Cancer Medicine Journal

Review Article | Vol 5 Issue 1

A Comprehensive Review of Management of Colorectal Liver Mets in the Current Era

Hassan Aziz[1*], Zubair Ahmed[2], Yi Lee[2], Gavin Drumm[3] and Muhammad Wasif Saif[4]

[1]*Department of Surgery, Division of Transplant and Hepatobiliary Surgery, Tufts Medical Center, Boston, MA, USA*

[2] *St. Joseph Mercy Oakland Hospital, Pontiac, MI, USA*

[3]*Boston University, Boston, MA, USA*

[4]*Department of Oncology, Northwell Health Cancer Institute and Feinstein Institute of Research, NY, USA*

Correspondence should be addressed to Hassan Aziz, Department of Surgery, Division of Transplant and Hepatobiliary Surgery, Tufts Medical Center, Boston, MA, USA

Received: November 02, 2021; Accepted: November 22, 2021; Published: November 29, 2021

ABSTRACT

Colorectal carcinoma is the third most common cancer in the US. The liver tends to be the most common site of metastasis. This review provides an in-depth analysis of non-transplant options available in the management of colorectal liver mets.

KEYOWRDS

Colorectal carcinoma; Cancer; Liver mets

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the US, preceded by prostate and bronchopulmonary cancer in males and breast and bronchopulmonary carcinomas in females [1]. It is the second most common cause of cancer-related mortality in the US [2]. In 2021, the American Cancer Society estimates the number of new colon and rectal cancer cases to be 104,270 and 45,230, respectively; meanwhile, 52,980 deaths from colorectal cancers accounting for 8.7% of all cancer deaths in 2021 [3].

In CRC, patients' metastases to other sites are the primary cause of death. The metastases may involve a single organ, tissue, or multiple locations; in solitary structural involvement, liver and lungs were the most frequently invaded sites [4]. The most common sites of metastases for CRC were in the liver (70%). Thorax is also a common metastatic site for both colon cancers (32%) and rectal cancers (47%). The third most common metastatic site was peritoneum 5% for colonic cancers, whereas rectal cancers invaded bones (12%) [5]. An estimated 60% of patients with CRC develop liver metastases during their illness. In addition, 85% of patients with CRC presented initially with unresectable disease to first healthcare services, and an estimated 60% of CRC patients developed liver metastasis during the cancer courses.

Scheele et al., in 1990, reported on a significant cohort of 1209 patients with CRLM that were divided into three main categories: 1) Un-resectable CRLM patients had a

Citation: Hasan Aziz, A Comprehensive Review of Management of Colorectal Liver Mets in the Current Era. Cancer Med J 5(1): 46-57.

median survival duration of 6.9 months. 2) Patients with resectable CRLM that was not resected had a median survival time of 14.9 months 3) CRLM patients in which resection was performed with negative margins had a median survival of 30 months and 5-years survival of 38%. They concluded that radical excision of liver segments invaded by colorectal cancer mets was an effective measure to achieve palliation and could offer a chance of cure in patients [6]. Trevino et al. reported that in the case of CRC patients who presented with liver metastases but did not undergo any treatment, a median survival time of 5 months to 20 months with 2-year survival is unusual, and 5-year survival is extremely high rare [7].

Up to the present, surgery is the only curative treatment for Colorectal carcinoma with Liver Metastases (CRLM) patients. With the advancement of multidisciplinary cancer care, including systemic chemotherapy, surgery, and radiation therapy, the survival outcomes of CRLM have significantly been improved [8].

IMPACT OF SURGERY ON OUTCOMES

Currently, surgical resection of the liver metastasis in CRC patients provides the best chance of long-term survival and cure. The 5-years survival of patients who have undergone liver resection is 24% to 40%, with a median survival of 28 months to 46 months. In contrast, patients who received only palliative therapy survived 7 months to 8 months only although surgical resection greatly improves the survival outcomes, unfortunately, not all patients are ideal candidates for surgical treatment due to unstable conditions, multiple sites of metastases, lack of sufficient functional liver segment post-resection (future liver remnant: FLR), or other associated comorbidities. However, patients could potentially qualify as surgical candidates after tumor size reduction with chemotherapy and other regimens. Subsequently, effective palliation could be achieved after liver resection.

Treatment modalities including systemic chemotherapy, intra-arterial chemotherapy, and radiofrequency ablation are commonly used as adjuncts to surgery. However, effective as a treatment option, they do not have as many benefits as liver resection when used alone. Therefore, therapies such as systemic chemotherapy or local ablative regimens should be utilized when a patient is considered not a candidate for surgery. Either alone or in conjunction with surgical resection, these therapeutic regimens form the basic CRLM treatment protocol [9,10]. When a patient is deemed unfit for surgery, locoregional therapies are used to reduce the tumor burden and slow disease progression to improve patient survival [11].

IMPACT OF CHEMOTHERAPY

Patients who undergo incomplete resection and who had inoperable CRC have similar prognostic outcomes. Patients who received preoperative chemotherapy could potentially become liver resection candidates. In an exhaustive study of 1104 patients with the unresectable disease treated with preoperative chemotherapy who were converted into resectable disease, a 5-years survival rate of 33% and 10-years survival of 23% were reported. The survival rates are similar with patients who presented with resectable disease [12].

A study was conducted to compare the survival and quality of life in patients treated with combination chemotherapy and supportive therapy alone. Patients were randomly assigned to two groups in ratio 2:1, one with chemotherapy and the other with supportive therapy alone based on their ECOG performance status, characteristics of metastatic disease, and weight loss 6 months before being included in the trial; the chemotherapy regimen included four cycles with leucovorin (LV/folinic acid [FA]) followed by 5-fluorouracil (FU) and cisplatin, each drug is given on the first four days of the cycle. Overall survival for chemotherapy was 11.0 months compared to 5.0 months for supportive therapy alone. Systemic chemotherapy was

concluded to be an effective treatment modality to achieve palliation [13]. The work of Saltz et al. involved 683 patients divided into three groups: 1st group received irinotecan, FU, and LV, 2nd group received FU and LV combination, and 3rd group was treated with irinotecan only. In an intention-to-treat analysis, the treatment with 3 drug combinations of irinotecan, FU, and LV yielded longer progression-free survival than fluorouracil and irinotecan only (median, 7.0 *vs.* 4.3 months; P = 0.004) and more prolonged overall survival (median, 14.8 *vs.* 12.6 months; P = 0.04) [14]. A Phase III randomized controlled trial by Kohne et al. reported that adding irinotecan to the standard regimen of FU/FA significantly affected survival outcomes and increased them from 16.9 months to 20.1 months (P = 0.2779) [15]. Capecitabine was found to be comparable in efficacy to parental 5-FU/FA; it also showed better safety profile and convenience of a peroral mode of administration [16]. Gramont et al. reported an increase in progression-free survival (PFS) with LV5FU2-oxaliplatin combination (median, 9.0 *vs.* 6.2 months; P = 0.0003) compared to the control group [17]. FOLFOX regimen of oxaliplatin with infused fluorouracil plus leucovorin was determined to be safe and suggested as a treatment regimen for the treatment of colorectal metastases [18]. 109 patients were assigned to FOLFIRI, and then FOLFOX 6 and 111 patients were placed on FOLFOX6 first and then FOLFIRI, the median survival times between the two groups of patients were 21.5 *vs.* 20.6 P = 0.99 [19]. Hurwitz et al. demonstrated that the addition of bevacizumab to fluorouracil-based combination chemotherapy improved survival times [20]. FOLFOXIRI was determined to improve PFS, RR, and OS outcomes compared with FOLFIRI [21]. After an intent to treat the study of 634 patients initially with the addition of 1400 patients later to a combined total cohort of 2034 patients, XELOX was reported as non-inferior to FOLFOX-4 as first-line therapy for metastatic CRC (MCRC) patients [22]. The inclusion of bevacizumab in oxaliplatin-based chemotherapy improved PFS but was not statistically significant [23]. In KRAS wild-type tumors, first-line therapy with cetuximab plus FOLFIRI reduced the risk of disease progression compared to when treated alone with FOLFIRI [24]. The evidence of increased toxicity and side effects along with decreased PFS by the inclusion of panitumumab with bevacizumab or oxaliplatin or irinotecan-based chemotherapy regimens were reported and suggested that their use be avoided in MCRC treatment [25,26] (Table 1).

Clinical Trial	Drugs		Median OS (Months)	OS Benefit (Months)	Median PFS (Months)
Y Chou M et al. (2018)	Arm 1	FOLFIRINOX	42.9	5.3	12.8
	Arm 2	FOLFOX/FOLFIRI with CET or BEV	37.6	-	10.7
T Gruenberger et al. (2015)	1	BEV + FOLFOX-6	-	-	11.5
	2	BEV + FOLFOXIRI	-		18.6
Tang W et al. (2020)	1	BEV + mFOLFOX-6	25.7	5.2	9.5
	2	mFOLFOX-6	20.5	-	5.6
Carrato A et al. (2017)	1	Pmab + FOLFOX-4	37	4	13
	2	Pmab + FOLFIRI	41	-	14
Tournigand C et al. (2015)	1	BEV	22.1	2.8	6
	2	BEV + Erlotinib	24.9	-	5.1
Heinmann V et al. (2014)	1	FOLFIRI + CET	28.7	3.7	10.0
	2	FOLFIRI + BEV	35.0	-	10.3
Oki E et.al. (2019)	1	mFOLFOX-6 + BEV	-	-	11.5
	2	mFOLFOX-6 + CET	-	-	14.8

Table 1: Study characteristics of clinical trials on CRC with liver mets.

Abbreviations: OS: Overall Survival; FOLFIRINOX: Folinic Acid, Fluorouracil (5FU), Irinotecan, Oxaliplatin; FOLFOX-4: Folinic Acid, Oxaliplatin, and 5-FU; FOLFOX-6: Folinic Acid, 5-FU, and Oxaliplatin; FOLFIRI: Folinic Acid, 5-FU, and Irinotecan; FOLFOXIRI: Fluorouracil, Folinic Acid, Oxaliplatin, and Irinotecan; mFOLFOX-6 (Modified FOLFOX-6): Folinic Acid, 5-FU and Oxaliplatin; CET: Cetuximab; BEV: Bevacizumab; Pmab: Panitumumab

A total of 256 patients were enrolled in METHEP 2 trial, 56 and 70 being allocated to FOLFIRI and FOLFOX4 groups, respectively, for a combined tally of 126 patients in 2 CT groups: 130 patients in 3CT groups

(FOLFIRINOX). 91 patients had KRAS mutation, whereas RAS mutation was detected in 109 patients [27]. Median OS time was 42.9 months in 3 CT arms *vs.* 37.6 months in 2 CT arms yielding a survival benefit of 5.3 months. Based on specific drug regimens, cetuximab (CET)-treated patients had OS of 43.6 months, and bevacizumab (BEV) - treated patients had OS of 34.2 months. This study suggested that FOLFIRINOX is a better treatment regimen when combined with CET or BEV when compared with FOLFIRI/FOLFOX for R0/R1 resection in patients who were initially classified as unresectable CRLM. T Gruenberger et al. conducted an open-label phase 2 study in 16 centers; 41 patients were placed in the bevacizumab-FOLFOXIRI group, 39 patients in bevacizumab - FOLFOX6; overall tumor response rates were 81% and 62%. Median PFS of 18.6 months *vs.* 11.5 months was reported with bevacizumab - FOLFOXIRI and Bevacizumab - FOLFOX6 when compared. A greater but manageable degree of toxicity was associated with bevacizumab - FOLFOXIRI therapy while generating a triad of clinical benefits, including higher tumor response rates, resection rates, and prolonged PFS [28]. An intention-to-treat analysis was performed in a population of 241 patients with RAS mutation CRLM, and a median follows of 37.0 months, where 121 patients were randomized to arm A (bevacizumab + FOLFOX6) and 120 to arm B (FOLFOX6 alone). Patients in arm A had a PFS of 9.5 months *vs.* 5.6 months and OS of 25.7 months *vs.* 20.5 months compared to arm B [29]. The CELIM randomized phase 2 study assessed the effectiveness of cetuximab and chemotherapy in unresectable CRLM patients. The median follow-up was 25 months. A total of 138 patients enrolled, with 70 in arm A and 68 in arm B treated with FOLFOX + cetuximab and FOLFIRI + cetuximab, respectively. Patients in arm A had significantly improved 3-years OS rate of 41% *vs.* 18% and increased survival time of 30.9 months *vs.* 21.0 months compared with arm patients [30]. In the PLANET-TTE study, 38 patients were treated with panitumumab (Pmab) - FOLFOX4, while 39 were treated with Pmab-FOLFIRI; data analysis concluded a median PFS of 13/14 months and median OS of 37/41 months [31]. In another randomized, open-label, phase 3 study conducted in France, Austria, and Canada, 700 patients were enrolled in trial after induction therapy into two arms via a minimization technique in a ratio in 1:1 ratio Arm A was bevacizumab only; arm B was bevacizumab and erlotinib as maintenance therapy until progression. The median follow-up period was 51.0 months *vs.* 48.3 months, and the median PFS from randomization was 4.9 months *vs.* 5.4 months in the final analysis. Median OS from maintenance was concluded to be 22.1 months *vs.* 24.9 months (stratified HR 0·79 [95% CI 0·63-0·99], p = 0.03). The study suggested that erlotinib might be used as a non-chemotherapeutic first-line agent in addition to bevacizumab after bevacizumab-based induction therapy [32]. 592 patients were enrolled in a clinical trial with KRAS exon 2 wild-type tumors, 297 were treated with FOLFIRI plus cetuximab, and 295 with FOLFIRI plus bevacizumab. Median PFS was reported as 10.0 months *vs.* 10.3 months among the two groups. Median overall survival was 28.7 months *vs.* 35.0 months in cetuximab *vs.* bevacizumab groups, respectively [33]. A randomized trial Atom assigned 122 patients with initially unresectable CRLM into two groups, one with mFOLFOX6 plus bevacizumab and mFOLFOX6 plus cetuximab, Median PFS of 11.5 *vs.* 14.8 was achieved in BEV *vs.* CET group, respectively [34].

BIOLOGY IS KING: PROGNOSTICATION

The Fong clinical risk score for colorectal cancer recurrence score (CRS) was established with five clinical criteria in CRLM patients: 1) Nodal status of primary, 2) Disease-free interval from the primary to the discovery of the liver metastases of <12 months, 3) The number of tumors >1, 4) preoperative CEA level >200 ng/ml, and 5) Size of the largest tumor >5 cm. Each of these 5 criteria was given one point, and the total score of each patient was

compared with their respective clinical outcomes after performing liver resection. The 5-years survival rate for patients with a zero on CRS was 60%, and those with 5 had a survival value of 14%. No patient with 5 scores on CRS survived 5 years ($p < 0.0001$). It is the most widely used score system for CRLM patients after resection, although built in 1999 by Fong et al. [35]. However, with the current advancement of multiple agents, score systems for DFS and OS should be further validated [36].

PATIENT SELECTION AND PROGNOSTIC VARIABLES

Creasy et al. followed a population of 1211 CRC patients for 11 years to obtain median survival times. Median disease-specific survival was 4.9 years, and 24.4% of patients were actual 10-years survivors. Cure model analysis yielded a cure rate of 20.6%. Several poor prognostic factors associated with cure were: 1) Node-negative primary, 2) Use of hepatic artery infusion pumps chemotherapy, 3) Metachronous disease, 4) Low clinical risk score (CRS) ≤2, 5) Margin negative resection, 6) Perioperative chemotherapy, 7) They estimated that the probability of cure in patients with high CRS and extrahepatic disease spread less than 5%. The study suggested that patients should be considered for treatment strategies such as neoadjuvant chemotherapy [37].

RESECTABLE COLORECTAL CANCER LIVER METASTASES

What is considered "resectable."

Technical resectability is defined as "the ability to achieve a margin-negative resection, adequate volume of the future liver remnant, preservation of vascular inflow, outflow, and biliary drainage." The number or size of metastases becomes irrelevant, and the real significance is of how much liver volume (%) was left behind; the patient must have an adequate future liver remnant (FLR) to be considered for liver resection [38]. The data suggests that a person with a normal liver can tolerate a reduction in liver size up to 20%. On the contrary, patients with chemotherapy-induced liver injury require an FLR of about 30%, and cirrhotic patients would need at least 40% of residual future liver volume [39].

WHEN AND WHY PERIOPERATIVE CHEMOTHERAPY

Systemic chemotherapy is an important treatment modality and can be used in both resectable and unresectable CRLM. It is broadly classified into two categories: 1) Conversion chemotherapy is used to convert a previously unresectable lesion into a resectable one. 2) Neo-adjuvant chemotherapy for resectable and potentially resectable lesion given before the surgical resection; other courses of chemotherapy post-surgery may follow [40]. Without a prior course of chemotherapy, complete resectability cannot be achieved in 70%-90% of CRLM patients. The survival of patients decreased considerably if complete resection is not achieved. The purpose of the conversion chemotherapy course is not to achieve complete tumor response but to achieve resectability. When chemotherapy is started to achieve resectability, the shortest course should be adopted, and resection of hepatic metastases should be performed as soon as possible [41].

One of the major reasons for perioperative chemotherapy is to achieve margin control of lesions. In chemo-responders, R0 and R1 are the goals post-resection; R0 indicates complete resection, whereas R1 resection indicates the removal of all macroscopic disease, but microscopic margins are positive for tumor. The resultant five-year survival was 29% in patients with R0 resection and 20% in patients who had undergone R1 resection; other benefits include downsizing and decreasing the degree of liver resection and assessing tumor morphologically and predicts its survival outcomes from pathological response to chemotherapeutic agents. This treatment protocol ensures that the patient receives some extent of chemotherapy and converts previously unresectable

lesions into resectable ones before surgery [42,43]. In the case of resectable lesions, perioperative chemotherapy also enables us to obliterate micro metastases and achieve tumor shrinkage to make R0 resection possible. However, it has limitations, such as tumor progression of an unresectable lesion, hepatotoxicity, and missing tumors in cases where chemotherapy achieves complete radiological response [43-46].

RESECTABLE CRLM NEO-ADJUVANT CHEMOTHERAPY

A phase 3 clinical study was carried out in which eligible patients aged 18 years - 80 years with a confirmed diagnosis of colorectal cancer histologically were randomly assigned to either of two groups, perioperative FOLFOX4 and surgical resection alone. The perioperative FOLFOX4 group was treated with oxaliplatin, FA, and FU. The treatment regimen consisted of six 14-days cycles of therapy before and after surgery. The cohort of 364 patients was randomly assigned to two groups, with a median follow-up of 8.5 years. The mortality rate was 59% in the FOLOX4 group and 63% in the surgical resection-only group- without an overall survival difference. However, the benefits of progression-free survival (PFS) obtained from perioperative therapy mean that it should be maintained as a treatment regimen for the CRLM population of patients [43].

CHEMOTHERAPY ASSOCIATED LIVER INJURY OXALIPLATIN

Blue Liver

Vauthey et al. assessed the impact of liver injury and chemotherapy on perioperative outcomes. 406 CRLM patients underwent hepatic resection,158 received no chemotherapy, and 248 were treated with chemotherapy. Patients who were treated with chemotherapy received either of one regimen out of four: 1) FU alone, 2) FU plus oxaliplatin, 3) FU with irinotecan, and 4) Others.

Patients who received oxaliplatin developed blue liver, i.e., sinusoidal dilatation, compared to no chemotherapy (18.9% *vs.* 1.9%; OR = 8.3%, 95% CI [2.9 - 23.6]), microvascular injury, and increased postoperative morbidity [43]. Oxaliplatin-induced sinusoidal injury is dose-dependent (>6 weeks); however, the impact can be reduced with Bevacizumab.

Yellow Liver

Chemotherapy with irinotecan resulted in liver injury, also referred to as yellow liver since it causes steatohepatitis compared to the patient group that received no chemotherapy (20.2% *vs.* 4.4%, OR = 5.4, 95% CI [2.2 - 13.5]). In addition, patients with steatohepatitis secondary to irinotecan were found to have higher 90-days mortality than those who received no chemotherapy following by resection.

Chemotherapy regimens were utilized in CRLM patients, whereas targeted therapy was safer and effective. Some argued that limiting chemotherapy cycles of certain regimens such as oxaliplatin could minimize unwanted complications and side effects of chemotherapy-induced liver injuries, and an optimum effect could be achieved [46]. It was suggested that curcumin could potentially alleviate the impact or treat oxaliplatin-induced liver injury since it reduces the oxidative stress in hepatocytes by activating the Nrf2 pathway and other less understood mechanisms [46]. Thus, chemotherapy has a significant toxic effect on liver parenchyma and must be administered carefully [47].

PORTAL VEIN EMBOLIZATION

Abdalla et al. described that the general indications of portal vein embolization (PVE) include patients with normal liver having an FLR of less than 25% [48]. One of the significant concerns about PVE is the rapid tumor progression following PVE, which indicates a poor prognosis [46,49]. Several studies have shown that PVE

can cause various complications such as inadequate FLR, high rates of disease recurrence, and increased tumor progression [45,46]. Post PVE, the hepatic atrophy-hypertrophy complex (AHC) and increased tumor volume Studies suggested that the hepatic atrophy-hypertrophy complex (AHC) and increased tumor volume post-PVE could be due to up-regulation of cytokines and growth factors, increased hepatic arterial perfusion, and evoked cellular host response; however, the mechanisms remain unclear [50]. Even though PVE has side effects and complications, it is still a preoperative regimen that aids in converting unresectable liver Mets into resectable preceding major hepatectomy by improving the future liver remnant volume. Further research is needed to identify potential tumors that could increase post-PVE and develop personalized treatment regimens in such patients [51].

TWO-STAGED HEPATECTOMY FOR BI-LOBAR METASTASES

When it is impossible to achieve complete resectability of all liver mets in a single procedure while sustaining an adequate future liver remnant of at least 30%, the treatment strategy is shifted into a sequential two-stage hepatectomy. Two-stage hepatectomy is a multi-regimen approach to manage patients with extensive liver metastases, including perioperative systemic chemotherapy, preoperative PVE, and two sequential resections [52].

WHY HEPATIC ARTERY INFUSION PUMP

The hepatic artery's preferential blood supply of liver mets enables us to leverage this anatomical fact and administer regional chemotherapy commonly referred to as hepatic artery infusion chemotherapy utilizing a subcutaneous pump [53]. Hepatic artery infusion pump (HAIP) chemotherapy, a locoregional therapy, is particularly beneficial in multi-focal liver mets. HAIP delivers chemotherapeutic agents selectively to tumor cells while sparing the liver parenchyma, which helps alleviate hepatotoxicity. It also helps maintain higher intratumor concentrations compared to systemic chemotherapy making it an effective treatment regimen [54,55].

HAIP FOR UNRESECTABLE CRLM

Buisman et al. reported that intrahepatic recurrences were lower with the HAIP+ systemic chemotherapy (SYS) combination (22.9% *vs.* 38.4%, $p<0.001$) [56]. HAIP has its own set of shortcomings, including technical complications with pump (22%), catheter blockage or dislodgement (6%), extrahepatic infusion (3%), and hematoma or infection (3%). Biliary sclerosis was also reported as a complication in as high as 23% of patients. However, the rate dropped when dexamethasone was administered along with floxuridine (FUDR) [57,58]. 64 patients with unresectable CRLM were enrolled in MSKCC where un-resectability was confirmed by a team of two hepatobiliary surgeons and one radiologist with the working definition of technical un resectability defined as a margin-negative resection being resection of all three hepatic veins, both portal veins, or the retrohepatic vena cava; or a resection would result in 6 metastases in a single lobe, with one lesion ≥5 cm; or ≥6 bilobar metastases). There was a significant difference in OS between chemotherapy-naive and previously treated patients (median, 76.6 months 95%CI: 38.6-NR] *vs.* 29.7 months [95%CI: 21.5 months - 40.2 months], $p = 0.022$). 5-years survival in patients with resectable liver mets was 63% compared to 12% in patients who did not meet resectability criteria [59].

PARENCHYMAL SPARING RESECTION *VS.* MAJOR HEPATECTOMIES

Tumor recurrence after curative resection of CRLM is seen in 50% to 75%, which is a significant unsolved issue [58,60]. The parenchymal sparing strategy maintains future liver-directed therapy options [61].

CHEMOTHERAPY IN PATIENTS WITH UNRESECTABLE COLORECTAL CANCER METASTASES

GONO et al. conducted a phase III study comparing fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI). 244 patients with unresectable CRM were randomized to FOLFIRI or FOLFOXIRI. The resectability rates of two groups FOLFIRI *vs.* FOLFOXIRI were 6% *vs.* 15% in all patients and 12% *vs.* 36% in patients with liver metastases only. Therefore, it was concluded that the FOLFOXIRI regimen was associated with improved RR, PFS, and OS compared with FOLFIRI [21].

CONCLUSION

We have made significant progress with metastatic CRLM. The goal is to get to surgical resection. Novel treatments are helping us push the boundaries and improve survival in these patients.

CONFLICT OF INTEREST

None.

REFERENCES

1. Siegel R, Ward E, Brawley O et al. (2011) Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA: A Cancer Journal for Clinicians 61 (4): 212-236.
2. Siegel RL, Miller KD, Goding Sauer A, et al. (2020) Colorectal cancer statistics, 2020. CA: A Cancer Journal for Clinicians 70(3): 145-164.
3. (2021) How common is colorectal cancer? Colorectal cancer statistics.
4. Vatandoust S, Price TJ, Karapetis CS (2015) Colorectal cancer: Metastases to a single organ. World Journal of Gastroenterology 21(41): 11767-11776.
5. Riihimäki M, Hemminki A, Sundquist J, et al. (2016) Patterns of metastasis in colon and rectal cancer. Scientific Reports 6(1): 1-9.
6. Scheele J, Stangl R, Altendorf-Hofmann A (1990) Hepatic metastases from colorectal carcinoma: Impact of surgical resection on the natural history. Journal of British Surgery 77(11): 1241-1246.
7. Valderrama-Treviño AI, Barrera-Mera B, Ceballos-Villalva JC, et al. (2017) Hepatic metastasis from colorectal cancer. Euroasian Journal of Hepato-gastroenterology 7(2): 166.
8. Xu F, Tang B, Jin TQ, et al. (2018) Current status of surgical treatment of colorectal liver metastases. World Journal of Clinical Cases 6(14): 716.
9. Mitchell D, Puckett Y, Nguyen QN (2019) Literature review of current management of colorectal liver metastasis. Cureus 11 (1): e3940.
10. Nieuwenhuizen S, Puijk RS, van den Bemd B, et al. (2020) Resectability and ablatability criteria for the treatment of liver only colorectal metastases: Multidisciplinary consensus document from the COLLISION trial group. Cancers 12(7): 1779.
11. Maher B, Ryan E, Little M, et al. (2017) The management of colorectal liver metastases. Clinical Radiology 72(8): 617-625.
12. Adam R, Delvart V, Pascal G, et al. (2004) Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: A model to predict long-term survival. Annals of Surgery 240(4): 644-657.

13. Scheithauer W, Rosen H, Kornek GV, et al. (1993) Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. British Medical Journal 306(6880): 752-755.
14. Salts LB (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer, Irinotecan Study Group. The New England Journal of Medicine 343(13): 905-914.
15. Kohne CH, Van Cutsem E, Wils J, et al. (2005) Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. Journal of Clinical Oncology 23(22): 4856-4865.
16. Van Cutsem E, Twelves C, Cassidy J, et al. (2001) Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. Journal of Clinical Oncology 19(21): 4097-4106.
17. de Gramont AD, Figer A, Seymour M, et al. (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. Journal of Clinical Oncology 18(16): 2938-2947.
18. Goldberg RM, Sargent DJ, Morton RF, et al. (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. Journal of Clinical Oncology 22(1): 23-30.
19. Tournigand C, André T, Achille E, et al. (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. Journal of Clinical Oncology 22(2): 229-237.
20. Hurwitz H, Fehrenbacher L, Novotny W, et al. (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. New England Journal of Medicine 350(23): 2335-2342.
21. Falcone A, Ricci S, Brunetti I, et al. (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The Gruppo Oncologico Nord Ovest. Journal of Clinical Oncology 25(13): 1670-1676.
22. Cassidy J, Clarke S, Díaz-Rubio E, et al. (2008) Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. Journal of Clinical Oncology 26(12): 2006-2012.
23. Saltz LB, Clarke S, Díaz-Rubio E, et al. (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. Journal of Clinical Oncology 26(12): 2013-2019.
24. Van Cutsem E, Köhne CH, Hitre E, et al. (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. New England Journal of Medicine 360(14): 1408-1417.
25. Hecht JR, Mitchell E, Chidiac T, et al. (2009) A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. Journal of Clinical Oncology 27(5): 672-680.
26. Gallagher DJ, Kemeny N (2010) Metastatic colorectal cancer: From improved survival to potential cure. Oncology 78(3-4): 237-248.
27. Ychou M, Rivoire M, Thezenas S, et al. (2018) Induction chemotherapy (CT) with FOLFIRINOX or FOLFOX/FOLFIRI, plus cetuximab (CET) or bevacizumab (BEV)(by RAS status), in patients (pts) with primarily unresectable colorectal

liver metastases (CRLM): Results of the randomized UNICANCER PRODIGE 14-ACCORD 21 (METHEP-2) trial. Journal of Clinical Oncology 36 (15_suppl): 3535-3535.

28. Gruenberger T, Bridgewater J, Chau I, et al. (2015) Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: The OLIVIA multinational randomised phase II trial. Annals of Oncology 26(4): 702-708.
29. Tang W, Ren L, Liu T, et al. (2020) Bevacizumab plus mFOLFOX6 versus mFOLFOX6 alone as first-line treatment for RAS mutant unresectable colorectal liver-limited metastases: The BECOME randomized controlled trial. Journal of Clinical Oncology 38(27): 3175-3184.
30. Folprecht G, Gruenberger T, Bechstein W, et al. (2014) Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). Annals of oncology 25(5): 1018-1025.
31. Tournigand C, Chibaudel B, Samson B, et al. (2015) Bevacizumab with or without erlotinib as maintenance therapy in patients with metastatic colorectal cancer (GERCOR DREAM; OPTIMOX3): A randomised, open-label, phase 3 trial. The Lancet Oncology 16(15): 1493-1505.
32. Heinemann V, von Weikersthal LF, Decker T, et al. (2014) FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): A randomised, open-label, phase 3 trial. The Lancet Oncology 15(10): 1065-1075.
33. Oki E, Emi Y, Yamanaka T, et al. (2019) Randomised phase II trial of mFOLFOX6 plus bevacizumab versus mFOLFOX6 plus cetuximab as first-line treatment for colorectal liver metastasis (ATOM trial). British Journal of Cancer 121(3): 222-229.
34. Fong Y, Fortner J, Sun RL, et al. (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. Annals of surgery 230(3): 309-318.
35. Creasy JM, Sadot E, Koerkamp BG, et al. (2018) Actual 10-year survival after hepatic resection of colorectal liver metastases: Wwhat factors preclude cure?. Surgery 163(6): 1238-1244.
36. Wu Y, Guo T, Xu Z, et al. (2021) Risk scoring system for recurrence after simultaneous resection of colorectal cancer liver metastasis. Annals of Translational Medicine 9(12): 966.
37. Charnsangavej C, Clary B, Fong Y, et al. (2006) Selection of patients for resection of hepatic colorectal metastases: Expert consensus statement. Annals of Surgical Oncology 13(10): 1261-1268.
38. Adams RB, Aloia TA, Loyer E, et al. (2013) Selection for hepatic resection of colorectal liver metastases: Expert consensus statement. HPB 15(2): 91-103.
39. Nordlinger B, Sorbye H, Glimelius B, et al. (2008) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomised controlled trial. The Lancet 371(9617): 1007-1016.
40. Nordlinger B, Vauthey JN, Poston G, et al. (2010) The timing of chemotherapy and surgery for the treatment of colorectal liver metastases. Clinical Colorectal Cancer 9(4): 212-218.
41. Pawlik TM, Scoggins CR, Zorzi D, et al. (2005) Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Annals of Surgery 241(5): 715-722.

42. de Haas RJ, Wicherts DA, Flores E, et al. (2008) R1 resection by necessity for colorectal liver metastases: Is it still a contraindication to surgery?. Annals of Surgery 248(4): 626-637.
43. Nordlinger B, Sorbye H, Glimelius B, et al. (2013) Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. The Lancet Oncology 14(12): 1208-1215.
44. Adam R, De Gramont A, Figueras J, et al. (2012) The oncosurgery approach to managing liver metastases from colorectal cancer: A multidisciplinary International consensus. The Oncologist 17(10): 1225-1239.
45. Benoist S, Nordlinger B (2009) The role of preoperative chemotherapy in patients with resectable colorectal liver metastases. Annals of Surgical Oncology 16(9): 2385-2390.
46. Vauthey JN, Pawlik TM, Ribero D, et al. (2006) Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. Journal of Clinical Pncology 24(13): 2065-2072.
47. Abdalla EK, Vauthey JN (2008) Chemotherapy prior to hepatic resection for colorectal liver metastases: Helpful until harmful?. Digestive Surgery 25(6): 421-429.
48. Lu Y, Wu S, Xiang B, et al. (2020) Curcumin attenuates oxaliplatin-induced liver injury and oxidative stress by activating the Nrf2 pathway. Drug Design, Development and Therapy 14: 73-85.
49. Abdalla EK, Hicks ME, Vauthey JN (2001) Portal vein embolization: Rationale, technique and future prospects. Journal of British Surgery 88(2): 165-175.
50. Simoneau E, Aljiffry M, Salman A, et al. (2012) Portal vein embolization stimulates tumour growth in patients with colorectal cancer liver metastases. HPB 14(7): 461-468.
51. Al-Sharif E, Simoneau E, Hassanain M (2015) Portal vein embolization effect on colorectal cancer liver metastasis progression: Lessons learned. World Journal of Clinical Oncology 6(5): 142-146.
52. Narita M, Oussoultzoglou E, Bachellier P, et al. (2011) Two-stage hepatectomy procedure to treat initially unresectable multiple bilobar colorectal liver metastases: Technical aspects. Digestive Surgery 28(2): 121-126.
53. Thiels CA, D'Angelica MI (2020) Hepatic artery infusion pumps. Journal of Surgical Oncology 122(1): 70-77.
54. Dzodic R, Gomez-Abuin G, Rougier P, et al. (2004) Pharmacokinetic advantage of intra-arterial hepatic oxaliplatin administration: Comparative results with cisplatin using a rabbit VX2 tumor model. Anti-cancer Drugs 15(6): 647-650.
55. Ensminger WD, Gyves JW (1983) Clinical pharmacology of hepatic arterial chemotherapy. In Seminars in Oncology 10(2): 176-182.
56. Buisman FE, Galjart B, van der Stok EP, et al. (2020) The impact of hepatic arterial infusion pump chemotherapy on hepatic recurrences and survival in patients with resected colorectal liver metastases. HPB 22(9): 1271-1279.
57. Allen PJ, Nissan A, Picon AI, et al. (2005) Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: An institutional experience of 544 consecutive cases. Journal of the American College of Surgeons 201(1): 57-65.
58. Kemeny N, Seiter K, Niedzwiecki D, et al. (1992) A randomized trial of intrahepatic infusion of fluorodeoxyuridine with dexamethasone versus fluorodeoxyuridine alone in the treatment of metastatic colorectal cancer. Cancer 69(2): 327-334.
59. Pak LM, Kemeny NE, Capanu M, et al. (2018) Prospective phase II trial of combination hepatic artery infusion and systemic chemotherapy for unresectable colorectal liver metastases: Long term results and curative potential. Journal of Surgical Oncology 117(4): 634-643.

60. Chan KM, Wu TH, Cheng CH, et al. (2014) Prognostic significance of the number of tumors and aggressive surgical approach in colorectal cancer hepatic metastasis. World Journal of Surgical Oncology 12(1): 1-8.
61. Alvarez FA, Claria RS, Oggero S, et al. (2016) Parenchymal-sparing liver surgery in patients with colorectal carcinoma liver metastases. World Journal of Gastrointestinal Surgery 8(6): 407-423.