ADITUM
Enrich your Research

Gastroenterology and Hepatology Research

Review Article

# Recent Advances in The Treatment of Liver Metastases from Colorectal Cancer. A Comprehensive Review

**Running head/ Short title: Colorectal Liver Metastases – An Overview of treatment.**

**Harshal Rajekar**
Consultant Hepatibiliary, Gastrointestinal and Liver Transplant Surgeon, Medicover Hospital, Bhosari, Pune, India.

**Article Info**

**Received:** August 2, 2024
**Accepted:** August 19, 2024
**Published:** September 02, 2024

***Corresponding author:** Harshal Rajekar, Consultant Hepatibiliary, Gastrointestinal and Liver Transplant Surgeon, Medicover Hospital, Bhosari, Pune, India.

**Citation:** Harshal Rajekar. (2024) "Recent Advances in The Treatment of Liver Metastases from Colorectal Cancer. A Comprehensive Review.", J of Gastroenterology and Hepatology Research, 5(2); DOI: 10.61148/2836-2888/GHR/049.



## Abstract

Colorectal cancer is the 3rd most common cancer in the United States and the 2nd most common cause of cancer related death in men, besides being the leading cause of cancer related death in males less than 50y of age [1]. More patients diagnosed with colorectal cancer are younger than 55y of age and a larger number of patients present more with advanced disease.

Developing countries are seeing an increase in the incidence of colorectal cancer, probably because of adopting the "western" way of life. Obesity, sedentary lifestyle, red meat consumption, alcohol, and tobacco are probably responsible for this increasing incidence of CRC (colo-rectal cancer) [2]. Besides, increase in testing and detection, better diagnostic and imaging modalities and better access to healthcare and information. Recent advances in early detection have resulted in lesser mortality and hence more patients live longer; and more patients develop advanced disease.

Thus, with improving knowledge and better understanding, with better investigations and better understanding of molecular biology, therapeutic opportunities involving pharmacological, genetic and biological barriers have helped identifying newer targets for treatment of metastatic CRC [3].

More than 90% of all CRC are Adenocarcinoma, while the remaining 10% comprise rarer types, like squamous cell carcinoma, adeno-squamous carcinoma, spindle cell carcinoma, undifferentiated carcinoma, etc. Most cancers of the colon are associated with non-hereditary and spontaneous mutations and epigenetic changes or micro-aberrations, occurring due to smoking, alcohol, processed foods, food additives, environmental factors, etc [4]. Not all colorectal cancers share the same genetic aberrations, and therefore a uniform molecular therapy or treatment plan has been difficult to devise.

**Key Words:** colorectal cancer; liver metastases; recent advances; liver resection for CRLM; CRLM

## Introduction:

Treatment of colorectal cancer depends on the stage of the disease at the time of diagnosis. Early-stage CRC can be cured by curative surgical resection where the primary tumor and loco-regional nodes are removed surgically resulting in a R0 (no residual disease resection) offering a chance of cure. Advanced stage disease cannot be cured by surgery alone and require some form of adjuvant therapy, which may be chemotherapy,

radiotherapy, immunotherapy, targeted immune boosting therapies, non-coding RNA-based therapies, probiotics, natural products, oncolytic viral therapies, and biomarker-driven therapies [5]. The number of therapeutic targets keeps on increasing, as we identify the factors involved in the various steps in the genesis and spread of CRC. Because there is a variety of factors that contribute to the genesis and spread of colorectal cancer; the number of possible targets for intervention and modification keeps on growing.

**Liver Metastases:**
**Pathogenesis and Mechanisms:**

Almost half the patients with CRC will develop liver metastases in their disease process, and more commonly in left sided tumours [6]. Although, once right sided colonic tumors develop liver metastases; they tend to be more numerous and more invasive [7]. In almost 25% of patients' hepatic metastatic disease can be identified clinically at the time of diagnosis, and 40 to 50% will develop during the first 3 years after the primary tumor [8].

Alteration in tumor suppressor genes and oncogenes, like APC, SMAD4, KRAS, BRAF, and TP53, etc are responsible for the initiation of the adenoma-carcinoma sequence leading to development of invasive CRC [9]. APC, KRAS and TP53 are the most frequently altered genes in patients with CRC and CRLM (Colo-rectal cancer liver metastases) [10]. The APC gene regulates the Wnt/ beta-catenin pathway is a common aberration in CRC and CRLM [11]. CRLM go through a complex step wise progression; evasion from the tumor, EMT (epithelial-to-mesenchymal transition), then ECM (migration through extra-cellular matrix, ten invading into neighbouring tissue, intravasation into circulation, survival in the circulation, extravasation into the target organ and finally seeding and colonization of the liver (or any other target organ) forming more aggressive CRLM. Previous research has suggested that BRAF, KRAS, NRAS, PI3KCA, TP53, NRAS, CDK12, EBF1 might be genes associated with high risk of CRLM [12,13,14,15]. Also, apparently NOTCH1 and PIK3C2B mutations offer a better response to treatment, and SMAD3 mutations are associated with the lowest cure rates [14].

**Diagnosis and Staging:**
Liver metastases are detected at the time of imaging studies done at the time of primary colonic tumor detection, for synchronous liver metastases; and surveillance and follow up imaging for metachronous liver metastases. The incidence of liver metastases form CRC is about 25% [16,17,18,19]. The incidence of synchronous liver metastases is between 13.8 and 17.1% and those of metachronous liver metastases between 7.6 to 15.1% 7, 17, 18. Upto 85% metachronous CRLM occur within 1 year and 97.5% within 3 years. Only 2 % may occur between 5 to 10 years after surgery of the primary tumor [20,19], 19. 33-40 % of metachronous CRLM are limited to the liver [21]. A meta-analysis of five randomised controlled trials published in 2002 showed a survival benefit associated with more intensive follow up regimes, with early detection of metachronous CRLM and surgery for CRLM [22]. However, Primrose et al., and Jeffery et al in 2014 and 2016 found that intensive surveillance led to increased identification of metachronous disease but failed to translate to improved survival; probably undermining the importance of the role of tumor biology [23,24].

**Surveillance:**
Cross sectional imaging and serum CEA levels constitute the 2 most important parts of CRC screening and surveillance.

**Ultrasound:**
Transabdominal ultrasound has a limited role in the detection and evaluation of CRLM and contrast enhanced USG (CEUS) is definitely far more sensitive than gray scale ultrasound in the detection of lesions smaller than 10mm [25]. Even CEUS cannot offer the comprehensive information required for surgical planning for resection of CRLM and is operator dependent. Intra-operative ultrasound has a definite role and has been shown to find new lesions intra-operatively in upto 16% [26]; that could change clinical management in 9% patients. CEUS intraoperatively has a much higher sensitivity, especially in the setting of disappearing lesions after neo-adjuvant chemotherapy [27].

**Computerized Tomography (CT):**
CT is the modality of choice for detection of CRLM and is the most commonly done investigation. Limitations include inability to characterise lesions smaller than 10mm and difficulty in patients with fatty liver, which is quite common after chemotherapy. CRLM are typically hypo-vascular with variable heterogeneity depending on size and previous treatment. Arterial phase images does not improve detection due to the low vascularity, but are helpful for pre-surgical or pre-embolization planning [28]. CT scans with volumetry are also useful for surgical planning, remnant size evaluation, and to detect extension to surrounding organs.

**MRI (Magnetic Resonance Imaging):**
Compared to computerised tomography, MRI has superior soft tissue distinguishing capabilities making it much better at detection of liver metastases, even smaller than 10mm [29]. CRLM are usually T1 hypointense, T2 hyperintense with often a rim enhancement in the arterial phase, and a low enhancement in the portal and delayed phase. DWI (diffusion weighted imaging) improves the sensitivity of MRI improving the resolution to detect lesions smaller than 10mm [30]. CRLM show a restricted DWI because of their hypercellularity with low diffusion coefficient values [31]. Hepatocyte specific contrast such as Gadobenate dimeglumine (MultiHance, Bracco) and gadoxetate disodium (Eovist, Bayer) are preferably taken up by hepatocytes and not by the tumor cells, thus providing an even better ability to detect small lesions and disappearing/ occult lesions [32].

**PET-CT (Positron Emission Technology + Computerised tomography scan):**

18FDG PET-CT (18 Fluro-deoxygenated Glucose) has been thought to be very sensitive for detection of CRLM and accurate and specific for diagnosis of extra-hepatic disease [33]. However, small CRLM <10mm and metastases from mucinous adenocarcinomas may be missed, as also not all CRLM tend to be PET-CT detectable [34,35]. The role of PET-CT as a routine investigation in addition to standard imaging (CT chest, abdomen and pelvis and MRI liver) remains uncertain. Still, it is a useful

complementary investigation to rule out extrahepatic disease.

**Surveillance:**
Optimal surveillance depends on the knowledge of the general patterns and timing of recurrence. In 2016 Hallet et al were able to show that, 89% recurrences occur within 3 years of colonic surgery; and tended to be intrahepatic alone in 46%, 31% in extrahepatic sites and combined intra- and extra-hepatic in 22% [36]. And yet, a small but significant number of recurrences happen after 5years. Pulitano et al reported that almost 11% patients who are disease free at 5 years, went on to develop recurrence after 5years [37]. Tomlinson reported 23% recurrences after 5 years [38], whereas Vigano reported recurrence in 15% after 5 years [39].

Surveillance methods are not standardized and Serum CEA level along with CT scan chest, abdomen and pelvis are the most commonly used modalities in surveillance, in addition to MRI and PET-CT. The frequency and methods of surveillance are not standardized. Galjart et al attempted a stratification risk score, based on grade, nodal status and disease-free interval to determine surveillance intensity [40].

**Molecular Landscape:**
Amongst prognostic and utilitarian models, the biomarkers KRAS, NRAS, BRAF, TP53, PIK3CA, APC, and Mismatch Repair Deficiency (MMRD), are useful, as they help in selection of chemotherapy and other biological treatments [41].
**KRAS:**
KRAS mutation is present in almost 30% CRC, is associated with more aggressive disease and a higher incidence of recurrence after resection of CRLM [42].
**BRAF:**
BRAF mutations occur in 5 to 15% patients with CRC and is associated with aggressive disease which is resistant to EGFR (epidermal growth factor receptor) blockage [43] and is associated with poorer overall survival. Because of aggressive and metastatic disease associated with BRAF mutation, BRAF mutation in patients undergoing resection of CRLM is low (2%-4%) [41].
**TP 53:**
TP53 mutations in patients with CRLM is between 40 to 60% [44]. Though its role in the pathogenesis of CRC is evident, its exact effect on the prognosis of CRC and the development of CRLM is not clear, with conflicting reports from different researchers [45,46].
**PIK3CA (Phosphoinositide 3-kinase catalytic subunit alpha):**
PIK3CA mutations result in loss of apoptosis, increased tumor invasiveness and resistance to EGFR blockage [47]. Mutant PIK3CA mutations are reported n 20% CRLM, and is associated with shorter time to recurrence, and worse overall survival [48].
**APC mutation:**
APC is reported in almost 50% of CRLM, but by itself it does not seem to carry any prognostic significance [49]. When occurring along with PIK3CA mutation it portends a poorer OS (overall survival).

**MMRD (Mismatch Repair Deficiency):**
MMRD mutations result in impaired ability to correct DNA errors. The usually affected proteins include MLH1, MSH2, MSH6, PSM2 [50]. Sporadic MMRD mutations occur more commonly in right sided colonic tumours, in elderly patients and in early-stage cancers [51].

Thus, the genes involved in CRC and CRLM are numerous, including k-RAS, BRAF, APC, MMRD, TP53, etc; which provide significant prognostic information, and information regarding mutation specific surveillance [52].

**Role of Biopsy:**
Biopsy of CRLM should be avoided. The problem of needle track seeding is well documented, and varies from 10-16% [53,54,55].

**Treatment of CRLM:**
**LOCO-REGIONAL vs SYSTEMIC:**
Loco-regional treatment is directed towards the site of the primary disease and the regional lymph nodes. In CRC, understanding the nature of disease has led to CRLM being recognized a loco-regional disease, and treatment direct to the liver, i.e. surgery, trans-arterial treatments, or ablation.

Theus multimodal treatment will be seen as the ideal CRLM treatment, as it can improve clinical outcomes. CRLM patients should be discussed in a multidisciplinary tumor board, in order to decide the optimal treatment, the sequence of treatment, operative time window, extent of surgery and adjuvant treatment.

***Prognostic variables in CRLM:***

| VARIABLE | EVIDENCE |
|---|---|
| Clinical indicator | |
| Node positive CRC<br>Recurrence within 12months<br>CRLM > 5cm<br>Multiple lesions<br>CEA > 200 | Fong et al 1999 [**Error! Bookmark not defined.**-. (CRS scoring system) |
| Extrahepatic disease<br>Response to chemotherapy<br>Fibrotic response to chemotherapy | Poultsides et al 2012 [56]. |
| Pathology Indicator | |
| Margin positive resection<br>High TIL cells | Turcotte et al 2014 [57]. |
| Molecular Indicators | |
| CXCR 4 | Yopp et al 2014 [58]. |

**Surgery:**
**Factors determining surgical options:**
1. Patient factors: Pre-existing liver disease, cardiopulmonary condition and other co-morbidities will greatly determine the patient's ability to withstand major surgery, post operative morbidity and the subsequent adjuvant therapy.
2. Tumor factors [59]: Most patients will receive a short course of induction chemotherapy in addition to a EGFR antibody or a VEGF antibody, partly to distinguish between favourable or unfavourable biology. Tumours responding to systemic therapy will fall into the more favourable pathology. Most patients will also have a clinicopathological assessment along with a mutation analysis to look for a prognostic guide to assess the best form of treatment. Several prognostic scoring attempts

have been made, trying to assess the risk of developing recurrent disease and extra-hepatic disease [60].

3. Anatomical factors: Initial restrictions placing limits on the size, number and distribution of CRLM is now largely superseded and now CRLM are deemed resectable if all viable tumor can be removed leaving a sufficient residual liver volume [61]. Extra-hepatic disease is also not a contra-indication, if the extra-hepatic sites can be resected with a negative margin [62].

CRLM can be divided into 3 types, resectable, borderline or potentially resectable after downstaging or unresectable. Surgery for CRLM should always be with a curative intent. The thing to always keep in mind is whether all the tumor can be removed leaving behind an adequate amount of functioning liver remnant (FLR). Too small a remnant can result in post operative liver failure which is a dreaded and potentially fatal complication [63].

Factors to remember: disease burden and location, disease biology, progression while on systemic therapy, relationship to vascular structures (inflow and outflow and relationship to major biliary radicles, and background liver health – fatty liver, chronic liver disease and chemotherapy associated liver injury; all of which may diminish the capacity of the liver to regenerate after resection [64]. Generally speaking, only 10% of CRLM are resectable up front. Another 20 % require downstaging before resection [65]. Downstaging is usually done with a 5-FU (% flouro-uracil) based treatment usually in combination usually with a targeted agent. Because of the availability of increasingly more effective chemotherapeutic regimens, all patients with CRLM should be given a trial of neo-adjuvant chemotherapy, in an attempt to preserve functional liver parenchyma, understand the tumor biology and try and avoid more radical surgery [66]. Patients with progression of disease while on systemic therapy would generally predict a poor prognosis, a higher chance of recurrence and reduced OS [67].

Currently, surgical resection of CRLM is the only proven cure for CRLM [68].

When the liver metastases are confined to a part of the liver, several loco-regional therapeutic options are available, such as surgical resection; radiologically guided ablation (cryotherapy or RFA (radio-frequency ablation); Hepatic artery high dose chemotherapy (HAC); TARE (trans-arterial radioembolization)/ SIRT (Selective internal Radiotherapy); systemic chemotherapy, targeted therapies or immunotherapy; singly or in combination, usually sequentially [69].

Surgery is the only strategy proven to cure hepatic metastases, it is a well-established treatment of CRLM achieving a 5-year survival of 39 to 58% in patients with isolated liver metastases [70,71].

**The 2006 proposed guidelines for surgery for CRLM included [72]:**

- All patients with resectable liver metastases from colorectal cancer, with the possibility of having R0 resection and achieve an adequate residual liver volume should be candidates for surgery.
- A biopsy is not required unless reasonable doubt exists regarding the diagnosis and pathology.
- PET (positron emission technology) scan is recommended only in patients with high-risk primary disease, i.e. T4 lesion, perforated malignancy, apical node (C2), or poorly differentiated carcinoma.

The aim is to remove all macroscopic disease with clear (negative) margins and leave sufficient functioning liver. Patients with CRLM with extrahepatic disease can be considered for liver resection if:

1. Resectable pulmonary metastases.
2. resectable isolated extrahepatic sites—for example, spleen, adrenal, or respectable local recurrence; OR
3. local direct extension to, diaphragm/adrenal that can be respected.

Morbidity and mortality following liver resection has vastly improves with advances in hepatobiliary surgery and are mainly related to post operative liver failure secondary to the volume of remnant liver [73]. Background liver disease, blood loss during surgery, bile leaks, cardiopulmonary complications and intra-abdominal sepsis affect the morbidity and mortality following liver resections [74,75]. Background liver disease like steatosis (fatty liver - NASH); chemotherapy associated steatosis - CASH, frank liver cirrhosis and alcoholic liver disease can affect the function of residual liver after resection and will need to be factored into the decision making for CRLM [76].

Initial experience suggested that a 1cm margin of resection was required, and 5-year survival reduced from 45% to 21% if the margin was less than 1cm [77]. Subsequently it has been shown that lesser margins are adequate if the tumor pseudo-capsule is not breached during resection [78,79].

The number and location of CRLM probably does not affect survival in patients with metastases from CRC as long as all macroscopic disease is resected. The CRS (Clinical Risk Score) is a widely used clinical scoring model to predict tumor biology. It includes 5 parameters: node positive primary colon cancer, tumor to metastases duration < 12months, largest CRLM > 5cm, CEA > 200, and solitary against multiple tumours [80].

With advances in techniques of liver resection, including PVE (portal vein embolization) extended resections are possible. Resection of one half of the liver with ablation, i.e. RFA/ alcohol injection or cryotherapy of small lesions in the other lobe or other solid organs becomes possible. 2 stage hepatectomy or ALPPS makes extended liver resection possible.

Resection of CRLM: Surgery involves various levels and types of a hepatectomy, required to remove all viable tumour leaving behind an adequate FLR (functional liver remnant). Options include:

- Parenchyma sparing liver resection – this type of liver resection involves a non-anatomical resection, preserving as much parenchyma as possible. This results in a lesser incidence of post operative liver failure and a lesser operative risk and seems oncologically adequate [81]. However, such liver resections

more often require repeat liver resection for recurrence in part of the liver that may have been resected in a anatomical hepatectomy [78].

- Formal anatomical resection – involves segment related anatomical resection according to anatomical landmarks, which may extend upto a formal left or right hepatectomy or a right or left tri segmentectomy or extended hepatectomy.
- Repeat hepatic resection, as is resection in the presence of oligometastatic disease; is justified [82].
- Portal vein embolization – in an attempt to promote hypertrophy of the future remnant. PVE (portal vein embolization) is now increasingly being with hepatic vein embolization (HVE) [83]. The DRAGON trial showed that PVE + HVE resulted in better hypertrophy of the liver remnant leaving a much higher FLR with improved resectability [84].
- Two stage hepatectomy - Classical two-stage hepatectomy involves an initial resection with contralateral portal vein ligation, followed by a second resection 4-8 weeks later. Portal vein ligation appears to cause a similar hypertrophy of the liver on the contralateral side [85].
- ALPPS – associating liver partition with portal vein ligation for staged hepatectomy. ALPPS (Associating liver partition with portal vein ligation for staged hepatectomy) involves right portal vein ligation with in-situ splitting of the liver. And induces rapid and extensive hypertrophy of the FLR allowing for a more extensive resection [86]. ALPPS seems to improve the resectability of CRLM more than TSH (two stage hepatectomy) (LIGRO trial) [87,88,89]. Advances in surgical techniques at specialist centres have demonstrated that a 70% hepatectomy can be achieved with a mortality rate of <5% [90].

**Timing of Surgery: Synchronous Liver Metastases:**
Synchronous CRLM can be offered surgery either primary colon first, liver metastases first or simultaneous liver and colon lesions at the same time. Irrespective of whether the colon or liver is treated first, or simultaneous, these patients should all get neo-adjuvant chemotherapy.

**The Primary first approach:**
This is the most common approach, especially true when the primary lesion is the cause of symptoms, like bleeding, perforation or obstruction [91]. Traditionally, surgery for synchronous liver metastases from CRC is approached in 2 phases, that include surgery for the colorectal cancer followed by chemotherapy and a delayed resection of the CRLM [66]. The problem with this approach is the possibility of progression of the liver disease till the time hepatectomy is done, and the higher chances of recurrence after resection [92]. Patients with symptomatic primary CRC will need a colonic surgery first, to relieve the obstruction, bleeding, pain or perforation.

**Simultaneous Liver and Colon approach:**
In 2007 Reddy et al analysed retrospectively the data from 135 simultaneous colon-liver resections with 475 staged resections. They found a shorter combined hospital stay after simultaneous resections and similar morbidity and mortality after minor liver resections in both the groups. When major liver resections were required, the combined severe morbidity and mortality were much higher after simultaneous colon and liver surgery [93]. In 2019 analysis of database, Jones et al reported that major complications were much higher in patients undergoing simultaneous liver and colon surgery [94]. Additionally, patients undergoing simultaneous liver and colon resection, seem to have a worse progression free survival and a poorer overall survival [95,96]. However, this interpretation may be biased, in view of patients undergoing simultaneous resections have received lesser chemotherapy, whereas also having had many more minor liver resections. Among patients having staged resections, natural progression of the disease between the two procedures would have automatically been excluded from analysis. Thus, there seems to be no major difference in morbidity and overall survival in simultaneous or staged resections [97].

**Liver first approach:**
Liver first has been advocated in certain scenarios, viz; [98,41]

1. following the downstaging of inoperable liver disease to operability and asymptomatic primary.
2. synchronous operable tumours, but the liver lesion is seemed more urgent in view of their size or location, where waiting may convert the liver to inoperable.
3. In the specific instance of rectal cancer, where radiation of the primary tumour and its resection after a prolonged course of radiation, provides a chance for resection of the liver metastases without significant delay.

There have been no RCTs comparing liver first versus colon first versus simultaneous resection in patients with synchronous CRLM; and it is understandable how it may be difficult to randomize patients. Thus, every center has offered individualized treatments, either liver first or colon first and there is an obvious selection bias. However, all the trials and studies since then, and the subsequent surveys and metanalyses, have shown no significant difference in disease free survival and overall survival in both the groups [99,100,101,102].

**Local Ablation Techniques:**
In medically unfit patients, many alternatives or adjuncts to surgery aided by interventional radiology are now available. At least if not replacement, these form auxiliary treatment strategies. The most useful procedures include percutaneous thermal ablation (Radiofrequency ablation – RFA OR Microwave ablation – MWA). In addition, there are trans-arterial therapies like TACE (trans-arterial chemoembolization) and TARE (trans-arterial radio-embolization) or SIRT (Selective internal Radiation Therapy) [103].

RFA/ MWA – is suitable for patients with small tumours (<3cm) and low number of lesions (<4). The AmCORE study concluded that RFA was non-inferior to surgical resection for CRLM for suitable size and location [104]. Some authors, in retrospective studies have reported that patients who received RFA had a survival rate similar to that observed in partial hepatectomy, while others found better survival after surgery [105]. Still RFA has a place in the management of patients with CRLM for patients who are not candidates for surgery, as adjunct to surgery, for early recurrences and intra-operatively for lesions in addition to surgical

resections.

Before the discovery of RFA/ MWA, cryotherapy or freezing was an option that was used intra-operatively. Cryotherapy of the involved or inadequate resection considerably improves local disease control and may allow a greater proportion of patients to undergo potentially curative treatment [106]. Of late MWA has gained more popularity over RFA for the advantages it provides. Faster, higher intra-tumour temperatures, larger volume and with no effect of heat dissipation, high impedance, and no effect of low conductivity or penetrance [107]. Tumours 5cm or more are unsuitable for RFA/ MWA and proximity to vascular structures is a limiting factor for RFA.

**Intra-arterial therapy:**

Hepatic trans-arterial chemoembolization (TACE) involves the infusion of drugs directly into the liver vessels, i.e. the arterial supply to the liver metastases. TACE cannot be used to treat metastases more than 5–6 cm in diameter [108]. TACE aims to infuse chemotherapy drugs into small-calibre arteries of liver metastases, thus combining both ischemic and cytotoxic effect that led to tumor cells' death. CRLM derive a predominantly arterial supply which is useful in TACE. Lipiodol-emulsified chemotherapy agents (including irinotecan, oxaliplatin or doxorubicin) are injected with embolic particles, often polyvinyl alcohol or gelfoam, into the hepatic arteries supplying metastatic lesions while sparing the surrounding normal liver parenchyma. Drug eluting beads have improved the delivery of cytotoxic chemotherapeutic agents to the CRLM, allowing a higher dose to the tumour over a prolonged time [109].

Hepatic Artery Infusion (HAI) therapy: Since the blood supply to CRLM is predominantly arterial, and the liver metabolizes the chemo-therapeutic agent allowing for a higher dose to the metastases and reducing the systemic side effects [110]. HAI is delivered via a surgically or percutaneously placed hepatic arterial catheter. The affection of quality of life with a procedure, and the adverse effects of the drug was thought to outset the benefit, however, with newer drugs the side effects are considerably lesser; and the procedure is used as a pretreatment to downstaging CRLM.

**TARE (Trans-arterial Radio-embolization):**

Administration of a radionuclide [yttrium (Y)-90, or holmium-166], connected to either resin/glass particles or bio-resorbable microspheres into the hepatic artery, which produce their therapeutic effect by irradiating the surrounding tissues. Y90 or Ho166 are beta particle emitters, with radiation penetration in tissues limited to 10mm [111]. Initial experience on SIRT/ TARE was quite promising in chemotherapy refractory disease; with significantly improves OS in these patients [112,113]. With the available evidence, now SIRT is recommended in patients with unresectable or ablatable colorectal liver metastases with progression or are refractory to both oxaliplatin-based and irinotecan-based chemotherapy, with five or fewer liver tumours, a percentage tumour to liver volume of ≤ 25% [114].

Treatment of CRLM and other liver directed therapies have shifted the cause of death in metastatic CRC to elsewhere. Lung metastases is second to liver in terms of incidence of metastases in CRC. Patients who have their lung metastases resected, have a much higher 5-year survival against those who don't; 57% vs 13% 5-year survival [115]. Approach to thoracic and mediastinal nodes is uncertain, and positive thoracic nodes may preclude surgery for lung metastases.

Peritoneal carcinomatosis happens in 25% patients with metastatic CRC. Treatment of peritoneal carcinomatosis is done by cytoreductive debulking and HIPEC (hyperthermic intra-peritoneal chemotherapy). HIPEC with cytoreduction results in palliation and prevention of adhesive obstruction, palliation of GI symptoms, and resultant interruptions of chemotherapy and hospitalizations [101]. A 2003 randomized trial of HIPEC versus standard chemotherapy showed nearly doubling of survival in patients undergoing HIPEC [116]. HIPEC remains popular because of acceptable morbidity and mortality in experienced centres with nearly 27% 5-year survival.

Bone, Extra-abdominal lymph node and brain metastases portent a poor outcome and are often treated symptomatically along with systemic chemotherapy. Modern chemotherapy along with biological agents and immunotherapy, have revolutionized the care of patients with metastatic disease from CRC.

Minimally invasive (laparoscopic and robotic surgery) for abdominal (colonic and hepatic resection) and for thoracic disease has made recovery faster with lesser peri-operative morbidity and faster recovery.

**Influencing Factors:**

**Role of chemotherapy:**

***Neo_Adjuvant Chemotherapy:***

The role of neo-adjuvant chemotherapy is not certain. Once upon a time, there was little doubt that neo-adjuvant therapy is helpful. But there is no level 1 evidence that neo-adjuvant therapy improves overall survival, but there is evidence that pre-operative chemotherapy prolongs recurrence free survival [117,61]. Furthermore, unresectable lesions may be rendered resectable following chemotherapy [118,119]. However, this improvement in recurrence free survival doesn't seem to translate into better overall survival. So, probably neo-adjuvant chemotherapy will probably no longer be a default option in resection of CRC and CRLM [120,121]. The JCOG0306 trial showed that routine pre operative chemotherapy was not beneficial. However, practice will take some time to change, due to lack of understanding and knowledge among all the doctors looking after these patients. The EPOC trial compared 6 cycles of perioperative FOLFOX (3 before and 3 after surgery) to no chemotherapy. They found an improvement in disease free survival (20.9 versus 12.5 months) but there was no difference in OS 61. Pre-operative chemotherapy does not seem to confer any advantage over adjuvant chemotherapy in terms of OS [122].

One also needs to consider the role of EGFR antibody in the neo-adjuvant or adjuvant setting. The new EPOC phase 3 trial randomized wtRAS mutation tumours to chemotherapy with or without cetuximab, before and after resection of CRLM. Cetuximab seems to have an adverse effect of progression free survival as also on the OS [123]. Also, the post relapse survival

was worse in the Cetuximab group.

The role of anti-angiogenesis is also unclear at this point in time. Constantinidou et al studied the effect of chemotherapy alone with bevacizumab with chemotherapy. They found pathologic complete response in 11 out of 94 patients in both groups and there was no difference in OS between responders and non-responders [124].

***Adjuvant Chemotherapy:***
It remains unclear whether adjuvant chemotherapy after R0 resection improves OS. It is now general practice to prescribe chemotherapy to patients with high-risk features with CRLM that have undergone complete resection. Patients with low-risk features (metachronous disease, oligometastatic, well differentiated, R0 resection and low risk mutation analysis) may be managed with surgery alone [125].

***Conversion Chemotherapy:***
In the event of primarily unresectable CRLM, upfront chemotherapy may be considered with a view to reducing tumor burden to render it resectable (conversion chemotherapy). Oxaliplatin based or Irinotecan based chemotherapeutic regimens, with or without targeted therapy may be tried for conversion or rescue chemotherapy.

The phase III TRIBE trial and phase II Olivia trial used a triplet regimen (FOLFOXIRI) ± bevacizumab, resulted in a high resection rate but increased toxicity [126,127]. Tomasello et al found that FOLFOXIRI-bevacizumab resulted in a surgical conversion rate of 39% with 28.1% of R0 resections [128]. Similarly, FOLFOX6-bevacizumab led to 23.1% being operated, including 15.4% of R0 resections. The TRICC0808 trial had a median 36.8 months survival in patients treated with hepatectomy after mFOLFOX6 and Bevacizumab, although most of the patients developed recurrence [129].

Similar findings were reported by the CELIM [104] and PLANET [130] phase 2 trials [131].

The phase 3 PARADIGM trial was the first to show the superiority of panitumumab in combination with chemotherapy over bevacizumab [132]. In the KEYNOTE-177 phase 3 trial an unprecedented PFS and OS was achieved with the use of immunotherapy with Pembrolizumab [133].

***Targeted Therapy:***
Targeted therapy involves blockage of receptors or growth factor, like anti EGFR (epidermal growth factor receptor) or VEGF (vascular endothelial growth factor); and international guidelines now recommend chemotherapy along with targeted agents as first line of therapy in suitable patients [134].

**EGFR antagonists:**
EGFR mutations are rare in CRC, rather the protein overexpression in 40-50% patients [135]. EGFR alterations in CRC are poorly distinguishable, and therefore their predictive role is unclear. But, the clinical role of two downstream members (KRAS and NRAS) are more clearly demonstrated [136]. The two main pathways activated by EGFR are the RAS–RAF–MAP kinase pathway and the PI3K–PTEN–Akt pathway which are responsible for cell proliferation, migration, differentiation, and apoptosis [137,138]. EGFR protein overexpression results in oncogenic point mutations in the KRAS, NRAS, BRAF, and PIK3CA genes (reported in approximately 40%, 5%, 10%, and 20% of CRC cases, respectively), and PTEN loss of function [124].

Intra-tumour heterogeneity explains the occurrence of cells with different cancer clones, carrying different genetic and molecular alterations [139]. This heterogeneity could explain the primary and secondary resistance to chemotherapeutic and biological agents [140]. A fraction of CRCR cells that carry a resistance mutation may not prevent a transient clinical response to a specific drug, but the duration of the response is relatively short for the rapid clonal expansion of the resistant cancer cells.

The CAPRI-GOIM trial tried to assess the relevance of heterogeneity of KRAS, NRAS, BRAF, and PI3KCA mutations on the clinical activity of anti-EGFR therapy. At that time cetuximab was the anti EGFR drug available.

A metanalysis of randomised trials by Petrelli et al, found that addition of cetuximab or panitumumab to oxaliplatin or irinotecan regimens increased response rates in patients with initially inoperable CRLM [141]. But surprisingly, in a trial with triplet therapy, FOLFOXIRI with or without panitumumab showed to difference in OS or PFS [142]! The CAPRI-GOIM study found; in 7/10 cases of low KRAS mutations; the presence of additional mutations in PIK3CA, TP53, BRAF, ERBB2, FGFR3, and/or FBXW7 genes, which could equally contribute to anti-EGFR cancer cell resistance. Thus, there is a certain subset of patients with mixed genotype, which could prove resistant to single targeted agent [143]. One third patients may develop secondary resistance to EGFR blockage, by development of RAS mutant cancer subclones; and by mutations in the EGFR extra-cellular domain [144].

EPHA2, AXL, are potential downstream receptors; mutation in which could contribute to EGFR blockage resistance. Cetuximab could promote the presentation of tumour antigen to the immune system and dendritic cells, through presentation of tumour antigen to T-cells [145]. Also, cetuximab may promote NK cell mediated antibody dependent cellular toxicity [146]. Based on these findings researchers are now investigation the combination of Cetuximab with immune check point inhibitors in various cancers. The CRC, the AVETUX trial (Avelumab + Cetuximab + FOLFOX) is showing promising results [147]. Boosted by the findings a re more intensive AVETRIC trial is underway (Avelumab + Cetuximab + FOLFIRI).

Rechallenge with EGFR blockage is another interesting prospect, which allows clonal selection before retreatment with EGFR blockage like Cetuximab or panitumumab [148]. The CRICKET trial was the first proof of concept study looking at the benefit of rechallenge with Cetuximab and irinotecan [149].

**Anti-Angiogenesis Agents:**
Bevacizumab is the only VEGF (vascular endothelial growth factor) antagonist that is approved for the treatment of metastatic

CRC. Bevacizumab improves OS and PFS on addition to any irinotecan based or oxaliplatin based chemotherapeutic regimen [150,151,152] regardless of the RAS status. The OLIVIA trial and the TRIBE trial both showed an overall improved response rate, PFS and improved R0 resection rates after addition of Bevacizumab [153,154].

The FIRE-3 trial compared the addition of cetuximab to FOLFIRI versus the addiction of bevacizumab to FOLFIRI, while the PEAK trial compared FOLFOX + Panitumumab versus FOLFOX + Bevacizumab; and both suggested a slightly better response to EGFR blockage [155,156]. While the CALGB trial showed no difference in the two arms, either EGFR blockage or VEGF blockage [157].

**Novel Agents:**

***Regorafenib:***

Regorafenib is a multi-kinase inhibitor, which blocks a wide range of kinases involving oncogenic pathways [158], and it has shown improved OS in many randomized control trials [159,160].

***Gefitinib/ Erlotinib:***

Gefitinib and Erlotinib are both non-specific EGFR tyrosine kinase inhibitors that inhibit the EGFR pathway. The DREAM trial tried a combination of Bevacizumab and Erlotinib and showed an improved OS and PFS with the combination [161]. Another study from 2017, showed that Erlotinib may benefit pts with KRAS-wild-type CRC, specifically those with left-sided primary tumours, and likely harms those with KRAS-mutated CRC [162].

***Vemurafenib:***

BRAF mutated CRLM tend to be aggressive and associated with a poor prognosis. Vemurafenib targets BRAF mutation with EGFR blockage with promising results in some reports [163,164].

***Selumetinib:***

Selumetinib is a MEK kinase inhibitor that targets patients with KRAS mutation CRC that have not responded to oxaliplatin [165].

Other agents being investigated for use in CRLM and metastatic CRC, like Famitinib [166], which inhibits multiple receptor tyrosine kinases. Dual blockage with immune check point inhibitor and angiogenesis or multi-kinase inhibitor is another strategy being investigated. An initial trial in a small group of patients combining Camrelizumab with Famitinib has shown effectiveness in rectal cancer patients [167].

Newer molecules being tested: Many new therapies are being evaluated. Many have been set aside due to unacceptable toxicity, but here is a list of the more promising ones: Fruquintinib, nintedanib, VGX-100, tanibirumab, vanucizumab, Tegafur-Gimeracil-oteracil, Saikosaporin-B2, Raltitrexed, Apatinib, Pyrivinium, Ramucirumab, Anlotinib, Olaparib, Axitinib, Encorafenib, Simtuzumab, Tivozanib, Tipifanib, Aflibercept, Berberine, Fucoidan, Resveratrol, Topotecan and many others [156]. All of these acts through interaction with VEGFR-3, VEGFR-3, VEGF-C, VEGF-A, Angiopoetin-2, and many other downstream proteins in the EGFR/ RAS pathway. Immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T cell therapy, T cell receptor (TCR) alterations, and cytokine therapy have recently emerged as effective treatments for CRC [168]. VEGF inhibitors, ramucirumab and aflibercept have already been approved for second-line therapy for the treatment of metastatic RC [169].

**Immunotherapy:**

Agents: Pembrolizumab, Dostarlimab, Relatimab, Avelumab, Atezolizumab, Cemiplimab, Nivolumab, etc have been used in metastatic CRC with some benefit. Immune therapy is based on the concept that cancer cells evade the immune system by several mechanisms [170]. Tumors suppress T-cell function, suppression of CD4 and CD*+ lymphocytes, loss of MHC expression and upregulate immune checkpoint molecules likePD-L1 [171]. The KEYNOTE 224 [172] trial studies Pembrolizumab, CHECKMATE 142 assessed Nivolumab [173], and then further Nivolumab + Ipilumumab [174]. All these showed 69 to 90% response in metastatic CRC. Responses appeared to be stable and 71% had remained progression free at 12 months regardless of PD-L1 expression of tumor tissue [175]. It seems that response is durable, lasted anywhere from 1.6 months to 22.7 months, with 78% of responses lasting more than 6 months [176]. But, there have also been trials where immunotherapy has failed. The IMBlaze 370 study failed to show response to a combination of Atezolizumab (PD-L1 inhibitor) with Cobemitinib [177]. The MODUL trial failed to show improvement when Atezolizumab with Bevacizumab with fluoropyrimidine [178].

There is obviously a lot we need to understand. Immunotherapy, targeted therapy and cytotoxic chemotherapy will surely see more improvements as the science and understanding progresses.

***Vaccine:***

Vaccination is another type of immunotherapy, where vaccination along with immune checkpoint inhibitor is expected to amplify the immune response. Dendritic cell (DC) vaccine therapy was tried in the past. DC vaccines have historically performed poorly in clinical trials for cancer, but renewed interest in this immunotherapeutic strategy has been sparked by the relative success of Sipuleucel-T for prostate cancer and immunomodulatory agents that may synergistically improve DC function [179].

***CAR-T (Chimeric Antigen Receptor-Transfer) therapy:***

CAR-T therapy has been a huge success in treating hematological cancers. In solid tumors may trials are underway. T cells expressing human GUCY2C-targeted chimeric antigen receptor have shown potential to eliminate CRC metastases in the mice model [180].

**Liver Transplantation:**

Given the success that surgery offers in cure and control of CRLM in comparison to chemotherapy alone, the possibility of total hepatectomy followed by OLT (Orthotopic liver transplant) was firdt attempted in the 1990s. The results were a dismal 12 to 21% 5-year survival [181,182]. In 2006, given the favourable deceased organ to recipient ratio in Norway, DDLT was assessed by the Oslo University Hospital Group in unresectable CRLM, (the SECA trial [183]). In this carefully selected group of 21 patients with unresectable CRLM, they achieved a 1, 3, and 5-year OS of 95%, 68%, and 60% [184].

With the lessons learnt from the SECA 1 trial, the SECA 2 trial is currently underway, with more stringent selection criteria, and with preliminary results showing overall survival at 1, 3, and 5 years of 100%, 83%, and 83%, respectively [185].

## Conclusion:

One of the major problems faced, is the lack of knowledge and understanding amongst medical professionals and specialists who are often involved in the care of patients with CRC and CRLM. As late as 2015, in a study from Michigan, even oncologists believed that bi-lobar disease, number of lesions, or tumor diameter; as contraindications to surgery [186]!! In an interesting observation from Netherlands, it was noted that involvement of specialists in HPB surgery and radiology resulted in 20% patients being assigned to locoregional therapy with curative intent, as opposed to palliative chemotherapy [187]!!

Targeted therapy, Immune therapy and advances in cytotoxic chemotherapy may increase the survival of patients with CRLM. As advances in surgical techniques improve, survival is expected to get better and cure is a realistic possibility. With the developments in organ transplantation and better organ donation rates liver transplantation for CRLM is set to revolutionize the treatment of colorectal cancer with liver metastases.

**Conflict of Interest:** None.

## References:


1. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018; 68(1): 31-54.
2. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019 Dec;16(12):713-732.
3. Tirendi S, Marengo B, Domenicotti C, Bassi AM, Almonti V, Vernazza S. Colorectal cancer and therapy response: a focus on the main mechanisms involved. Front Oncol. 2023 Jul 19;13: 1208140.
4. Giovannucci E. Modifiable risk factors for colon cancer. Gastroenterol Clin North Am. 2002 Dec;31(4):925-43.
5. Kumar A, Gautam V, Sandhu A, Rawat K, Sharma A, Saha L. Current and emerging therapeutic approaches for colorectal cancer: A comprehensive review. World J Gastrointest Surg 2023; 15(4): 495-519 [PMID: 37206081
6. Price TJ, et al. Does the primary site of colorectal cancer impact outcomes for patients with metastatic disease? Cancer. 2015; 121:830–835.
7. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Cancer. 2018; 18:78.
8. Chua TC, Saxena A, Chu F, Zhao J, Morris DL. Predictors of cure after hepatic resection of colorectal liver metastases: an analysis of actual 5- and 10-year survivors. J Surg Oncol. 2011 Jun;103(8): 796–800.
9. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990; 61:759–767.
10. Feng L, Hong S, Gao J and Li J (2019) Whole-exome sequencing characterized the landscape of somatic mutations and pathways in colorectal cancer liver metastasis. J Oncol 2019: 2684075.
11. Kuipers EJ, et al. Colorectal cancer. Nat Rev Dis Primers. 2015 doi: 10.1038/nrdp. 2015.65.
12. Margonis GA, et al. Association of BRAF Mutations with Survival and Recurrence in Surgically Treated Patients with Metastatic Colorectal Liver Cancer. JAMA Surg. 2018; 153: e180996.
13. Shi R, et al. Prediction of KRAS, NRAS and BRAF status in colorectal cancer patients with liver metastasis using a deep artificial neural network based on radiomics and semantic features. Am. J. Cancer Res. 2020; 10:4513–4526.
14. Tsilimigras DI, et al. Clinical significance and prognostic relevance of KRAS, BRAF, PI3K and TP53 genetic mutation analysis for resectable and unresectable colorectal liver metastases: a systematic review of the current evidence. Surg. Oncol. 2018; 27:280–288.
15. Pitroda SP, et al. Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. Nat. Commun. 2018; 9:1793.
16. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Cancer. 2018; 18:78.
17. van der Geest LG, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clin Exp Metastasis. 2015; 32: 457–465.
18. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg. 2006; 244: 254–259.
19. Hackl C, Neumann P, Gerken M, Loss M, Klinkhammer-Schalke M, Schlitt HJ. Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. BMC Cancer. 2014; 14: 810.
20. Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. Int J Colorectal Dis. 2015; 30: 205–212.
21. Landreau P, Drouillard A, Launoy G, Ortega-Deballon P, Jooste V, Lepage C, Faivre J, Facy O, Bouvier AM. Incidence and survival in late liver metastases of colorectal cancer. J Gastroenterol Hepatol. 2015; 30: 82–85.
22. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. BMJ. 2002; 324: 813.
23. Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, George S, Mant D FACS Trial Investigators. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. JAMA. 2014; 311: 263–270.
24. Jeffery M, Hickey BE, Hider PN, See AM. Follow-up strategies

for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev. 2016; 11: CD002200.
25. Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L, Giovagnoni A. Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. J Magn Reson Imaging. 2010;31:19–31.
26. an Vledder MG, Pawlik TM, Munireddy S, Hamper U, de Jong MC, Choti MA. Factors determining the sensitivity of intraoperative ultrasonography in detecting colorectal liver metastases in the modern era. Ann Surg Oncol. 2010; 17: 2756–2763.
27. Takahashi M, Hasegawa K, Arita J, Hata S, Aoki T, Sakamoto Y, Sugawara Y, Kokudo N. Contrast-enhanced intraoperative ultrasonography using perfluorobutane microbubbles for the enumeration of colorectal liver metastases. Br J Surg. 2012; 99: 1271–1277.
28. Preoperative imaging for hepatic resection of colorectal cancer metastasis. J Gastrointest Oncol. 2012; 3:11–18.
29. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology. 2010; 257: 674–684.
30. Bruegel M, Holzapfel K, Gaa J, Woertler K, Waldt S, Kiefer B, Stemmer A, Ganter C, Rummeny EJ. Characterization of focal liver lesions by ADC measurements using a respiratory triggered diffusion-weighted single-shot echo-planar MR imaging technique. Eur Radiol. 2008; 18: 477–485.
31. Bruegel M, Holzapfel K, Gaa J, Woertler K, Waldt S, Kiefer B, Stemmer A, Ganter C, Rummeny EJ. Characterization of focal liver lesions by ADC measurements using a respiratory triggered diffusion-weighted single-shot echo-planar MR imaging technique. Eur Radiol. 2008; 18: 477–485.
32. Vilgrain V, Esvan M, Ronot M, Caumont-Prim A, Aubé C, Chatellier G. A meta-analysis of diffusion-weighted and gadoxetic acid-enhanced MR imaging for the detection of liver metastases. Eur Radiol. 2016; 26: 4595–4615.
33. Rohren EM, Paulson EK, Hagge R, Wong TZ, Killius J, Clavien PA, Nelson RC. The role of F-18 FDG positron emission tomography in preoperative assessment of the liver in patients being considered for curative resection of hepatic metastases from colorectal cancer. Clin Nucl Med. 2002; 27: 550–555.
34. Sahani DV, Kalva SP, Fischman AJ, Kadavigere R, Blake M, Hahn PF, Saini S. Detection of liver metastases from adenocarcinoma of the colon and pancreas: comparison of mangafodipir trisodium-enhanced liver MRI and whole-body FDG PET. AJR Am J Roentgenol. 2005; 185: 239–246.
35. Deng J, Tang J, Shen N. Meta-analysis of diagnosis of liver metastatic cancers: comparison of (18) FDG PET-CT and gadolinium-enhanced MRI. J Med Imaging Radiat Oncol. 2014; 58: 532–537.
36. Hallet J, Sa Cunha A, Adam R, Goéré D, Bachellier P, Azoulay D, Ayav A, Grégoire E, Navarro F, Pessaux P French Colorectal Liver Metastases Working Group, Association Française de Chirurgie (AFC) Factors influencing recurrence following initial hepatectomy for colorectal liver metastases. Br J Surg. 2016; 103: 1366–1376.
37. Pulitanò C, Castillo F, Aldrighetti L, Bodingbauer M, Parks RW, Ferla G, Wigmore SJ, Garden OJ. What defines 'cure' after liver resection for colorectal metastases? Results after 10 years of follow-up. HPB (Oxford) 2010; 12: 244–249.
38. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, Kemeny N, Brennan MF, Blumgart LH, D'Angelica M. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007; 25: 4575–4580.
39. Viganò L, Ferrero A, Lo Tesoriere R, Capussotti L. Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. Ann Surg Oncol. 2008; 15: 2458–2464.
40. Galjart B, van der Stok EP, Rothbarth J, Grünhagen DJ, Verhoef C. Posttreatment Surveillance in Patients with Prolonged Disease-Free Survival After Resection of Colorectal Liver Metastasis. Ann Surg Oncol. 2016; 23: 3999–4007.
41. Martin J, Petrillo A, Smyth EC, Shaida N, Khwaja S, Cheow HK, Duckworth A, Heister P, Praseedom R, Jah A, Balakrishnan A, Harper S, Liau S, Kosmoliaptsis V, Huguet E. Colorectal liver metastases: Current management and future perspectives. World J Clin Oncol. 2020 Oct 24;11(10):761-808.
42. Brudvik KW, Kopetz SE, Li L, Conrad C, Aloia TA, Vauthey JN. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. Br J Surg. 2015; 102: 1175–1183.
43. Tie J, Desai J. Targeting BRAF mutant metastatic colorectal cancer: clinical implications and emerging therapeutic strategies. Target Oncol. 2015; 10: 179–188.
44. Nakayama M, Oshima M. Mutant p53 in colon cancer. J Mol Cell Biol. 2019; 11: 267–276.
45. Tanaka K, Shimada H, Miura M, Fujii Y, Yamaguchi S, Endo I, Sekido H, Togo S, Ike H. Metastatic tumor doubling time: most important prehepatectomy predictor of survival and nonrecurrence of hepatic colorectal cancer metastasis. World J Surg. 2004; 28: 263–270.
46. Yang Y, Forslund A, Remotti H, Lönnroth C, Andersson M, Brevinge H, Svanberg E, Lindnér P, Hafström L, Naredi P, Lundholm K. P53 mutations in primary tumors and subsequent liver metastases are related to survival in patients with colorectal carcinoma who undergo liver resection. Cancer. 2001 ;91: 727–736.
47. Samuels Y, Diaz LA, Jr, Schmidt-Kittler O, Cummins JM, Delong L, Cheong I, Rago C, Huso DL, Lengauer C, Kinzler KW, Vogelstein B, Velculescu VE. Mutant PIK3CA promotes cell growth and invasion of human cancer cells. Cancer Cell. 2005; 7: 561–573.
48. Løes IM, Immervoll H, Sorbye H, Angelsen JH, Horn A, Knappskog S, Lønning PE. Impact of KRAS, BRAF, PIK3CA, TP53 status and intraindividual mutation heterogeneity on outcome after liver resection for colorectal cancer metastases. Int J Cancer. 2016; 139: 647–656.
49. Yamashita S, Chun YS, Kopetz SE, Maru D, Conrad C, Aloia TA, Vauthey JN. APC and PIK3CA Mutational Cooperativity Predicts Pathologic Response and Survival in Patients Undergoing Resection for Colorectal Liver Metastases. Ann Surg. 2017.

50. Sinicrope FA. DNA mismatch repair and adjuvant chemotherapy in sporadic colon cancer. Nat Rev Clin Oncol. 2010; 7: 174–177.
51. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA., Jr PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015; 372: 2509–2520.
52. Kawaguchi, Y.; Kopetz, S.; Lillemoe, H.A.; Hwang, H.; Wang, X.; Tzeng, C.-W.D.; Chun, Y.S.; Aloia, T.A.; Vauthey, J.-N. A new surveillance algorithm after resection of colorectal liver metastases based on changes in recurrence risk and RAS mutation status. J. Natl. Compr. Cancer Netw. 2020, 18, 1500–1508.
53. Jones OM, Rees M, John TG, Bygrave S, Plant G. Biopsy of resectable colorectal liver metastases causes tumour dissemination and adversely affects survival after liver resection. Br J Surg. 2005; 92: 1165–1168.
54. Rodgers MS, Collinson R, Desai S, Stubbs RS, McCall JL. Risk of dissemination with biopsy of colorectal liver metastases. Dis Colon Rectum. 2003; 46: 454–8; discussion 458-9.
55. Robertson EG, Baxter G. Tumour seeding following percutaneous needle biopsy: the real story! Clin Radiol. 2011; 66: 1007–1014.
56. Poultsides GA, Bao F, Servais EL, Hernandez-Boussard T, DeMatteo RP, Allen PJ, et al. Pathologic response to preoperative chemotherapy in colorectal liver metastases: fibrosis, not necrosis, predicts outcome. Ann Surg Oncol. 2012. September;19 (9): 2797–804.
57. Turcotte S, Katz SC, Shia J, Jarnagin WR, Kingham TP, Allen PJ, et al. Tumor MHC class I expression improves the prognostic value of T-cell density in resected colorectal liver metastases. Cancer immunology research. 2014. June; 2(6): 530–7.
58. Turcotte S, Katz SC, Shia J, Jarnagin WR, Kingham TP, Allen PJ, et al. Tumor MHC class I expression improves the prognostic value of T-cell density in resected colorectal liver metastases. Cancer immunology research. 2014. June; 2(6): 530–7.
59. Wimmer K, Schwarz C, Szabo C, et al. Impact of neoadjuvant chemotherapy on clinical risk scores and survival in patients with colorectal livermetastases. Ann Surg Oncol. 2017; 24(1): 236–43.
60. Roberts KJ, White A, Cockbain A, et al. Performance of prognostic scores in predicting long-term outcome following resection of colorectal liver metastases. Br J Surg. 2014; 101(7) :856–66.
61. Eadens, M J, Grothey A. Curable metastatic colorectal cancer. CurrOncolRep. 2011;13(3):168–76.
62. Charnsangavej C, Clary B, Fong Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006; 13(10): 1261–8.
63. Søreide JA, Deshpande R. Post hepatectomy liver failure (PHLF)—Recent advances in prevention and clinicalmanagement. Eur JSurg Oncol. 2021; 47(2): 216–24.
64. Khan AS, Garcia-Aroz S, Ansari MA, et al. Assessment and optimization of liver volume before major hepatic resection: current guidelines and a narrative review. Int J Surg. 2018; 52: 74–81.
65. Nordlinger, B, Van Cutsem, E, ,Gruenberger T, et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: Recommendations from an expert panel. Ann Oncol. 2009;20(6):985–92.
66. H. Uetake, M. Yasuno, M. Ishiguro, S. Kameoka, Y. Shimada, K. Takahashi, T. Watanabe, K. Muro, H. Baba, J. Yamamoto, N. Mizunuma, H. Tamagawa, I. Mochizuki, Y. Kinugasa, T. Kikuchi, K. Sugihara, A multicenter phase II trial of mFOLFOX6 plus bevacizumab to treat liver-only metastases of colorectal cancer that are unsuitable for upfront resection (TRICC0808), Ann. Surg Oncol. 22 (2015) 908–915.
67. Nordlinger, H. Sorbye, B. et al. EORTC gastro-intestinal tract cancer group, cancer research UK, arbeitsgruppe lebermetastasen und-tumoren in der Chirurgischen arbeitsgemeinschaft onkologie (ALM-CAO), australasian gastro-intestinal trials group (AGITG), fédération francophone de Cancérologie digestive (FFCD), perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC intergroup trial 40983): a randomised controlled trial, Lancet 371 (2008) 1007–1016.
68. Primrose JN. Surgery for colorectal liver metastases. Br J Cancer. 2010 Apr; 102(9): 1313–1318.
69. Valderrama-Treviño AI, Barrera-Mera B, Ceballos-Villalva JC, Montalvo-Javé EE. Hepatic Metastasis from Colorectal Cancer. Euroasian J Hepatogastroenterol. 2017 Jul-Dec;7(2): 166-175. doi: 10.5005/jp-journals-10018-1241. Epub 2017 Sep 29.
70. Anderson PS, Hornbech K, Larsen PN, Ravn J, Wettergren A. Surgical treatment of synchronous and metachronous hepatic- and pulmonary colorectal cancer metastases- The Copenhagen experience. Eur Surg. 2012 Dec;44(6):400–407.
71. Shah SA, Bromberg R, Coates A, Rempel E, Simunovic M, Gallinger S. Survival after liver resection for metastatic colorectal carcinoma in a large population. J Am Coll Surg. 2007 Nov;205(5):676–683.
72. Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, Primrose JN, Parks RW. Guidelines for resection of colorectal cancer liver metastases. Gut. 2006 Aug;55 Suppl 3(Suppl 3): iii1-8.
73. Schindl M J, Redhead D N, Fearon K C.et al The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut 2005, 54; 289–296.
74. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. Br J Surg 1990, 77; 1241–1246.
75. Fong Y, Cohen A M, Fortner J G.et al Liver resection for colorectal metastases. J Clin Oncol 199;71; 5; 938–946.
76. Kooby D A, Fong Y, Suriawinata A.et al Impact of steatosis on perioperative outcome following hepatic resection. J Gastrointest Surg 2003; 7; 1034–1044.
77. Hughes KS, Simon R, Songhorabodi S, Adson MA, Ilstrup DM, Fortner JG, Maclean BJ, Foster JH, Daly JM, Fitzherbert D, et al. Resection of the liver for colorectal carcinoma

metastases: a multi-institutional study of patterns of recurrence. Surgery. 1986 Aug;100(2):278-84.
78. Yamamoto J, Sugihara K, Kosuge T, Takayama T, Shimada K, Yamasaki S, Sakamoto M, Hirohashi S. Pathologic support for limited hepatectomy in the treatment of liver metastases from colorectal cancer. Ann Surg. 1995 Jan;221(1):74-8.
79. Rees M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. Br J Surg. 1997 Aug;84(8):1136-40.
80. Fong, Y.; Fortner, J.; Sun, R.L.; Brennan, M.F.; Blumgart, L.H. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. Ann. Surg. 1999, 230, 309–318; discussion 318–321.
81. Farid SG, Aldouri A, Morris-Stiff G, Khan AZ, Toogood GJ, Lodge JP, et al. Correlation between postoperative infective complications and long-term outcomes after hepatic resection for colorectal liver metastasis. Ann Surg. 2010; 251(1): 91–100.
82. Adair RA, Young AL, Cockbain AJ, Malde D, Prasad KR, Lodge JP, et al. Repeat hepatic resection for colorectal liver metastases. Br J Surg. 2012; 99(9): 1278–1283
83. Le Roy B, Gallon A, Cauchy F, Pereira B, Gagniere J, Lambert C, et al. Combined biembolization induces higher hypertrophy than portal vein embolization before major liver resection. HPB (Oxford). 2020; 22(2): 298–305.
84. Heil J, Korenblik R, Heid F, Bechstein WO, Bemelmans M, Binkert C, et al. Preoperative portal vein or portal and hepatic vein embolization: DRAGON collaborative group analysis. Br J Surg. 2021; 108(7): 834–842.
85. Pandanaboyana S, Bell R, Hidalgo E, Toogood G, Prasad KR, Bartlett A, et al. A systematic review and meta-analysis of portal vein ligation versus portal vein embolization for elective liver resection. Surgery. 2015; 157(4): 690–698.
86. Schnitzbauer, Andreas A., Sven A. Lang, Holger Goessmann, Silvio Nadalin, Janine Baumgart, Stefan A. Farkas, Stefan Fichtner-Feigl et al. "Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings." Annals of surgery 255, no. 3 (2012): 405-414.
87. Sandström, Per; Røsok, Bård I.; Sparrelid, Ernesto; et al.. ALPPS Improves Resectability Compared with Conventional Two-stage Hepatectomy in Patients with Advanced Colorectal Liver Metastasis: Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial). Annals of Surgery. 267(5):833-840, May 2018.
88. Mittler, J., Baumgart, J., Lang, H. (2022). Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Colorectal Liver Metastasis. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham.
89. Bednarsch, J., Czigany, Z., Sharmeen, S. et al. ALPPS versus two-stage hepatectomy for colorectal liver metastases——a comparative retrospective cohort study. World J Surg Onc 18, 140 (2020).
90. von Heesen M, Schuld J, Sperling J, Grunhage F, Lammert F, Richter S, Schilling MK, Kollmar O. Parenchyma-preserving hepatic resection for colorectal liver metastases. Langenbecks Arch Surg. 2012 Mar; 397(3): 383–395.
91. Philip Kron, Peter Lodge; New trends in surgery for colorectal liver metastasis. Ann Gastroenterological Surgery; 2024 April; 8; 4; 553-565.
92. Misiakos EP, Karidis NP, Kouraklis G. Current treatment for colorectal liver metastases. World J Gastroenterol. 2011 Sep;17(36):4067–4075.
93. Reddy SK, Pawlik TM, Zorzi D, Gleisner AL, Ribero D, Assumpcao L, Barbas AS, Abdalla EK, Choti MA, Vauthey JN, Ludwig KA, Mantyh CR, Morse MA, Clary BM. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol. 2007;14:3481–3491.
94. Jones TJ, Murphy AE, Tameron A, Hussain LR, Grannan K, Guend H, Dunki-Jacobs EM, Lee DY. Trends and Outcomes of Synchronous Resection of Colorectal Metastasis in the Modern Era-Analysis of Targeted Hepatic NSQIP Database. J Surg Res. 2019; 238: 35–40.
95. de Haas RJ, Adam R, Wicherts DA, Azoulay D, Bismuth H, Vibert E, Salloum C, Perdigao F, Benkabbou A, Castaing D. Comparison of simultaneous or delayed liver surgery for limited synchronous colorectal metastases. Br J Surg. 2010; 97: 1279–1289.
96. Bogach J, Wang J, Griffiths C, Parpia S, Saskin R, Hallet J, Ruo L, Simunovic M, Serrano PE. Simultaneous versus staged resection for synchronous colorectal liver metastases: A population-based cohort study. Int J Surg. 2020; 74: 68–75.
97. Gavriilidis P, Katsanos K, Sutcliffe RP, Simopoulos C, Azoulay D, Roberts KJ. Simultaneous, Delayed and Liver-First Hepatic Resections for Synchronous Colorectal Liver Metastases: A Systematic Review and Network Meta-Analysis. J Clin Med Res. 2019; 11: 572–582.
98. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. Br J Surg. 2006; 93: 872–878.
99. Brouquet A, Mortenson MM, Vauthey JN, Rodriguez-Bigas MA, Overman MJ, Chang GJ, Kopetz S, Garrett C, Curley SA, Abdalla EK. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? J Am Coll Surg. 2010; 210: 934–941.
100. Andres A, Toso C, Adam R, Barroso E, Hubert C, Capussotti L, Gerstel E, Roth A, Majno PE, Mentha G. A survival analysis of the liver-first reversed management of advanced simultaneous colorectal liver metastases: a LiverMetSurvey-based study. Ann Surg. 2012; 256: 772–8; discussion 778-9.
101. Jegatheeswaran S, Mason JM, Hancock HC, Siriwardena AK. The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: a systematic review. JAMA Surg. 2013; 148: 385–391.
102. Lam VW, Laurence JM, Pang T, Johnston E, Hollands MJ, Pleass HC, Richardson AJ. A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases. HPB (Oxford) 2014; 16: 101–108.
103. Tsitskari, M, Filippiadis, D, Kostantos, C, Palialexis, K, Zavridis, P, Kelekis, N, et al. The Role of Interventional Oncology in the Treatment of Colorectal Cancer Liver Metastases. Ann Gastroenterol (2019) 32:147–55.
104. Dijkstra, M, Nieuwenhuizen, S, Puijk, RS, Timmer, FEF, Geboers, B, Schouten, EAC, et al. Primary Tumor Sidedness, RAS and BRAF Mutations and MSI Status as Prognostic

Factors in Patients With Colorectal Liver Metastases Treated With Surgery and Thermal Ablation: Results From the Amsterdam Colorectal Liver Met Registry (AmCORE). Biomedicines (2021) 9:962.
105. Minami Y, Kudo M. Radiofrequency ablation of liver metastases from colorectal cancer: a literature review. Gut Liver. 2013 Jan;7(1):1-6.
106. Seifert JK, Morris DL. Prognostic factors after cryotherapy for hepatic metastases from colorectal cancer. Ann Surg 1998;228:201-8.
107. Lubner, MG, Brace, CL, Hinshaw, JL, and Lee, FT. Microwave Tumor Ablation: Mechanism of Action, Clinical Results and Devices. J Vasc Interv Radiol (2010) 21(8 Suppl. l):S192–S203.
108. Swierz, MJ, Storman, D, Riemsma, RP, Wolff, R, Mitus, JW, Pedziwiatr, M, et al. Transarterial (Chemo)embolisation Versus No Intervention or Placebo for Liver Metastases. Cochrane Database Syst Rev (2020) 2020. Issue 3.
109. Wang, DS, Louie, JD, and Sze, DY. Intra-Arterial Therapies for Metastatic Colorectal Cancer. Semin Intervent Radiol (2013) 30:12–20.
110. Chapelle N, Matysiak-Budnik T, Douane F, Metairie S, Rougier P, Touchefeu Y. Hepatic arterial infusion in the management of colorectal cancer liver metastasis: Current and future perspectives. Dig Liver Dis. 2018; 50: 220–225.
111. Moslim, MA, and Jeyarajah, DR. Narrative Review of the Role of Yttrium-90 Selective Internal Radiation Therapy in the Surgical Management of Colorectal Liver Metastases. J Gastrointest Oncol (2021) 12(5):2438–46.
112. Cosimelli M, Golfieri R, et al. Italian Society of Locoregional Therapies in Oncology (SITILO) Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer. 2010; 103: 324–331.
113. Kennedy A, Cohn M, Coldwell DM, Drooz A, Ehrenwald E, Kaiser A, Nutting CW, Rose SC, Wang EA, Savin MA. Updated survival outcomes and analysis of long-term survivors from the MORE study on safety and efficacy of radioembolization in patients with unresectable colorectal cancer liver metastases. J Gastrointest Oncol. 2017 ;86 :14–624.
114. NHS England Specialised Services Clinical Reference Group for Radiotherapy. Clinical Commissioning Policy: Selective internal radiation therapy (SIRT) for chemotherapy refractory / intolerant metastatic colorectal cancer (adults).
115. Stewart CL, Warner S, Ito K, Raoof M, Wu GX, Kessler J, Kim JY, Fong Y. Cytoreduction for colorectal metastases: liver, lung, peritoneum, lymph nodes, bone, brain. When does it palliate, prolong survival, and potentially cure? Curr Probl Surg. 2018 Sep; 55(9): 330-379.
116. Vic J. Verwaal, Serge van Ruth, Eelco de Bree, Gooike W. van Slooten, Harm van Tinteren, Henk Boot, Frans A.N. Zoetmulder. Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients With Peritoneal Carcinomatosis of Colorectal Cancer Journal of Clinical Oncology 2003 21:20, 3737-3743.
117. Padmanabhan C, Parikh A. Perioperative chemotherapy for resectable colorectal hepatic metastases-what does the EORTC 40983 trial update mean? Hepatobiliary Surg Nutr. 2015; 4(1): 80–83.
118. Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010; 11(1): 38–47.
119. Alberts SR, Horvath WL, Sternfeld WC, Goldberg RM, Mahoney MR, Dakhil SR, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a north central cancer treatment group phase II study. J Clin Oncol. 2005; 23(36): 9243–9249.
120. Kanemitsu Y, Shimizu Y, Mizusawa J, Inaba Y, Hamaguchi T, Shida D, et al. Hepatectomy followed by mFOLFOX6 versus hepatectomy alone for liver-only metastatic colorectal cancer (JCOG0603): a phase II or III randomized controlled trial. J Clin Oncol. 2021; 39(34): 3789–3799.
121. Booth CM, Berry SR. Perioperative chemotherapy for resectable liver metastases in colorectal cancer: do we have a blind spot? J Clin Oncol. 2021; 39(34): 3767–3769.
122. Allard, MA, Nishioka, Y, Beghdadi, N, Imai, K, Gelli, M, Yamashita, S, et al. Multicentre Study of Perioperative Versus Adjuvant Chemotherapy for Resectable Colorectal Liver Metastases. BJS Open (2019) 3:678–86.
123. Kawaguchi, Y, and Vauthey, JN. The Landmark Series: Randomized Control Trials Examining Perioperative Chemotherapy and Postoperative Adjuvant Chemotherapy for Resectable Colorectal Liver Metastasis. Ann Surg Oncol (2020) 27:4263–70.
124. Constantinidou, A, Cunningham, D, Shurmahi, F, Asghar, U, Barbachano, Y, Khan, A, et al. Perioperative Chemotherapy With or Without Bevacizumab in Patients With Metastatic Colorectal Cancer Undergoing Liver Resection. Clin Colorectal Cancer. (2013) 12:15–22.
125. Filoni E, Musci V, Di Rito A, Inchingolo R, Memeo R, Mannavola F. Multimodal Management of Colorectal Liver Metastases: State of the Art. Oncology Reviews; 17; 2024; DOI=10.3389/or.2023.11799
126. Cremolini, C, and Loupakis, F. Early Tumor Shrinkage and Depth of Response Predict Long-Term Outcome in Metastatic Clorectal Cancer Patients Treated With First-Line Chemotherapy Plus Bevacizumab: Results From Phase III TRIBE Trial by the Gruppo Oncologico del Nord Ovest. Ann Oncol (2015) 00:1–7.
127. Gruenberger, T, Bridgewater, J, Chau, I, García Alfonso, P, Rivoire, M, Mudan, S, et al. Bevacizumab Plus mFOLFOX-6 or FOLFOXIRI in Patients With Initially Unresectable Liver Metastases From Colorectal Cancer: The OLIVIA Multinational Randomised Phase II Trial. Ann Oncol (2015) 26:702–8.
128. Tomasello, G, and Petrelli, F, FOLFOXIRI Plus Bevacizumab as Conversion Therapy for Patients With Initially Unresectable Metastatic Colorectal Cancer. Jama Oncol (2017) 3(7).
129. Yasuno, M, Uetake, H, Ishiguro, M, Mizunuma, N, Komori, T, Miyata, G, et al. mFOLFOX6 Plus Bevacizumab to Treat Liver-Only Metastases of Colorectal Cancer that Are Unsuitable for Upfront Resection (TRICC0808): A Multicenter Phase II Trial Comprising the Final Analysis for Survival. Int J Clin Oncol (2019) 24:516–25.

130. Carrato A, Abad A, Massuti B, Grávalos C, Escudero P, Longo-Muñoz F, Manzano JL, Gómez A, Safont MJ, Gallego J, García-Paredes B, Pericay C, Dueñas R, Rivera F, Losa F, Valladares-Ayerbes M, González E, Aranda E; Spanish Cooperative Group for the Treatment of Digestive Tumours (TTD). First-line panitumumab plus FOLFOX4 or FOLFIRI in colorectal cancer with multiple or unresectable liver metastases: A randomised, phase II trial (PLANET-TTD). Eur J Cancer. 2017 Aug; 81: 191-202.
131. Vogel, A, and Kirsten, M. First-Line Molecular Therapies in the Treatment of Metastatic Colorectal Cancer – A Literature-Based Review of Phases II and III Trials. Innov Surg Sci (2018) 3(2):127–38.
132. Yoshino, T, and Watanabe, J. Panitumumab (PAN) Plus mFOLFOX6 Versus Bevacizumab (BEV) Plus mFOLFOX6 as First-Line Treatment in Patients with RAS Wild-Type (WT) Metastatic Colorectal Cancer (mCRC): Results from the Phase 3 PARADIGM Trial. United States: American Society of Clinical Oncology (2022).
133. André, T, Shiu, K-K, Kim, TW, Jensen, BV, Jensen, LH, Punt, C, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. New Engl J Med (2020) 383:2207–18.
134. Van Cutsem E, Cervantes A, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016; 27: 1386–1422.
135. Ogino S, Meyerhardt JA, Cantor M, et al. Molecular alterations in tumors and response to combination chemotherapy with gefitinib for advanced colorectal cancer. Clin Cancer Res. 2005; 11: 6650–6656.
136. Saletti P, Molinari F, De Dosso S, Frattini M. EGFR signalling in colorectal cancer: a clinical perspective. Gastrointestinal Cancer: Targets and Therapy. 2015 ;5: 21-38.
137. Talapatra S, Thompson CB. Growth factor signalling in cell survival: implications for cancer treatment. J Pharmacol Exp Ther. 2004; 298: 873–878.
138. Custodio A, Feliu J. Prognostic and predictive biomarkers for epidermal growth factor receptor-targeted therapy in colorectal cancer: beyond KRAS mutations. Crit Rev Oncol Hematol. 2013; 85: 45–81.
139. Dagogo-Jack I., Shaw A.T., Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol. 2018; 15: 81-94.
140. Martinelli E, Ciardiello D, et al. Implementing anti-epidermal growth factor receptor (EGFR) therapy in metastatic colorectal cancer: challenges and future perspective. Annals of Oncology, 31; 1; P30-40, Jan 2020.
141. Petrelli F, Barni S Anti-EGFR agents for liver metastases. Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: a meta-analysis. Int J Colorectal Dis. 2012; 27: 997–1004.
142. Modest DP, Martens UM, et al. FOLFOXIRI Plus Panitumumab As First-Line Treatment of RAS Wild-Type Metastatic Colorectal Cancer: The Randomized, Open-Label, Phase II VOLFI Study (AIO KRK0109) J Clin Oncol. 2019; 37: 3401–3411.
143. Rachiglio A.M., Lambiase M., Fenizia F., et al. Genomic profiling of KRAS/NRAS/BRAF/PIK3CA wild-type metastatic colorectal cancer patients reveals novel mutations in genes potentially associated with resistance to anti-EGFR agents. Cancers. 2019; 11: 859.
144. Identification of a mutation in the extracellular domain of the epidermal growth factor receptor conferring cetuximab resistance in colorectal cancer. Nat Med. 2012; 18: 221-223.
145. Botta C., Bestoso E., Apollinari S., et al., Immune-modulating effects of the newest cetuximab-based chemoimmunotherapy regimen in advanced colorectal cancer patients. J Immunother. 2012; 35: 440-447.
146. Dechant M., Weisner W., Berger S., et al. Complement-dependent tumor cell lysis triggered by combinations of epidermal growth factor receptor antibodies. Cancer Res. 2008; 68: 4998-5003.
147. Stein A., Binder M., Al-Batran S.-E., et al. Avelumab and cetuximab in combination with FOLFOX in patients with previously untreated metastatic colorectal cancer (MCRC): Results of the safety run-in phase of the phase II AVETUX trial (AIO-KRK-0216). J Clin Oncol. 2018; 36: 3561.
148. Morelli M.P., Overman M.J., Dasari A., et al. Characterizing the patterns of clonal selection in circulating tumor DNA from patients with colorectal cancer refractory to anti-EGFR treatment. Ann Oncol. 2015; 26: 731-736.
149. Cremolini C., Rossini D., Dell'Aquila E., et al. Rechallenge for patients with RAS and BRAF wild-type metastatic colorectal cancer with acquired resistance to first-line cetuximab and irinotecan: a phase 2 single-arm clinical trial. JAMA Oncol. 2019; 5: 343-350.
150. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004; 350: 2335–2342.
151. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008; 26: 2013–2019.
152. Macedo LT, da Costa Lima AB, Sasse AD. Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups. BMC Cancer. 2012; :89.
153. Gruenberger T, Bridgewater J, et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. Ann Oncol. 2015; 26: 702–708.
154. Loupakis F, Cremolini C, et al. A. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med. 2014; 371: 1609–1618.
155. Heinemann V, von Weikersthal LF, et al. 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. Lancet Oncol. 2014; 15: 1065–1075.
156. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, Yu H, Oliner KS, Go WY. PEAK: a randomized, multicenter phase II study of panitumumab plus modified

fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol. 2014; 32: 2240–2247.
157. Venook AP, Niedzwiecki D, et al. Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. JAMA. 2017; 317: 2392–2401.
158. Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, Thierauch KH, Zopf D. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011; 129: 245–255.
159. Grothey A, Van Cutsem E, et al. Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013; 381: 303–312.
160. Li J, Qin S, et al. CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2015; 16: 619–629.
161. Tournigand C, Chibaudel B, et al. Bevacizumab with or without erlotinib as maintenance therapy in patients with metastatic colorectal cancer (GERCOR DREAM; OPTIMOX3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2015 ;16: 1493–1505.
162. Daniel Adam Breadner, Stephen Welch, et al; Phase II trial of capecitabine +/- erlotinib in advanced colorectal cancer, with retrospective KRAS and primary tumor site analysis. Cancers of the Colon, Rectum, and Anus; March 21, 2017; Vol 35, No $ supl.
163. Wang Z, Dai WP, Zang YS. Complete response with fluorouracil and irinotecan with a BRAFV600E and EGFR inhibitor in BRAF-mutated metastatic colorectal cancer: a case report. Onco Targets Ther. 2019; 12: 443–447.
164. Ducreux M, Chamseddine A, Laurent-Puig P, et al. Molecular targeted therapy of BRAF-mutant colorectal cancer. Ther Adv Med Oncol. 2019; 11: 1758835919856494.
165. Lee SY, Oh SC. Advances of Targeted Therapy in Treatment of Unresectable Metastatic Colorectal Cancer. Biomed Res Int. 2016; 2016: 7590245.
166. Sai Ge, et al. Famitinib exerted powerful antitumor activity in human gastric cancer cells and xenografts. Oncol Lett. 2016 Sep;12(3):1763-1768.
167. Tianshu Liu et al., Camrelizumab plus famitinib in patients with metastatic colorectal cancer: Results from an open-label, multicenter phase II basket study. JCO 40, 3577-3577(2022).
168. Kumar A, Gautam V, Sandhu A, Rawat K, Sharma A, Saha L. Current and emerging therapeutic approaches for colorectal cancer: A comprehensive review. World J Gastrointest Surg 2023; 15(4): 495-519.
169. Mody K, Baldeo C, Bekaii-Saab T. Antiangiogenic therapy in colorectal cancer. Cancer J 2018; 24: 165–170.
170. Golshani G, Zhang Y. Advances in immunotherapy for colorectal cancer: a review. Therap Adv Gastroenterol. 2020 Jun 1; 13: 1756284820917527.
171. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014; 515: 568–571.
172. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018; 19: 940–952.
173. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017; 18: 1182–1191.
174. André T, Lonardi S, Wong M. et al. Nivolumab + ipilimumab combination in patients with DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer: first report of the full cohort from CheckMate-142. Paper presented at 2018 Gastrointestinal Cancers Symposium, 20 January 2018 Abstract 553. San Francisco, CA, USA.
175. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017; 357: 409–413.
176. Marcus L, Lemery SJ, Keegan P, et al. FDA approval summary: pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res 2019; 25: 3753–3758.
177. Eng C, Kim TW, Bendell J, et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol 2019; 20: 849–861.
178. Grothey A, Tabernero J, Arnold D, et al. LBA19Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy. Ann Oncol 2018; 29: LBA19.
179. Amanda L. Wooster, Lydia H. Girgis, Hayley Brazeale, Trevor S. Anderson, Laurence M. Wood, Devin B. Lowe. Dendritic cell vaccine therapy for colorectal cancer, Pharmacological Research, Volume 164, 2021, 105374, ISSN 1043-6618,
180. Magee MS, Abraham TS, Baybutt TR, et al. Human GUCY2C-targeted chimeric antigen receptor (CAR)-expressing T cells eliminate colorectal cancer metastases. Cancer Immunol Res 2018; 6: 509–516.
181. Mühlbacher F, Huk I, Steininger R, Gnant M, Götzinger P, Wamser P, Banhegyi C, Piza F. Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? Transplant Proc. 1991; 23: 1567–1568.
182. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery. 1991; 110:726–34; discussion 734-5.
183. Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, Boberg KM, Mathisen O, Gladhaug IP, Egge TS, Solberg S, Hausken J, Dueland S. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013; 257:800–806.
184. Dueland S, Guren TK, Hagness M, Glimelius B, Line PD, Pfeiffer P, Foss A, Tveit KM. Chemotherapy or liver transplantation for nonresectable liver metastases from

colorectal cancer? Ann Surg. 2015; 261:956–960.
185. Dueland S, Syversveen T, Solheim JM, Solberg S, Grut H, Bjørnbeth BA, Hagness M, Line PD. Survival Following Liver Transplantation for Patients with Nonresectable Liver-only Colorectal Metastases. Ann Surg. 2020; 271:212–218.
186. Krell, R.W.; Reames, B.N.; Hendren, S.; Frankel, T.L.; Pawlik, T.M.; Chung, M.; Kwon, D.; Wong, S.L. Surgical Referral for Colorectal Liver Metastases: A Population-Based Survey. Ann. Surg. Oncol. 2015, 22, 2179–2194.
187. Hellingman, T.; de Swart, M.; Joosten, J.; Meijerink, M.; de Vries, J.; de Waard, J.; van Zweeden, A.; Zonderhuis, B.; Kazemier, G. The value of a dedicated multidisciplinary expert panel to assess treatment strategy in patients suffering from colorectal cancer liver metastases. Surg. Oncol. 2020, 35, 412–417.