



## **REDUCTIONS IN PRESCRIBED ACTIVITY OF SIR-SPHERES® MICROSPHERES**

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The “**SIR-Spheres Microspheres Prescribed Activity Calculator**” employs the body surface area (BSA) method for the calculation of the prescribed activity of SIR-Spheres microspheres to implant into an individual patient.

Sirtex recommends the use of the body surface area (BSA) method on the basis of its more favorable safety and toxicity profile, based on its extensive use both within formal clinical trials and in the non-trial setting of routine clinical practice.

This recommendation is also supported by the Radioembolization Brachytherapy Oncology Consortium (REBOC) consensus panel of experts which reported its recommendations for the radioembolization of hepatic malignancies using <sup>90</sup>Y-microspheres in 2007 (Kennedy 2007). The panel, comprising experts in the field of selective internal radiation therapy (radioembolization) from the specialties of Radiation Oncology, Nuclear Medicine, Interventional Radiology, Medical Oncology and Surgical Oncology, published 14 recommendations that were made with category 2A consensus. Recommendation 10 of 14 was that:

- “The prescribed activity estimated by the body surface area method for SIR-Spheres microspheres is more consistent with the delivered dose in clinical practice and therefore should be the method of choice”.

Nevertheless, despite the favorable safety and efficacy profile conferred by the use of the BSA method, the clinical circumstances of patients being considered for treatment with SIR-Spheres microspheres may in some cases warrant a reduction in the prescribed activity as calculated from the BSA method.

### **Reduction in Prescribed Activity of SIR-Spheres Microspheres in Patients Heavily Pre-treated with Systemic Chemotherapy and/or Biologic Therapies**

Since SIR-Spheres microspheres were approved by the FDA in 2002 and a CE Mark granted in the same year, there have been significant advances in the chemotherapy options available for patients with metastatic colorectal cancer (mCRC), with the integration of irinotecan and

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oxaliplatin substantially improving disease control rates and survival duration. More recently, the biologic agents bevacizumab and cetuximab have resulted in further increases in survival as demonstrated in large randomized controlled trials.

It is as a result of this increased range of therapeutic options available to Medical Oncologists, that patients who undergo treatment with SIR-Spheres microspheres have often been heavily pre-treated with multiple regimens of these agents.

Recently, two multicenter prospective clinical trials have reported the safety and efficacy of the use of SIR-Spheres microspheres in mCRC patients heavily pre-treated with, and refractory to all standard chemotherapy and available biologic therapy options (Cosimelli 2009, Van den Eynde 2009). In both of these clinical trials, the BSA method was used to calculate the prescribed activity of SIR-Spheres microspheres, without a reduction in prescribed activity other than for lung shunting greater than 10%.

Despite these encouraging clinical data, in some patients who have been heavily pre-treated with systemic chemotherapies and/or biologic therapies, there may be clinical evidence of either compromised hepatic reserve and/or angiographic evidence of reduced hepatic vascular capacitance. In such circumstances, the implantation of the full prescribed activity of SIR-Spheres microspheres – as calculated by the BSA method – could lead to progressive hepatic decompensation and/or may not be able to be delivered due to angiographic stasis developing in the tumor feeding vasculature.

There are not currently accepted guidelines as to how much to reduce the prescribed activity if a patient's liver function or estimated reserve is only just good enough to be a candidate for SIRT. Generally, it is recommended that the prescribed activity of SIR-Spheres microspheres be reduced by 25% (i.e. prescribed activity calculated by the BSA method minus 25%) for patients with poorer liver function but who are still candidates for SIRT according to the established criteria.

### **Reduction in Prescribed Activity of SIR-Spheres Microspheres in Patients with HCC**

Primary hepatocellular carcinoma (HCC) commonly develops in patients who have pre-existing chronic liver disease and cirrhosis. This is related to the etiology of these conditions. Chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), or chronic alcohol abuse are the most common causes of chronic liver disease. In each case, chronic exposure to the underlying etiologic agent leads to repeated hepatocyte damage and then regeneration, ultimately leading to permanent loss of structure and function within hepatic lobules, the basic functional unit of the liver. Cirrhosis represents the end state of liver damage and is commonly further complicated by two processes: 1) liver failure, i.e. inadequate synthetic and excretory function within sufficient liver lobules to be compatible with life; and 2) malignant transformation of a cirrhotic nodule and the development of primary hepatocellular carcinoma.

Treatment of inoperable HCC with SIR-Spheres microspheres has been shown to be a safe and effective treatment (Sangro 2006; Lau 1998). However, patients with pre-existing liver damage, as in chronic liver disease and cirrhosis may have an impaired ability to tolerate any further

insult to the non-tumorous liver parenchyma. It is for this reason, that patients with HCC commonly cannot have their tumor removed surgically, as removal of only a small portion of the remaining non-tumorous liver parenchyma will lead to progressive liver failure.

Patients with chronic liver disease and cirrhosis also have an impaired ability to tolerate SIR-Spheres microspheres. This is because the small radiation doses that are tolerated by healthy liver parenchyma may cause irreversible damage to chronically diseased or cirrhotic liver parenchyma. Therefore, the radiation dose delivered to the non-tumorous liver compartment must be reduced in these patients.

There are two ways to reduce the chance of seriously damaging the non-tumorous liver parenchyma in patients with chronic liver disease and cirrhosis, viz; selectively targeted delivery of SIR-Spheres microspheres or reduction of prescribed activity.

### **1. Selectively targeted delivery of SIR-Spheres microspheres in patients with HCC**

When HCC develops as a single or small number of tumor masses, it is frequently possible to selectively catheterize the arteries supplying only the tumor and deliver SIRT directly to the tumor, with preservation of the remaining non-tumorous liver parenchyma. This method of delivering SIR-Spheres microspheres has two advantages. Firstly, the radiation dose received by the tumor is far greater than when the SIR-Spheres microspheres are delivered into the general hepatic circulation at the level of the proper hepatic artery; secondly, as the non-tumorous liver parenchyma is not being irradiated, it provides a greater margin of safety. This method of delivering SIRT is the preferred method of treating these patients, and is referred to as “radio-ablation”, “radiation segmentectomy”, or “radiation lobectomy”.

### **2. Activity reduction in patients with HCC**

If the HCC tumor masses are numerous and it is consequently not possible to selectively target only the tumor via selective catheterization and delivery of SIR-Spheres microspheres, then the prescribed activity of SIR-Spheres microspheres should be reduced by 25% (i.e. prescribed activity of SIR-Spheres calculated by the BSA method minus 25%).

In patients with severely impaired liver function, when the serum bilirubin is  $\geq 2.0\text{mg/dL}$  or when serum albumin is  $< 3.0\text{g/dL}$ , then SIRT treatment is absolutely contra-indicated.

## References

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3. Lau W, Ho S, Leung T *et al.* Selective internal radiation therapy for non-resectable hepatocellular carcinoma with intraarterial infusion of <sup>90</sup>-yttrium microspheres. *Int J Radiation Oncology Biol Phys.* 1998; 40:583-592.
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5. Van den Eynde M, Hendlisz A, Peeters M *et al.* Prospective randomized study comparing intraarterial injection of yttrium-90 resin microspheres with protracted IV 5FU continuous infusion versus IV 5FU continuous infusion alone for patients with liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *ASCO Annual Meeting Proceedings Journal of Clinical Oncology* 2009; 27 (Suppl 7s): Abs 4096.