



# Liver-Directed Therapy for Metastatic Colon Cancer: Update

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## Abstract

**Purpose of Review** To discuss the emerging technologies in the field of Interventional radiology (IR) for the management of metastatic colorectal cancer (mCRC). We review the field of selective internal radiation therapy (SIRT), and well-known IR treatments, with a more focused investigation of radioembolization with Yttrium-90 (Y-90).

**Recent Findings** State-of-the-art treatment modalities for unresectable hepatic malignancies are crucial to increased patient survival. There are many options for the treating physician to manage and potentially cure patient's disease, with Y-90 as the cornerstone of liver neoplasm treatment. Additionally, current research in the fields of dosimetry and radiomics may allow for more optimized patient specific radiation doses.

**Summary** Continued advancements in colorectal surgery and interventional radiology have improved survival outcomes for patients with mCRC. Current treatment options are numerous and often include partial hepatectomy and SIRT. We review current literature and discuss our experiences in treating patients with advanced liver malignancies.

**Keywords** Metastatic colorectal carcinoma (CRC) · Hepatocellular carcinoma (HCC) · Radioembolization · Yttrium 90 (Y90) · Microspheres · Interventional radiology (IR)

## Introduction

Colorectal cancer (CRC) is one of the most common types of cancer, accounting for 850,000 world-wide deaths per year worldwide, while being the 3rd leading cause of cancer death in the USA [1]. Twenty percent of patients diagnosed with colorectal cancer present with synchronous metastases, and 50% develop metastatic disease at some point [2]. The NCI estimates the 5-year survival rate of stage IV mCRC is 14% [1]. Liver metastases are the most common metastatic site, with pulmonary metastases coming in second, and peritoneal surface third [3, 4]. Multiple treatment options, including chemotherapeutic agents, minimally invasive treatments, and surgery, are available for metastatic disease; however, surgical resection remains the only curative treatment option [5, 6]. Many minimally

invasive treatments performed by interventional radiologists prolong life and can even be a bridge to surgical resection in a select patient population, making these treatments of utmost importance. Other important factors influencing time to surgical resection include improvement in detection of CRC and mCRC and immunotherapies for disease control and/or treatment. Current research in the interventional radiology (IR) field includes Y90 voxel-based dosimetry and radiomics and recent FDA approval for Theraspheres continues to expand treatment options for patients with mCRC. This review will focus on current research in the field of IR-driven locoregional therapies and their enhancements in the treatment and survival of mCRC. Protocols regarding diagnosis and treatment of mCRC are beyond the scope of the present review, and will not be discussed.

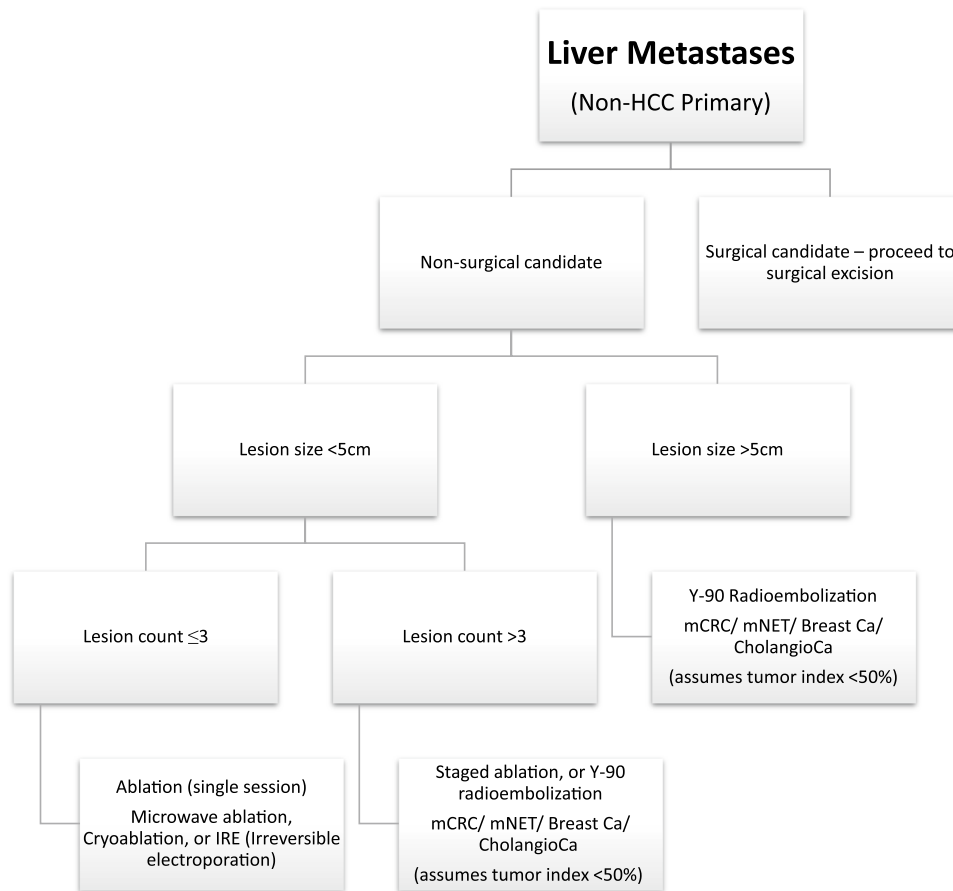
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### Detection and Systemic Treatment

No significant strides have been made in the field of earlier detection of CRC. Colonoscopy, biopsy, and imaging remain the cornerstone for diagnosis and staging of mCRC. Tumor markers such as CEA have been well known in the literature and in clinical practice to be useful for detecting recurrence of mCRC, but not in the initial detection.

In recent years, microRNA as a predictive marker has been researched [7]. MicroRNA is a non-coding RNA that functions in the regulation of gene expression by regulating messenger RNA (mRNA). mRNA is responsible for repressing or translating proteins, thus making miRNA pivotal in carcinogenesis. Elevated expression levels of miRNA have been hypothesized to be a predictive and diagnostic factor in certain cancers, such as colorectal cancer, specifically miR-410 (a subtype of microRNA found to be increased with mCRC). A study performed demonstrated increased expression of miR-410 in malignant tissue and was correlated with worse overall clinical features and survival outcomes [7].

An additional innovative and evolving method in assessing for CRC is measuring the circulating tumor

derived cell-free DNA (ctDNA). This is defined as DNA that is found in the non-cellular blood components, 150–200 base pair fragments long, and released by circulating, active, and/or necrotic tumors cells (8). Current tumors markers (CEA and CA 19–9) lack high sensitivity and specificity, leading many oncologists and surgical oncologists to investigate the role of ctDNA in tumor detection, surveillance, and restaging [8, 9]. The impact on patient care of ctDNA is not yet known, though some studies suggest it has an increased sensitivity (89.7%) and specificity (86.8%) for detection of CRC [8, 10]. This will be crucial to monitor in the coming years as it could have an impact for our patients.

Target immunotherapy remains a cornerstone for mCRC treatment. Research in the microsatellite instability subtype of colorectal cancer continues, as this remains one of the most aggressive forms of mCRC. Specific immunotherapies targeting RNAs associated with increased metastases are evaluated, specifically long coding RNAs involved in metastases, tumorigenesis, and regulation [11].

Continued development of VEGF/VEGFR treatments, with new systemic agents, is coming on to the market. For example, in clinical trials, ramucirumab has

demonstrated usefulness in prolonging mCRC survival, specifically when the patient has diffuse liver metastases [12].

Avelumab is an immunotherapy agent targeting the anti-programmed cell death ligand (anti-PDL1). This drug is currently in phase III trials, and shows promise in patients with mCRC when first-line treatment fails, when compared to standard second line chemotherapy [13].

## IR Treatment Options

### Radiofrequency Ablation (RFA)

The technique of radiofrequency ablation (RFA) of liver lesions played a bigger role prior to the development of microwave ablation (MWA), transarterial chemoembolization (TACE), and Y90 [14•]. RFA uses electric current generated from external electrodes placed into the liver lesions under CT guidance by interventional radiologists. As electric current acts as a large heat sink within the liver tissue, there are many limitations to using RFA, including number, size, and location of the lesion [2]. Only smaller lesions can be ablated, and the lesion cannot be near a bile duct or large vessel (peripheral location only). Despite these limitations, however, there are many retrospective trials reporting comparable results of RFA to surgery in terms of life expectancy [15].

### Microwave Ablation (MWA)

MWA is used frequently in the treatment of mCRC [16]. MWA uses electromagnetic waves (EMW), allowing for a larger treatment area. EMW produce shorter wavelengths, allowing for a higher temperature to be reached in a shorter amount of time. This creates less of a heat sink within the liver tissue and thus poses less risk to surrounding liver tissue [2]. When comparing to hepatectomy, MWA is just as effective at disease-free survival, plus MWA demonstrates shorter hospital stays, lower healthcare costs, and lower complication rates [16].

### Transarterial Chemoembolization (TACE)

TACE uses the principle of differential blood supply to liver metastases vs normal liver tissue to embolize liver lesions while preserving normal liver. The current technique uses drug-eluting beads (DEB) containing a chemotherapeutic agent (such as doxorubicin) injected arterially to directly target the metastases [2]. TACE is indicated as an adjuvant treatment for mCRC, but is not currently recommended for primary treatment [2].

### Yttrium-90 (Y90)

The use of radiation therapy for primary liver carcinoma and liver metastases is the cornerstone of liver neoplasm treatment. The traditional radiation options for local control of liver disease include whole liver treatments with external beam radiation or targeted therapy with the radioactive isotope yttrium-90 (Y90) [17–21]. Selective internal radiation therapy (SIRT) uses resin or glass microspheres to carry the Y90 directly into the hepatic arterial system for treatment of liver metastases. The primary advantage of radioembolization with Y90, when compared to external beam radiation therapy, is the ability to deliver local tumoricidal effects while causing minimal effects to surrounding normal hepatic tissue [19, 22, 23]. Thus, SIRT has replaced external beam radiation by interventional radiologists for liver-directed therapy.

The use of Y90 was first noted in the 1960s, with case reports describing its use in treatment of hepatic malignancies. Results were limited but showed improvement in symptoms. A few landmark trials built on these findings and revolutionized Y90 treatment. In the 1970s, Grady et al. demonstrated efficacy of Y90 resin microspheres in five trial patients with metastatic colon cancer [24]. These patients had decreased tumor size after treatment. The development of glass and resin microspheres in the 1980s and the early 1990s ushered numerous phase I trials. This led to a humanitarian device exemption in 1999 by the FDA for the use of glass microspheres in patients with unresectable HCC. In 2004, Salem et al. demonstrated that Y90 glass microspheres are safe in unresectable HCC patients with portal vein thrombosis (PVT) [25•]. Since glass is minimally embolic, this trial opened doors for sequencing treatment.

Owing to Salem et al., sequencing trials involving Y90 began in the late 2000s. The PREMIERE trial demonstrated longer median time to progression for patients receiving Y90 compared to TACE, but no difference in survival outcomes [26]. It also was able to downstage patients, placing them higher on the transplant list. The SARAH trial evaluated Y90 vs sorafenib in patients with primary HCC, and results showed no difference in overall survival (OS), but objective response rate was higher in Y90, and had lower complication rates [27]. The SIRveNIB trial evaluated primary HCC and demonstrated similar results to SARAH trial [28]. The SORAMIC trial is a recent investigation whose primary results showed no change in OS between Y90 and sorafenib, but patients < 65 years old with non-alcoholic cirrhosis seemed to benefit from the addition of resin Y90 [29].

## Y90 Combination Therapy

In 2016, SIRFLOX was the first randomized control trial evaluating the efficacy of adding SIRT using Y90 to the standard FOLFOX based chemotherapy treatment in patients with chemo-naïve metastatic colorectal cancer. This was a landmark randomized clinical trial, demonstrating the efficacy of SIRT in combination with modified FOLFOX chemotherapy (plus/minus bevacizumab) vs chemotherapy alone [30]. Results showed no difference in progression-free survival (PFS), but SIRT did delay disease progression. Furthermore, the addition SIRT to modern chemotherapy improves the surgical resectability of liver metastases, 28.9% versus 38.1%,  $p < 0.01$  (\*\*).

Since the SIRFLOX trial, numerous parallel studies (FOXFIRE and FOXFIRE Global for primary HCC, FOLFOXIRI, FOLFIRI) have emerged studying different combinations of chemotherapy, SIRT, and the timing of each [31]. While trials are ongoing, results demonstrate importance of SIRT in treatment of liver metastases.

## New Frontiers in the Field of Y90

### Dosimetry

One of the new and upcoming developing landscapes in IR is the use of voxel-based dosimetry in Y90 treatment. A current large issue with Y90 is under-dosing patients with the radioactive substance for obvious fear of over-exposing normal lung (causing radiation pneumonitis) and liver tissue (causing hepatonecrosis) [32, 33].

To calculate the liver dose and prevent over-exposure of normal liver tissue, there are two widely used methods: the body-surface-area (BSA) and partition models. The BSA method is simplest and therefore most widely used. However, the BSA method has limitations utilizing only the patient's overall size, without factoring the actual size of the liver or the regions of tumor necrosis. The BSA model also assumes a homogeneous uptake of Y90 microspheres throughout the liver. The partition model is based on the pretreatment MAA scan, the patient's treatment goal (treatment vs palliative), and Child–Pugh status [34]. The tumor mass is estimated based on the estimated imaging volume and then multiplied by a fixed density value. Limitations of the partition model are similar to those of the BSA model; however, the partition model has been shown to correlate with treatment response and survival [35].

By using voxel-based dosimetry, a more accurate evaluation of tumor dose, absorption, and treatment outcome can be predicted [36, 37]. In a retrospective study conducted by the Montpellier University Hospital, 42 procedures were analyzed to evaluate the ability of BSA to predict

tumor-absorbed dose and treatment outcome through retrospective voxel-based dosimetry [38]. The average dose was 60 Gy, with only 6 patients (14%) receiving a radioactive dose greater than 120 Gy. Treatment outcomes demonstrated that if the dose was above 120 Gy, the patient had an objective response (OR) (disease had either complete or partial response to treatment). If the liver dose was less than 40 Gy, the patient had a non-response (NR), (disease was either stable or progressive at the 6-month mark). In 62% of treatments, 120 Gy could have been delivered to the tumor while maintaining appropriate liver and lung thresholds. Under the current systems in place, this would have been impossible due to the liver and lung radiation safety thresholds.

In this study, the majority of patients could have tolerated an increased dose of Y90. Using the voxel-based dosimetry model, higher doses of Yttrium can be delivered during each treatment, which correlated to an OR. This method takes into account tumor to normal liver ratio (T/N), liver volume, and dose distribution heterogeneity (tumor necrosis), whereas the current BSA model does not. Unfortunately, there are limited studies using the voxel-based dosimetry method to calculate Y90 dosing. Current research is promising, and further investigation is needed to validate the use of this model.

### Lung Shunt Fraction

The lung shunt fraction must be calculated for each patient to minimize the risk of radiation pneumonitis. To evaluate the lung shunt fraction (LSF), a test dose of technetium albumin aggregated (99mTc-MAA) is infused at the same hepatic arterial location as anticipated for subsequent Y90 treatment. The 99mTc-MAA is used as it has similar properties to Y90 microspheres. The LSF is then calculated with a single photon emission computed tomography (SPECT) gamma camera. Treatment is generally contraindicated in patients with an LSF higher than 20% or estimated lung exposure of more than 30 Gy [39]. Many factors influence LSF, for example, blood flow, treatment technique, dosage, and route of delivery. In one of our studies, patients treated with glass demonstrated a higher average lung shunt fraction compared to those treated with resin 7.9% vs 6.0%, respectively [17]. However, this may have been slightly confounded due to there being a larger group of HCC patients in the glass group. HCC is a more vascular tumor, resulting in more arteriovenous shunting, i.e., higher lung shunting.

### Glass vs Resin

Another consideration in Y90 treatment planning is the choice of radioactive bead to use. There are two Y90 treatment options available: resin (SIR-Spheres®, Sirtex Medical Inc., Woburn, MA, USA) and glass (TheraSphere®,

BTG Inc. West Conshohocken, PA, USA) microspheres. Nationally there has been much research into exploring the differences between glass and resin treatments. There is a difference in particle size between glass (20–30  $\mu\text{m}$ ) and resin beads (20–60  $\mu\text{m}$ ). The glass beads deliver a much larger activity per bead (2500 Bq vs 50 Bq, for resin) [26, 40–42]. Due to their larger size, resin beads tend to produce a greater degree of embolization (39). This provides insight into why patients treated with resin microspheres tend to have longer survival times than patients treated with glass. This “embolization” effect causes additional tumor ischemia on top of the radiation effect. This phenomenon is further compounded by the sheer number of microspheres needed to achieve treatment doses, due to the lower density of Y90 per sphere in the resin than glass [43]. Complete dose delivery for glass microspheres is accomplished without detectable angiographic evidence of embolization, whereas full delivery of resin microspheres is not always possible, as the target artery can develop stasis prior to completion of infusion [39]. Ultimately, these differences may result in increased tumor ischemia by resin microspheres rather than increased radiation dose (although this has not been formally studied).

At our institution, glass microspheres were utilized as the primary form of Y90 treatment from 2008 to 2012. In 2012, our institutional Y90 use gradually shifted to incorporate resin microspheres at the discretion of the treating interventional radiologist, allowing us to have a substantial internal database of both treatment modalities. Studies comparing glass and resin show that glass has double the prescribed dose due to intrinsic properties of the beads [44]. For example, one of our studies found that the average glass dosage was 2.66 giga-becquerel (GBq) and 1.06 GBq for resin across all cancer types [17]. In a subset of colorectal cancer patients ( $n=46$  people, 80 treatments), significantly lower actual and projected resin activities were documented when compared to glass treatments.

To date, there is no clear survival benefit using glass vs resin beads. A meta-analysis comparing the treatment of HCC and mCRC liver metastases with glass versus resin Y90 microspheres demonstrated no significant difference between glass and resin treatment in mCRC patients though reported a significant benefit in HCC patients when treated with resin compared to glass [45]. One of our retrospective reviews showed that patients who received Y90 treatment with resin microspheres had statistically significantly longer survival times compared to those treated with glass, with resin patients experiencing a 44% reduction in the likelihood of death within 1 year after initiation of Y90 treatment [42]. However, when examined by liver disease pathology and presence of portal vein invasion (PVI), no statistically significant differences could be determined for patients with HCC, mCRC, or other pathologies. This inability to detect statistically significant differences in these subgroups may

be attributable to their relatively small sample sizes, though this remains somewhat perplexing [42, 46]. Future research with more patients into these treatment groups will help establish if there truly is a statistically significant difference between glass and resin survival rates.

After 20 years of Humanitarian Device Exemption (HDE) status, the Food and Drug Administration (FDA) approved the use of TheraSpheres glass microspheres for use as SIRT for local tumor control of solitary tumors in patients with unresectable HCC [47]. While this approval currently stands for HCC, approval of TheraSpheres for metastatic CRC won't be far behind, given its proven efficacy, low toxicity profile, and already widespread use.

Sir-Sphere will begin an FDA approved trial, DOOR-waY90, which will evaluate the safety and efficacy of SIRT using the company's resin beads as a first line treatment for HCC patients [48]. This study will be a multicenter study, conducted at MD Anderson Cancer Center at University of Houston, Texas, and at University of Kansas and is set to begin in mid-2021.

## Radiomics

Radiomics is a promising new field in radiology which aims to find associations between qualitative and quantitative information based off of medical images [49–51]. Imaging features, texture, shape, and spatial relationships are evaluated via reconstruction algorithms and are converted to mineable data [50]. Radiographic patterns may, for example, reveal tumor signatures and further quantify tumor response and outcomes.

Currently, the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria is used to evaluate tumor response to treatment [52]. However, this criterion is imperfect by only taking into account tumoral size, which can be variable depending on the type of treatment administered. A recent study evaluated the use of radiomics to predict outcomes in patients with metastatic colorectal cancer [53•]. Using a number of morphologic criteria, such as homogeneity, density, and border lines, a radiomic signature was created and validated. Results showed that the radiomic signature was better able to identify “good responders” on follow-up imaging when compared the RECIST1.1 criteria.

Similar results were found in a separate study, which assessed the association between clinical features, radiomic features, and a combined clinical-radiomic model (CRM) based on medical imaging [54•]. Significant clinical features were bilobar disease and complete pathologic response. Significant radiomic features were minimum pixel value and a small area of emphasis. When these features were combined in a CRM, they were more prognostic than each alone.

These studies emphasize the importance of using pre-treatment imaging features when assigning treatment

therapies. Patients who are stratified as “poor responders” may start off on a more aggressive treatment therapy to improve disease free survival, whereas ‘good responders may take an easier treatment course to avoid side effects. Future research should value radiomic signatures for mCRC recurrence or patients with CRC who are at high risk for developing metastases.

## Conclusion

IR provides pivotal treatments for the management of both liver metastases and primary liver cancer, with treatment goals ranging from palliative symptom management to complete tumor response and obliteration [55]. Current research aims to employ voxel-based dosimetry and radiomics to further characterize liver metastases and calculate the optimum radioembolization dose for each individual patient.

## Declarations

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Conflict of Interest** John J. Waddell, Patricia H. Townsend, Zachary S. Collins, and Carissa Walter each declare no potential conflict of interest.

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