METASTATIC COLORECTAL CANCER (mCRC) IN THE LIVER: BACKGROUND AND RATIONALE FOR THE SIRFLOX STUDY

Overview

When primary colorectal cancer metastasises, it spreads primarily to the patient’s liver. As a result, mCRC in the liver is the most frequent cause of death. Until the present century, the prognosis for patients with metastatic colorectal cancer was grim, particularly so if the patient’s liver metastases could not be surgically resected. Since 2002, great strides have been made in respect to chemotherapy and biological treatment for mCRC, but these advances have slowed.

Radiation therapy, the traditional “third leg” of all cancer treatment, has not until now played a significant role in the treatment of liver metastases. There is no question that radiation can kill tumours in the liver, but the problem has been the sensitivity of healthy liver tissue to radiation, which greatly limits the size of the radiation dose that can be administered.

Beginning in the 1990s, an innovative interventional technology called SIR-Spheres® Y-90 resin microspheres has sought to circumvent this problem, by delivering powerful doses of radiation carried by microscopic-sized particles through the liver’s arterial blood supply, directly to the liver tumour beds. Approved as a medical device by regulatory authorities and commercially available since 2002 in the US and Europe, as well as many other countries, this technology has already found a place in the treatment of mCRC that is unresectable and refractory to chemotherapy and biologics. Beginning in 2006, the developers of SIR-Spheres Y-90 resin microspheres have conducted a randomised controlled study called SIRFLOX. This study is designed to test whether the addition of Y-90 resin microspheres to standard first-line mFOLFOX6 chemotherapy (with or without bevacizumab) can further delay disease progression in unresectable mCRC liver tumours.

Colorectal cancer is the fourth biggest cancer-related cause of death

According to the World Health Organization, colorectal cancer (CRC) is the third most common cancer (after lung and breast cancer) and the fourth leading cause of cancer-related mortality worldwide, following lung, liver, and stomach cancers respectively. It is reported to kill 693,933 people globally a year, with this figure expected to increase by 85% over the next two decades.

Colorectal cancer most commonly metastasises to the liver

The liver is the most common site for the metastasis of colorectal cancer; over 70% of mCRC cases involve the liver, either alone or with other organs. This is due to the direct vascular connection between the bowel and liver. The lungs are the second most common site of metastasis, accounting for 20–30% of secondary colorectal tumours. Other organs, such as the central nervous system, adrenal glands, spleen, skeleton, or skin together account for less than 10% of all colorectal metastases.

The prognosis for patients with colorectal liver metastases is very poor

![Colorectal Cancer and Liver Metastases Diagram](https://example.com/diagram.png)
• About half of CRC patients will eventually develop liver metastases;\textsuperscript{4,5}
• It is estimated that around 15–25\% of CRC patients will present with liver metastases at diagnosis, with a further 25–35\% developing liver metastases over the course of their disease;\textsuperscript{6,7}
• It is estimated that the majority of patients (66–99\%) with liver metastases from CRC will die from hepatic failure caused by liver tumours;\textsuperscript{5,8–11}
• Surgical resection of the liver tumours is currently the only potentially curative intervention for patients with liver metastases from mCRC. However, only around 10–20\% of patients will be eligible for surgical resection;\textsuperscript{5,12}
• Among patients undergoing resection for liver metastases, 5-year survival has been reported as a median of 30\% (range 14–58\%), compared with 0–6\% for patients who do not undergo surgery;\textsuperscript{13}
• In some cases, the use of chemotherapy, biological drugs and/or Selective Internal Radiation Therapy (SIRT), can reduce initially unresectable liver tumours sufficiently to allow surgical intervention.

**Available mCRC Treatments**

Wherever possible, the standard of care for liver metastases from CRC is surgical resection. Although a recurrence of disease in the liver occurs in around one third of patients, repeat resection may be possible given the liver’s regenerative properties.\textsuperscript{13} Chemotherapy alone is a palliative treatment, but may prolong the lives of patients with unresectable liver metastases. However, it can also reduce the size of liver tumours sufficiently to allow resection.

1. **Surgical techniques**

Surgical resection to remove the cancer provides the only realistic possibility of providing a cure for liver metastases from CRC. Advances in surgery and chemotherapy over the last few years have increased the number of liver tumours considered resectable.\textsuperscript{5}

Other surgical techniques are based on the ablation of tumours. Either cold (cryoablation) or heat (through an electric current or laser) can be applied directly to the liver tumours in this way. However, these methods are generally used alongside conventional surgery for small, poorly located lesions, and are not considered equivalent to conventional surgical resection.\textsuperscript{10}

2. **Chemotherapy**

Chemotherapy for mCRC has three main aims:\textsuperscript{5}

- to reduce the size of unresectable metastases enough to allow resection;
- to reduce the risk of recurrence through treatment of unseen micro-metastases;
- to provide potential post-operative (adjuvant) benefits.

3. **Biological therapy**

Biological therapies available for mCRC include cetuximab and bevacizumab, which are monoclonal antibodies to epidermal growth factor receptor (EGFR) and vascular endothelial growth factor-A (VEGF-A) respectively. They are generally used as an add-on to 5-FU-containing chemotherapy rather than as an alternative treatment. Used in this way, they are associated with longer overall and progression-free survival but also with increased toxicity.\textsuperscript{16} They have also been shown to improve resection rates.\textsuperscript{5,17,18}

4. **Selective Internal Radiation Therapy (SIRT)**

SIRT (also known as radioembolisation) is an innovative type of radiation therapy that targets high doses of radiation directly to liver tumours. The therapeutic agent consists of microscopic resin beads (microspheres) carrying the radioactive element Yttrium-90 (Y-90). These are injected directly into the hepatic artery, via a catheter inserted through an incision in the femoral artery near the groin. The microspheres become lodged in the capillaries in and around the liver tumours. The short-range radiation – which on average penetrates 2.4 mm in tissue – is delivered in high doses to the immediate location of the tumour, while having little effect on surrounding healthy tissue.

**Developing the case for SIRT with SIR-Spheres® Y-90 resin microspheres**

Studies have shown that the addition of a single dose of SIR-Spheres to chemotherapy increased response rate in the liver from 17.6\% to 44\% and time to disease progression in the liver from 9.7 to 15.9 months.\textsuperscript{19}
The rationale for combining SIRT with traditional chemotherapy is that although SIRT is effective in controlling the liver disease, it has no effect on extra-hepatic disease. Therefore, the addition of systemic chemotherapy is necessary for treating extra-hepatic disease.20

As a result of these positive outcomes, a number of subsequent trials have been, and are being, undertaken to test the combination of SIRT with systemic chemotherapy, including the SIRFLOX study.

The SIRFLOX study

Based on the earlier, smaller studies just described, SIRFLOX was launched in 2006 as an international research study (70 centres in Australia, Asia-Pacific, Europe, Israel and the United States) to evaluate whether mFOLFOX6 chemotherapy (+ bevacizumab) in combination with SIRT, in the form of SIR-Spheres Y-90 resin microspheres, is more effective than chemotherapy alone in the first-line management of unresectable mCRC. The study is the first time that these treatments have been assessed together as part of a large randomised controlled study of first-line therapy (i.e. in patients who have not previously received chemotherapy for their liver metastases). With 530 patients, it is also the largest study ever to investigate the combination of chemotherapy and interventional radiology in oncology.1

SIRFLOX completed patient enrolment in April 2013. The results were reported at the May 2015 Annual Meeting of the American Society of Clinical Oncology (ASCO) and published on-line as a Rapid Communication in the *Journal of Clinical Oncology* in February 2016.1 The editors stated that this “paper is required reading and is considered practice-changing”, which suggests that the SIRFLOX regimen could potentially change the treatment journey for patients with mCRC.

The SIRFLOX study results show a modest and not statistically significant trend in progression-free survival (PFS) at any site in the patients who received chemo-radiotherapy. This was not surprising as SIR-Spheres Y-90 resin microspheres are a liver-directed therapy and do not have an effect on metastases outside the liver. However, the investigators reported a significantly prolonged PFS in the liver – from a median of 12.6 months for control patients to 20.5 months for patients receiving SIR-Spheres Y-90 resin microspheres – resulting in a 31% reduction in the risk of progression in the liver, which is the organ in which the radiotherapy targets tumours.

Two similar studies, ‘FOXFIRE’ and ‘FOXFIRE Global’ have been designed to be combined with the SIRFLOX study, allowing for the pooling of data on safety and efficacy outcomes, with the combined studies powered to demonstrate potential benefit in overall survival. Both studies completed recruitment at the end of 2014, and results of the combined overall survival analysis are expected in 2017.

The primary objective of the FOXFIRE and FOXFIRE Global studies is to determine if there is an Overall Survival (OS) benefit of adding targeted radiation (in the form of SIR-Spheres Y-90 resin microspheres) to a current systemic chemotherapy regimen, compared to chemotherapy alone, in patients with non-resectable liver metastases from primary colorectal cancer, with or without evidence of metastases outside the liver.

In both studies, the chemotherapy regimen used is FOLFOX (oxaliplatin plus 5FU and leucovorin), with or without the biologic agents bevacizumab or cetuximab (prescribed at the investigators’ discretion).

The total sample size in the three studies combined is 1,103 patients, which is expected to provide adequate statistical power to detect a clinical significant difference in OS between the experimental and control arms.

Results from SIRFLOX, FOXFIRE and FOXFIRE Global have the potential to transform first-line treatment options for liver metastases from colorectal cancer and lead to better patient outcomes.

*For more information please visit: www.sirtex.com*