Three of the patients with breast cancer liver metastases were sufficiently down-sized to enable RFA to be used with curative intent and these remain alive without recurrence in the liver at 12–24 months post-radioembolisation.[36]

Overall, this initial experience with SIR-Spheres among patients with a poor prognosis is encouraging and compares favourably with the largest analyses in breast cancer patients with liver metastases. In an analysis of 500 patients with breast cancer liver metastases receiving first-line chemotherapy by Pentheroudakis and colleagues, median survival was 16.3 months following diagnosis, with a predicted five-year survival of 8.5%.[37] However, notably Eichbaum and colleagues observed that median survival could be significantly improved in patients who received regional therapy to lower the burden of hepatic metastases compared with those who received systemic chemotherapy only (30 versus 11 months; p<0.001),[33] and this was reflected in the reported experience with SIR-Spheres.

Investigations into Other Metastases

A number of investigators have reported on efficacy and safety of SIR-Spheres in the treatment of variety of liver metastases (see *Tables 4* and *5*).[17,38–49] The results suggest that there is significant reduction of hepatic metastatic load as evaluated objectively by PET after 90Y radioembolisation for the treatment of unresectable metastatic disease to the liver.

In their analysis of patients with treatment-refractory liver tumours, Jakobs and colleagues noted that radioembolisation was safe and produced response rates by imaging and tumour markers that were sufficiently high to support more widespread use of the modality in various tumour types.[40] In a similar population, Wong and co-workers reported a significant reduction in hepatic metastatic load as evaluated objectively by PET, with 79% of patients responding to radioembolisation.[45] Comparable findings have been reported by many other groups, including my own institution, using radioembolisation to treat a range of liver metastases from different tumour types.[17,38,39,41,42,46,49] At the Hammersmith Hospital, we found that in our first cohort of patients, all of whom had chemorefractory disease, it was notable that half were still alive 18–24 months after receiving radioembolisation.[16,17]

Discussion

Overall, the results so far using radioembolisation with SIR-Spheres are encouraging, showing that treatment can arrest the progression of metastatic cancer in the liver. Whether these objective responses result in favourable long-term clinical outcomes is currently unknown and further clinical trials are warranted. However, a number of studies

Table 5: Liver Tumours from Primary Cell Types Reported To Have Been Treated with Radioembolisation Using SIR-Spheres[5,7–14,16,17,23–28,34,35,37–50]

Breast	Malignant melanoma
Cancer of unknown primary	Mouth
Cervical	Neuroendocrine tumour
Cholangiocarcinoma	Ocular melanoma (choroidal; uveal)
Colorectal	Oesophagus
Endometrial	Ovarian
Gastric	Pancreatic
Gall bladder	Prostate
GI sarcoma	Renal
GIST	Sarcoma
Hepatocellular carcinoma	Squamous cell
Hepatic angiosarcoma	Thymus
Lung	Thyroid

GI = gastrointestinal; GIST = gastrointestinal stromal tumour

suggest that SIRT alone or in combination with chemotherapy is effective in slowing disease progression and improving survival. The published clinical experience across many treatment centres also shows that the therapeutic ratio with SIRT compared with EBRT is significantly superior, and tumoricidal doses can be delivered with a relatively high safety margin. Therapeutic efficacy can further be improved by utilisation of dosimetric techniques and careful treatment planning in order to mitigate serious complications.[50,51]

Correlation between increased response rates and ability to surgically resect liver metastases has recently been demonstrated following adjuvant chemotherapy in patients with mCRC liver metastases.[52] Even in chemo-refractory patients, radioembolisation using SIR-Spheres has recently been shown to downstage tumours for potentially curative ablation in patients with breast, pancreatic and colorectal cancer.[36]

The Future

Current clinical experience shows that radioembolisation using SIR-Spheres has the potential to provide significant clinical benefits for patients with liver metastases at various points in the treatment paradigm, from first-line setting through to salvage therapy. However, the experience in mCRC suggests that these benefits (in terms of reducing tumour burden) are greatest early in the disease process when the liver vasculature is also less compromised. Earlier referral of patients with unresectable liver-only or liver-predominant tumours, a life expectancy >12 weeks and a good performance status (ECOG performance score of 0–2 [PS 0-2] is likely to yield further improvement in treatment outcome, particularly when combined with an appropriate systemic chemotherapy regimen in some tumour types.

Large phase II/III international studies are now ongoing to investigate the efficacy and safety of combining SIR-Spheres with FOLFOX (i.e. the SIRFLOX and FOXFIRE studies) as a first-line treatment for mCRC.[53] Other studies are examining the role of combining radioembolisation with chemotherapy and biologicals in mCRC (SIR-Spheres plus FOLFOX plus bevacizumab, and SIR-Spheres plus irinotecan plus cetuximab).

Two phase II studies evaluating SIR-Spheres combined with chemotherapy in pancreatic cancer are ongoing, as is a phase II study of SIR-Spheres alone in chemotherapy-refractory breast cancer. Further prospective studies are planned in neuroendocrine tumours. ■

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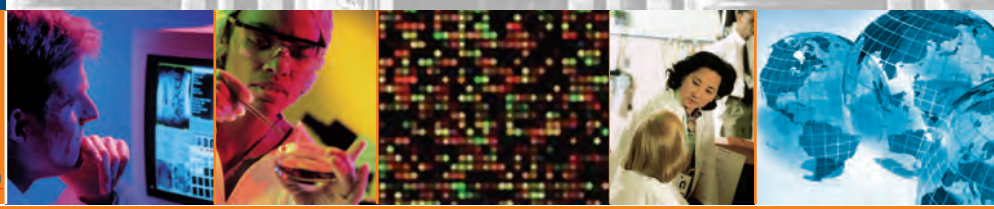

Priming Knowledge in Liver Cancer across Disciplines

- *State-of-the-art lectures*
- *Cutting edge symposia*
- *Special lectures*
- *Interactive workshops*

www.ilca2009.org