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Pathogenetic development, diagnosis and clinical therapeutic approaches for liver metastasis from colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC) is a prevalent malignancy and a significant proportion of patients with CRC develop liver metastasis (CRLM), which is a major contributor to CRC-related mortality. The present review aimed to comprehensively examine the pathogenetic development and diagnosis of CRLM and the clinical therapeutic approaches for treatment of this disease. The molecular mechanisms underlying CRLM were discussed, including the role of the tumour microenvironment and epithelial-mesenchymal transition. The present review also highlighted the importance of early detection and the current challenges in predicting the development of CRLM. Various treatment strategies were reviewed, including surgical resection, chemotherapy and immunotherapy, and the potential of novel therapies, such as selective internal radiation therapy and Traditional Chinese Medicine. Despite recent advancements in treatment options, the treatment of CRLM remains a therapeutic challenge due to the complexity of the liver microenvironment and the heterogeneity of CRC. The present review emphasized the need for a multidisciplinary approach and the integration of emerging therapies to improve patient outcomes.

Contents

1. Introduction

Colorectal cancer (CRC) is one of the most prevalent malignancies of the digestive system, ranking third in terms of global cancer incidence and second in global cancer mortality rates (1). Of all the patients with CRC, ~20% are initially diagnosed with metastatic CRC (mCRC) and 50% will develop metastases at a later stage (2). Distant metastasis is a leading cause of death among patients with CRC, with liver metastasis being the most common route for distant spread in advanced stages. At the time of diagnosis, 20-25% of patients with CRC already exhibit liver metastasis, while up to 50% may develop metachronous liver metastasis following excision of the primary tumour. Early detection of liver metastases from CRC and subsequent curative resections can result in a 5-year survival rate ranging from 30-57%. By contrast, patients who are not eligible for resection face a 5-year survival rate of <5% (3-5). Of all the patients with CRC, ~90% cannot undergo curative liver resection at the time their liver metastasis is diagnosed (6). Therefore, early detection of CRC-related liver metastases and targeted interventions are crucial for improving patient prognosis; however, there is currently no efficient method for the early prediction of these liver metastases in clinical practice.

In the past century, numerous hypotheses have been proposed regarding the molecular mechanisms underlying the metastasis of malignant tumours, with Paget's 'seed and soil' theory being the most prominent (7). This theory suggests that tumour metastasis results from the interaction between the 'seed' (tumour cells) and the 'soil' (tumour microenvironment). Additionally, epithelial-mesenchymal transition (EMT) is recognized as a critical factor in facilitating the initiation of metastasis (8-10). EMT is a biological process wherein epithelial cells undergo transformation into mesenchymal cells

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under specific conditions, significantly influencing distant tumour metastasis (8).

The treatment of liver metastases in patients with CRC poses significant challenges and remains a leading cause of mortality. The prognosis for individuals diagnosed with colorectal liver metastasis (CRLM) is generally poor, with survival outcomes closely associated with various clinical and pathological factors, including the type of pathology, tumour grade and extent of tumour spread and invasion (11). Specific determinants, such as tumour size, proximity to the anal margin and the number of metastatic liver lesions also serve critical roles in the prediction of patient prognosis (12). The primary treatment options for CRLMs include surgical resection and chemotherapy. However, only ~10-20% of these patients are deemed suitable for surgical intervention at the time of diagnosis (13). For patients who undergo surgery, the 5-year survival rate after surgery varies considerably, ranging from 20-50%. This variability is influenced by factors such as age, comorbid health conditions and tumour characteristics (14). Conversely, patients who are not candidates for surgery face a poorer prognosis (15). Despite advancements in chemotherapy regimens, the effectiveness of these treatments is frequently compromised by the development of side effects and resistance, particularly concerning therapies based on fluorouracil and platinum compounds (16). This situation highlights the urgent necessity for the development of more precise and effective treatment strategies aimed at improving the long-term survival prospects for patients with CRLMs. The present review aimed to summarise the mechanisms underlying the pathogenetic development of CRLM, examine current diagnostic strategies and explore clinical therapeutic approaches, with a particular emphasis on integrating emerging therapies alongside conventional treatments.

2. Pathogenetic development of CRLM

Tumour cells metastasize to the liver. Cancer cells can often be found in specific organs when cancer cells encounter an organ environment that allows them to proliferate, leading to metastasis (17). The liver is favoured by various types of cancer, including cancers of the colon, stomach, breast and lungs, which often spread to the liver (18). The liver is an organ with both an active metabolism and immune function, and fosters certain conditions that can promote the proliferation of cancer cells (19). Colon cancer, for example, has been reported to commonly metastasize to the liver (20), largely due to the structure of the liver as it receives blood from both the portal vein and the hepatic artery, which provides cancer cells an easier path to enter the liver (21). Additionally, the proximity of the colon to the liver, particularly from areas such as the hepatic flexure, can make it easier for cancer cells to directly invade the liver from nearby tumours (22). Moreover, factors such as the high permeability of hepatic sinusoidal endothelial cells combined with slow blood flow within the liver may further promote tumour colonization (23). In addition, the liver has immune properties that allow it to tolerate foreign cells and this immunosuppressive environment may contribute to cancer growth (24,25). Certain chemokines produced by liver cells can help promote the spread of cancers, such as colon cancer, to the liver (26). The C-X-C motif chemokine ligand 12/C-X-X motif chemokine receptor (CXCR) 4/CXCR7 pathway has been associated with CRC recurrence and its metastasis to the liver (27). Furthermore, extracellular vesicles released by CRC cells may enhance liver metastasis through the activation of hepatic stellate cells while modulating the surrounding tumour microenvironment (28). In conclusion, the liver provides a suitable environment or 'soil' for the spread and growth of CRC cells (Fig. 1).

EMT. EMT is a biological process in which epithelial cells change and take on features of mesenchymal cells. This can occur at different times, such as when embryos are developing, tissues are forming, healing is occurring or when there is fibrosis in tissues (29). In cancer, EMT has been linked to the early stages of tumour growth, spread and resistance to treatments (30). As cells undergo EMT, they start losing epithelial cell features, causing them to be less adherent to other cells and the surrounding matrix. The key to this shift is a decrease in the expression level of E-cadherin, an epithelial marker, whereas the expression levels of N-cadherin and vimentin, markers of mesenchymal cells, increase (31). Consequently, the ability of the cells to move or migrate strengthens, allowing them to invade neighbouring tissues and blood or lymphatic vessels, thereby travelling to distant organs (31). Therefore, targeting the EMT may prevent tumours recurring after surgery. However, directly targeting EMT for drug development poses significant challenges due to the complexity and heterogeneity of the involved pathways. Nevertheless, EMT inhibitors together with chemotherapy may have potential for use in patients with cancer to help prevent drug resistance, particularly in metastatic CRC. Using such inhibitors after tumour removal could reduce the chances of tumour recurrence (32,33).

Circulating tumour cells (CTCs). During EMT, there is a major decrease in cell adherence (34). This allows tumour cells to move and invade surrounding tissues more easily. As these cells enter blood vessels or the lymphatic system, they can travel to establish new tumours (35). The cells that are able to travel in the blood are CTCs (36). However, most CTCs do not successfully spread, as immune cells in the blood target and eliminate them (36). CTCs that have undergone EMT have an increased ability to migrate, invade and escape the immune system compared with those that have not undergone EMT (37). CTCs with mesenchymal traits and stem-like properties are more likely to form new tumour colonies when they encounter suitable environments for growth. Recent research has shown that CTCs can travel in the bloodstream as individual cells or in clusters (38,39). Cell clusters are smaller in number but exhibit greater transfer capacity compared with individual CTCs due to their greater ability to metastasize, causing phenotypic changes in the tumour cells in the cell cluster. It has previously been reported that the DNA in cancer cells from CTC clusters has lower methylation levels compared with the DNA in single CTCs, particularly in genes related to stemness and cell growth. The hypomethylation of genes such as Oct4 and Nanog leads to the upregulation of their expression, giving cancer cells the ability to self-renew and undergo multidirectional differentiation, similar to stem cells, which is critical for tumour metastasis formation in distant organs (38).

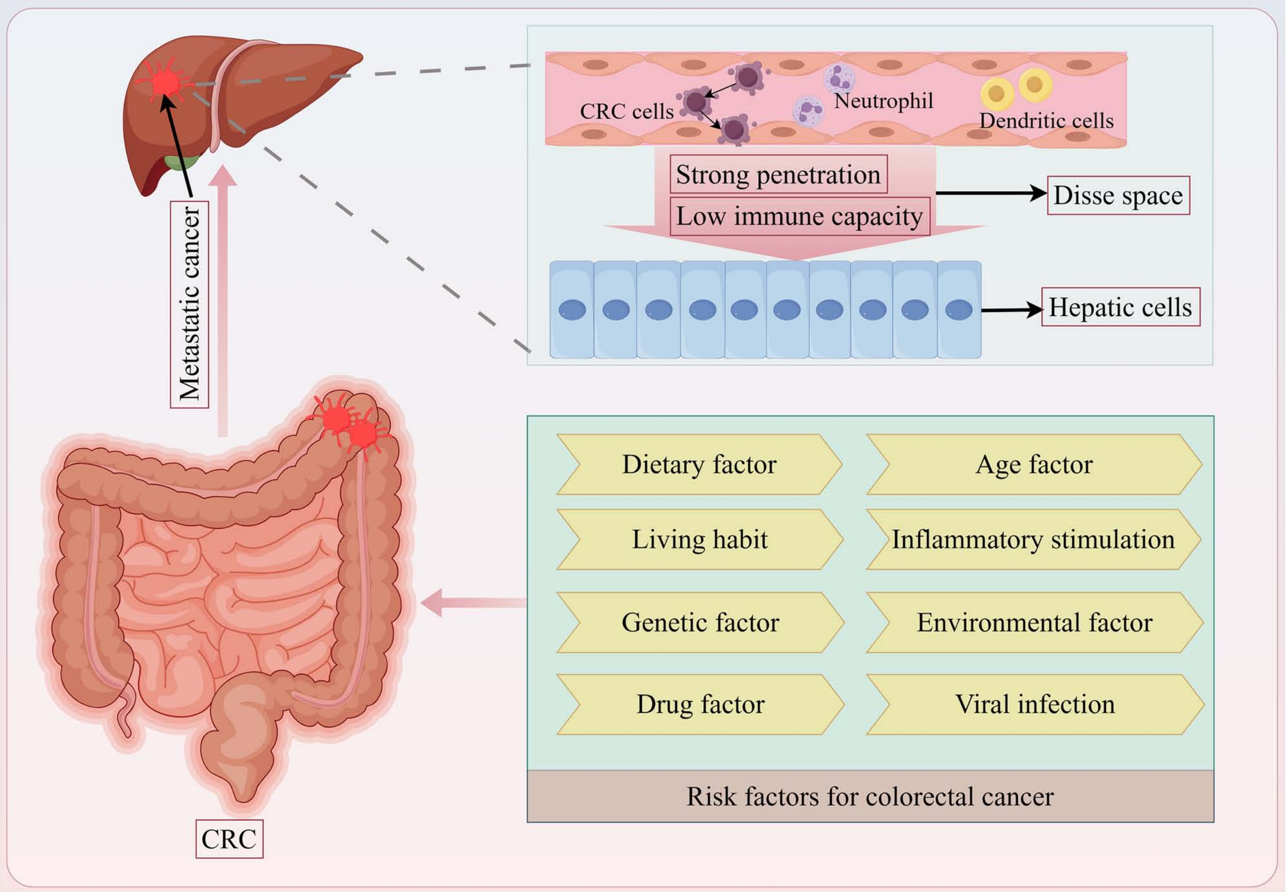

Figure 1. Molecular mechanism of liver metastasis in CRC. CRC, colorectal cancer.

Additionally, EMT markers are more highly expressed in CTC clusters compared with isolated cells (40). Moreover, these clusters include other cells from the tumour environment, such as platelets, immune cells and fibroblasts, which help tumour cells as they spread (41). Platelets form a physical barrier on the surface of tumour cells to evade the attack of the immune system (42). When platelets bind to CTCs, they secrete TGF-β, which helps to maintain the EMT state of tumour cells and promote tumour cell metastasis (43). It has previously been reported that neutrophils in CTC clusters can regulate the cell cycle of tumour cells, thereby promoting tumour metastasis (44). Furthermore, Duda *et al* (45) reported that fibroblasts in CTC clusters also serve a role in tumour cell metastasis.

Cytological study of CRLM. Upon entering the liver, metastatic cells interact with native liver cells, thereby establishing a unique niche (46). This specialized microenvironment comprises various cell types, including parenchymal hepatocytes, liver sinusoidal endothelial cells (LSECs), Kupffer cells, hepatic stellate cells (HSCs) and natural killer (NK) cells (47). These resident intrahepatic cells have specific functions and can interact with tumour cells, affecting the metastasis and progression of tumour cells. These reactions are complex and are important for understanding how metastasis works. It has been previously suggested that different types of liver cells cooperate with tumour cells and this cooperative relationship has a dual nature. On one hand, this relationship may aid with the invasion and metastasis of tumour cells, facilitating the spread of tumours within the body, whilst on the other hand it also has the potential to activate the body's immune defence mechanisms, helping the body recognize and effectively kill tumour cells (Fig. 2) (48).

Hepatocytes. Hepatocytes account for ~60% of the cellular composition of the liver and participate in several metabolic activities, such as glycogen synthesis and decomposition, fat and protein metabolism and the biosynthesis of hormones (49). These cells are distinguished by their high mitochondrial content and extensive endoplasmic reticulum, which facilitate the synthesis of coagulation factors, albumin and other serum proteins that are crucial for the metabolic and detoxification functions of the liver (49). In response to hepatic injury, hepatocytes can undergo rapid proliferation, contributing to the regenerative capacity of the liver (50). However, elucidating the precise mechanisms underlying liver regeneration remains an active area of research. Specifically, whether this process is driven primarily by stem or progenitor cells or through the replication of existing hepatocytes is still under investigation (51). With respect to their interaction with neoplastic cells, it has been reported that hepatocytes can express integrins capable of binding to malignant cells via osteopontin. They may also form desmosomes with tumour cells, facilitating cell aggregation within the liver (52). In addition, fibrinogen like 1, which is secreted by hepatocytes, can help cancer cells survive by preventing attacks from T cells. This interaction between

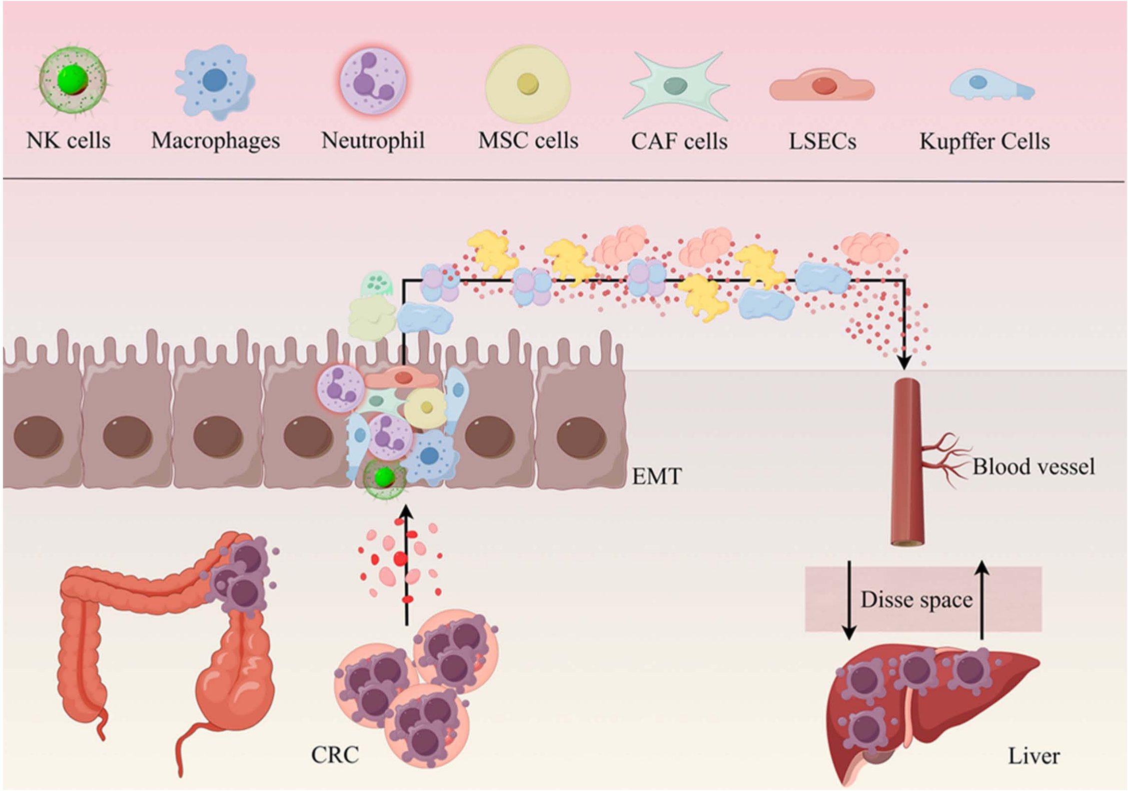

Figure 2. Connections between colorectal liver metastasis cells. NK, natural killer; LSEC, liver sinusoidal endothelial cells; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition. CAF, cancer-associated fibroblasts; MSC, mesenchymal stem cells.

hepatocytes and cancer cells is currently under investigation, though it is suggested that liver cells serve a significant role in cancer progression (53).

LSECs and Kupffer cells. LSECs serve important roles in both immune and physiological actions, such as filtering, carrying out endocytic processes and antigen presentation (54). As selective filters, LSECs facilitate the passage of various molecules, such as plasma proteins, pharmaceuticals and viruses <200 nm into the Disse space while effectively preventing cellular entry (55). Kupffer cells, which are found in the liver and make up a small portion of liver cells, are critical for certain processes, such as removing infectious agents, processing cholesterol and assisting the immune system (56). Kupffer cells originate from the yolk sac early in development and travel to the liver where they renew and help maintain the immune balance, cellular homeostasis and metabolic balance of the liver (57). When mature, Kupffer cells express several types of surface receptors, such as scavenger receptors, Toll-like receptors and nucleotide-binding and oligomerization domain-like receptors, which help identify and eliminate harmful pathogens or dying cells (58). When they are activated, Kupffer cells can produce chemicals such as cytokines and chemokines, including TNF-β and IL-1, which attract other immune cells to sites of infection (58). When tumour cells enter the liver, they first meet LSECs and Kupffer cells in the sinusoids and can often be killed quickly because of physical stress or mechanical problems, such as shear forces caused by blood flow in the liver sinus environment, mechanical stresses caused by the pressure from surrounding cells and occurrences of tumour cells getting stuck in the liver sinus, which can cause cell death. Moreover, Kupffer cells can resist tumour metastasis by killing tumour cells through phagocytosis using receptors such as Dectin-2 (59). Like LSECs, Kupffer cells also produce inflammatory chemicals, such as TNF-α, nitric oxide and reactive oxygen species (ROS), which contribute to cancer cell apoptosis. NK cells from the liver also help to kill cancer cells, releasing perforin or granzyme or activating the Fas/FasL pathway to cause cancer cell death (60). After cancer cells die, IL-1, IL-6, IL-8 and C-C motif chemokine ligand (CCL) 5 are released, facilitating the mobilization and activation of additional immune cells to eliminate additional cancer cells (61). However, this process can create a local immune response that increases the expression of certain adhesion receptors on LSECs, such as E-selectin, vascular cell adhesion molecule 1 and intercellular-adhesion molecule 1, which mediate cancer cell adhesion and transmigration into the Disse space (62). Notably, LSECs can increase EMT, which helps tumour cells move and invade more easily, allowing them to escape immune detection (62,63). While Kupffer cells initially display antitumour properties, they can also have adverse effects, including the release of growth factors, such as hepatocyte growth factor, and angiogenic factors, such as VEGF, which can help cancer cells migrate (61). Kupffer cells also attract other immune cells that help cancer spread, such as macrophages and myeloid-derived suppressor cells (MDSCs), fostering an immune-tolerant microenvironment (64). Therefore, LSECs not only serve an antitumour role but also serve an immunosuppressive role and ultimately impair the antitumour response of the immune system (65).

NK cells. Typically, the liver harbours a substantial population of NK cells, which serve crucial roles in combating infections and eliminating malignancies (66). When NK cells interact with cancer cells, they can release chemicals such as perforin and granzymes, which cause the target cells to break apart and undergo programmed cell death (67). NK cells can also destroy tumour cells directly via other methods, such as the use of TNF-related apoptosis-inducing ligands to induce tumour cell death (68). Their role in tumour immunosurveillance encompasses the induction of inflammatory responses via the secretion of various cytokines and chemokines (69). For example, granulocyte-macrophage colony-stimulating factor secreted by NK cells can stimulate the bone marrow to produce more granulocytes and macrophages. These immune cells are recruited to the tumour site to participate in the inflammatory response and the killing of tumour cells. Additionally, TNF-α secreted by NK cells is also an important factor in inducing the inflammatory response. In liver cancer, TNF-α can also promote the infiltration of inflammatory cells together with IFN-γ (69). IL-8 secreted by NK cells can attract inflammatory cells, such as neutrophils, to migrate to the tumour site and alter the tumour microenvironment to be unfavourable for the growth of tumour cells (68). NK cells are also key in preventing the spread of tumours as they can attack cancer cells that have already spread to other parts of the body (70), and a high concentration of these cells often correlates with improved overall survival in patients with CRLM (71). However, the glycolytic conditions prevalent in CRLM create an environment rich in lactic acid, which leads to NK cell apoptosis via the reduction of intracellular pH levels (72). Moreover, MDSCs can also reduce the power of NK cells by releasing nitric oxide, which disrupts functions mediated by Fc receptors, including antibody-dependent cellular cytotoxicity and cytokine production (73). A previous study utilizing a murine model of CRLM has demonstrated that liver-resident NK (LrNK) cells exhibit increased expression of retinoid-related orphan nuclear receptor alpha (RORα), a regulator that is essential for LrNK cell maintenance but does not affect conventional NK cells (74). The targeted deletion of RORα in these models exacerbates CRLM, highlighting the necessity of RORα for LrNK cell-mediated antitumour immunity. Additionally, treatment with the RORα agonist SR1078 has been shown to slow CRLM progression (74). In clinical contexts, the number of liver NK cells is often reduced in patients with CRLM due to the negative effects of lactate produced by the tumour cells (72). Furthermore, NK cells are capable of promoting a proinflammatory metastatic environment in CRC, leading to increased levels of IFN-γ, IL-2, IL-12p70 and IFN-α within the CRC microenvironment while simultaneously decreasing IL-6 levels. This finding indicates their effective antitumour activity (75). Overall, NK cells exhibit significant antitumour effects in patients with CRLM and are closely associated with patient prognosis, positioning them as promising specific therapeutic targets for this condition.

Macrophages. Macrophages function as APCs with multiple functions that are essential in mediating immune responses against tumours (76). They present exogenous antigens to T cells through the major histocompatibility complex (MHC)-I and MHC-II pathways, utilizing costimulatory and inhibitory signals, along with cytokines, to modulate T cell activation (76). Macrophages that are recruited to tumour sites are referred to as tumour-associated macrophages (TAMs), which serve a comprehensive regulatory role in metastasis (77). TAMs contribute to an immunosuppressive tumour environment through the upregulation of inhibitory receptors such as programmed death-ligand (PD-L) 1 and PD-L2 (78). TAMs also produce cytokines such as IL-10 and TGF-β. These molecules activate regulatory T cells, which further reduce the ability of the immune system to fight tumours (79). Moreover, TAMs secrete remodelling factors that alter the extracellular matrix (ECM) and enzymes that breakdown ECM components, aiding in the dispersal of colorectal tumour cells (80).

Novel analytical techniques, such as single-cell analysis and spatiotemporal transcriptomics, have significantly enhanced our understanding of the specific TAM subsets that drive CRC metastasis (81). A previous study compared tumour cells from the colon with their metastatic counterparts found in the liver and reported the presence of a type of TAM that expresses secreted phosphoprotein 1 (SPP1). This type of TAM is associated with more aggressive cancers and poorer outcomes for patients (82,83). SPP1$^+$ TAMs interact with fibroblasts that express fibroblast activation protein (FAP). This interaction likely hinders lymphocyte infiltration and is associated with decreased patient survival rates. These findings underscore the complex interactions between stromal and immune components within the tumour microenvironment (84,85). In alignment with these observations, another study identified a group of M2-like TAMs positive for mannose receptor c-type 1 and CCL18 with elevated SPP1 expression within CRLM. These macrophages have different metabolic profiles and are also immunosuppressive. This suggests that TAMs can have complex characteristics that contribute to cancer progression (86). These findings indicate that targeting the interactions between FAP$^+$ fibroblasts and SPP1$^+$ TAMs could be a potential strategy for improving CRC treatment outcomes. However, this approach needs further research to fully explore its effectiveness (87).

Hepatic stellate cells (HSCs). HSCs constitute ~15% of the nonparenchymal cell population in the liver and serve a crucial role in mediating the liver's response to injury (88). Typically, they are not active; rather, they rest within the Disse space. However, upon liver damage, activated hepatic stellate cells expressing smooth muscle actin are activated and differentiate into a myofibroblast-like phenotype and begin to produce ECM. The ECM is mostly made up of collagen types I and IV, which are key parts of the fibrotic processes that occur in the liver (88). In addition to producing ECM, HSCs also produce various growth factors, such as TGF-β, and molecules that aid in the production of blood vessels, such as VEGF and angiopoietin-1. HSCs also release cytokines and chemokines such as CCL2 and CCL21 (89,90), which help attract immune cells to injured areas of the liver. HSCs also produce matrix metalloproteinases (MMPs), including MMP-2, MMP-9 and MMP-13, which are involved in remodelling the ECM (89,90). Angiogenesis is significantly enhanced by the synergistic actions of VEGF, angiopoietin-1, ECM components and MMPs. Together, these factors facilitate the migration of cancer cells (20,91). Activated HSCs secrete CCL20, which further activates the CCL20/C-C motif chemokine receptor 6/ERK1/2/ETS transcription factor ELK1/microRNA-181a-5p positive feedback loop. This pathway affects how the tumour microenvironment functions and helps form a niche to which cancer cells can be transferred (28). While HSCs can engage in antigen presentation to T cells and potentially initiate an adaptive immune response, they more commonly promote immune tolerance, particularly through the PD-L1/programmed cell death protein 1 (PD-1) pathway and by inducing regulatory T cells (92,93). Additionally, they influence the transformation of monocytes into MDSCs, a process that depends on CD44, further augmenting the immunosuppressive microenvironment. Together, these actions help create conditions where immune responses are dampened, which is beneficial for the survival of tumour cells in the liver (94).

$CD4^+$ and $CD8^+$ T cells. $CD4^+$ T cells serve an important role in the immune system, particularly in terms of tumour immunity. They modulate the function of $CD8^+$ T cells and increase tumour resistance (95). $CD4^+$ T helper 1 cells produce IFN-γ and TNF-α and create a microenvironment that favours cell-mediated cytotoxicity. Conversely, $CD4^+$ Th2 cells secrete IL-4, which allows the activation of humoral immunity (96).

Furthermore, $CD4^+$ T cells can polarize into different subsets, including T helper (Th) 9 and Th17 cells. The role of Th17 cells in cancer is currently unclear (97). Notably, a high ratio of Th1:Th17 cells in liver metastases is associated with an improved prognosis in patients with CRLM (98), which is consistent with observations in patients with primary CRC (99).

$CD8^+$ T cells serve crucial roles in the clearance of intracellular pathogens and tumour cells, as well as in maintaining long-term protective immunity (100-102). In addition, $CD8^+$ T cell populations represent important biomarkers with high predictive value for prognosis and response to treatments in patients with cancer (103).

Upon encountering tumour cells, $CD8^+$ T cells are activated by antigens recognized by the T cell receptor. This activation initiates rapid proliferation and differentiation into cytotoxic T lymphocytes (CTLs), which kill tumour cells via direct contact. Following their interaction with cancer cells, CTLs release cytotoxic granules and discharge various lethal proteins, such as perforin, granzymes and granulysin, leading to the destruction of the targeted cells (104). A greater proportion of CTLs has been associated with improved prognosis in patients with CRC (105). However, to maintain hepatic immune tolerance, effector T cells may undergo exhaustion, differentiation or apoptosis (106). Chronic exposure to tumour antigens forces $CD8^+$ T cells into an intermediary state that is considered a pre-exhausted state of $CD8^+$ T cells (107). Based on the central role of cancer reactive CTLs in cancer immunity, reactivating $CD8^+$ T cells may be essential for inhibiting the progression and metastasis of CRC.

B lymphocytes. B cells are among the most abundant immune cell types in the liver (108,109). They serve important roles in the initiation, progression and metastasis of tumours (110,111). In the context of CRLM, B cells contribute to humoral immunity by producing antibodies that mediate various effector functions. These include antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity and enhanced antigen presentation (112,113).

B cells are a major component of the tumour microenvironment and are generally associated with tertiary lymphoid structures (TLSs) (114). TLSs are lymphoid-like aggregates that form in nonlymphoid tissues (115). Their main function involves facilitating the immune response in nonlymphoid tissues, especially in states of malignancy (115). It has been reported that in some CRLMs, the proportion of B cells that produce antibodies is significantly increased and concentrated around TLSs and these antibodies are associated with antitumour immunity (116). However, another study reported the immunosuppressive role of B cells within the tumour microenvironment (117).

In conclusion, the activity of B cells in liver metastases from colorectal carcinoma has many facets; however, B cells contribute to tumour growth via immunosuppressive mechanisms and are also active in TLSs in the production of antitumour antibodies and participation in antitumour responses.

The establishment of a microenvironment prior to metastasis in the liver is a consequence of interactions between certain cells. Resident cells of the liver interact with CRC cells, altering the hepatic microenvironment by accumulating inflammatory mediators, remodelling the ECM and enhancing tumour-induced immunosuppression. Consequently, these concurrent processes create a supportive 'soil' that facilitates the establishment and proliferation of CRC cells within the hepatic landscape.

3. Diagnosis of liver metastasis from CRC

CRLM is present in ~20% of patients with CRC, which are liver metastases that are diagnosed either before or at the time of CRC diagnosis (118). Biomarker testing is routine for the correct diagnosis of synchronous liver metastasis. Serum CEA is typically a first-line test, whereas CA19-9 serves a subsidiary role in patients in whom CEA levels are not informative (119). RAS mutation status is considered a predictive biomarker that affects the effectiveness of anti-EGFR therapies and therefore influences treatment options. Thus, mutation testing of NRAS exons 2, 3 and 4 and KRAS exons 2, 3 and 4 is recommended for all patients with CRC (120). Furthermore, it is suggested that patients with CRLM undergo BRAF mutation testing, as BRAF is a prognostic biomarker (121,122).

The basic diagnostic workup for CRC patients should combine serum tumour markers and pathology staging with imaging studies, including routine liver ultrasound and abdominal contrast-enhanced CT (123). In patients with a high suspicion of CRLM based on ultrasound or CT images that cannot be confirmed, further tests may include serum alpha-fetoprotein, liver contrast-enhanced ultrasound and both plain and enhanced MRI of the liver (124). MRI is generally recommended preoperatively in cases where metastasis to the liver is resectable, whereas PET-CT is not a routine standard modality. However, in specific clinical situations where there is a need to accurately assess the extent of disease beyond the liver, or to distinguish between viable tumour and post-treatment changes, PET-CT has its indications. Needle biopsies of liver metastases are generally not required as biopsies may

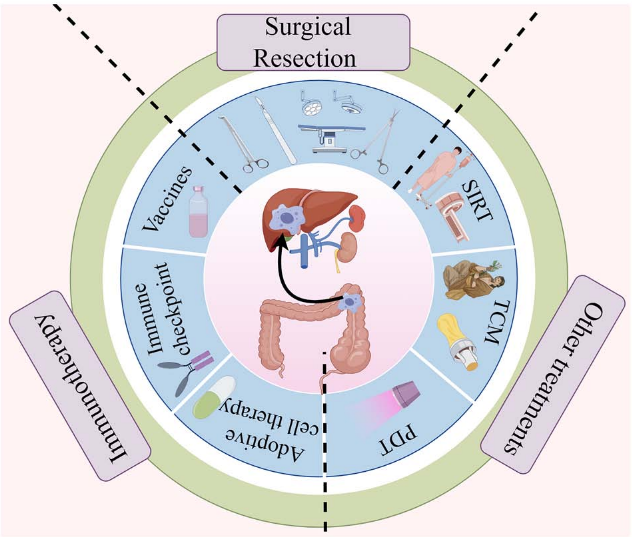

Figure 3. Current treatments for colorectal cancer. SIRT, selective internal radiotherapy; TCM, Traditional Chinese Medicine; PDT, photodynamic therapy.

cause tumour cells to spread along the needle track and may lead to bleeding, especially when the tumour is located near major blood vessels. Meanwhile, non-invasive imaging techniques such as CT, MRI and PET-CT can provide thorough diagnostic information (125). Intraoperative exploration of the liver should be a routine part of surgery for CRC to exclude metastatic disease and any suspicious nodule detected at the time of surgery may necessitate biopsy (125).

Regular follow-up examinations are necessary after surgery to identify the occurrence of metachronous liver metastases. CEA and CA19-9 levels must be measured every 3-6 months for 2 years after surgical resection, with regular monitoring every 6 months for the following 3 years and yearly monitoring after 5 years (126). In cases of high suspicion on ultrasound or CT, liver MRI should be considered and abdominal/pelvic enhanced CT scan or liver MRI enhancement should be performed every 3 months for 2 years after surgery, with liver cell-specific contrast agent enhanced MRI, if deemed necessary. Imaging, using a consistent modality, is recommended every 6-12 months for a total of 5 years (127). Routine PET-CT scans are not indicated. Finally, electronic colonoscopy should be performed within 1 year following surgery. In the case of abnormalities, re-examination should be performed within 1 year. If no abnormality is found, then re-examination at 3 years after surgery and every 5 years thereafter is recommended (128).

4. Clinical therapeutic approaches for liver metastasis from CRC

The clinical therapeutic approaches for liver metastasis from CRC primarily involve surgical resection, immunotherapy and other treatments (Fig. 3). The surgical removal of liver metastatic foci is optimal for curing liver metastases and achieving significant cure rates. Immunotherapy, particularly in combination with other cancer therapies, may activate antigen-specific T cells to overcome tumour immunosuppression. Comprehensive therapeutic strategies are crucial for improving outcomes in patients with liver metastasis from CRC.

Surgical resection. Surgical removal of liver metastatic foci remains the optimal approach for curing liver metastases in patients with CRC (129). Therefore, it is critical that eligible patients receive surgical treatment when appropriate. For patients with liver metastases, resection can achieve a 20% cure rate (130), with a 5 year survival rate >50% (131). Additionally, for patients whose dissemination is accompanied by lymph node infiltration and occult micrometastasis who are suitable for complete surgical resection, adjuvant radiotherapy, chemotherapy and targeted therapy are required (16). However, ~70% of patients are ineligible for surgical treatment due to widespread disease, multiple tumours, significant systemic diseases or poor liver reserve function (132).

Moreover, the best surgical strategy for patients with liver metastases from CRC remains controversial. The METASYNC trial is a published prospective controlled trial (133) in which the outcomes of patients who underwent simultaneous tumour resection were compared with those of patients who underwent staged surgical resection. A total of 85 patients with liver metastasis of CRC were analysed. There was no significant difference in the rate of postoperative complications between the two groups. After 2 years, patients who underwent simultaneous resection had improved overall survival (OS) and disease-free survival (DFS) compared with patients who underwent staged resection. However, OS improvement was not statistically significant after 47 months, which may be due to several limitations, including the small sample size of the trial and the long time period over which the trial was conducted, which could lead to the loss of patient follow-up data.

In brief, while surgical treatment of liver metastases from CRC has limitations, the criteria for surgery are not uniform and further investigations based on well-designed prospective, multicentre studies are needed. Additionally, the prognostic factors of liver metastasis of CRC mainly include the size, differentiation and depth of invasion of the primary tumour, the number, size and distribution of liver metastases, the age, sex and physical condition of the patient and the levels of serological markers such as CEA and CA19-9, as well as the mutation status of genes such as KRAS and BRAF (134,135). For liver metastases of CRC, surgical resection may be considered if there are a small number and size of tumours and they have not metastasized. Among the prognostic factors, the primary tumour and metastases directly affect the feasibility and effect of surgery. For example, patients with highly differentiated tumours have an improved prognosis and experience increased surgical removal success rates (136).

Immunotherapy. The purpose of immunotherapy is to enhance the intrinsic immunity and antitumour capabilities of T cells, target immunosuppressive TAMs and amplify the antitumour actions of the patient's own immune system (137). Immunotherapy encompasses immune checkpoint inhibitors (ICIs), cancer vaccines and other biologics such as chimeric antigen receptor (CAR) T cells. However, due to the suppressive effect of the tumour immune microenvironment, the efficacy of immunotherapy may not be ideal (138).

PD-1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) are receptors that inhibit T cell responses to ensure peripheral tolerance, permitting the proliferation of tumour cells rather than the elimination of tumour cells by the immune system. ICIs can enhance the anticancer immune response by inhibiting the expression of the suppressive receptor PD-L1 on the surface of T cells and malignant cells, particularly CRC cells (139). The PD-1/PD-L1 inhibitors commonly used in current mCRC clinical trials include nivolumab, pembrolizumab, durvalumab, atezolizumab and avelumab (140-144). These medications have shown significant effectiveness in treating microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) mCRC, though they have demonstrated poor efficacy in the majority (>90%) of patients with microsatellite stable (MSS)/metastatic MMR-proficient (pMMR) mCRC (145). Specifically, the blockade of PD-1 by pembrolizumab or nivolumab has resulted in frequent and lasting remission for ~75% of patients with dMMR mCRC (146). Patients with mCRC with high microsatellite instability or mismatch repair defects did not have significantly improved overall survival rates compared with those achieved with chemotherapy. Nevertheless, the median progression-free survival (PFS) for those treated with pembrolizumab was 16.5 months compared with 8.2 months for the chemotherapy group (range, 6.1-10.2 months), indicating that the PFS of the patients in the pembrolizumab group was at least twice that of those receiving chemotherapy, with fewer treatment-related adverse events (147). Increased infiltration of CD8$^+$ T cells and expression of immune checkpoint molecules, including PD-L1 (137), are characteristics of dMMR CRC, which may partially explain why PD-1/PD-L1 inhibitors have achieved significant efficacy in patients with MSI-H or dMMR mCRC.

Ipilimumab, a CTLA-4 inhibitor antibody, can be used in conjunction with PD-1/PD-L1 inhibitors for the clinical treatment of MSI-H/dMMR mCRC. The combination of nivolumab with a low dose of ipilimumab has provided sustained clinical benefits, marked by an objective response rate (ORR) of 65% (complete response rate of 13%) and a disease control rate of 81% after a median follow-up of 50.9 months, with durable responses (148). While this therapy can be highly effective for dMMR CRC, pMMR tumours exhibit no response.

Immunotherapy targeting the PD-1/PD-L1 axis is a promising strategy for eliminating cancer. However, patients with CRC with MSS do not respond to anti-PD-1/PD-L1 therapies. The efficacy of immunotherapy is largely determined by the intensity of the immune response and the limited effectiveness can be explained by the immunosuppressive state of the tumour microenvironment (149). Currently, various combination therapies against PD-1/PD-L1 have enhanced the regeneration of an immunogenic TME, however, their synergistic effects and clinical efficacy for patients with MSS CRC remain underexplored (150). For patients with refractory CRC, there is a need to develop an increased number of potential combination therapies to overcome the ineffectiveness of anti-PD-1/PD-L1 treatments (151). Furthermore, patients with MSI-H or dMMR status have a better response to immunotherapy and an improved prognosis and are more suitable for immunotherapy (152).

Cancer cells elicit an immune response due to the expression of altered self-antigens; thus, cancer vaccines induce a potent immune reaction against one or several tumour-specific antigens (153,154). Currently, there are three main types of cancer vaccines for CRC liver metastases: Molecular-based vaccines, cancer cell vaccines and dendritic cell vaccines. Among these, the most widely used approach is the use of dendritic cell vaccines for treating CRC liver metastases. However, no product has yet been approved for the development of cancer vaccines targeting CRC. A previous study demonstrated that patients with CRC metastases who received a dendritic cell vaccine and were disease-free after metastasectomy and perioperative chemotherapy had a survival rate that surpassed that of the contemporary unvaccinated group, with a relapse-free median survival time of 25.7 months and a median OS of 44.1 months (155). A randomized phase II clinical trial of dendritic cell vaccination following the resection of CRC liver metastases showed that, compared with the observation group (median DFS, 9.53 months), the vaccine group had fewer and later disease recurrences (median DFS, 25.26 months) (156). Therefore, the combination of DC vaccines with other cancer therapies such as chemotherapy, radiotherapy and ICIs could activate antigen-specific effector T cells and potentially overcome tumour immunosuppression.

Adoptive T cell therapy is an antitumour treatment that involves the transfer of T cells from a donor to the patient (157). The process involves isolating T cells with antitumour activity, followed by their extensive *ex vivo* expansion, activation and infusion into patients for tumour treatment (158). In solid tumours, three main types of adoptive T-cell therapies have been developed: Tumour-infiltrating lymphocytes, CAR-engineered T cells and high-affinity T cell receptor-engineered T cells (159). In CRC, CAR T cell therapy remains a primary focus of research. In a mouse model of CRC liver metastasis, the administration of anti-CEA CAR T cell therapy significantly controlled tumour growth, inhibited tumour proliferation and improved liver function (160). For patients with CEA-positive mCRC, CAR T cell therapy stabilized the condition of 7 patients who had progressive disease in previous treatments after receiving CAR T cell therapy. Of these individuals, 2 patients maintained stable disease for >30 weeks and a reduction in both tumour size and number was observed in 2 patients through PET/CT and MRI analysis. Additionally, after long-term observation, a significant reduction in serum CEA levels was evident in ~60% of patients. Moreover, a sustained presence of CAR T cells in the peripheral blood was noted in patients treated with high doses of CAR T cell therapy (161). Another previous study demonstrated the application of HER2-specific CAR T cells for the treatment of mCRC. HER2 CAR T cells displayed potent specific killing activity against CRC cells and their antitumour efficacy was confirmed in both *in vitro* and mouse model studies (162). Zhou *et al* (163) reported that the use of mesothelin-targeted CAR T cells for the treatment of mouse CRLMs demonstrated good efficacy and safety. When a local administration method was used, the treatment effectively reduced the tumour burden and enhanced cytotoxic T cell infiltration without significant toxicity. CAR T cell therapy, which targets specific antigens such as HER2 and mesothelin, has shown potential in the treatment of mCRC, with preclinical models demonstrating a reduced tumour burden and increased survival rates. The use of localized delivery methods, including portal vein administration, has improved both the safety and effectiveness of treatment (164). Nevertheless, there are still challenges to address, such as overcoming the immunosuppressive tumour microenvironment and ensuring the longevity and effectiveness of CAR-T cells within solid tumours. Ongoing research and clinical trials aim to refine CAR T cell treatment strategies for mCRC, with a focus on overcoming these obstacles to fully exploit their therapeutic potential.

Targeting therapies. EGFR is overexpressed in 60-80% of patients with CRC (165), making it a target for therapeutic intervention. Cetuximab, a chimeric monoclonal antibody that binds to EGFR, competes with ligands such as EGF to inhibit receptor activation and has been shown to reduce the risk of disease progression when combined with chemotherapy, as evidenced by the CRYSTAL trial (166).

Among the most frequently used targeted therapies in clinical practice, anti-VEGF and anti-EGFR treatments have resulted in favourable outcomes in patients with mCRC. However, the optimal first-line approach for a more precise and personalized therapeutic strategy continues to be a subject of debate (167). The results of several large clinical studies comparing the combination regimens of bevacizumab and cetuximab with FOLFOX/FOLFIRI were fairly consistent, with no significant difference in response rate or PFS between the two groups and prolonged OS in the cetuximab group (168,169). Similarly, the PEAK trial, which evaluated the combination of panitumumab and bevacizumab with FOLFOX, reported comparable response rates and PFS rates, with a slight OS advantage for panitumumab compared with bevacizumab with FOLFOX (34.2 vs. 24.3 months) (170).

However, one-sided evaluation of the efficacy of these two treatment methods on the basis of the results of the above clinical trials still has a large bias. To clarify the potential role of tumour heterogeneity in the effectiveness of these targeted therapies, the latest research further explores the mechanism of action of drugs and the impact of differences in the mutation sites of genes.

Post hoc analyses of the FIRE-3 trial suggested that cetuximab might be superior to anti-VEGF therapy in patients with wild-type RAS, achieving higher objective response rates (72.0 vs. 56.1%) and faster tumour regression (68.2 vs. 49.1%) (171). Meta-analyses encompassing the FIRE-3, CALGB and PEAK trials have reinforced the preference for anti-EGFR over anti-VEGF in patients with CRC with wild-type RAS (172).

Moreover, anatomical location appears to modulate the efficacy of targeted therapies. Left-sided tumours, characterized by higher EGFR expression when compared with right-sided lesions, result from a variety of complex biological and molecular mechanisms and tend to exhibit superior responses to anti-EGFR agents, whereas right-sided tumours are more responsive to anti-VEGF drugs (173,174). The FIRE-3 trial corroborated these observations, with left-sided tumours demonstrating a greater sensitivity to cetuximab compared with bevacizumab (OS, 38.3 vs. 28.0 months) and right-sided tumours showing the opposite pattern (OS, 8.3 vs. 23.0 months) (175). Similar trends were observed in the CALGB study (174) and panitumumab trial (176), indicating that even in the absence of BRAF mutations, right-sided cancers may derive minimal benefit from anti-EGFR therapy (176).

For second-line therapy, transitioning from a bevacizumab maintenance regimen to cetuximab or panitumumab did not yield significant improvements in patients with progressing RAS wild-type CRC, as per findings from the independent phase II trial (177).

Consistent with the findings of a number of studies regarding mCRC, the use of anti-EGFR drugs in combination with chemotherapy has the potential to be effective in patients with surgically resectable liver metastases of CRC if the KRAS gene is wild type (178-180). However, the EPOC trial showed that incorporating cetuximab into perioperative chemotherapy did not confer a survival advantage and was associated with a shorter PFS (14.1 vs. 20.5 months) (179,181), highlighting the uncertainty surrounding the role of cetuximab in this setting. Conversely, the perioperative administration of bevacizumab in conjunction with chemotherapy has been linked to prolonged survival in patients with liver-limited mCRC, although recurrence remains a common outcome (182-185).

The mutation status of KRAS and BRAF is a key factor affecting the selection and effectiveness of targeted therapy (186). For example, patients with abnormal EGFR expression may be treated using a drug that targets EGFR, such as cetuximab. Patients with mutations in KRAS, NRAS and BRAF genes should be treated with other corresponding targeted drugs. The status of gene mutation in prognostic factors not only affects the selection of targeted drugs, but also directly affects the therapeutic effect and prognosis of patients (187). Despite advancements in the targeted treatment landscape of CRC, the requirement for more efficacious therapeutic modalities persists. Future endeavours should focus on refining the combination of targeted therapies with conventional chemotherapy and using precision medicine paradigms to optimize patient outcomes and prolong survival.

Other treatments. In addition to surgery and immunotherapy, a range of other treatments exists, including selective internal radiation therapy (SIRT) and Traditional Chinese Medicine (TCM). Furthermore, new developments in cancer nanotechnology and photodynamic therapy (PDT) may offer potential solutions for the diagnosis and treatment of mCRC in the liver.

SIRT is a process in which microspheres filled with the β-emitting radionuclide Yttrium-90 (Y-90) are embolized into the arterial supply of the liver to enhance the management of liver metastases (188). Currently, the European Society for Medical Oncology consensus guidelines consider SIRT as a potential treatment option only for patients who are unresponsive to chemotherapy drugs (189). In a previous systematic review and network meta-analysis, SIRT with Y-90 resin microspheres demonstrated positive therapeutic effects for patients with chemotherapy-resistant or chemotherapy-intolerant mCRC. The analysis, which included 15 studies, showed that all active treatments enhanced OS compared with best supportive care, with SIRT having the longest OS, albeit without reaching statistical significance. Specifically, compared with best supportive care, SIRT has a hazard ratio for OS of 0.48 (95% CI, 0.27-0.87), demonstrating its potential advantages in terms of safety and efficacy (190). The unique delivery mechanism of SIRT, which targets liver metastases while minimally affecting healthy tissues, renders it a feasible choice in the mCRC treatment landscape, warranting additional exploration and consideration in clinical settings.

In China, TCM has been widely used as an adjunct therapy for cancers, including mCRC (191). TCM, which serves as a supportive therapy, can diminish the adverse effects of cancer treatments and may increase the effectiveness of chemotherapy (192,193). A previous study integrating Huangci granules, a TCM, with chemotherapy and either cetuximab or bevacizumab for the treatment of mCRC. These results indicated that, compared with the placebo group, the treatment group experienced significantly prolonged PSF, improved quality of life and fewer related grade 3 or 4 adverse events (194). A cohort study by Zhang *et al* (195) compared the results of 110 patients treated with a combination of Chinese and Western medicine with those of 225 patients treated exclusively with Western medicine. These findings indicated that combined therapy notably increased the OS and PFS in women, patients with right-sided colon lesions and those receiving first-line treatment. Studies regarding the correlation between Chinese herbal medicine (CHM) and stage II and III CRC have shown that long-term use of CHM (>18 months) can significantly reduce the postoperative recurrence and metastasis of CRC (196). At present, the study of TCM in the treatment of CRC has focused largely on the molecular level. The lack of robust evidence-based studies and standardization of herbal products are major barriers to the globalization of TCM (197). With the advent of new technologies, such as whole-genome sequencing, genome editing and quantitative proteomics analysis, a deeper and more accurate understanding of the molecular targets and signalling pathways involved in the antimetastatic effects of CRC can be gained. With further research in this area, TCM interventions for CRC can be combined with other treatment methods being developed, leading to safer, evidence-based use of these herbs.

Photodynamic therapy (PDT) is an emerging minimally invasive treatment method with promising outcomes for CRC treatment. PDT involves the administration of a photosensitizer that accumulates selectively within cancer cells. When exposed to light at the appropriate wavelength, PDT can destroy cancer cells by generating ROS (16,198). In a phase I study, 24 patients with mCRC to the liver were treated with PDT with the photosensitizer 5,10,15,20-tetrakis(m-hydroxyphenyl)bacteriochlorin, which caused tumour necrosis in all treated lesions 1 month after PDT (199). The treatment of 18 patients with CRC with PDT using Hematoporphyrin resulted in a significantly longer OS in the PDT group compared with the non-PDT group, with a 44.4% ORR and 88.9% disease control rate 2 months after PDT (200). Currently, the primary challenges of PDT are the limited depth of penetration by the activating light source, inadequate immunogenicity induction and complexity of the tumour microenvironment, all of which restrict the effectiveness of PDT. These challenges have been addressed through the use of nanotechnology. The combined use of meta-tetrahydroxy-phenylchlorin in PDT with hepatitis B virus core-like particles for treating mice with CRC effectively controlled tumour growth and significantly improved the survival rates of the treated mice (201). Liang *et al* (202) used perfluorocarbon@porphyrin nanoparticles to assist PDT in treating mice with CRC, which resulted in an enhanced therapeutic effect of PDT and downregulation of COX-2 expression, eliminating tumour hypoxia and directly inhibiting hypoxia-driven CRLM. In addition to conventional treatment methods, the development of a variety of new interdisciplinary methods are required for the successful treatment of patients with CRC.

5. Conclusion

The management of CRLMs remains a significant challenge in oncology due to the intricate interactions between tumour cells and the hepatic microenvironment. Early detection and a comprehensive understanding of the molecular mechanisms driving CRLM are crucial for improving patient prognosis. Surgical resection offers the best chance for a cure, though many patients are ineligible due to advanced disease or poor liver function. Chemotherapy and targeted therapies have shown promise, yet resistance and side effects are common. Immunotherapy, particularly in patients with dMMR CRC, has emerged as a promising treatment modality, but its efficacy in the majority of patients with CRC remains limited. The use of SIRTs and TCMs offers alternative approaches, highlighting the potential benefits of integrating these approaches with conventional treatments. Continued research is imperative to refine therapeutic strategies, overcome treatment resistance and develop personalized medicine for patients with CRLM. The future of CRLM management lies in the combination of novel therapies with a deeper understanding of the tumour microenvironment, ultimately aiming to increase the survival and quality of life of patients.

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Availability of data and materials

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Authors' contributions

MW and ZJ designed the study. YL and HY wrote the manuscript. SD, CW and WZ produced the figures using Figdraw (https://www.figdraw.com/). ZZ read the literature search. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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