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REVIEW

Liver-Directed and Systemic Therapies for Colorectal Cancer Liver Metastases

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Epidemiology, Predisposing Factor and Pathology

Colorectal cancer (CRC) is the third most common cancer worldwide, resulting in an estimated 140,250 new cases and 50,630 deaths in 2018 [1, 2]. Liver is the most common visceral metastatic site due to the portal venous drainage from the colon. About 15% of patients present with synchronous liver metastases at initial diagnosis, which is an independent poor prognostic factor [3]. Approximately 50% of patients ultimately develop liver metastasis during the course of the disease.

The risk factors for CRC are classified to *non-modifiable* (age, family history, hereditary predisposition, inflammatory bowel disease and adenomatous polyp) and *modifiable* (diets, smoking, obesity and high alcohol consumption) [4].

Left-sided and right-sided CRCs harbor different clinical and biologic characteristics with different exposures to potential carcinogenic toxins and microbiota, which can potentially impact the prognosis. Right-sided primary CRCs are more likely to have genome-wide hypermethylation via the CpG island methylator phenotype (CIMP), hypermutated state via microsatellite instability, *BRAF* mutation [5], greater proportions of the "microsatellite unstable/immune" CMS1 and the "metabolic" CMS3 consensus molecular subtypes. Molecular tumor subtypes (different from primary tumor) have been defined for colorectal liver metastases (CLMs) [6] and impact prognosis.

KRAS mutation is detected in 35–45% of CRCs, and it is a strong negative *prognostic* biomarker (associated with more infiltrating/migratory characteristics of cancer cells [7]) and a negative *predictive* biomarker in terms of resistance to anti-EGFR treatment [8], higher incidence of positive and narrow margins at surgery [9] and worse oncologic outcomes after ablation of CLM [10, 11]. BRAF-mutant cancers, comprising 10% of all CRCs, represent a distinct subset of CRC with its own clinical implications with regard to prognosis, treatments and emerging therapeutic strategies. BRAF-mutant CRCs tend to be microsatellite instable (MSI-high), mucinous histology, poorly differentiated, less likely to have metastatic disease amenable for surgical resection as well as poorer overall survival (OS) [12]. Approximately 15–20% of colorectal cancers display MSI with prognostic and therapeutic implications as these tumors are highly immunogenic and can be targeted with immunotherapy [13].

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Main limitations of the studies, analyzing outcomes of CLM include heterogeneity in terms of prior therapies (treatment-naïve, patients after first-, second-, or subsequent treatment lines) and tumor subtypes.

Summary of the most important facts about liver-directed and systemic therapies for CLM is presented in Table 1.

Diagnosis and Initial Workup

Most primary CRCs are diagnosed through colonoscopy either through regular screening or due to symptoms such as change in bowel habits, GI bleeding (hematochezia, melena, occult blood loss, iron deficiency anemia) or abdominal pain. Some cases are diagnosed due to signs or symptoms caused by metastatic disease.

CRCs can spread by lymphatic and hematogenous dissemination, as well as contiguous and transperitoneal spread. The most common metastatic sites are regional lymph nodes, liver, lung and bones.

This article reviews management of CLM. The only potentially curative treatment option for CLM is surgical resection and/or complete ablation [15]. Recent advances in chemotherapy, surgical and interventional techniques allow a subset of initially unresectable CLMs to be downsized to resection or ablation. Thus, precise assessment of the extent of disease is critical to determine the resectability. Several imaging modalities are used to identify CLM. Commonly used imaging modalities are ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), ^{18}F-FDG PET/CT and more recently fully integrated ^{18}F-FDG PET/MR. The utility of different imaging modalities is described in Table 2.

Our recommendation of working up CLMs is to start with CT chest/abdomen/pelvis with triphasic liver protocol. If the patient is potentially resectable, liver MRI should be the next step to further define the extent of disease to ensure a proper selection for surgery. ^{18}F-FDG PET/CT is also advisable, especially prior to resection or ablation of metastatic disease [26].

Approved/Recommended Treatments

Liver resection is considered to be a "gold standard" for CLM treatment, with median OS in liver-resected patients of 28–46 months [27]. However, only 15–20% of the patients are considered to be eligible for liver surgery [28, 29]. Patients with oligometastatic disease (OMD), located in anatomically favorable territory, and low tumor burden may be considered to have upfront liver metastasectomy, followed by 6-month adjuvant therapy. National Comprehensive Cancer Network (NCCN) guidelines recommend surgery or ablation alone or in combination as long as all visible metastases can be eradicated [26].

When liver metastases are completely resected and/or ablated, long-term survival and potential cure could be achieved. In patients who can undergo liver resection followed by adjuvant systemic therapy plus HAI, 5-year OS as high as 78% can be achieved [30], which is significantly better than 5-year OS of the patients treated with chemotherapy alone, which is around 10%. Clinical risk score (CRS) and margins impact surgical outcomes and potential for cure [15, 16].

Cytotoxic chemotherapies remain the mainstream therapy for metastatic CRC, even in patients with resectable or amenable to ablation disease. Chemotherapy combined with resection or ablation of all metastatic sites significantly improves outcomes in this patient population [14].

Adjuvant Therapies After CLM Resection

Adjuvant therapy options following liver resection include systemic chemotherapy with FOLFOX or 5-FU/LV [31] and hepatic arterial infusion chemotherapy (HAI) with floxuridine (FUDR) alone or in combination with systemic chemotherapy in certain institutions.

HAI FUDR demonstrated liver PFS and OS benefit, based on four randomized trials in the adjuvant setting [32–35] (*please see Supplement 1 for detailed HAI data*). NCCN guidelines conclude that HAI infusion with or without systemic chemotherapy is an option as adjuvant or perioperative therapy in the setting of liver metastasectomy. In addition to FUDR, several other chemotherapeutic agents can be administered through HAI, including 5-FU, mitomycin, oxaliplatin and irinotecan [36–38]. However, due to the complexity of hepatic pump placement, management of HAI pump and administration of chemotherapy via HAI, this approach has only been utilized in certain institutions with relevant expertise.

Neoadjuvant Conversion Therapy

Among patients with CLM, up to 30% of initially unresectable patients could have disease converted to surgically resectable after receiving systemic therapy. The options of conversion therapy are as follows:

(1) *FOLFOX or CAPOX ± bevacizumab* for the patients without prior oxaliplatin exposure [39–41]. Bevacizumab has modest benefit when in combination of FOLFOX or XELOX in the perioperative setting but with potential complications such as arterial thromboembolic events, hemorrhage, delayed wound healing, gastrointestinal perforation, biliary complications or severe hypertension. Its use in the perioperative

Table 1 Liver-directed therapies for colorectal cancer liver metastases

Liver-directed therapies for colorectal cancer liver metastases	
10 most important points of the cancer	Colorectal cancer (CRC) is the third most common cancer worldwide. Liver is the most common metastatic site, with synchronous metastasis being an independent poor prognostic factor [3].
	Genetic molecular profiles not only have impact on prognosis, but also provide therapeutic values. KRAS mutation is detected in 35–45% of CRCs, and it is a strong negative *prognostic* biomarker and *predictive* biomarker. BRAF-mutant cancers comprise 10% of all CRCs and are associated with poorer overall survival.
	Systemic chemotherapies are proven to have survival benefit in all clinical settings from post-liver metastasectomy, to converting unresectable liver metastasis to resectable, to maintaining quality of life.
	Cytotoxic chemotherapies remain the mainstream therapy for metastatic CRC, even in patients with resectable or amenable to ablation disease. Chemotherapy combined with resection or ablation of all metastatic sites significantly improves outcomes in this patient population [14].
	Treatment options for liver-only or dominant metastasis include surgical resection/ablation, locoregional debulking interventions, systemic cytotoxic chemotherapy, intra-arterial pump chemotherapy, biological therapy as well as immunotherapy, with immune checkpoint inhibitors benefiting small percentage of patients whose tumor is MMR-deficient.
	When liver metastases are completely resected and/or ablated, long-term survival and potential cure could be achieved. Clinical risk score (CRS) and margins impact surgical outcomes and potential for cure [15, 16].
	Despite a relevantly high recurrence rate following resection and or ablation of liver metastases, ablation (with or without resection) of CLM in addition to chemotherapy prolongs patient survival [14]. Modified CRS impacts outcomes of ablation similarly to surgery. Ablation with margins over 10 mm offers the best local tumor control [17–19].
	Intra-arterial therapies and in particular Y-90 radioembolization is recommended for CLM treatment in the salvage setting with liver disease progression while on or after second line chemotherapy with encouraging oncologic outcomes [20].
	Liver-directed chemotherapy through hepatic arterial pump demonstrated survival benefit in multiple clinical settings including adjuvant, neoadjuvant and metastatic.
	Locoregional interventions are also being combined with different systemic therapies to enhance anti-tumor effect and to facilitate drug delivery.
5 most important numbers of the cancer	There are estimated 140,250 new cases of CRC, and 50,630 patients will die from CRC in 2018 in the USA.
	15% of patients present with synchronous liver metastases, and 50% of patients with CRC will ultimately develop liver metastasis.
	Only around 15–20% of the patients with CLM are eligible for liver resection.
	The recurrence rate following resection of liver metastases from CRC is in the order of 60–70%.
	Up to 38% of patients with initially unresectable liver metastases could have disease converted to surgically resectable after receiving proper therapy.
3 major pivotal studies for the last 5 years	Ruers T, et al. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. J Natl Cancer Inst. 2017;109. https://doi.org/10.1093/jnci/djx015
	Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative hepatic arterial infusion pump chemotherapy is associated with longer survival after resection of colorectal liver metastases: a propensity score analysis of 2368 consecutive patients. J Clin Oncol. 2017;35:1938–44
	Wasan HS, Gibbs P, Sharma NK, Taieb J, Heinemann V, Ricke J, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 2017;18(9):1159–71
2 messages about the cancer	All metastatic colorectal cancer with liver metastasis should be managed by multidisciplinary teams including medical oncologist, surgical oncologist, interventional oncologist/radiologist as well as diagnostic radiologist.
	All patients should be considered for clinical trials.
1 prediction for the 5 future years	Combination of locoregional plus systemic therapies might be the leading approach in this patient population in an effort to prolong overall survival.

setting requires caution; in general, it is recommended avoiding bevacizumab 4 weeks before and after invasive operations [41].

(2) *FOLFIRI ± cetuximab or panitumumab* for the patients with prior oxaliplatin as adjuvant therapy,

Table 2 Imaging modalities used for colorectal liver metastases (CLM) detection and follow-up

Nr.	Imaging modality	Description
1.	CT of the chest/abdomen/pelvis with triphasic liver protocol	It is the most commonly used imaging modality in diagnosis of both intrahepatic and extrahepatic metastases as well as post-treatment follow-up [21–23]; however, CT is not sensitive enough to detect lesions smaller than 1 cm
2.	MRI with liver-specific contrast agents and diffusion-weighted imaging	It is more sensitive than CT for detecting smaller CLM, and it is more often chosen by surgeons when planning metastasectomy [21–23]
3.	^{18}F-FDG PET/CT imaging	It is not routinely used in CRC workup; however, if CT or MRI detects suspicious but inconclusive abnormalities, ^{18}F-FDG PET/CT may be considered. It is recommended for restaging prior to resection or ablation of metastatic disease
4.	^{18}F FDG PET/MRI imaging	It is gaining some popularity for its sensitivity and specificity in diagnosing CLMs [24]; however it is not available in many institutions
5.	Traditional ultrasound (US), contrast-enhanced ultrasound (CEUS) and intra-operative US	They all have a role in detecting CLM [25], especially useful for image-guided needle biopsy of CLM

left-sided primary cancer and wild-type KRAS [42–44];

(3) *FOLFOXIRI ± bevacizumab*. This regimen is generally used in younger, healthier patients; thus, the patients with high tumor burden and risk of chemotherapy-related toxicity should be under consideration when choosing this regimen. This regimen was associated with conversion rate of up to 40% with significantly prolonged OS [45–48].

Locoregional therapies include the following:

(1) HAI therapy alone or with systemic chemotherapy. HAI with FUDR plus systemic chemotherapy (FOLFOX, FOLFIRI) as conversion therapy resulted in CLM resectability in nearly 50% of the patients [49, 50].
(2) Neoadjuvant ^{90}Y radiation lobectomy [51] or transarterial chemoembolization with drug-eluting beads (DEBIRI-TACE) [52].

Unresectable CLMs

If complete resection/ablation of CLM is not feasible or patients are not fit surgical candidates, other locoregional therapies, such as HAI, percutaneous ablation, chemoembolization, radioembolization (RE) and radiation therapy (RT), including stereotactic body RT (SBRT) can all be considered for the patients with OMD (see "Role of Interventional Oncology/Radiology (IO/IR)" section for detailed discussion). Also, in selected patients percutaneous ablation within the "test of time" concept may be preferable to surgery as the initial local cure while observing the disease biology in potentially resectable patients. In the event of local failure in the ablation site, in patients without multifocal progression during the follow-up period, surgery remains a subsequent option. "Test of time" allows expression of disease biology and can spare patients with an aggressive tumor biology the morbidity of a non-beneficial surgery [53]. Percutaneous ablation can also be useful for disease control without systemic chemotherapy administration in selected patients, allowing for "chemotherapy holiday."

Systemic Palliative Therapies

For this category, goals of therapy focus on palliative and non-curative measures with expectation of maintaining quality of life and potentially prolonging OS. Many combinations are available, consisting of cytotoxic chemotherapeutic agents including irinotecan, oxaliplatin, capecitabine; monoclonal antibodies targeting VEGF and EGFR pathways such as bevacizumab, ramucirumab, cetuximab, panitumumab; tyrosine kinase inhibitor regorafenib, recombinant fusion protein aflibercept and trifluridine/tipiracil, as well as immunotherapy. Overall principle is to expose patients to all active agents sequentially if they can tolerate. Enrollment in a clinical trial is always recommended in this setting.

First-line and beyond first-line locoregional and systemic treatment options for the patients with CLM are described in Table 3.

Role of Interventional Oncology/Radiology (IO/IR)

The main focus of IO/IR in mCRC is oligometastatic disease (OMD). OMD is characterized by disease localization to a few sites and tumors allowing the option to use local and ablative treatments (LATs) aiming to improve disease control and therefore clinical outcome in these patients [72]. Although the mortality of CRC patients has dramatically decreased in the last 20 years following the

Table 3 Treatment options for the patients with colorectal liver metastases, adopted from several current guidelines

Treatment regimen	Description
First-line systemic palliative chemotherapy options	
FOLFOX and FOLFIRI ± bevacizumab or cetuximab [54, 55]	Left-sided wild-type KRAS colorectal cancer (CRC) patients have significant survival benefit from cetuximab, while right-sided CRC patients have survival benefit from bevacizumab [56]
	Combining both anti-VEGF and anti-EGFR agents is not recommended due to poorer outcome [57, 58]
FOLFOX or FOLFIRI + panitumumab	For the patients with RAS wild-type tumor [59, 60]
S-1 plus oxaliplatin or irinotecan	S-1 is only used in selected countries, such as Japan and Korea [61, 62]
FOLFIRINOX or FOLFOXIRI	This regimen is used only in selected younger patients with high tumor burden and RAS or BRAF mutation
HAI with FUDR or in combination with FU/LV, FOLFOX or FOLFIRI	For patients with unresectable liver metastasis [49, 50]
Beyond first-line systemic chemotherapy options	
Irinotecan-based chemotherapy	For patients received oxaliplatin-based initial therapy, irinotecan-based chemotherapy is considered to be the next treatment choice.
	The following regimens are recommended:
	FOLFIRI
	FOLFIRI + bevacizumab (for patients with tumor bearing RAS mutation)
	FOLFIRI + cetuximab/panitumumab (for patients with RAS wild-type tumor)
	FOLFIRI with intravenous aflibercept [63, 64]
	FOLFIRI with ramucirumab [65]
Oxaliplatin-based chemotherapy	For patients received irinotecan-based initial therapy, changing to oxaliplatin-based chemotherapy with or without biological agents depending on RAS mutational status would be reasonable
	For RAS wild type, anti-EGFR therapy would be appropriate, anti-VEGF agent can be also be considered, although only anti-VEGF agent would be indicated if RAS mutations present
Regorafenib or trifluridine/tipiracil	For the patients who have received and failed both oxaliplatin- and irinotecan-based therapy, additional treatment should be based on performance status and organ functions. We suggest single agent regorafenib or trifluridine/tipiracil [66, 67]
HAI therapy	HAI therapy remains effective treatment for patients who had prior systemic chemotherapy exposure [49, 50, 68]
Immunotherapy (in selective patients)	Mismatch repair protein (MMR) deficient or MSI-high tumors may benefit from check point inhibitors
	Patients with MMR-deficient metastatic CRC had a 50% objective response rate (ORR) and a 89% disease control rate (DCR) when treated with pembrolizumab, while in contrast, the ORR and DCR were 0 and 16%, respectively, in MMR-proficient mCRC [69, 70]
	Similar results were also seen in CheckMate-142, in which patients received nivolumab with or without ipilimumab. Significantly higher ORR and PFS were demonstrated in MMR-deficient mCRC [71]
Reutilizing the regimen initially used in the treatment sequence	During the often lengthy phase of sequential therapy, tumors may regain sensitivity to the previously used agents
Locoregional treatment options	
HAI therapy	For liver-dominant metastatic CRC (early-stage multifocal liver-only disease)
Transarterial chemoembolization or radioembolization	For liver-dominant metastatic CRC (late-stage multifocal liver-only disease)

introduction of new systemic treatments, the management of metastatic CRC remains a major challenge with surgical resection and ablation being the only potentially curative options.

IO/IR plays an important role in the management of mCRC from disease diagnosis through tissue sampling, treatment of unresectable OMD, bridging potentially resectable patients or treating chemorefractory metastatic disease in the salvage setting [73] to palliation. Therefore, there is a strong international consensus that the interventional oncologist/radiologist should be a standing member of the institutional tumor board [74].

Most frequent clinical scenarios for LAT include the following:

(1) *Neoadjuvant setting.* In this setting, LAT can be used as:
   - Potentially curative treatment for unresectable patients with limited metastatic tumor burden;
   - Induction therapy in order to downsize tumor in potentially resectable patients [52];
   - Percutaneous ablation can be applied within the "test of time" concept, when it is used instead of surgery in order to observe the disease biology in potentially resectable patients [53].

(2) *Adjuvant setting.* In this setting, LAT can be used for:
   - Combination with first-line chemotherapy in carefully selected patients [52, 75];
   - Treatment of CLM by means of combined percutaneous and endovascular therapies [76–80];
   - Induction of distant tumor response by combining LAT with immunotherapy;
   - Disease control without systemic chemotherapy administration in selected patients, allowing for "chemotherapy holiday."

(3) *Salvage setting* for chemorefractory patients with a goal to improve disease control and OS with minimal impact on the quality of life [81].

Percutaneous Ablative Techniques

Percutaneous ablative techniques include a wide range of modalities, which are divided into two groups:

(1) Thermal modalities (heat and cold based). They include radiofrequency (RFA) [82–87], microwave (MWA) [17, 88–90], cryoablation [91], laser ablation [92–94] and high-intensity focused ultrasound [95];
(2) Non-thermal modality, which includes irreversible electroporation [96–98].

RFA is the most extensively studied ablation modality with multiple larger retrospective case-matched comparisons as well as meta-analyses available, comparing RFA to surgical resection or using RFA in addition to systemic chemotherapy [14, 99–104].

For treatment of CLM, hepatocellular carcinoma algorithm of the West and Japan is often applied, which recommends RFA for < 3 cm liver metastases in unresectable patients with ≤ 3 tumors [105–107]. However, for CLM the lesion number is not an absolute limiting factor for RFA, if successful treatment of all metastases can be accomplished, with most centers preferentially treating patients with ≤ 5 lesions. Several studies demonstrated highest rates of complete tumor destruction with RFA for lesions of ≤ 3 cm [108–110], with oncological outcomes similar to surgical resection [18, 108, 111–114].

Recent thermal ablation literature focuses on improving the relatively high local tumor recurrence rates (2–60%) [17, 86, 115–117]. This can be achieved by creating sufficient (ideally > 10 mm) minimal ablation margins ("A0 ablation" concept) [17, 118], incorporating metabolic image-guidance for tumor ablation by means of ^{18}F FDG-PET [119] as well as stratifying the patients based on modified clinical risk scores and genetic mutation profile, such as KRAS mutation [11, 18, 19, 86, 118, 120]. Essentially ablation with margins of > 10 mm is associated with few if any local failures [17, 18]. Similarly ablation margins of > 5 mm with immediate post-ablation zone center and margin biopsy confirming complete tumor necrosis offered over 97% local progression-free survival 30 months post-RFA [19].

The CLOCC trial is extremely important as it is the only randomized-controlled trial (RCT), providing the evidence of OS advantage when using LAT (by means of RFA) in combination with systemic chemotherapy versus systemic chemotherapy alone, with OS at 8 years of 36% and 8%, respectively [14, 102]. However, due to trial's limitations, new multicenter prospective COLLISION trial has been initiated, comparing thermal ablation (TA) and liver resection outcomes for CLM [121]. The main hypothesis is that TA might enable to achieve similar local tumor control and OS rates to surgical resection while reducing morbidity, mortality, direct economic costs, hospitalization days and improving quality of life [121]. Achieving similar local tumor control and OS with TA compared to surgery will further establish the terms "resectable" and "ablatable" as synonyms.

The outcomes following RFA and MWA in terms of safety and toxicity are comparable. Although there are data on MWA superiority than RFA for CLM [122], when stratified by margin size there was no difference in LTPFS [17] with no LTP for tumors ablated with margins > 10 mm. The latest-generation MWA systems offer technical advantages such as greater intra-tumoral temperature, deeper penetration of energy, propagation across the poorly conductive tissues, less sensitivity to the heat-sink effect and larger ablation volume, enabling to treat larger tumors with adequate safety margin when compared to RFA [123–125].

Endovascular Approaches

While ablation and resection are the only potentially curative options for mCRC, only around 20% of CLM patients are eligible for these treatments. Endovascular approaches, such as transarterial chemoembolization (TACE) [126–132] and ^{90}Y radioembolization (RE) [26, 75, 133–141], demonstrated improvement in OS and quality of life in chemorefractory CLM.

RE

^{90}Y RE is an FDA approved liver brachytherapy, recommended through the NCCN and the ESMO guidelines for the treatment of CLM in the salvage setting with liver disease progression while on or after second-line chemotherapy with encouraging oncologic outcomes [26, 72, 75, 133, 136, 137, 142–153]. It is also used to treat unresectable non-colorectal liver metastases [154–156]. However, when the patients present to the RE in salvage setting with advanced tumor load, unfavorable biological tumor characteristics and comorbidities, the range of outcomes post-RE is highly variable, with objective response rates varying between 10 and 48% when RE is applied in the third and subsequent chemotherapy regiment setting [146, 152, 157, 158].

The main effect of RE is attributed to radiation as it has a minimal embolic effect. Three types of particles are currently being used for RE: ^{90}Y microspheres (resin or glass based) and ^{166}Ho microspheres.

^{90}Y microspheres are the most commonly used microspheres for RE. ^{90}Y is β-emitter, with 96% of radiation delivered within 12 days in the tumor, with up to 1-cm penetration depth around each microsphere, enabling to achieve treatment margins around the tumor, similarly to surgical resection or thermal ablation [159].

Physical properties of glass-based and resin microspheres are different due to the size and number of the particles required to deliver the same radiation dose. RE with resin microspheres enables to deliver higher number of microspheres with potentially more homogeneous tumor coverage with a risk of embolic effect and stasis prior to total dose delivery [133, 160, 161]. ^{90}Y microspheres are not radiopaque, making real-time infusion monitoring challenging. Modified infusion methods using diluted or undiluted contrast medium have been explored with resin microspheres and resulted in decrease in incidence of stasis as well as fluoroscopy time [153, 162]. No substantial difference between the oncological outcomes when using resin or glass microspheres for CLM has been shown [20].

^{166}Ho microspheres emit γ-radiation and are paramagnetic; thus, they are getting increased attention due to a facilitated imaging with MRI, enabling real-time infusion and tumor coverage monitoring [163]. In addition, ^{166}Ho microspheres scout dose is used for treatment planning, enabling more accurate prediction of intra-and extrahepatic distribution of radiation activity. The differences between the RE particles are summarized in Table 4.

Although recent RCT failed to demonstrate the OS benefit of combination of RE with systemic chemotherapy compared with systemic chemotherapy alone in the first-line CLM treatment setting [164], subset of the patients with right-sided CRC showed OS advantage from this combinational treatment [165]. This is very important as the patients with right-sided CRC have less treatment options available than the left-sided CRC. Further investigation is of course needed to further assess this preliminary finding prior to its acceptance as a standard of care recommended in guidelines.

TACE

The objective of TACE is to generate a hypoxic/ischemic environment as well as to synergistically induce chemotherapeutic tumor destruction. TACE showed promising results for patients progressing on irinotecan-based systemic chemotherapy. TACE is usually applied to treat unresectable CLM in chemorefractory setting [72]. The data on second- and third-line TACE are collected from RCT [130] as well as from observational studies demonstrating wide variation of response (35–85%) and median OS of 13.3–37 months [166], which compares favorably to other standard of care therapies for CLM.

DEBIRI-TACE [52] have been imposed as a novel drug-delivery vehicle allowing for higher concentrations of drugs (irinotecan) within the target tumor and lower systemic concentrations compared with conventional TACE (cTACE) [167]. cTACE is usually administered selectively/sub-selectively, whereas DEBIRI-TACE is commonly administered in the lobar fashion due to the fact that irinotecan is a prodrug, activated by normal liver parenchyma, enabling to treat potentially occult liver lesions.

DEBIRI-TACE has been also explored for endovascular induction (neoadjuvant therapy) to target resectable CLM in PARAGON II study, with demonstrated low morbidity and 77% major response rate on pathology [168]. Radiopaque DC Bead LUMI™ beads (*BTG plc, the USA*), loaded with irinotecan, are the first radiopaque beads, which have been recently approved for CLM treatment, enabling to achieve much more precision for targeting, visualization of tumor coverage and defining the endpoints [169, 170].

To date, there is very limited evidence for bland embolization in CLM.

Table 4 Comparison of ^{90}Y (resin and glass based) and ^{166}Ho microspheres for radioembolization

	SIR-Spheres^{TM}	TheraSphere^{TM}	QuiremSpheres^{TM}
Matrix	Resin	Glass	PLLA
Diameter	20–60 μm (mean 32 μm)	25 μm	30 μm
Isotope	Yttrium-90		Holmium-166
T 1/2	64.5 h		26.8 h
Density	1.6 g/cm^3	3.4 g/cm^3	1.4 g/cm^3
Number of spheres	33–50 mln	4 mln	33 mln
Amount per dose	900–1370 mg	110 mg	600 mg
Activity per sphere	50 Bq	1250–2500 Bq	200–400 Bq
Activity per dose	2–3 GBq	5–15 GBq	6–12 GBq
Imaging	Y-90 PET or Bremsstrahlung SPECT/CT		SPECT/MRI/CT
Test dose	99 m Tc-MAA		Ho-spheres/Tc-MAA
Company	Sirtex Medical Limited, NSW, Australia	BTG, London, UK	Terumo, Nijmegen, NL
Year of creation	1974	1989	1994
CE trade mark year	2002	1999	2014
CE mark and indications/ FDA approval and indications	CE maked class III active medical device, indicated for treatment of inoperable liver tumors. FDA approved for unresectable colorectal liver metastases in combination with intrahepatic floxuridine	CE marked class III active medical device, indicated for treatment of hepatic neoplasia. Has FDA humanitarian device exemption for unresectable HCC	CE marked class III active medical device, indicated for treatment of unresectale liver tumors. Not FDA cleared in the US for sale
Activity calculation	BSA, partition model	MIRD-based approach	Two-compartment-based dosimetry

New IR Treatments on the Pipeline and Possible Molecular Drivers

New IR treatments on the pipeline, including treatment of earlier stage metastatic disease, combinational LAT therapies, ablative dose RE as well as combination of immunotherapy and LAT are described in detail in Supplement 2.

Shift of the Research Scope in mCRC

At the time of OMD term introduction (2016), the main focus of IO/IR has been integration of new LATs, such as RFA, MWA, irreversible electroporation, RE and (chemo-) embolization, into mCRC treatment guidelines, improvement of techniques efficacy, identification of prognostic factors and multidisciplinarity [72]. LATs were administered for OMD patients with curative or palliative intents [72].

However, since the year 2018, main research focus has been shifted to mCRC molecular determination, identification of the patients with curable OMD based on RNA analysis, exploration of tumor–stromal interaction as well as systemic effects following LAT and immunomodulation to induce abscopal effect (non-targeted tumor response) [171]. Also, mCRC OMD treatment concept has been modified, with recommendation to administer LAT with cytoreduction and curative intent to allow for “chance for cure” [171].

Identification of Curable mCRC for Better Patient Selection

It is crucial to be able to distinguish patients with potentially curable oligometastatic disease (OMD) from patients whose OMD is a part of a large cascade of widespread disease. This is very important as patients with new lesions following LAT of mCRC have been shown to have a poor prognosis. Prognostication strategies of CLM patients, based on RNA analysis, have been developed, indentifying three distinct CLM similarity network fusion subtypes (SNFs) with unique patterns of mRNA and miRNA expression as well as with distinct histological and genetic features and prognosis, which could help to identify OMD patients with potentially curable disease [6]. Further investigation is needed to define to what extent these concepts apply to patients undergoing LAT and, more generally, to patients with more widespread disease.

Key Mutations in LAT for mCRC

Most explored prognostic genetic signatures in LAT for mCRC include KRAS and PI3K mutations. KRAS mutation was found to be an independent prognostic factor of poor outcomes following ^{90}Y RE [172, 173] and thermal ablation of CLM [10, 11, 174]. Concordant data indicate that a minimum ablation margin of > 10 mm is recommended when ablating KRAS-mutant CLM [113, 174]. A minimal margin under 5 mm in KRAS-mutant CLM carries 16.8 times the risk of local failure when compared to wild-type CLM ablated with MM over 10 mm [113]. PI3K mutation was found to be associated with longer liver progression-free survival following ^{90}Y RE of CLM [138].

Artificial Intelligence (AI) in IR

AI has the potential to improve mCRC patient outcomes following LAT by improving patient selection and response assessment via the identification of imaging features associated with oncological outcomes. Texture analysis has demonstrated its utility in the assessment of response to RE for CLM, allowing for the detection of disease progression, on average, 3.5 months before it was visible on RECIST 1.1 [175].

Also, AI has a potential to improve catheter navigation, ablation probe placement, imaging registration and estimation of ablation margins [176].

Conclusion

In conclusion, there is expanding evidence regarding the value of LAT to improve liver and overall progression-free survival in mCRC. Evidence regarding the effect of LAT on patient OS is lacking [14, 75]. At this time, prospective studies comparing different locoregional modalities or ablative modalities to surgery are limited and decision making relies on limited data and a multidisciplinary decision-making process. As IO techniques strive to take additional roles in the management of CLM, progress will ultimately be dependent on the ability to produce substantial prospective trial-based evidence.

Suggested Readings

a. Cancer Societies

- Society of Interventional Oncology (SIO): http://www.sio-central.org/.
- Society of Interventional Radiology (SIR): https://www.sirweb.org/.
- Society of Cardiovascular and Interventional Radiology of Europe (CIRSE): https://www.cirse.org/.
- European Society of Oncologic Imaging (ESOI): http://www.esoi-society.org/.
- European Organization for Research and Treatment of Cancer (EORTC): http://www.eortc.org/.
- European Society for Medical Oncology (ESMO): https://www.esmo.org/.

b. Guidelines

- European Society for Medical Oncology (ESMO) consensus guidelines for the management of patients with metastatic colorectal cancer [72];
- NCCN Clinical Practice Guidelines in Oncology for Colon Cancer [26];
- Image-guided tumor ablation: standardization of terminology and reporting criteria—a 10-year update [177];
- Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy [178];
- Radioembolization of Hepatic Malignancies: Background, Quality Improvement Guidelines, and Future Directions [179];
- Transcatheter Therapy for Hepatic Malignancy: Standardization of Terminology and Reporting Criteria Reporting Standards [180].

c. Publications

- Ruers T, et al. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. J Natl Cancer Inst. 2017;109. https://doi.org/10.1093/jnci/djx015.
- Wasan HS, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 2017;18: 1159–71. https://doi.org/10.1016/s1470-2045(17)30457-6.
- Pitroda SP, et al. Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. Nat Commun. 2018;9:1793. https://doi.org/10.1038/s41467-018-04278-6.
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- Kurilova I, et al. Factors affecting oncologic outcomes of 90Y radioembolization of heavily pre-treated patients with colon cancer liver metastases. Clin Colorectal Cancer. 2019;18(1):8–18.

Compliance with Ethical Standards

Conflict of interest Authors Jia Li, Ieva Kurilova and Juan C Camacho declare that they have no conflict of interest. Nancy Kemeny received research fund from Amgen. Constantinos T. Sofocleous declares Research Support: Ethicon J&J, BTG, Consultant/Advisory Board: Terumo, Ethicon J&J, GE.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

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