Abstract

Colorectal Cancer (CRC) is one of the common cancer types and a great proportion of the CRC patients develop metastasis to liver. Innovative treatment methods for liver CRC metastasis (mCRC) have improved the patients’ survival rate and quality of life. Modern treatment of CRC employs combination of surgery, ablative therapies, and (neo) adjuvant chemotherapy. This review discusses recent developments in the treatment of mCRC in terms of ablation, drug therapy and surgery with an general overview of the recent literature.

Keywords: Chemotherapy, Colorectal Cancer, Liver metastases, Molecular mechanism, Radiotherapy, surgery.

Introduction

Colorectal Carcinoma (CRC) is the third most common cancer in the Western World and CRC has the second most common cause of cancer related mortality after lung cancer in North America. An annual new cases of 130,000 colorectal cancer and nearly 50,000 cases of death due to CRC were estimated for 2015 [1]. In the last decade, a significant improvement has achieved in the management of CRC patients with improvements in screening strategies, diagnostic methods, and implementation of novel chemotherapeutics with biological agents. The 10-year survival rate is 90% in early stage disease but is lower than 5% in patients with inoperable metastatic stage [2].

Liver is known to be the most common metastasis site for CRC. More than 50% of patients with CRC will develop liver metastases during their life (metachronous liver metastasis) [3]. At the time of diagnosis, 25% of CRC patients have already hepatic metastasis (synchronous liver metastasis) [4]. One third of the patients with liver metastases have an
isolated metastatic site limited to the liver and the survival of this specific population is directly related to biological behavior and number of hepatic lesions. Hepatic metastasis accounts for more than half of colorectal cancer deaths which emphasize the importance of effective managements strategies of liver metastasis [5]. Nowadays, especially in liver-only metastatic disease the 5-year Overall Survival (OS) rate has increased up to 35-58% [6,7]. The multidisciplinary therapeutic approach can be classified into three parts; i. new and more effective chemotherapeutic agents administered as a single agent or in combination with other anti-cancer agents (Table 1), ii. An advanced role of interventional radiology and nuclear medicine iii. New strategies and techniques for hepatic resections for CRC and mCRC patients. These therapeutic strategies improved resectability rate of metastases and increased the survival rate, as a result the unresectable cases decreased approximately to 20-30%.

Surgery is the bony frame in the management of any stage CRC. In metastatic setting, surgery still remains the only curative option for patients. Historically, only 5-10% of hepatic lesions were reported to be resectable. With advances in diagnostic methods, new staging systems for resections and new therapies resectability have increase up to 25%. [8]. Emerging strategies that increase the potential for resection are neo-adjuvant chemotherapy, preoperative portal vein occlusion and the two-stage resection approaches. In this manuscript, the treatment modalities for liver metastatic colorectal carcinoma along with molecular perspectives will be outlined.

Treatment Methods of Mcrc

Surgical resection

In patients with limited liver CRC metastasis, hepatic resection is the gold standard approach for curative treatment. Nowadays, the most common indication for hepatectomy in western countries is metastatic CRC (mCRC) [9]. Surgery increases the cure rate to 20-50% and gives long-term survival chance for patients after complete R0 hepatic resection [10]. Generally, limited liver mCRC cases can be categorized into three groups: resectable, potentially resectable, and definitely unresectable.

The criteria for resectability of liver lesions were defined as having less than three lesions (an estimated resection margin of more than one cm), absence of extrahepatic disease, and expected sufficient postoperative liver volume. This definition limits the curability option of more than 70-80% of mCRC patients. Recent debates enabled substantial data to change the resectability criteria. Malik et al. reported that liver resection still have a favorable outcome in patients with 4 to 7 hepatic lesions or even more than 7 lesions [11]. Several studies have indicated that actual surgical margin after possible R0 resection did not affect survival rates [12,13]. The presence of extrahepatic disease is no longer considered an absolute contraindication for liver resection. The requirements for remaining sufficient liver volume after surgery can be different. In a healthy liver at least 20% of liver volume should be preserved but this proportion may increase due to underlying liver damage and/ or chemotherapy associated liver injury [14,15].

The optimal timing of surgery in patients with synchronous liver metastasis is controversial. There are three options for surgical treatment of primary and metastatic tumors: 1) simultaneous resection of both the primary and liver metastasis 2) primary tumor resection followed by hepatic resection and 3) upfront hepatectomy approach. The decision of choice lies behind a thought of surgical complexity, patient characteristics, biological behavior and genetic status of the disease and surgeon expertise [16,17]. In the past, due to high mortality and morbidity, simultaneous surgical approach was not widely accepted. However, more recently, with improved techniques and improved postoperative care of patients, simultaneous resection is more widely adopted. In a systemic analysis which includes trials that compared the two approaches, no significant difference had been found in 5-year overall survival [18]. However, preoperatively planned extend of liver resection is
important. Major hepatectomy (i.e. resection of three or more hepatic segments) have still a significantly higher mortality and morbidity [16,19]. A new paradigm called “liver first strategy” is introduced due to the potential risk of significantly increased complications. This method includes primary liver resection without neo-adjuvant chemotherapy, after surgery chemotherapy and finally primary tumor resection. This method is more suitable for patients with potentially resectable liver metastasis, but can be applied also to resectable metastatic disease. A potential detrimental effect of this approach can be progression of primary tumor and requiring an emergency surgery. Hence, for locally advanced stage tumors or urgent surgery requiring patients, upfront liver strategy is not suitable.

Liver mCRC cases may be initially unresectable. However, there might be a potential for future resection option by the aid of chemotherapy, interventional radiology, and nuclear medicine therapeutic strategies. The chemotherapy approach that enables an initially unresectable metastatic liver lesion to be removed is called “conversion chemotherapy”. This phenomenon has been known for two decades and improved with introduced biological molecularly targeted agents. This topic will be discussed separately in chemotherapy section.

It is well known that liver is a metamorphic organ that can replace itself to some extent. Preserving sufficient liver volume after liver resection is a major obstacle for especially extensive liver metastatic cases. In the situation, Portal Vein Embolization (PVE) can help to increase the remnant contralateral liver volume to fulfill the resectability criterion. The right liver lobe volume is generally sufficient as a remnant when left hepatectomy is planned. PVE is usually necessary when extensive right lobe resection is required.

A single hepatectomy session might not be enough for complete resection of all metastasis even with neoadjuvant chemotherapy or PVE. In that circumstance “two stage hepatectomy” may be planned. This approach resulted better for unresectable metastatic cases when compared to palliative chemotherapy only. Usually 4-6 cycles of chemotherapy is applied initially and in accordance with response in diagnostic imaging techniques, first stage hepatectomy is done. After the healing period, chemotherapy is continued with achieved response criteria and the patient is prepared for a second stage hepatectomy. Often PVE may be necessary before the second stage. Adam et al. conducted a study that involves this strategy in 2000 [20]. The updated results showed that 5-year OS was a 42% but more than 30% of the patients were not completed a second hepatectomy session due to higher postoperative morbidity and mortality. It is important to consider the future morbidity of first stage hepatectomy. The survival results of this approach is a reflection of both the intrinsic biology of tumor and overall complete resection of metastasis. Hence, case selection is important when considering a two-stage hepatectomy.

**Ablative therapies**

Interventional radiology plays an important role in management of liver mCRC. Ablation therapies include Radiofrequency Ablation (RFA), Microwave Ablation (MWA), cryoablation, radioembolization, and chemoembolization. Thermal ablation results in delivering extreme temperatures to neoplastic tissue to cause immediate cell death and tumor necrosis [21]. Thermal ablation techniques have a low morbidity, allow for future adjunct therapy approaches and resections and do not to damage the liver parenchyma extensively.

Radiofrequency ablation is the most commonly used approach. An electrode is placed and high frequency alternating current causes thermal damage and coagulation necrosis. Open surgical approach, laparoscopic or percutaneous techniques are possible for RFA. The reported local recurrence rate varies from 17% to 46% [22-24]. In circumstances when a liver resection is planned, RFA can be done intraoperatively. RFA is generally recommended for lesions less than 3 cm since for bigger lesions recurrence rates increases dramatically [22]. RFA has some limitations. There is a risk of heat transfer via blood vessels (heat sink phenomenon) and increasing the damage area and further there is a risk of biliary damage.
The median survival rate after RFA ranges from 24 to 45.3 months [25-28]. Previously, RFA was found to be inferior to liver resection for mCRC due to high local recurrence rate [25,29]. However, RFA not alone but combined with liver resection can be helpful in cases with extensive liver metastasis and/or inadequate remnant liver volume. The use of RFA may obviate the need for a two-stage hepatectomy. The CLOOC (EORTC 40004) trial addressed this question [27]. In this study, the 5-year OS was reported as 56%. The CLOOC trial also compared the RFA with chemotherapy vs. chemotherapy alone. Although RFA alone arm had better PFS results (16.8 months vs. 9.9 months) it was not ultimately powered to evaluate the OS.

Microwave ablation is a thermal ablation technique in which the electrode generates a rapid heat source with microwave energy. Rapid oscillation of water molecules creates coagulation necrosis. MWA is advantages over RFA in way that it is more rapid, safer to administrate with lower recurrence rate [30].

Cryoablation involves rapid nitrogen or argon gas being delivered to tumor tissue by the guidance of ultrasound. It causes freezing of tissue below the degrees of survival and cause necrosis. It has more complication and recurrence rates hence it has fallen out of favor [31,32].

Chemoembolization is not a thermal ablative approach rather than a local ablative technique that involves either emulsions of ethiodized oil or drug eluting beads. The median duration of response was reported as 6 months with median survival of 25 months [33]. There is a risk of post-embolization syndrome characterized with right upper quadrant pain, fever, nausea and increase in transaminases.

Radioembolization (RE) is the best known local ablative technique for liver adverse effects are lung and Gastrointestinal (GI) toxicity. They occur as the microspheres go through the vessels of lung and major GI organs. The vasculature diversity should be known well before the application of this technique. A Lung Shunt Fraction (LSF) is calculated based on imaging and dose reductions can be made accordingly if LFS is between 10-20%. The response rate varies between 12.9-35.5% [34-36]. The median OS following RE is 10.2-12.6 months [36].

For the majority of patients with hepatic metastasis there are no curative option rather than a significant benefit in OS and quality of life can be achieved. Palliative surgery of primary tumor is indicated for symptomatic patients or in emergent cases related to intestinal obstruction or partial mechanical ileus, intractable bleeding, anemia or perforation. The value of primary tumor resection for asymptomatic patients with unresectable metastasis is still vague. There will be a risk for future emergent conditions related to primary tumor progression during palliative chemotherapy which may increase the mortality and morbidity of compulsory surgery. In previous series, Cook et al. reported that 66% of patients received primary tumor resection [37]. The Memorial Sloan-Kettering Cancer Center reported that only 7% of patients recommended after surgery during treatment [38]. Thus, US National Comprehensive Cancer Network (NCCN) recommends beginning chemotherapy with primary tumor unresected. Besides the role of surgery, palliative chemotherapy with/ without ablation techniques plays an important role for unresectable metastatic cases and this will be discussed in the following sections.

**Chemotherapy**

**Molecular mechanism of clinically used mCRC drugs**

5-Fluorouracil, capecitabine, oxaliplatin, cetuximab, bevacizumab, and panitumumab are FDA approved anticancer drugs that are clinically used in advanced chemotherapy for mCRC patients (Table-1).
<table>
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<th>ADMINISTRATION TYPE</th>
<th>BRAND NAME</th>
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<td>Thymidylate synthase</td>
<td>Intravenous</td>
<td>Adrucil®&lt;sup&gt;®&lt;/sup&gt; Carac®&lt;sup&gt;®&lt;/sup&gt; Carzonal®&lt;sup&gt;®&lt;/sup&gt; Efudex®&lt;sup&gt;®&lt;/sup&gt; Efudix®&lt;sup&gt;®&lt;/sup&gt; Efurix®&lt;sup&gt;®&lt;/sup&gt; Fluoroplex®&lt;sup&gt;®&lt;/sup&gt; Fluracril®&lt;sup&gt;®&lt;/sup&gt;</td>
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<tr>
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<td>Oral</td>
<td>Xeloda®&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Roche</td>
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<td>Topoisomerase I</td>
<td>Intravenous</td>
<td>Campto®&lt;sup&gt;®&lt;/sup&gt; Camptosar®&lt;sup&gt;®&lt;/sup&gt;</td>
<td>YakultHonsha Co. Ltd. Pfizer</td>
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<td>Intravenous</td>
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<td>growth factor-A (VEGF-A)</td>
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<td>receptor (EGFR)</td>
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Table 1: FDA approved anticancer drugs in treatment of mCRC.

Especially, the combination of 5-fluorouracil, irinotecan and leucovorin (FOLFIRI), 5-fluorouracil, oxaliplatin and leucovorin (FOLFOX) and capecitabine with oxaliplatin (XELOX) are increased therapeutic efficiency in these patients. Recently, target specific monoclonal antibodies (cetuximab, bevacizumab and panitumumab) have been included in these drug combinations in order to achieve successful treatment results [39-41].

**5-Fluorouracil and capecitabine**

5-Fluorouracil (also known as 5-FU or 5-fluoro-2,4-pyrimidinedione) is pyrimidine analog which is still a widely used anticancer drug for the treatment of various cancer types (colon, rectum, breast, head and neck, pancreas, skin, stomach and esophagus) as an anticancer agent over the past 40 years [42,43].

For most mCRC patients, 5-FU is the first line treatment drug; however, 5-FU is used in combination with oxaliplatin, irinotecan and leucovorin in advanced stages of metastasis [39,40]. Due to its chemical structure, 5-FU interacts with DNA and leads to irreversible inhibition of thymidylate synthase (Figure-1) [42,44].

![Figure 1: Mechanism and metabolic pathway of 5-FU. FUH₂ (5-Fluorodihydrouracil), FUPA (5-Fluorouridopropionic Acid), FBAL (α-fluoro-β-alanine), FdUrd (5-Fluorodeoxyuridine), FdUMP (5-Fluorodeoxyuridine Monophosphate), dUMP (Deoxyuridine Monophosphate) and dTMP (Deoxythymidine Monophosphate) (Redrawn from Ref. 47)](image)

Thymidylate synthetase (EC 2.1.1.45) is an essential precursor for DNA biosynthesis,
and catalyzes the methylation of Deoxyuridine Monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). This reaction is necessary for DNA biosynthesis and repair processes. 5-FU is metabolized to form active FdUMP (fluorodeoxyuridine monophosphate) metabolite that binds covalently to the nucleotide-binding site of thymidylate synthase. Consequently, this interaction blocks binding of the dUMP and interferes with dTMP synthesis in cancer cells [45,47]. Therefore, thymidylate synthase has been accepted as a critical target in cancer drug design studies.

Apart from these advantages, drug resistance and poor bioavailability reveal some limitations to the clinical use of 5-FU. 5-FU has a short biological life (0.4-2.1 hours) due to rapid metabolism and its non-oral form administration. Further, 5-FU shows toxic side effects especially on bone marrow, gastrointestinal tract and unselective effect on normal healthy cells [42,48-49]. To resolve all these limitations, capecitabine was designed and approved by FDA. Capecitabine is an orally-administered pro-anticancer drug which is converted to 5-FU via three-step enzymatic cascade. Oral administration provides rapid absorption of the capecitabine through the gastrointestinal wall and prevents direct contact of 5-FU with intestinal tissue [50-52].

Formation of rapid 5-FU resistance is important limiting factor for clinical efficiency. Multiple factors may contribute to 5-FU resistance in cancer cells. According to the experimental studies, overexpression of thymidylate synthetase is the main reason for the resistance development of 5-FU. Further, increased expression level of multidrug resistance-associated protein 2 and increased glutathione S-transferase activity generate drug resistance against 5-FU activity in mCRC patients [48,53].

**Irinotecan**

Irinotecan is a water-soluble and semi-synthetic camptothecin derivate which is mainly used against colorectal cancer and its metastases as first and second-line chemotherapeutic. It is used in treatment of advanced CRC and liver metastases with 5-FU and leucovorin. Further, irinotecan shows anticancer activity in advanced non-small cell lung cancer, either alone or in combination with cisplatin. Irinotecan inhibits the action of topoisomerase 1 enzyme in cancer cells [47,54-56]. Topoisomerase 1 (EC 5.99.1.3) is ubiquitous and abundant enzyme in eukaryotic cells and plays critical role in DNA replication, transcription, translation, and repair processes. Topoisomerase 1 is highly expressed in CRC tissues, and therefore inhibition of topoisomerase 1 is the significant therapeutic aspect in treatment of CRC and liver metastases. Double strand structure of DNA exist in supercoil state and it is tightly packed into chromatin in normal cellular conditions. During transcription and DNA replication processes, DNA must be in unwound state. Topoisomerase 1 binds to the double strand DNA and catalyzes breaking of the phosphodiester bonds between nucleotides in DNA replication process [57,60].

After administration, irinotecan is converted to SN-38 by catalysis of the carboxylesterase 2 (CES2) enzyme in the liver. SN-38 is active metabolite of irinotecan and metabolized by uridine diphosphate glucuronosyltransferase (UGT1A1) enzyme. SN-38 is 1000 times more active than irinotecan. SN-38 binds to the topoisomerase DNA complex in order to prevent breaking of the single strand of DNA (Figure-2).

![Image](image.png)

**Figure 2**: Mechanism and metabolism pathway of irinotecan. **APC** (7-ethyl-10-(4-amino-1-piperidino) carbonyloxy-camptothecin), **NPC** (7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxy-camptothecin), **SN-38G** (SN-38 glucuronide). (Redrawn from Ref. 47)
As a result, DNA replication and transcription mechanisms are inhibited and blocked, and they ultimately lead to cancer cell death [47,58-61].

**Oxaliplatin**

Platinum-based anticancer agents (for example: cisplatin, carboplatin, and oxaliplatin) have been extensively used in treatment of cancer for a long time [62,63]. Oxaliplatin is a third-generation platinum-based antineoplastic agent which is extensively used in treatment of first line advanced CRC and liver metastases along with 5-FU, leucovorin, and capecitabine. Oxaliplatin demonstrate well aqueous solubility, less drug resistance and significant antitumor activity than cisplatin and carboplatin. Like other platinum-based compounds, the anticancer action of oxaliplatin is based on formation of DNA damage in cancer cells. Oxaliplatin causes breaking of the DNA strand and inhibition of DNA replication unselectively [47,64,65].

Oxaliplatin has planar structure and consists of a central platinum atom (Pt), a 1,2diaminocyclohexane group (DACH) and a bidentate oxalate ligand. Pro-drug oxaliplatin is converted to highly reactive dichloro, monoaquo, and diaquocomplexes by non-enzymatic hydrolysis (Figure-3).

![Figure 3: Bioactive derivatives of oxaliplatin.](image)

These complexes covalently bind to sulphur and amino groups of DNA, RNA, and proteins. Particularly, its anticancer feature is formed by formation of oxaliplatin-DNA interaction. Oxaliplatin binds to the guanine and cytosine moieties of DNA and causes cross-linking of DNA. As a result DNA synthesizes and transcription is inhibited and cancer cell proliferation is interrupted unspecifically [47,66,67].

**Cetuximab and Panitumumab**

Cetuximab and panitumumab are monoclonal antibodies which are clinically used in treatment of a wide spectrum of human malignancies including metastatic colorectal cancer, non-small cell lung cancer, and head and neck cancer. Cetuximab is a chimeric (mouse/human) monoclonal antibody; however, panitumumab is a fully human monoclonal antibody. Especially, cetuximab and panitumumab are used as first-line therapeutics for the treatment of patients with Epidermal Growth Factor Receptor (EGFR)-expressing,
ras wild-type metastatic colorectal cancer in combination with FOLFOX and FOLFIRI [68-70].

EGFR is the transmembrane receptor which is member of the Erb-B/ HER tyrosine kinase receptors family. EGFR is involved in the pathogenesis and progression (cancer cell proliferation, survival, migration, apoptosis, and differentiation) of different cancer types. Therefore, aberrant expression of EGFR is to be a significant prognostic feature for many tumor types, especially for CRC and liver metastases. EGFR is activated by binding of several specific ligands: Epidermal Growth Factor (EGF), Transforming Growth Factor α (TGFα), and heparin-binding EGF (HB-EGF). Numerous oncogenic signaling pathways (JAK-STAT, PI3K/AKT/mTOR, MAPK/ERK, and PLC-γ signaling pathways) are stimulated by EGFR. These pathways lead to the inhibition of apoptosis and activation of metastases, cell proliferation, angiogenesis, cell migration, adhesion and invasion in tumor pathogenesis (Figure-4).

Cetuximab and panitumumab bind specifically to the ligand binding domain of EGFR as competitive inhibitors of the EGF and TGFα. These interactions support internalization of the EGFR from cell surface to cytoplasm. Therefore, inhibition of EGFR has become important therapeutic strategy in oncology [71-74].
Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody that is known as the first FDA approved angiogenesis inhibitor in treatment of mCRC, HER2-negative metastatic breast cancer, and advanced non-squamous non-small cell lung cancer. Angiogenesis is an essential process for the development and progression of cancer. Bevacizumab inhibits Vascular Endothelial Growth Factor A (VEGF-A), and blocks prevents and/or reduces the formation of blood vessels (angiogenesis) in cancer cells. Therefore, bevacizumab is more effective on metastatic solid tumors [75-77].

The VEGF family consists of six members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta induced growth factor. Especially, VEGF-A comes to the forefront in angiogenesis pathways. VEGF-A is a dimeric glycoprotein and it is involved in vascular development and blood-vessel formation. VEGF-A is the key pro-angiogenic factor that stimulates tumor angiogenesis and the survival of tumor endothelial cells. VEGF-A is overexpressed in almost all cancer tissues and it is induced by Hypoxia-Inducible Factor 1 (HIF-1); Platelet Derived Growth Factor (PDGF), Tumor Necrosis Factor A (TNF-a), and transforming growth factor-b (TGF-b) and by inactivation of the von Hippel-Lindau (vHL) gene. RAS/RAF/MEK/ERK (MAPK) and PI3K/PTEN/AKT (AKT) are two major signaling pathways and are related with angiogenesis. Bevacizumab binds to the VEGFR-1 and VEGFR-2, and this interaction inhibits angiogenesis process [78-82].

Clinical applications of drugs in mCRC treatment

Historically, the first line combined chemotherapy for mCRC was 5-FU and leucovorin (5-FU-Lv). Over the past decade, addition of oxaliplatin and irinotecan lead to improvement in treatment of patients. More recently, insights of pathophysiologic mechanism of metastasis have been highlighted and therefore, biologic mechanisms of CRC tumors were targeted with bevacizumab, cetuximab, and panitumumab (Table-2).

<table>
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<tr>
<th>Author</th>
<th>Phase</th>
<th>Arms</th>
<th>Sample size (n)</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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</table>

Table 2: Clinical trials in metastatic colorectal cancer.

ORR: Overall response rate PFS: Progression free survival OS: Overall survival
*KRAS wild type, ** Only cases with liver metastasis
Oxaliplatin in addition with 5-FU-Lv regimen (FOLFOX) was compared with 5-FU-Lv alone in a randomized controlled trial [83]. The addition of oxaliplatin improved Progression Free Survival (PFS) by 2.7 months (9.0 months vs. 6.3 months, p=0.0001). In this study, 6.7% of the patients who received FOLFOX regimen were able to get their liver metastasis resected. In contrary, 5-FU-Lv group had only 3.3% of liver metastasis resection. The most common grade 3-4 side effects of oxaliplatin containing chemotherapy were neutropenia and neurosensory toxicity.

Saltz et al. compared irinotecan, irinotecan with 5-FU-Lv combination (IFL) and 5-FU-Lv combination alone in patients with Mcrc [84]. The Objective Response Rate (ORR) was higher with IFL than that of FU-Lv (p<0.001; 50% vs 28%, respectively). The combination therapy with irinotecan was shown to be superior FU-Lv regimen in terms of PFS, response rate, and OS times. PFS was 7.0 months in the arm of IFL vs. 4.3 months in FU-Lv arm. Median OS was 14.8 and 12.6 months, respectively (P=0.04).

In another study, Douillard et al. had similar results [85]. In their study, ORR, PFS, and OS were superior with irinotecan compared to non-irinotecan combined chemotherapy (ORR: 69% vs. 41%; PFS: 6.7 vs. 4.4 months; OS: 17.4 vs. 14.1 months). Metastasectomy was not a study end point for both of these trials. Diarrhea, neutropenia, mucositis were the most common side effects observed during the treatment.

In GERCOR study, the authors compared oxaliplatin- (FOLFOX) and irinotecan plus 5-FU+Lv (FOLFIRI) combination regimens [86]. FOLFOX regimen was compared initially with irinotecan+ 5-FU-Lv (FOLFIRI) regimen in this study [86]. In the first-line, while PFS was 8.5 months with FOLFIRI and 8.0 months with FOLFOX, PFS was 4.2 and 2.5 months in the second line, respectively. FOLFOX had a similar therapeutic benefit to FOLFIRI with less gastrointestinal adverse effects and neutropenia at a cost of more neuropathy. However, metastasectomy rate was 22% for FOLFOX and 9% for FOLFIRI (p=0.02).

In 2004, in a German study, addition of bevacizumab to IFL regimen resulted in 4.9 months increase in OS [87]. The median OS was 20.3 months in the arm of bevacizumab and 15.6 in the arm of IFL. The PFS and response rates were superior in bevacizumab added arm (10.6 and 6.2 months, respectively). The ORR was superior in the experimental arm compared to the control (44.8% vs. 34.8%). Newer infusional irinotecan-5-FU-Lv regimens were not inferior to IFL regimen [88,89].

Capecitabine is a 5-FU analog used alone or in combination with oxaliplatin and/or irinotecan including regimens. The addition of bevacizumab to FOLFOX or capecitabine-Oxaliplatin Regimen (XELOX) was tested by Saltz et al [90]. The only statistical difference was shown in PFS (9.4 months vs. 8.0 months, p=0.0023). There was no difference in either OS duration or response rates (DFS: 38% vs. 38% and OS: 19.9 vs. 21.3 months). Of 1401 patients recruited in that study, 8.4% in bevacizumab arm and 6.0% in chemotherapy only arm had the chance of curative metastasectomy.

CRYSTAL study was published in 2009 in which addition of cetuximab to irinotecan based protocol was tested [91]. Cetuximab with FOLFIRI had resulted in better PFS (8.9 vs. 8.0 months) and ORR (47% vs. 39%), but no difference in OS (19.9 vs. 18.6 months). There was another endpoint of study that showed a higher rate of R0 liver resection in cetuximab arm (4.8% vs. 1.7%, p=0.0002). Subgroup analysis yielded that KRAS status is the determinant of efficacy of cetuximab and also in FOLFIRI only arm KRAS wild type tumors were more prevalent (66.9% vs. 62.1%). However, the difference surgery rate according to KRAS status was not reported.

KRAS status was tested for cetuximab efficacy in OPUS study [92]. OPUS study was a phase II study which enrolled patients in FOLFOX 4 and FOLFOX4-cetuximab arms. ORR was higher in cetuximab arm (46% vs. 36%; p=0.064). But, PFS and OS were similar in the study groups. Further, the patients were tested for KRAS status and Wild Type (WT) tumor harboring patients had better survival results with cetuximab. However, in patients with KRAS wild-type, ORR and PFS improved with cetuximab (ORR: 57% vs. 34% and PFS 8.3
vs. 7.2 months). The addition of cetuximab to KRAS WT patients also led to increased liver surgery rates (12% vs. 3%, p=0.242).

A phase 3 multicenter trial, the Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME), was investigated panitumumab in combination with FOLFOX4 chemotherapy as first-line treatment for patients with mCRC [93]. In patients with KRAS WT, ORR was significantly higher in the panitumumab arm compared to the control group (57% vs. 48%; p=0.02). Also, PFS improved in the arm of panitumumab-FOLFOX4 than the control group (10.0 vs. 8.6 months; p=0.01). However, in patients with KRAS mutation, the treatment effect of panitumumab was found inferior. The median OS was superior in the combination group than the control group, but the difference was no significant (23.9 vs. 19.7 months; p=0.17). The complete resection rate in patients with KRAS WT mCRC was similar in the groups (10% vs. 8%). In patients with KRAS WT mCRC with baseline metastasis in the liver, the rate was higher in the experimental arm than the FOLFOX4 alone arm (28% vs. 18%).

The results of subset analyses of these trials suggested that KRAS was a well-established biomarker predictive of anti-EGFR monoclonal antibody efficacy in patients with mCRC. Wild type KRAS is an obligatory biomarker for patients to get benefit from anti-EGFR targeted therapy. (Table 3).

<table>
<thead>
<tr>
<th>CRYSTAL</th>
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<th>PRIME</th>
<th>Arms</th>
<th>PFS</th>
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Table 3: The outcomes of anti-EGFR therapies in patients with metastatic colorectal cancer according to KRAS mutation.

Given these findings, it can be interpreted that a proportion of patients with initially unresectable liver disease may have a chance in future with careful patient selection and proper chemotherapy implementation. However, in the studies that are described latter, the primary end point was not resectability nor the patients were defined as potentially resectable in the initial recruitment. Therefore, the results should be carefully investigated.

The role of chemotherapy for patients with initially resectable disease is controversial. The aims of neoadjuvant chemotherapy in this setting are: i) to eradicate micrometastasis that already exists in the initial diagnosis and may progress during the surgery period, ii) to evaluate the chemosensitivity and biologic behavior of tumor and, iii) to decrease the size of liver metastasis in order to have a low surgical morbidity.

Neoadjuvant chemotherapy response can be a selection criterion for further surgery and treatment modalities. This hypothesis has been tested since 2004. In a French study, the patients who had progressive disease during neo-adjuvant therapy course had a lower 5-year OS probability [94]. Allen et al. had a similar result showing that progressive disease is a negative prognostic factor [95]. However, if the patient remained resectable despite the disease progression, than the surgery is still beneficial. The 5-year OS rate for which the surgery was offered was better than for patients who were withheld from surgery.

EORTC 40983 trial addressed the same question of real evidence for neo adjuvant chemotherapy [96]. An upfront surgery arm was compared with pre- and post-operative chemotherapy (FOLFOX4) + surgery arm. The median PFS durations were not statistically
significant between the two arms (11.7 months vs. 18.7 months, p=0.058). Seventeen percent of the patients were excluded from analysis since they were found to have more extensive state of the disease. After the exclusion, the 3-year PFS was found to be 36.2% for combination modality arm and 28.1% for surgery alone arm which was statistically significant (p=0.025). Forty-four percent of the patients could not complete postoperative 6 cycles of chemotherapy whereas 79% of the patients completed preoperative chemotherapy cycles. Chemotherapy resulted in high but reversible postoperative complication rate.

Adam et al. showed that with better case selection neoadjuvant chemotherapy can be more beneficial. They retrospectively analyzed the data from Liver Met Survey International Registry [97]. In patients with >5 cm liver lesion, neoadjuvant chemotherapy has resulted in better 5-year OS rate (58% vs. 33%, p<0.01).

A recent systematic review summarized the evidence on the beneficence of neoadjuvant chemotherapy for patients with initially resectable live metastasis [98]. Eight retrospective studies were included. The 5-year OS rate for neoadjuvant chemotherapy received patients ranged from 38.9 % to 74%. For the surgery patients, the range was from 20.7% to 56%. No statistically significant difference between the groups was found in 7 of 8 studies. The authors concluded that there is no clear evidence on the role of neoadjuvant chemotherapy for resectable liver lesions.

The role of adjuvant chemotherapy after the liver resection is also not clear. According to results of MOSAIC trial, FOLFOX was superior to FU-Lv in terms of 5-year disease free survival in patients with stage III, resected liver lesions. Irinotecan has not been shown superior over 5-FU-Lv in adjuvant setting [99]. A meta-analysis of four studies of perioperative chemotherapy found no OS benefit but did find a 25% PFS benefit [100]. The addition of bevacizumab to FOLFOX6 or cetuximab to FOLFOX6 in KRAS WT tumors have not been clearly shown adding benefit in adjuvant setting for resected stage III mCRC. (Figure 5)

![Cell membrane diagram](image)

**Figure 5:** Mechanism pathway of bevacizumab (Redrawn from Ref. 82).
Herein, we described latest advancement in mCRC treatment by surgical and oncological approaches. Specially, combined drug therapy improves the life quality of mCRC patients and help surgical treatments

References


