METASTATIC COLORECTAL CANCER (mCRC) IN THE LIVER: BACKGROUND AND RATIONALE FOR THE FOXFIRE COMBINED ANALYSIS

Overview

When primary colorectal cancer metastasizes, 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. Metastatic Colorectal Cancer (mCRC) is now understood to be a heterogeneous disease with differing histological features, outcomes and clinical responses. Over the past decade, researchers have also found increasing evidence that primary tumor location within the colon is an important prognostic factor for both early and advanced colorectal cancer.[1]

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 tumors 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 tumor 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 conducted a randomized controlled study called SIRFLOX. This study was designed to test whether the addition of SIR-Spheres Y-90 resin microspheres to standard first-line mFOLFOX6 chemotherapy (with or without bevacizumab) could further delay disease progression in unresectable mCRC liver tumors.[2]

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.[3]

For mCRC patients, the prognosis worsens for patients whose primary tumor was right-sided. The risk of death in those patients with left-sided primary tumors is 27% lower; mCRC patients who present with a right-sided primary tumor are also clinically more difficult to treat, because these are less responsive to standard of care chemotherapies and do not respond to some biologic agents such as EGFR inhibitors (cetuximab and panitumumab).[4]

Colorectal cancer most commonly metastasizes 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 tumors. Other organs, such as the central nervous system, adrenal glands, spleen, skeleton, or skin together account for less than 10% of all colorectal metastases.[5]

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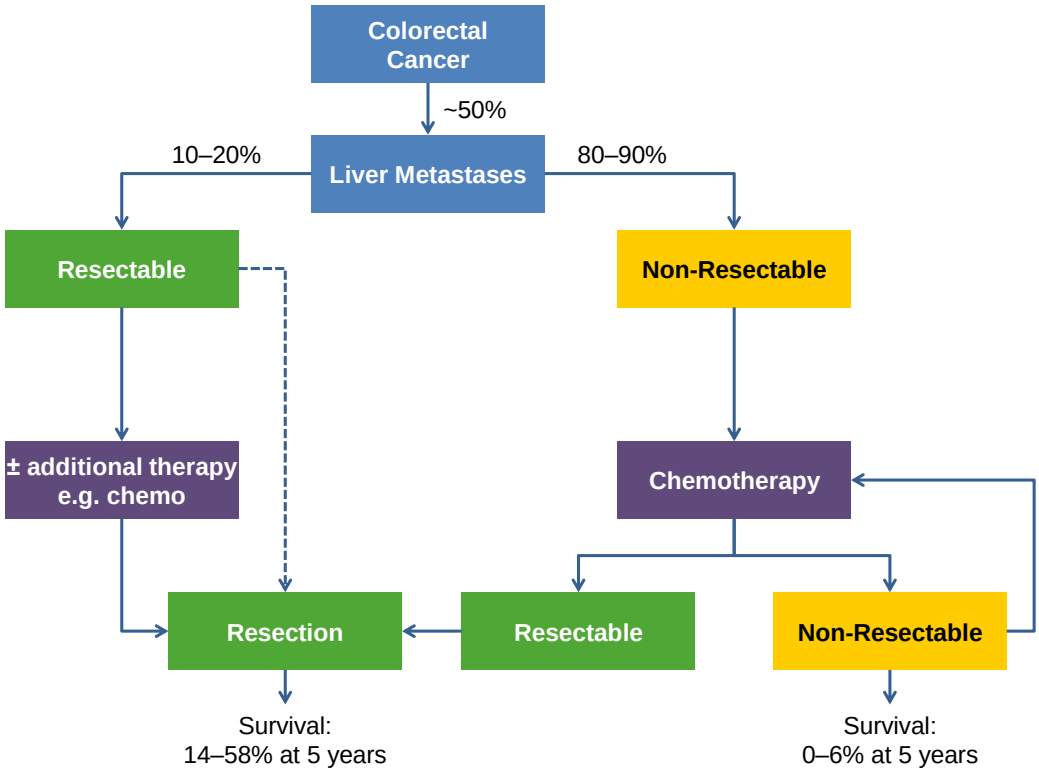
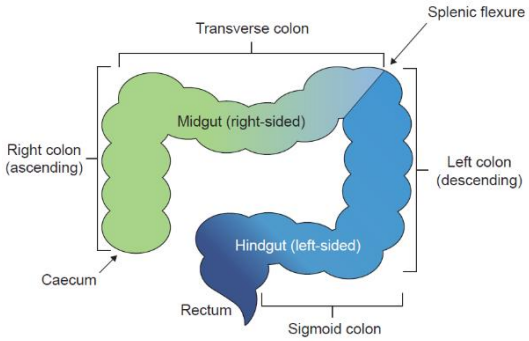
The prognosis for patients with colorectal liver metastases is very poor



- About half of CRC patients will eventually develop liver metastases;[6,7]
- 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;[8,9]
- It is estimated that the majority of patients (66–90%) with liver metastases from CRC will die from hepatic failure caused by liver tumors;[7,10-13]
- Around 35-38% of mCRC patients have metastases arising from right-sided primary colon cancers, based on clinical studies and population-based analysis.[1,14]
- Surgical resection of the liver tumors 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;[7,15]
- 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;[16]
- In some cases, the use of chemotherapy, biological drugs and/or Selective Internal Radiation Therapy (SIRT), can reduce initially unresectable liver tumors sufficiently to allow surgical intervention.

Primary tumor location as a prognostic factor in mCRC

Metastatic Colorectal Cancer (mCRC) is not a homogeneous disease. Tumors that arise in the right side of the colon (located up to the proximal two-thirds of the transverse colon) are now known to be clinically and biologically distinct from tumors on the left side of the colon (located within the distal third of the transverse colon or beyond).[4] The current National Comprehensive Cancer Network (NCCN) guidelines for first-line treatment of mCRC, recently modified its treatment recommendations based on the location of the primary tumor.[17]



A meta-analysis of 66 studies representing 1.4 million CRC patients showed an 18% reduced risk of death from a left-side primary tumor versus a right-side primary tumor regardless of the patient's disease stage for all CRC stages.[4]

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.[16] 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 tumors 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 tumors considered resectable.[7]

Other surgical techniques are based on the ablation of tumors. Either cold (cryoablation) or heat (through an electric current or laser) can be applied directly to the liver tumors 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.[12]

2. Chemotherapy

Preoperative chemotherapy for liver-only mCRC has three main aims [7]

- 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.

Standard chemotherapy regimens for mCRC include combinations of 5-fluorouracil/ folinic acid (5-FU/FA) with irinotecan, oxaliplatin or both. While chemotherapy is usually administered by intravenous (IV) infusion, it can also be delivered directly to tumor sites through hepatic artery infusion (HAI). However, the benefits of HAI over the latest systemic chemotherapy regimens are not conclusive, and the two delivery methods are more often used in combination.[8]

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.[18] They have also been shown to improve resection rates.[7, 19, 20]

However, it has been shown that patients who present with a right-sided primary tumor do not respond to some biologic agents such as EGFR inhibitors (cetuximab and panitumumab).[4, 21, 22] Therefore, the NCCN guidelines no longer recommend EGFR inhibitors for this patient population.

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 tumors. The therapeutic agent, SIR-Spheres Y90 resin microspheres, 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 tumors. The short-range radiation – which on average penetrates 2.4 mm in tissue – is delivered in high doses to the immediate location of the tumor, 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 Y-90 resin microspheres 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.[23]

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.[24]

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 and the combined SIRFLOX FOXFIRE, FOXFIRE Global analysis

Based on the earlier, smaller studies just described, SIRFLOX was launched in 2006 as an international research study (70 centers 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, was more effective than chemotherapy alone in the first-line management of unresectable mCRC. Results of the 530 patient SIRFLOX study 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.[2]

Two similar studies, 'FOXFIRE' and 'FOXFIRE Global' were designed to be combined with the SIRFLOX study, with more than 1,100 patients, allowing for a pooling of data on safety and efficacy outcomes, with sufficient statistical power to demonstrate a potential overall survival benefit. Both studies completed recruitment at the end of 2014, and results of the combined overall survival analysis were presented at ASCO 2017.

Although the combined analysis showed no difference in overall survival between patients treated with SIR-Spheres Y-90 resin microspheres plus first-line treatment *vs* treatment alone, there were clinical benefits shown by the study.[25] A post-hoc analysis of data from the 739-patient SIRFLOX and FOXFIRE Global was presented at the World Congress of GI Cancers in Barcelona, 28 June - 1 July 2017.[26] The results indicated that adding SIR-Spheres Y-90 resin microspheres to standard first-line mFOLFOX6 chemotherapy for liver-only or liver-dominant mCRC in patients with right-sided primary (RSP) tumors led to a statistically significant and clinically meaningful 4.9-month median overall survival benefit (HR: 0.64 [95% CI: 0.46–0.89]; p=0.007). This translates into a 36% reduction in the risk of death at any given time compared to patients who received chemotherapy alone.

For more information please visit:
www.sirtex.com

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