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# Local Therapy Modalities in Management of Colorectal Cancer Liver Metastasis

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**Abstract:** *Liver is the most common site of metastasis in colorectal cancers, and metastatic liver disease is found nearly 25% of the patients at diagnosis. Additionally, liver metastasis occurs in approximately half of the cases during the course of the disease. Liver metastases are important in colorectal cancer morbidity and mortality. So, management of liver metastases of colorectal cancer is important. Recently, many treatment modalities have been introduced in addition to surgery. Liver-directed therapies increase treatment options and improve outcomes in metastatic disease. In this paper, we reviewed and summarized these treatment options in patients with colorectal liver metastases.*

**Keywords:** *Colorectal cancer; liver; metastasis.*

## 1. INTRODUCTION

Colorectal cancers (CRC) are the third leading cause of cancer-related mortality in both genders in the United States [1]. In 2019, an estimated 145,600 adults will be diagnosed with CRC [1]. Up to 25% of CRC admit initially with colorectal liver metastasis (CRLM), and approximately 50% develop CRLM during the course of the disease. The stage 4 CRC has the lowest 5-year survival rates; 12 % for colon cancer, 13% for rectal cancer. Liver metastasectomy may improve overall survival, and these patients may have long-term relapse free survival. So the management of liver metastasis becomes more important. The local liver therapies can expand the options of management and improve outcomes for CRLM patients.

## 2. SURGERY

There is no definite definition for resectable CRLM. Ekberg and colleagues reported traditionally resectability criteria as 4 intrahepatic metastases, no extrahepatic metastatic disease and being able to achieve at least 1 cm resection margin [2]. However, liver 3-dimensional reconstruction imaging technology, portal vein embolization, and associated liver partition and portal venous ligation for staged hepatectomy can increase the resectability. So, current resectability criteria are stable or resectable extrahepatic metastatic disease (excluding portal lymphadenopathy), amen able to venous resection or reconstruction, beyond 1 mm with a tumor-free margin, >20% remnant liver for normal liver and slight chemotherapy-associated liver dysfunction and >30-40% for severe chemotherapy-associated liver disease [3]. The number and distribution of liver metastasis are not decisive for resectability. Preoperative imaging procedures, such as computed tomography (CT), magnetic resonance imaging and positron emission tomography-CT are helpful to evaluate resectability. Especially CT is optimal to evaluate the relation between metastatic mass and vascular, biliary structures, and to identify the volume of remnant liver. Requiring resection of all hepatic veins, both portal veins, or the retrohepatic vena cava to achieve negative margins are considered unresectable, and also the resection of liver metastasis should not advised in the presence of unresectable extrahepatic disease [4].

Surgery can be performed in synchronous CRLM with 3 surgical strategies. The first is known classic or bowel first technique include removal of primary colorectal tumor, followed by chemotherapy and 3-6 months later with resection of metastatic lesion. In combined technique, resection of the primary tumor and metastatic liver lesion are performed together. The last technique is known as liver first technique and involves resection of liver

metastasis followed by chemotherapy and removal of the primary tumor [4].

The only curative treatment option in isolated CRLM is combination of hepatic resection with systemic therapy. However, this combination is curative in only 20% of the patients, and disease recurrence primarily to the liver is occurred in approximately 70% of the patients after resection [5, 6].

### 2.1. Biological Targeted Therapy and Chemotherapy

Biological targeted therapy and chemotherapy are used to reduce metastatic disease in cases of unresectable CRLM and delay the progression. The chemotherapy can be administered as adjuvant or neoadjuvant for initially resectable CRLM. However there are not enough data that adjuvant chemotherapy improves overall survival [7]. In the EORTC 40983 trial, the researchers compared overall survival between perioperative chemotherapy group with leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) and surgery alone group, and there were no statistically significant differences [8]. Data show us clinicians should avoid using preoperative chemoradiotherapy, but chemotherapy may be used to downstage CRLM for parenchymal preserving resection [9].

Combination of chemotherapy with biological agents targeting vascular endothelial growth factor (bevacizumab) or epidermal growth factor receptor (cetuximab) are recommended for unresectable CRLM in NCCN guidelines with the aim of conversion to resection [10]. The phase 2 CELIM trial evaluated cetuximab combination with FOLFOX or leucovorin, fluorouracil, and irinotecan (FOLFIRI) in unresectable CRLM and 34% of the cases included in this study achieved to undergo complete resection of liver metastasis [11]. Additionally, the phase 2 OLIVIA trial evaluated bevacizumab with modified FOLFOX-6, or leucovorin, 5-fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) in unresectable CRLM. This study showed significantly higher overall tumor response rate, and complete resection rates in bevacizumab-FOLFOXIRI group. However, grade 3 or higher adverse events such as neutropenia, diarrhea, and febrile neutropenia were seen 95% of bevacizumab-FOLFOXIRI group, and 84% of bevacizumab-mFOLFOX-6 group [12].

### 2.2. Radiofrequency and Microwave Ablation

The standard local treatment method for CRLM is resection, but oligometastatic cases can be considered for radiofrequency ablation (RFA). This is the most widely used non-surgical technique in CRLM [13]. The use RFA is a reasonable treatment option for non-surgical candidates. Shady and colleagues published the results of 162 patients with 233 CRLMs treated with RFA, and the method was found successful in 94% of the cases [14]. In this study, progression-free survival and overall survival were found 26 and 36 months respectively, and tumor size larger than 3 cm and more than 1 extrahepatic disease were the independent predictors of shorter overall survival [14]. Also, randomized phase 2 EORTC 40004 trial compared FOLFOX +/- bevacizumab (systemic treatment alone) and systemic treatment with RFA (combined modality), and there were no difference in overall survival initially, but prolonged follow-up showed improved overall survival in combined group. Additionally, progression-free survival was improved at 3 years in the RFA group [15]. Kwan*et. al* evaluated a total of 63 CRLM patients (109 tumors) treated with RFA, and they identified that average tumor-free survival was 14.4 ± 1.4 months (range, 1-43 months), and local recurrence was occurred in 31.2% of treated tumors (34/109) [16].

Microwave ablation is another technique for ablation that is used for particularly small metastases in CRLM. There is an ongoing prospective, randomized, phase 3 COLLISION trial comparing surgery versus ablation modality (RFA or microwave ablation) in 618 patients with 3 cm or less CRLM, and the primary endpoint is overall survival [17]. Ablation alone or in combination with surgical resection should be chosen in CRLM patients especially who are not optimal candidates for resection.

### 2.3. Radioembolization

Radioembolization is a minimally invasive method include both embolization and radiation therapy to treat liver cancer. The radioactive isotope yttrium 90 (Y-90) is used in this procedure. Also, this method can be named as transarterial radioembolization, internal radiation therapy, and intra-arterial brachytherapy. Generally Y-90 radioemboli zation is suggested in chemotherapy resistant or refractor cases with predominant liver metastasis (18). Radioembolization with chemot herapycan lengthen time to progression in CRLM [19].

The phase 3 randomized controlled SIRFLOX trial (Y-90 resin microspheres with FOLFOX+/- bevacizumab vs. FOLFOX+/- bevacizumab) results showed significant prolonged progression-free survival in FOLFOX/Y-90 group (20.5 vs. 12.6 months) [20]. Additionally, the FOXFIRE and FOXFIRE Global studies showed prolonged progression-free survival similar with SIRFLOX trial [21]. Radioembolization with low systemic toxicity is a feasible treatment option for chemotherapy refractor unrespectable CRLM cases.

### 2.4. Hepatic Artery Infusion Therapy

Treatment with liver-directed chemotherapy through hepatic arterial infusion (HAI), besides systemic chemotherapy, is a method that can be used to downsize the disease in the liver with the aim of conversion to surgical resection [22]. This procedure is administered in the gastroduodenal artery by surgically implanted pump, hepatic artery port, or through a catheter connected to an external pump placed percutaneously. HAI provides less systemic toxicity. The clinicians should choose the chemotherapeutic agent for HAI in order to increase the local concentration, which increases therapeutic response and to decrease the systemic exposure. Floxuridine has short half-life and high first-pass metabolism rate, so it is the most widely used agent [23]. Also irinotecan [24] and oxaliplatin [25] have been used for intrahepatic infusion. Additionally, some investigators used irinotecan, oxaliplatin and floxuridine by HAItogether with systemic chemotherapy as first-line treatment of unresectable liver metastasis [26].

Floxuridine may cause diarrhea or gastric and duodenal ulcers because of extrahepatic profusion, and the common side effect is biliary toxicity. So that, the clinicians should monitor liver function tests every 2 weeksto adjust the dose of floxuridine [23]. Biliary toxicity of floxuridine can be decreased with combination of dexamethasone. Also using fluorouracil alternatively is a way to prevent biliary toxicity [27, 28].

HAI with floxuridine alone may increase the objective responses compared to systemic chemotherapy with floxuridine or 5-flourouracil [29]. Fiorentini *et. Al* compared HAI combination with bolus 5-flourouracil/leucovorin or HAI alone, and they identified an increase in survival in the combined group (20 vs. 14 months, p=0.0033) [30].

In unrespectable CRLM, the only randomized comparison of HAI versus systemic chemotherapy is the phase 3 CALGB 9481 trial [31]. This trial showed that, improved median survival (24.4 vs. 20 months, p=0.0034) and objective response rate (47 vs. 24%, p=0.12) was associated with HAI. This trial also identified the toxicity status, and the common toxicity was biliary toxicity (Bilirubin elevation >3mg/dL; 18.6 vs. 0%, p=0.006). Combination of HAI with systemic chemotherapy is used to achieve conversion to complete resection of liver metastasis. In the phase 2 MSKCC trial initial report [5] and expansion cohort [32] demonstrated 47% and 52% conversion to liver metastasis respectively. Additionally adjuvant HAI after resection of CRLM has been shown to delay hepatic recurrence [33].

There are some possible complications of HAI therapy. These are hemorrhage, thrombosis, extrahepatic perfusion, incomplete perfusion as arterial complications, infection, hematoma, pump migration as pocket complications, and occlusion, dislodgement, erosion, pump malfunction as catheter complications. Also biliary sclerosis is a rare important complication associated with abnormal postoperative flow scans, postoperative infectious complications, and larger doses of floxuridine per cycle [34].

## 3. Conclusion

Improving treatment modalities in CRLM provide options to clinicians with improving clinical outcomes. Surgical resection of CRLM is curative approximately in 20% of patients, so that these local treatment modalities become more important especially in unrespectable CRLM. Some of these potentially improve overall survival or progression-free survival. More studies, clinical trials are required for unrespectable CRLM.

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