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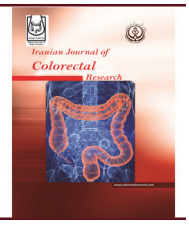

Current Concepts in the Management of Colorectal Liver Metastases: A Narrative Review

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Abstract

Colorectal cancer is a leading cause of cancer mortality worldwide, ranking as the third most common cause of death in men and the second in women. In Sub-Saharan Africa, the estimated incidence is 4.04 per 100,000, with slightly higher rates in men compared to women. The liver is the most common site for colorectal cancer metastases, with approximately 50% of patients developing liver metastases during the disease. Multidisciplinary approaches involving colorectal and liver surgeons, oncologists, radiologists, and other specialists have become critical in managing colorectal liver metastases (CRLM). We conducted a search on PubMed and Google Scholar using related keywords. Articles discussing the management of CRLM were included in this review. Historically, liver resections began in the late 19th century, with significant advancements such as the development of ultrasonic scalpels, preoperative portal vein embolization, and vascular staplers. Understanding CRLM progression involves recognizing mutations in tumor suppressor genes and oncogenes, which lead to uncontrolled cell growth, invasion, and metastasis. Surgical approaches include classical, synchronous, and liver-first strategies. Resectable CRLM typically involves wedge or anatomic resections. For unresectable cases, therapies such as radiofrequency ablation, microwave ablation, and hepatic artery infusion may be used. Novel techniques, including two-stage hepatectomy and associated liver partition and portal vein ligation for staged hepatectomy, along with conversion chemotherapy, have improved resection rates and survival outcomes. The management of CRLM has evolved significantly due to advancements in surgical techniques and therapies, emphasizing the need for specialized training and a multidisciplinary approach, particularly in regions such as Sub-Saharan Africa.

Keywords: Colorectal neoplasms; Liver neoplasms; Hepatectomy

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Introduction

Colorectal cancer is the third most common cause of mortality among men and the second leading cause of mortality among women worldwide (1). In 2012, more than one million new cases and approximately 693,900 deaths were recorded globally (2). The overall incidence remains low in various

regions of Africa, Hence in Sub-Saharan Africa, the estimated incidence is 4.04 per 100,000 with approximately 4.38 for men and 3.69 for women (1).

The liver is the most common site of colorectal cancer metastasis. Approximately 50% of colorectal cancer patients will develop liver metastases (3). Initially, fewer than 10% of colorectal cancer patients were considered for surgical intervention; however, with advancements in surgical techniques, an increasing number of such patients with colorectal liver metastases (CRLM) are now being considered for surgical treatment. Currently, hepatic tumor resections are performed in one-third of patients with CRLM (4). This has been made possible through various protocols and strategies aimed at increasing the number of patients eligible for surgical intervention (4-6). Hence, the involvement of a multidisciplinary team has become essential (7, 8). This team includes specialized surgeons (colorectal and liver), medical oncologists, pathologists, radiologists, and nurses (8). This article aims to review the historical perspective, natural history, classification, and various treatment protocols for CRLM.

Historical Perspective

The first recorded hepatectomy for a tumor was performed by Lius of Italy in 1886, when a pedicled mass was excised from the left hepatic lobe (9). In 1887, Carl Langenbuch also removed another pedicled mass from the liver (10). Eventually, the 30-year-old underwent re-exploration for reactionary hemorrhage, but she survived. All these initial liver resections were conducted under the belief that the falciform ligament separated the right lobe from the left lobe of the liver. In 1897, Cantlie described the imaginary plane that separates the right and left lobes of the liver, which connects the gallbladder bed to the inferior vena cava (11). Hence, Keen of Philadelphia performed the first left lateral sectionectomy in 1899 (12). Meanwhile, Wendell conducted the first successful right hepatectomy with ligation of the hepatic hilum in 1911 (13).

An extended right hepatectomy was performed on a 22-year-old patient with CRLM by Ichio Hinjo in 1955 (14). The liver was divided into eight segments based on the distribution of the portal vein branches by Couinuad in 1954 (Figure 1) (15). In 1963, Thomas Starzl conducted the first orthotopic liver transplant in humans (16). Starzl also performed the first extended left hepatectomy, known as left trisegmentectomy (17). To reduce intra-operative hemorrhage, Hodgson (1979) developed an ultrasonic scalpel that fragments liver parenchyma while preserving the vessels and bile ducts (18). In 1982, Makuuchi et al. perfected the technique of preoperative portal vein embolization to induce atrophy in the segment proposed for resection (19). McEntee introduced the use of a vascular stapler (20).

Search Strategy

The research question was: What are the current methods for treating colorectal liver metastases? We conducted a search on the PubMed and Google Scholar using the following keywords and medical subject headings (MeSH) terms: colorectal neoplasm, liver metastases, high-intensity focused ultrasound, radiofrequency ablation, microwave ablation, irreversible electroporation, hepatic artery infusion therapy, transarterial chemoembolization, liver transplantation, selective internal radiation therapy.

The literature search was completed in October 2024. The inclusion criteria consisted of articles discussing the treatment modalities for various scenarios of colorectal liver metastases. We excluded conference papers and abstracts.

Natural History of the Malignant Cells

The normal colonocytes undergoe mutation due to changes in tumor suppressor genes, DNA repair genes, and/or oncogenes. As a result, they experience uncontrolled proliferation and reduced apoptosis, leading to in situ tumor formation (21, 22).

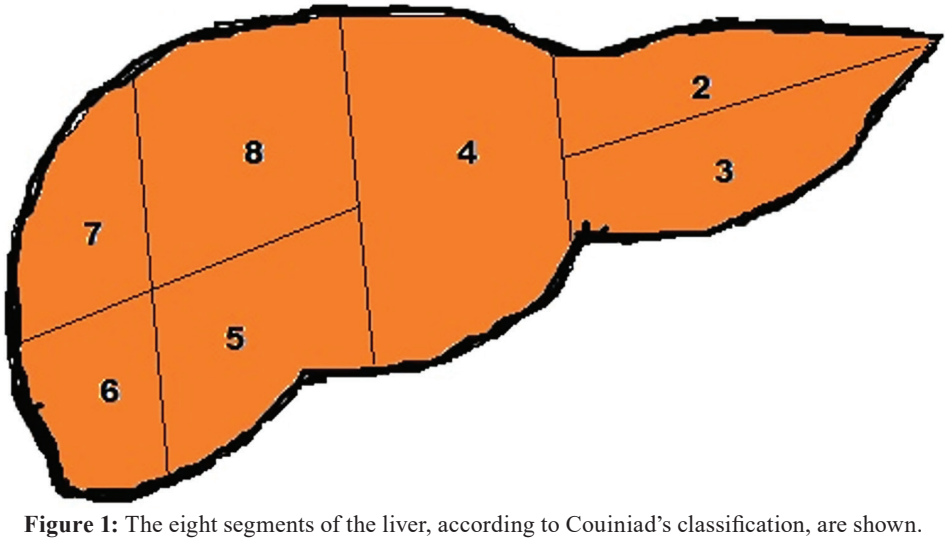

Figure 1: The eight segments of the liver, according to Couiniad's classification, are shown.

Further growth and metastasis of the tumor cells are caused by epithelial-mesenchymal dissociation and stromal invasion, neoangiogenesis and lymphangiogenesis, evasion of tumor cell destruction in the blood; and liver colonization.

The progressive growth of malignant cells in the colon leads to an epithelial-mesenchymal transformation, during which the epithelial cells are converted to mesenchymal cells; stimulated principally by transforming growth factor-beta (TGF-β) (23). Consequently, there is E-Cadherin/β-Catenin dissociation with associated disruption of the normal intercellular adhesion (24, 25). This will lead to detachment of tumor cells. Further production of proteases will stimulate their stroma invasion.

Angiogenesis occurs in carcinomas, particularly in the presence of hypoxia or low oxygen tension. Hypoxia leads to downregulation of the angiogenesis suppressing factors such as thrombospondin while increasing the secretion of angiogenic factors by tumor cells, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) (26, 27). The blood vessels that forms in tumors are leaky and exhibit a disorganized arrangement, leading to oxygen depletion within the tumor and permitting intravasation of tumor cells (26, 28). Additionally, concurrent lymphangiogenesis occurs under the influence of VEGF-C and VEGF-D *in vivo* (29, 30). A high level of lymphangiogenesis in colorectal cancer (CRC) is associated with metastasis to the liver, aside from lymph node metastasis (31).

There is an increased survival rate of metastatic tumor cells within blood vessel. Ideally, the destruction of the tumor cells is mediated by mechanical forces, such as stress forces, shearing forces, and endothelial contractions, which generate free oxygen radicals, as well as immune destruction by cytokines (e.g., interleukin-2 [IL-2], interleukin-12 [IL-12], and interleukin-18 [IL-18]) produced by T lymphocytes and natural killer cells (32, 33). The mechanical forces are evaded by circulating tumor cells through binding with platelets to form emboli or by activating the adhesion pathway with subsequent adherence to the endothelial cells (34). The tumor cells evade immune destruction by forming tumor emboli and a large volume of acute-phase glycoproteins (35).

Within the liver, tumor cells form dormant micro- or macro-metastases, and they also adhere to sinusoidal endothelial cells, which is important for colonization (36). The progressive growth of metastatic tumor deposits depends on the evasion of the liver's defense mechanisms and adequacy of blood supply.

A recent research has demonstrated that colorectal tumors exhibiting superoxide dismutase 3 (SOD3), reduce the expression of Ki-67 and liver metastases in mouse tumor models. It is hoped that this could be used to predict prognosis in the care of CRLM (37).

Classification of CRLM

CRLM can be classified as either synchronous or metachronous. Synchronous liver metastases are diagnosed at the same time as the primary tumor and tend to have a poor prognosis (8), while early metachronous metastases are identified within 12 months after diagnosis or surgical removal of the primary tumor. Late metachronous metastases are detected after 12 months following diagnosis or removal of the primary tumor (38).

Evaluation of Patients with CRLM

Investigations are conducted to diagnose, prognosticate, and determine the resectability of tumors in patients with CRLM. The imaging modalities that can be utilized include Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scans. FDG-PET has demonstrated the highest sensitivity at 94.1%. However, MRI remains the most sensitive method for detecting lesions smaller than 10 mm (39). Consequently, MRI is considered the first-line imaging technique for detecting CRLM. Nevertheless, the choice of imaging should be guided by availability and expertise of local radiologists. Yoon et al. found that employing machine learning techniques for liver MRI shows promising potential in predicting treatment responses, particularly in patients undergoing biologic therapy (40).

A biopsy of the lesion is necessary to confirm the diagnosis and rule out other differential diagnoses. However, there is a minimal risk of tumor seeding (41). The biopsy can be performed using percutaneous, laparoscopic, or open techniques.

Carcinoembryonic Antigen (CEA) levels may be elevated in approximately 90% of individuals with CRLM (42). A persistent elevation of CEA after an initial decline may serve as the first indication of either local or distant recurrence in asymptomatic patients (42). Bone scintigraphy can be ordered for individuals suspected of having bone metastases. Additional investigations may include liver function tests, electrolytes levels, urea and creatinine measurements, coagulation studies, and complete blood counts.

The evaluation of liver resectability can be conducted through various methods. The metabolic function of the liver can be assessed using Indocyanine Green (ICG) clearance and hepatic scintigraphy (43). ICG clearance is the most commonly utilized functional study; however, its limitations include the fact that uptake is influenced by elevated bilirubin levels, and it does not provide a characterization of the metabolic function of different regions of the liver (44). Hepatic scintigraphy employs Technetium-99m-labeled mebrofenin, with a cut-off value of 2.7%/min·m² considered indicative for both normal

and diseased livers. This method serves as a better predictor of liver failure after liver resections (45). CT volumetry can also be used due to its ability to ensure an adequate future liver remnant (FLR). The minimum FLR value is 25% for a healthy normal liver and 40% for a cirrhotic liver (46).

Fong's Clinical Score is effective in stratifying patients with CRLM. This is based on: CEA>200 ng/ml, the largest tumor>5 cm, a disease-free interval of less than 12 months from the primary diagnosis to the onset of metastasis, and the number of tumors of more than one (47). The Model for End-Stage Liver Disease (MELD) Score predicts survival, while the Child-Pugh-Turcotte (CPT) Score is used to assess patients for potential resection in CRLM. However, these two scoring systems do not recognize postoperative liver failure, so they are not useful in the preoperative setting (48-50).

Approaches to Surgical Treatment for Resectable Synchronous Disease

Resection of hepatic metastases can be performed using classical, synchronous, or liver-first approaches. In the classical approach, the initial resection of the primary CRC is followed by a later liver metastasectomy (51). This method avoids potential complications of the primary tumor, such as obstruction and invasion into adjacent organs. However, there is a risk of disease progression in CRLM and a high rate of treatment dropout, with less than one-third of patients completing the treatment. The synchronous approach involves the simultaneous removal of both the primary tumor and CRLM during a single operation. This method typically results in a shorter hospital stay compared to staged procedures and does not affect perioperative morbidity or long-term prognosis. In the liver-first approach, the liver metastases are resected prior to addressing the primary tumor. This approach is used in cases of asymptomatic primary tumors with large-volume CRLM or when the primary tumor is locally advanced, such as rectal carcinoma that requires chemoradiation (52).

Surgical Treatment

The resection of CRLM results in a median survival of over three years, with perioperative complication and mortality rates of 20% and 1-5%, respectively (53). Different types of resections include wedge resections and anatomic resections. The extent of surgical resection is determined by the location and size of the metastases, as well as the distance of the tumor from the main vasculature and bile ducts. Wedge resections are employed for small peripheral tumors that are located far from the liver hilum. Due to minimal blood loss, this procedure can be performed without vascular occlusion (52). Anatomic resections, which may involve uni- or polysegmentectomy, require the ligation of the segmental vascular and biliary pedicles (Figure 2).

The segmental anatomy of the liver can be identified using an ultrasonic aspirator or by injecting methylene blue into the portal pedicle (54). Multi-segmental resections depend on the primary right and left portal pedicles and include: a) left lateral sectionectomy; b) left hemi-sectionectomy (Segments two, three, four, five, and eight); c) right hepatectomy (Figure 3); d) right anterior sectionectomy (Segments five and eight); and e) right posterior sectionectomy (Segments six and seven).

Contraindications to the resection of hepatic metastases include the presence of unresectable extrahepatic disease, inability to have adequate functional hepatic tissue, portal or celiac lymph nodes metastases (55, 56).

The principles of preoperative care include: a) maintaining a normal coagulation profile; b) administering prophylactic antibiotics; c) performing biliary decompression through endoscopic or percutaneous intubation in cases of bile duct obstruction; d) implementing infection control; and e) ensuring that there is no risk of postoperative liver failure (52).

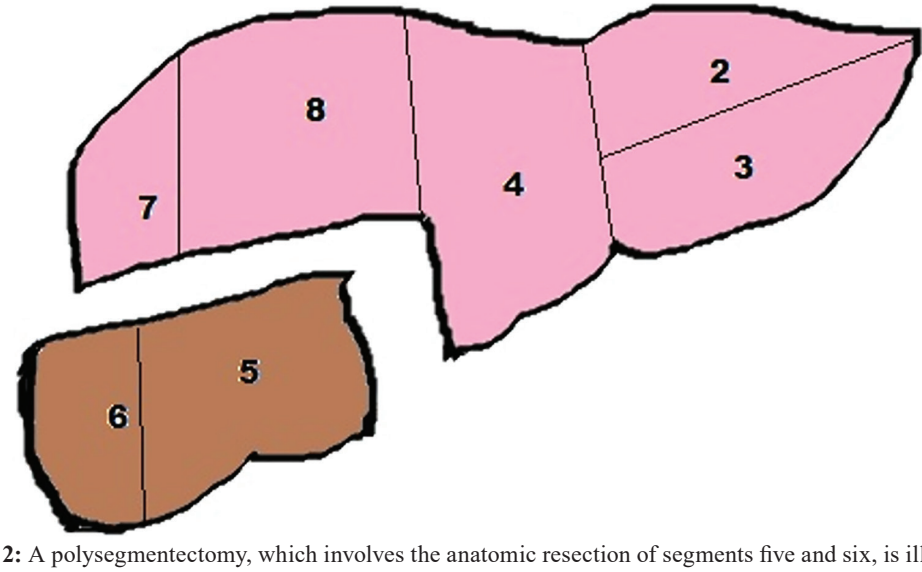

Figure 2: A polysegmentectomy, which involves the anatomic resection of segments five and six, is illustrated.

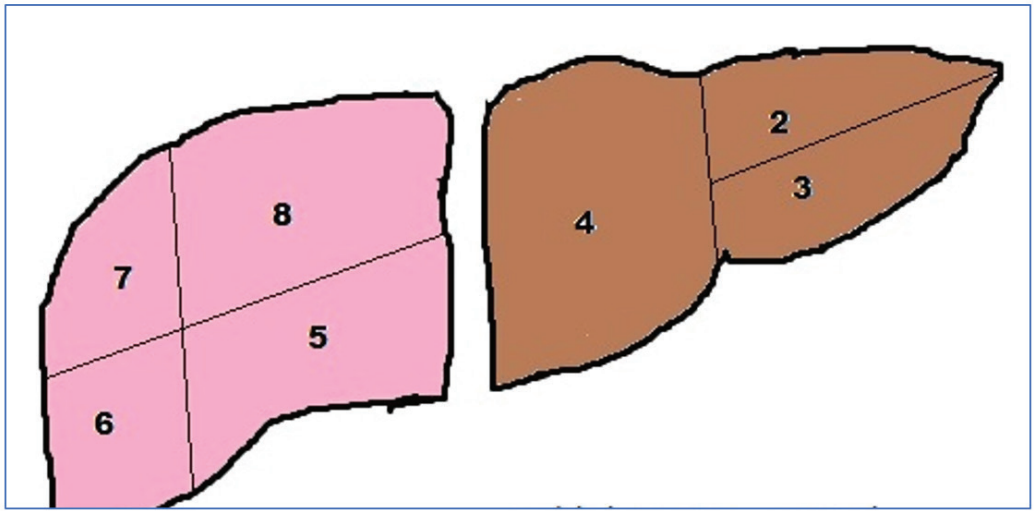

Figure 3: A right hepatectomy which involves the excision of segments five, six, seven, and eight of the liver is illustrated.

During surgery, the principles of care include: a) the use of large-bore intravenous access for rapid resuscitation; b) hypotensive anesthesia to reduce parenchymal blood loss; c) ensuring a negative tumor margin in the resection; and d) preserving the afferent and efferent vasculature of the liver.

In the postoperative period, the following principles should be adhered to: a) the administration of appropriate fluids, including, the addition of albumin to the standard crystalloid regimen to reduce weight gain; b) ensuring normal urine output; c) effective pain control to improve pulmonary function; d) the use of broad-spectrum antibiotics; e) deep vein thrombosis prophylaxis.

Two-stage hepatectomy (TSH) involves the removal of CRLM in two separate surgical procedures. This approach is used for selected patients with advanced disease involving the two lobes of the liver. With a single procedure, excising all lesions with a negative margin is impossible. Preoperative chemotherapy can be administered to selected patients to aid in complete resection (57).

Associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a novel surgical procedure that involves the ligation of the portal vein and liver transection during the initial surgery, followed by the resection of the liver segment containing metastases approximately 7 to 14 days later. This technique causes more FLR hypertrophy (58), and has a higher rate of resection than TSH in advanced CRLM (59). It has a higher morbidity and mortality rates than TSH (58).

Parenchymal-sparing hepatectomy (PSH) enables the possibility of serial or repeated resections in the event of intrahepatic recurrence. In patients experiencing recurrence, PSH is associated with salvage surgery, resulting in improved 5-year survival rates (60).

Liver-Directed Treatment in Unresectable CRLM

Radiofrequency ablation (RFA) utilizes an electrode to deliver heat through high-frequency alternating current. This technique is associated with a significant local recurrence rate, which varies between 5% and 60% across different studies. Additionally, RFA can lead to tissue desiccation (charring) and a heat-sink effect that impacts energy delivery (61).

Microwave ablation (MWA) produces heat energy from the oscillating molecules of water. It has a lower recurrence rate compared to RFA and also produces less heat sink effect and charring; therefore, it offers a better safety profile for the treatment of lesions close to major hepatic vessels (62, 63).

Irreversible electroporation (IRE) utilizes high-voltage, direct current to induce cellular membrane disruption through the formation of large pores, causing apoptosis. Its mode of action is nonthermal. It is used for treating unresectable tumors close to vessels and bile ducts, where RFA is considered less effective (61). It is a better salvage option than ablation for unresectable CRLM (64).

Hepatic artery infusion (HAI) therapy is a localized treatment indicated for patients with liver-only or liver-predominant metastatic disease. Tumoricidal and/or embolizing agents are selectively infused into the branches of the hepatic artery to improve their delivery to liver tumors while minimizing systemic toxicity. The selection criteria include: a) the presence of more than 30% tumor-free liver parenchyma; b) normal hepatic function without features of portal hypertension; and c) patients exhibiting a good performance status (65). In the literature, various studies describing the use of Fluorodeoxyuridine (FDR), oxaliplatin, 5-fluorouracil, and mitomycin C in HAI therapy of CRLM (66-68). However, the use of FDR has been limited due to the need for continuous infusion over 14 days and its associated biliary toxicity (69). In contrast, oxaliplatin is associated with lower toxicity, has an infusion time of approximately 2 hours, and demonstrates a conversion rate of 25% (70-72).

Trans-arterial chemoembolization (TACE) is a procedure that targets cancer cells through the

induction of ischemia and the administration of high concentrations of cytotoxic agents. Drug-eluting bead (DEB)-TACE utilizes microspheres that contain cytotoxic drugs such as doxorubicin or irinotecan. It is considered useful in CRLM that cannot be resected or ablated (65). When administered after the failure of first-line therapy, it has the potential to increase progression-free survival (73).

Selective internal radiation therapy (SIRT) involves the infusion of radiolabeled microspheres (Yttrium-90) into the hepatic arterial system. This method allows for targeted radiation delivery to the tumor while minimizing or eliminating toxicity to the surrounding healthy liver tissue (74).

Portal vein embolization (PVE) is used for patients with unresectable liver metastases to facilitate potential surgical resection. It is indicated when the functional FLR is less than 25% of the initial hepatic volume. Following compensatory hypertrophy of the hepatic remnant, surgical resection can be performed 4 to 6 weeks after the procedure (75).

High-Intensity Focused Ultrasound (HIFU) is an innovative ablative technique for treating CRLM. Its application is promising due to the absence of organ injury and pain associated with the use of percutaneous probes, which are common in other forms of ablation. A study conducted by Yang et al. reported that HIFU demonstrated an objective response rate of 97.7%, with a median overall survival of approximately 31 months (76). Additionally, HIFU provided improved local control and extended the median progression-free survival (77). Future research should include randomized controlled trials to compare various ablative techniques for the treatment of liver metastases.

Liver transplants may also be used for patients with unresectable CRLM. It has been found that patients who underwent liver transplants experienced better overall survival rate compared to those who received PVE (78). There is still a need for a large, randomized controlled trial to compare liver transplants with other modalities for treating CRLM.

There is a high risk of radiotherapy-induced liver disease when conventional radiotherapy is used to treat CRLM (79). Therefore, stereotactic body radiation therapy (SBRT) is an evolving technique for treating CRLM, especially in patients with oligometastases. It reduces the adverse effects of radiation on the liver and surrounding healthy tissues (80).

Conversion Chemotherapy Regimen

Some patients with initially unresectable CRLM may become resectable following conversion chemotherapy, which has been associated with improved survival rates (81). The most effective conversion chemotherapy regimen remains uncertain. The use of doublet chemotherapy, such as FOLFOX or FOLFIRI, is associated with conversion rates ranging from 9% to 33% (82). Triplet chemotherapy, specifically FOLFOXIRI, demonstrate a higher R0 resection rate and improved survival; however, it is also associated with increased toxicity (83). The use of targeted therapy during conversion chemotherapy results in a higher overall response rate compared to chemotherapy alone (68% vs. 43%), although it does not enhance survival. Examples of targeted therapies include Bevacizumab, an anti-vascular endothelial growth factor (VEGF) agent, and Cetuximab, an epidermal growth factor receptor (EGFR) inhibitor.

Adjuvant Chemotherapy Regimen: According to the latest ESMO guidelines (84), there is no evidence to support the use of adjuvant chemotherapy in patients who have undergone R0 resection. Therefore, the use of adjuvant therapy is indicated for patients with unfavorable prognostic criteria or those who have not received any previous chemotherapy for metastatic disease. In the adjuvant setting following the resection of CRLM, there is no concrete evidence to support the combination of chemotherapy and targeted therapy. Furthermore, the addition of targeted therapy does not prolong survival but also causes increased biliary toxicity (85).

Treatment Under Special Circumstances

Disappearing liver metastases (DLM) are CRLMs that have diminished on cross-sectional imaging following neoadjuvant treatment. MRI is preferred due to its high sensitivity (86). The application of Augmented Reality, which involves the fusion of reconstructed pre-treatment CT images with real-time patient images, has facilitated the localization of DLM during surgery (87). While Some DLMs may remain unresected, this decision should be made in consultation with a multidisciplinary team (88). Ablation of DLM sites is also a potential option; however, current evidence does not support its efficacy. DLM can be prevented by restaging the CRLM after the administration of three cycles of neoadjuvant therapy, and the overall course of chemotherapy should not exceed four to six cycles.

There is a unique challenge in managing borderline resectable disease due to insufficient FLR. Various treatment methods can be employed, including PVE, which can increase FLR volume by a 43.1%; ALPPS or a TSH.

For unresectable CRLM, the treatment approach is multidisciplinary. The two approaches include conversion therapy with curative resection and the use of liver-directed therapies.

Conclusion

The management of CRLM has evolved into a multidisciplinary approach. Recent advances in management have resulted in improved patient outcomes. Surgical resection of CRLM remains the cornerstone of curative treatment. There is an urgent need for training Hepato-Pancreato-Biliary

(HPB) surgeons capable of performing ablative liver interventions in Sub-Saharan Africa and other developing countries.

Authors' Contribution

Both the first and second authors contributed to the conception and design of the work. They were also involved in the acquisition, analysis, and interpretation of the data. Additionally, both authors participated in drafting and reviewing the manuscript and approved the final version. They also agree to be accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part of the work are thoroughly investigated.

Conflict of interest: None declared.

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