CLINICAL PRACTICE GUIDELINE

Assessment and treatment considerations for patients with colorectal liver metastases: AHPBA consensus guideline and update for surgeons

Members of the AHPBA Professional Standards Committee[1]

Abstract

Background: Colorectal cancer most commonly metastasizes to the liver. While various treatment strategies have been developed, surgical management of these patients has vital implications on the prognosis and survival of this group of patients. There remains a need for a consensus guideline regarding the surgical evaluation and management of patients with colorectal liver metastases (CRLM).

Methods: This review article is a consensus guideline established by the members of the AHPBA Professional Standards Committee, as an amalgamation of existent literature and a guide to surgeons managing this complex disease.

Results: These guidelines reports the benefits and shortcomings of various diagnostic modalities including imaging and next-generation sequencing in the management of patients with CRLM. While surgery has established survival benefits in patients with resectable disease, this report notes the importance of treatment sequencing with non-surgical modalities as well as between colon and liver resection. Finally, the guidelines address the various treatment modalities for patients with unresectable disease, that may have significant impact on survival.

Conclusion: CRLM is a complex diagnosis which warrants multidisciplinary approach with early surgical involvement in both assessment and management of the disease, to optimize patient outcomes and survival.

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Colorectal cancer is one of the most common malignancies associated with liver metastasis, with more than a quarter of patients developing liver metastasis within 5 years of diagnosis.[1] Complete resection is an effective treatment modality for well selected patients with colorectal liver metastases (CRLM), given its well-documented impact on survival and curative potential.[2,3] Over the past two decades, several consensus conferences by leading surgical societies have emphasized management advances in CRLM including imaging technology, molecular diagnostics, sequencing of treatment modalities, systemic therapy, and locoregional treatments including resection, ablation, local chemoradiotherapy and transplant.[4,5] With expansion of available therapies, more patients are considered candidates for curative-intent therapy such as surgery. Wide variations in surgical referral patterns and management strategies for CRLM are well-documented.[6,7] The need to include surgeons early in evaluation and management of patients with this disease is increasingly recognized.[8,9]

Acknowledging the need for informed surgical perspective in evaluation of patients with CRLM, the purpose of these practice guidelines is to inform surgeons and surgical care providers of up-to-date perspectives on appropriate initial assessment and treatment considerations for this challenging patient population. Areas considered include imaging modalities, contemporary risk assessment, role of molecular profiling, treatment sequencing considerations, and approach to initially unresectable disease.

[1] The Members of the AHPBA Professional Standards Committee are listed in Appendix 1 at the end of the article.

Methodology

The following guidelines were developed by members of the professional standards committee of the AHPBA (Americas Hepato-Pancreato-Biliary Association). The data presented is based on a consensus review of the literature, including final review by all members of the executive council of AHPBA.

Imaging modalities

Accurate assessment of the burden of metastatic disease is essential to assess feasibility of surgery or other liver-directed therapies and establish patient prognosis. The ideal imaging modality must identify all liver lesions with their corresponding anatomic relationships, assess the presence of extrahepatic disease, and allow estimations of liver volumetry. Additionally, it should allow assessment of chemotherapy response, and chemotherapy-associated liver injury (CALI), as well as be safe and readily available for surveillance once resection or other locoregional therapies have occurred.

Primary imaging modalities that are widely available and utilized include multiphasic contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI) with and without diffusion weighted imaging (DWI), and positron emission tomography (PET) scans.

As reviewed in the 2012 AHPBA/SSO/SSAT Consensus Conference on Multidisciplinary Treatment of Colorectal Cancer Liver Metastases, MRI with hepatobiliary contrast-enhanced delayed imaging and diffusion-weighted imaging is recognized as the most sensitive modality for detecting and characterizing liver metastases, particularly lesions under 1 cm in size.[10] This is supported by a meta-analysis performed by Choi *et al.* that reported a sensitivity for MRI, CT, and PET/CT of 93.1 %, 82.1 % and 74.1 % respectively, for lesion detection and or localization in chemo naïve patients.[11] Asato *et al.* confirmed a higher overall sensitivity of combined DWI plus Gd-EOB-DTPA MRI (91.4 %) over CT (80.9 %), observing a higher sensitivity especially in smaller-sized lesions, when compared to the gold standard of surgically confirmed liver metastasis.[12] These results concur with earlier meta-analyses supporting the use of MRI in the detection of CRLM.[13,14] The combination of DWI and hepatobiliary-contrast enhanced MRI has been found to have the highest sensitivity for detecting liver metastases on a per-lesion basis.[15] Similarly, hepatobiliary-contrast enhanced MRI is currently the best available image technique for assessing CALI, including sinusoidal obstructive syndrome and steatohepatitis.[16] Comparing the cost of the three modalities, MRI is felt to be the most cost-effective modality to assess CRLM.[17]

Computed Tomography (CT): Despite marginally lower sensitivity and specificity, the easy availability, and acceptable accuracy makes a multidetector row CT scan of the chest, abdomen and pelvis with iodinated contrast the standard for one session whole-body staging of patients with CRLM, allowing evaluation of extra-hepatic disease while also assessing liver pathology.[11,18] A conventional multiphase CT with a slice thickness of 2–4 mm is recommended for axial and volumetric three-dimensional rendering of the liver. Vascular reconstruction enables the demonstration of arterial and portal venous anatomy for surgical planning. CRLM metastasis on CT scan most commonly have a hyperattenuating rim during the hepatic arterial phase and become diffusely hypoattenuating during the portal venous phase. The sensitivity is lower for smaller CRLM which are often hyperattenuating and difficult to characterize and in patients treated with neoadjuvant therapy.[19]

Magnetic resonance imaging (MRI): MRI can be helpful to better characterize indeterminate lesions (i.e. identifying benign lesions) and has a higher yield in evaluating lesions after having received chemotherapy, as decreased metabolic activity and chemo-related changes in the liver (e.g. steatosis) may affect detection by other modalities.[20] T2-weighted images are helpful to differentiate small hypoattenuating metastatic lesions from benign cysts. Further, DWI provide a functional assessment of the lesion/s, adding specific features to help characterize indeterminate findings. Newer contrast agents with hepatobiliary excretion furnish both the dynamic phases (non-contrast, arterial, portal, and delayed phases) and the hepatobiliary phase (delayed 20-min phase). Normal hepatocytes uptake these agents remaining iso- or hyper-intense during the hepatobiliary phase, while metastatic lesions remain dark (hypoattenuating) in contrast to the surrounding parenchyma, as they do not retain these contrast agents.

Positron emission tomography (PET): The routine use of PET scans in evaluation of patients with CRLM is useful less for demonstration of liver disease than in characterization of extra-hepatic disease. Despite equivalent specificity compared to MRI, PET-CT has the lowest sensitivity in detection of CRLM as it is limited in its ability to detect metastases less than 1 cm in size.[11] One randomized trial concluded that the routine us of PET imaging in patients with resectable CRLM is not associated with significant changes to surgical plans or improved survival, but can have unique benefits, as it relates to characterizing indeterminate lesions ($\geq$8 mm).[21] There is a growing interest in utilizing PET-MRI to increase the sensitivity and specificity of detecting CRLM as well as extra-hepatic disease.[22] However, comparative studies have reported similar accuracy compared to PET-CT.[23]

Tumor volumetrics: When considering major liver resection for CRLM, preoperative imaging is essential for volumetric analysis of the future liver remnant (FLR). A small FLR is associated with an increased risk of post-hepatectomy liver failure (PHLF). Studies evaluating patients with normal livers, compared to those with CALI and cirrhosis (compensated and

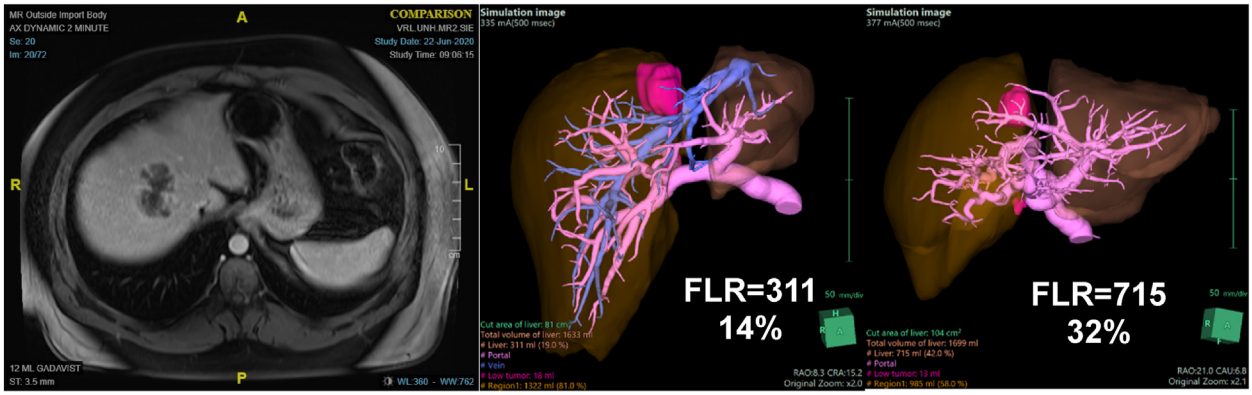

Figure 1 MRI depicting dominant tumor in dome of liver around segments 7/8/4A (**a**). 3D-reconstruction with volumetric analysis using specialized software (Synapse - FUJIFILM®) of the future liver remnant (left lateral section) before (**b**) and after (**c**) right portal vein embolization. Note: sTLV = 2,223 cm^3 is significantly higher than the measured TLV = 1,699 cm^3. Outcomes have been validated using the sTLV formula

without portal HTN), have accepted safe FLR thresholds of ≥20–25 %, ≥30 %, and ≥40 %, respectively.[24] As such, FLR volumetry is used to identify patients that will benefit from interventions geared to induce contralateral liver hypertrophy – including preoperative portal vein embolization (PVE), dual venous deprivation with portal and hepatic venous embolization, or portal vein ligation (PVL) as a component of an ALPPS procedure (Associating Liver Partition and Portal Vein Ligation for staged hepatectomy). The appropriate use of volumetry and each of these strategies is critical, as they expand the pool of patients that are candidates for resection by maximizing the amount of preoperative healthy liver required to reduce the risk of PHLF.

Different approaches exist to measure and quantify the FLR. The total liver volume can be standardized to the individual patient's weight or body surface area (BSA), and space-occupying lesions must be subtracted so as not to affect the accuracy of the total liver volume (TLV) specific to the patient. Two such formulas to estimate the *standardized* TLV (sTLV) have been well-validated in the western population and found to be most predictive of the actual TLV.[25,26]

The FLR volume is obtained through actual measurement of the liver segments that will remain after the planned operation, using available software with 3D-reconstruction (Fig. 1). Most commonly, images derived from CT are used for 3D-reconstruction and subsequent volumetry, although MRI images can be used as well. A liver-protocol study, as described, is adequate with no additional features required. Notably, the right lobe represents in average 65 % of the TLV[27]; in accordance with the established FLR thresholds as described above, liver volumetry should therefore be considered when considering resection of the right liver and routinely performed for more extensive resections, particularly in the setting of preoperative chemotherapy. Finally studies also recommend calculating remnant liver volume (RLV) calculated using (FLR volume)/(total liver volume) × 100, which has been associated with PHLF.

Repeat volumetric analysis using a new CT scan following PVE/PVL is required to obtain and assess the overall new volume of the FLR (%) and FLR growth rate (kinetic growth rate – KGR) prior to proceeding with the planned resection.[28] Repeat imaging and volumetric analysis are recommended 3–4 weeks post-intervention.[29] Retrospective analysis have noted that a kinetic growth rate or remnant growth rate of less than 2.66 % per week is a predictor of liver failure post resection.[30] Functional studies focused on examining the segmental contribution of liver function have become more relevant in the context of an associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), as the rapid volume increase is thought to overestimate the actual gain in function of the hypertrophied FLR. Scintigraphy liver studies, including 99mTc-labeled iminodiacetic acid (IDA) derivatives (mebrofenin being the most commonly used) have shown promising results, with its use in current practice limited to assess functional gain after the first stage of the ALPPS procedure.[31]

sTLV = (18.51 X body weight) + 191.8

sTLV= -794.41 + (1267.28 X BSA)

Intra-operative ultrasound (IOUS): While not part of the pre-operative multidisciplinary planning for colorectal liver metastases, consideration of imaging modalities pertinent to the liver surgeon must include the use of IOUS. Once considered the gold standard for detection of CRLM,[32] IOUS has largely been replaced by cross-sectional imaging for the purposes of treatment planning. Nonetheless, surgeons considering operations for liver metastases must be facile with IOUS for intraoperative planning (e.g. vascular anatomy/flow, vascular relation to lesion/s, transection guidance, and identification or confirmation of additional lesions). Systematic use of IOUS during surgery for CRLM can lead to detection of additional lesions in up to 10 % of cases.[33] This is particularly important when preoperative chemotherapy is utilized, for intraoperative localization of the disappearing liver metastasis on CT and to a lesser extent on MRI. MRI is particularly effective at detecting disappearing lesions on CT, as the difficulty in visualizing is often related to fatty changes in the liver which can be subtracted by MRI[34] Retrospective analysis have noted non-visualization of disappearing liver metastasis on MRI is an independent predictor of complete response[34](). Arita and colleagues demonstrated use of intraoperative ultrasound as a critical means to detect such metastases but demonstrated that the use of contrast enhanced IOUS with perflubutane which accumulates in Kuppfer cells had superior detection of disappearing liver metastases compared to contrast enhanced CT and standard IOUS ($p < 0.04$).[35] In addition, use of IOUS aids in defining anatomy and guiding resection plans for safe resection and is a vital tool for ablation targeting.

The most recent advancement in imaging for CRLM includes radiomics or radiogenomics. Radiomics involves examination of pixel-level relationships known as texture. These textures are being studied for their association with the tumor pathology, pathologic response to chemotherapy and molecular patterns.[36,37] Early studies have shown promise in its ability to assess for microsatellite instability and *KRAS* mutation in the metastatic lesions, which may be utilized to predict treatment response.[38,39]

Contemporary risk assessment

Despite excellent outcomes with resection of CRLM, most patients will experience disease recurrence. A number of scoring systems have been developed to help discriminate which patients might most benefit from liver resection, using available clinical information to inform disease biology and prognosis. Evaluation of patients with CRLM benefits from applying such scoring systems less as definitive determinants of which patients should undergo surgery, but rather to risk-stratify patients for informed decision-making.

Nordlinger *et al.* proposed the first prognostic scoring system to evaluate the chance for cure after hepatectomy for colorectal metastases.[40] Examining patients from 85 French institutions, the authors reported a scoring system with each of the following factors accounting for one point: extension into the serosa of primary cancer, lymph node involvement of primary tumor, the interval between primary tumor to metastases (<2 years), number of metastases (>4), margin status, and preoperative CEA level (5–30 μg/L: 1 point; >30 μg/L: 2 points). The cohort was divided into three risk groups: "Low risk" (0–2 risk factors); "Intermediate risk" (3–4 risk factors); and "High risk" (5–7 risk factors). The 2-year OS decreased from 79 % for the low-risk group to 60 % and 43 % for the intermediate and high-risk groups, respectively.

Analyzing a large single-center cohort of 1001 patients who underwent resection of colorectal metastases between 1985 and 1998, Fong *et al.* created the Clinical Risk Score (CRS).[41] Five clinical criteria that were identified to be highly predictive of OS, with one point assigned for each: nodal status of primary tumor, the interval between primary to liver metastases (<1 year), number of metastases (>1), preoperative CEA level (>200 ng/ml), and size of the largest tumor (>5 cm) were included in this scoring system, which was widely used at the time of its conception (Table 1). Although positive surgical margins and extrahepatic metastases were the most influential predictors of survival, they were not included in the model, as positive surgical margins would be unavailable in the pre-operative setting and extrahepatic metastasis was often found intraoperatively and overall was considered a contraindication for hepatectomy. The CRS accurately predicted the 5-year OS, whereas patients with CRS of 0 had a 60 % survival rate vs 14 % for patients with CRS of 5. Similar risk scoring systems have been developed in recent decades, including by Iwatsuki *et al.*,[42] as well as the Basingstoke Predictive Index,[43] largely using similar clinical information. Since patients with high scores still have the potential for long-term survival and even cure, albeit at a lower rate, the clinical applicability of these scoring systems remain limited and vary between institutions.[44]

More recently, Margolis *et al.* proposed a new score that incorporates *KRAS* mutation status[45] with validation in 747 patients from another high-volume institution. Primary lymph node status, CEA level (≥20 mg/ml), extrahepatic disease, presence of *KRAS* mutation, and the number of metastases (3–8 and ≥9) were incorporated in the predictive model. They defined the Genetic and Morphological Evaluation (GAME) score, as low risk (GAME 0–1), medium risk (GAME 2–3), and high risk (GAME ≥4). External validation showed that patients with a GAME score: 0–1 had a 5-year OS of 73.4 % vs 11.3 % for patients with a GAME score: ≥4 (Table 1). The authors also demonstrated the GAME score outperformed the CRS (Fong score) with an area under the curve of 0.625 vs 0.584 for the CRS, Harrell's C-index $P = 0.047$.

Role of molecular profiling

Incorporation of genomic information in the management of cancer patients holds great promise. It is now possible to obtain enormous amounts of data by performing DNA sequencing of

Table 1 Prognostic implications of various mutations seen in colorectal liver metastasis

Mutation	Prognostic impact	Literature
KRAS	Wild type associated with poor OS in right side tumors	Belias M *et al. Cancers (Basel)*. 2022.[103]
	KRAS mutation associated with poor OS and RFS	Brudvik KW *et al. Br J Surg*. 2015.[104]
	KRAS mutation does not impact liver metastasis or OS	Chan AKC *et al. Cancers (Basel)*. 2022.[105]
	KRAS mutation associated with worse OS and DFS after ALPPS for CRLM	Serenari M *et al. Dig Surg*. 2018.[106]
	KRAS mutation is poor prognostic marker of OS in patients who received neoadjuvant chemotherapy	Takeda Y *et al. Ann Surg Oncol*. 2022.[107]
	KRAS mutation is associated with poor OS, HRFS, DFS	Morató O *et al. Healthcare (Basel)*. 2022.[108]
	KRAS mutation is associated with poor OS and RFS	Brudvik KW *et al. Br J Surg*. 2015.[104]
	KRAS discordance (mutation in CRLM with wild type primary) is associated with poor OS	Ardito F *et al. Cancers (Basel)*. 2021.[109]
	KRAS mutation is associated with poor DFS with non-anatomical resection	Margonis GA *et al. Ann Surg*. 2017.[110]
	Cetuximab improves survival in wild type *KRAS*, unresectable CRLM	Lv W *et al. Gastroenterol Res Pract*. 2017.[111]
BRAF	*BRAF* associated with poor prognosis after surgery, that improves in converted tumors	Margonis GA *et al. Ann Surg*. 2023.[112]
	BRAF mutation is associated with poor OS and RFS in CRLM	Gau L *et al. Eur J Surg Oncol*. 2021.[113]
	Surgery improves survival in *BRAF V600E* positive tumors	Javed S *et al. World J Surg Oncol*. 2022.[114]
	BRAF mutation is associated with poor OS and DFS	Pikouli A *et al. Am J Surg*. 2022.[115]
	BRAF mutation associated with oncologically unresectable CRLM	Kobayashi S *et al. Cancer Med*. 2021.[116]
	BRAF mutation associated with worse OS, DSS and RFS	Pikoulis E *et al. Anticancer Res*. 2016.[117]
TP53	*TP53* mutation is associated with improved OS	Maki H *et al. J Gastrointest Surg*. 2023.[118]
	RAS/TP53 co-mutation is associated with worse OS in CRLM	Lillemoe HA *et al. Ann Surg*. 2022.[119]
	RAS/TP53 co-mutation is associated with worse DFS in CRLM	Kawaguchi Y *et al. J Am Coll Surg*. 2019.[120]
	TP53 mutation associated with poor OS after NAT	Pilat N *et al. Eur J Surg Oncol*. 2015.[121]
	TP53 mutation has no impact on OS in CRLM	de Jong KP *et al. Clin Cancer Res*. 2005.[122]
MSI	MSI associated with worse OS	Dijkstra M *et al. Biomedicines*. 2021.[123]
	MSI associated with worse OS	Turner KM *et al. Am J Surg*. 2023.[124]
	MSI not associated with survival in CRLM	Haddad R *et al. Ann Surg Oncol*. 2004.[125]
SMAD4	*SMAD4* mutation is associated with worse OS	Mizuno T *et al. Eur J Surg Oncol*. 2018.[126]
	SMAD4 expression is associated with higher risk of recurrence in CRLM	López-Gómez M *et al. Clin Transl Oncol*. 2015.[127]
	Loss of *SMAD4* expression is associated with development of CRLM	Losi L *et al. Oncol Rep*. 2007.[128]
	ERK pathway is a potential therapeutic pathway in *SMAD4* inactivated CRLM	Ai X *et al. Cancer Biol Ther*. 2013.[129]
HER2	*HER2* is associated with poor survival in CRLM (left side, wild type RAS mutation)	Han J *et al. J Surg Oncol*. 2022.[130]
	High discordance of *HER2* between primary CRC and metastatic lesion	Shan L *et al. J Cancer Res Clin Oncol*. 2018.[131]
	Dual therapeutic target for *HER2* positive CRLM	Sartore-Bianchi A *et al. Lancet Oncol*. 2016.[132]
NRAS	*NRAS* is associated with poor OS in CRLM	Schirripa M *et al. Int J Cancer*. 2015.[133]
	RAS mutation is associated with poor OS and DFS in CRLM	Chuang SC *et al. Oncol Lett*. 2020.[134]

patient's tumor at a reasonable cost. While this is remarkable progress over the last decade, the implementation of these molecular 'tools' in the clinic remains an area of investigation. Using next generation sequencing (NGS), there is the potential to detect mutations that may either inform patients and clinicians about prognosis, inform systemic therapy, and potentially allow participation in clinical trials. While certain mutations are characterized by poor prognosis after liver resection, there is currently insufficient data to preclude liver resection in these sub-groups, nor is there sufficient data to allow use of mutational status to guide surgical approaches (anatomic versus non-anatomic resection) or the utility of other liver-directed therapies including hepatic arterial infusion. Further studies are needed to establish independent prognostic value of molecular testing beyond traditional clinical risk scores, and incorporation of genomic risk scores in clinical decision-making requires external prospective validation.

CRC and CRLM can harbor *RAS*, *BRAF* and *TP53* mutations with *KRAS* being identified most commonly in 25–52 % of the patients.[46] While their impact on the prognosis, survival and

therapeutic planning has been analyzed with studies reporting contradictory results, *KRAS* and particularly *BRAF* mutations are most often associated with worse prognosis (Table 1).

Potential prognostic information can be obtained from the presence or absence of *RAS* mutations (*KRAS, HRAS* and *NRAS*), which occur in nearly half of all patients with metastatic colorectal cancer but with lower rates in patients undergoing liver resection. In patients undergoing liver resection, *RAS* mutations are associated with worse prognosis (3-year overall survival 52 % vs. 81 % for *RAS* wildtype, $P = 0.002$).[47,48] In addition, *BRAF* mutations occur in 5–11 % of patients with metastatic colorectal cancer. Patients with *BRAF* mutations are less likely to present with liver limited disease. After resection, compared to patients with *BRAF* Wild Type (*BRAF WT*) tumors, patients with *BRAF* mutation have worse overall survival at 2 years (61 % vs. 86 % *BRAF WT*, $P = 0.003$).[49,50] Almost all patients (>90 %) with *BRAF* mutation will eventually develop a recurrence after liver resection. Mutations in *TP53* and *SMAD4* occur in 89 % and 11 % of patients with metastatic colorectal cancer undergoing liver resection, respectively. Accounting for clinical risk factors, *RAS, TP53* and *SMAD 4* are each independently associated with worse overall survival.[51,52] Additionally, co-mutation analysis has noted worse survival in patients with concurrent *RAS/BRAF* alteration with *SMAD* mutation with resectable disease, as well as in patients with *RAS/BRAF* alternation with *TP53* mutation in unresectable liver metastasis.[53] *HER2* amplification occurs in 2–9% of patients with metastatic colorectal cancer. Given the rarity of *HER2* mutations, most studies are under-powered to detect an association between *HER2* status and survival.[54] Therefore, the prognostic role of *HER2* in metastatic colorectal cancer remains uncertain.

Molecular profiling helps guide systemic therapy for CRLM in some scenarios. Anti-EGFR therapy has been utilized for patients with wild type *KRAS* and is ineffective in patients with altered KRAS. However, alterations in genes such as *HER-2* impact the downstream expression of the RAS pathway leading to treatment resistance. *HER-2* mutational testing followed by anti-*HER-2* based therapies may be utilized in patients with anti-EGFR resistance.[54,55] Approximately 3.5–5 % of metastatic colorectal cancer are characterized as microsatellite instability high (MSI-H or dMMR). In the KEYNOTE-177 trial[56] comparing Programmed death 1 (PD-1) blockade with Pembrolizumab to standard first-line systemic therapy for patients with advanced dMMR colorectal cancer, Pembrolizumab led to significantly longer progression-free survival than chemotherapy with fewer treatment-related adverse events. Similarly, in the CheckMate-142 trial[57] Nivolumab combined with ipilimumab demonstrated an objective response rate of 69 % with acceptable toxicity. While these trials did not specifically evaluate patients planned for liver resection, the use of PD1 checkpoint blockade should be considered standard in the peri-operative setting for patients with dMMR status. In a subset of patients with dMMR tumors, PD1 blockade is associated with early progression compared to systemic therapy and therefore efficacy of immunotherapy in the peri-operative setting should be closely monitored.

In the New-EPOC trial,[58] patients with resectable or borderline resectable colorectal liver metastases with *KRAS* wildtype tumors, the addition of cetuximab to peri-operative systemic therapy conferred an overall survival detriment of 2 years on average (Median 55·4 months [95 % CI 43·5–71·5] vs 81·0 months [59·6 to not reached]; HR 1·45, 95 % CI 1·02–2·05; $p = 0·036$). Anti-EGFR therapy therefore should not be routinely used in patients with resectable or borderline resectable liver metastases. Interestingly, in the non-resectable setting, addition of anti-EGFR therapy to first-line systemic therapy was associated with improved response rates compared to systemic therapy alone. Then in the VOLFI Phase II trial[59] patients with non-resectable *RAS*-wildtype metastatic colorectal cancer were randomized to mFOLFOXIRI in combination with panitumumab vs. mFOLFOXIRI alone. Conversion to resectability was higher in the combination arm (33 %) compared to control (12 %). Molecular profiling therefore helps decide if anti-EGFR (cetuximab or panitumumab) therapy is appropriate. Patients with *KRAS* or *NRAS* mutations are insensitive to anti-EGFR therapy.[60,61] Further, patients with *KRAS* and *NRAS* wildtype tumors that originated in the right side of the colon are also insensitive to anti-EGFR treatment.[62] Finally, patients with *BRAF* V600E mutant tumors, similar to *RAS* mutant tumors are insensitive to anti-EGFR therapy (unless administered as part of a *BRAF* inhibitor regimen).[63] Of note, *BRAF* mutations are nearly always mutually exclusive with *RAS* mutations.

So while a tumor's mutation profile is shown to affect prognosis after metastasectomy, there is currently insufficient data to recommend the avoidance of surgery in given subgroups nor is there sufficient data suggesting that mutation profile should guide surgical approach.

Considerations for treatment sequencing

A crucial consideration in the multidisciplinary evaluation of patients with CRLM is the sequencing of treatment modalities, particularly whether to recommend chemotherapy in the pre-operative setting. Neoadjuvant chemotherapy has the theoretical advantage of downstaging tumors to allow a higher likelihood of margin-negative resection, addressing clinically occult systemic disease, and allowing observation of disease biology and treatment response prior to resection. Furthermore, therapy delivered solely in the adjuvant setting risks delayed administration in the setting of postoperative complications. In designing a multimodality therapeutic plan, one must always consider whether any kind of perioperative systemic therapy improves outcome in the context of complete resection. Some patients (in this case a small proportion – generally around 5 %) undergoing neoadjuvant chemotherapy experience disease progression that may alter surgical approaches or render metastatic disease unresectable.[64]

Progression of disease during neoadjuvant chemotherapy has also been noted as evidence of previously occult disease and therefore neoadjuvant therapy can be used as a selection tool. Smaller lesions may entirely regress radiographically; up to 83 % of so-called vanishing metastases on CT scan have microscopic residual disease resulting in a local recurrence rate of up to 70 % if left *in situ*,[65] though the overall effect of these lesions on survival is less clear.[66] Despite the various theoretical advantages of neoadjuvant therapy, most studies have failed to show any beneficial impact of neoadjuvant chemotherapy on the survival and progression of patients with CRLM.[67–69] This is especially important in patients with otherwise resectable disease at diagnosis, thus warranting strong consideration to upfront surgery for patients with resectable CRLM. Another significant concern with neoadjuvant chemotherapy is also the potential for chemotherapy-associated hepatotoxicity, which may increase the risk of resection and health of the postoperative liver remnant.[70–72]

Decisions regarding treatment sequencing are particularly important in the setting of synchronous presentation of colorectal metastases, especially with rectal cancer where preoperative chemotherapy and/or radiotherapy may be administered or in which staged colorectal and liver resections are planned. Patients with symptomatic primary tumors may require modifications of treatment sequencing depending on the need for upfront resection, intestinal diversion, or endoluminal stenting.

Data to inform evidence-based decision making regarding the use of perioperative chemotherapy for CRLM are limited. No randomized controlled trials compare perioperative to neoadjuvant or adjuvant chemotherapy, with most data including hepatectomy alone as the control arm. Table 2 depicts the various randomized controlled trials that have attempted to compare adjuvant therapy with surgery alone, different modalities of adjuvant therapy, as well as the impact of immunotherapy in the adjuvant setting. A recent Japanese trial investigating the potential benefit of adjuvant chemotherapy following hepatectomy alone reported that mFOLFOX6 conferred an improvement in 5-year disease-free survival (49.8 % versus 38.7 %; HR 0.67 (95 % CI 0.50–0.92); $p = 0.006$) but not 5-year overall survival (71.2 % versus 83.1 %; HR 1.25 (95 % CI 0.78–2.00); $p = 0.42$).[73] The most influential contribution concerning the benefit of perioperative chemotherapy was reported in 2008 following an international trial sponsored by the European Organization for Research and Treatment of Cancer, which found that perioperative chemotherapy consisting of six cycles of FOLFOX4 before

Table 2 Adjuvant therapy in CRLM: Randomized controlled trials

Trial	Result
Nordlinger B *et al. Lancet Oncol*. 2013.[75]	No difference in survival with addition of peri-operative chemotherapy in patients with resectable CRLM
Schimanski CC *et al. Oncoimmunology.* 2020.[135]	No benefit in survival with tecemotide as well as no impact of MUC1 mutation
Bridgewater JA *et al. Lancet Oncol.* 2020.[58]	Worse overall survival with the addition of cetuximab to peri-operative chemotherapy in resectable and sub-optimally resectable CRLM
Kokudo T *et al. Surgery*. 2021.[136]	Adjuvant uracil- tegafur therapy prolongs recurrence free survival with no impact on overall survival, when compared to surgery alone in CRLM
Modest DP *et al. Eur J Cancer*. 2022.[137]	No benefit to survival with addition of panitumumab to adjuvant chemotherapy in CRLM
Hasegawa K *et al. PLoS One*. 2016.[138]	Adjuvant uracil- tegafur therapy prolongs recurrence free survival with no impact on overall survival, when compared to surgery alone in CRLM
Schulze T *et al. Cancer Immunol Immunother*. 2009.[139]	Adjuvant ASI-NDV associated with improved overall survival in CRLM
Ogata Y *et al. PLoS One*. 2015.[140]	Antineoplaston associated with improved cancer specific survival with adjuvant HAI in CRLM
Portier G *et al. J Clin Oncol*. 2006.[141]	Adjuvant therapy is associated with improved DFS, with no impact on OS
Snoeren N *et al. Neoplasia.* 2017.[142]	Bevacizumab is safe in patients with CRLM, with unestablished impact on DFS
Feng WM *et al. Hepatogastroenterology*. 2012.[143]	Adjuvant HAI improves DFS and OS in CRLM
Ychou M *et al. Ann Oncol*. 2009.[144]	No difference in DFS between FOLFIRI and 5FU in adjuvant setting in resectable liver metastasis
Kemeny NE *et al. Ann Surg*. 2021.[145]	Panitumumab in adjuvant setting (with HAI pump and systemic therapy) associated with trends towards improved DFS and OS
Kemeny NE *et al. J Clin Oncol.* 2011.[146]	Bevacizumab in adjuvant setting (with HAI pump and systemic therapy) has no benefit on survival and worsens biliary toxicity
Chun YJ *et al. Clin Colorectal Cancer*. 2020.[147]	Peri-operative chemotherapy (and bevacizumab) improves overall survival compared to post-operative therapy
Laffer U *et al. Int J Colorectal Dis*. 2008.[148]	Peri-operative chemotherapy with 5-flurouracil and mitomycin C is not associated with disease free and overall survival.
Kusano M *et al. J Cancer Res Ther*. 2017.[149]	No difference in the survival between adjuvant systemic therapy and HAI pump

and after surgical resection of colorectal metastasis, compared to surgical resection alone, was associated with improved 3-year progression-free survival (42.4 % versus 33.2 %; HR 0.73 (95.66 % CI 0.55–0.97); $p = 0.025$), but with a similarly high rate of resection in both groups did not substantially help with patient selection for surgery.[74] Importantly, at long-term follow-up of a median of 8.5 years, no overall survival difference was identified.[75]

Utilizing hepatic artery infusion (HAI) in the adjuvant and peri-operative setting has also been noted to improve outcomes in patients with resectable CRLM. A randomized control trial examining the impact of adjuvant utilization of HAI pump utilizing floxuridine with and without 5-flurouracil based systemic therapy, noted a 2.34 risk ratio of death with systemic therapy compared to systemic therapy with HAI pump.[76] These findings were supported by a large retrospective analysis utilizing propensity matched analysis of more than 2000 patients, treated at a single center, who received perioperative systemic therapy with and without HAI pump. This study noted HAI pump was utilized in more in patients with N2 disease, number of liver lesions, and synchronous liver tumors. Despite this discrepancy with higher utilization of HAI pumps in patients with advanced disease, perioperative utilization of HAI pump was associated with a 2 year longer overall survival.[77] However, the study also noted no benefit with HAI pump in patients with extrahepatic disease, positive resection margin and worse clinical risk score. This is an important consideration while selecting patients who would benefit from this modality.

Based on available data, patients with resectable colorectal liver metastasis have shown no added benefit with peri-operative chemotherapy and should be considered for upfront surgery, to allow them the maximum benefit of a curative resection. Preoperative chemotherapy may be beneficial in patients who are not resectable at diagnosis, demonstrate high risk features or would be better candidates for ablation rather than surgical resection.[69,78,79] In light of the paucity of data to guide treatment decisions, sequencing tailored to the individual patient must be guided by multidisciplinary consensus. It is essential that liver surgeons are involved at the time of initial assessment of patients with CRLM rather than after the administration of chemotherapy, to ensure the entirety of metastatic burden and resectability are assessed given the risks of prolonged chemotherapy to the liver remnant.

An important consideration in treatment sequencing also includes the decision of simultaneous versus staged surgical resection as well as liver or primary first resection. Various studies have shown improved safety as well as survival in patients undergoing staged resections.[80,81] A large analysis of the LiverMetSurvey registry also noted that decision regarding liver first versus primary first may be based on the liver tumor burden.[82] Other studies, however, have shown that simultaneous surgery, even in the context of rectal surgery and major liver resections can be safely performed in experienced centers.[83] The most compelling case for staged resection is the combination of a major hepatectomy combined with a complex rectal resection. In the case of minor colon resections and minor liver resections it is reasonable to perform simultaneous resection. The evidence on this topic is nearly all retrospective and plagued by selection bias. Therefore approaches must be individualized based on the details of the clinical presentation and the experience of the treating center.

Considerations for initially unresectable colorectal liver metastases

Surgeons evaluating patients with metastatic colorectal cancer will frequently be called on to evaluate patients with metastatic burden that is unresectable for a variety of reasons. While the treatment of initially unresectable metastatic colorectal disease to the liver with surgery or locoregional treatments may seem far-fetched, curative-intent therapies remain possible. Indicators of tumor biology and prognosis, including components of the clinical risk scores as reviewed above, are crucial to decision making in this patient subset. Considerations for the treatment of initially widespread hepatic metastases include systemic therapy, combined ablation-resection strategies, two-stage hepatectomy with or without portal vein embolization (PVE), associating liver partition and portal vein ligation (ALPPS), and Ytrrium-90 therapy. Throughout the therapy for unresectable disease, surgeons should remain involved in decision making since tumors can be downstaged to the point where complete resection becomes possible.[84,85] For truly unresectable disease, two modalities that warrant special consideration on initial evaluation are hepatic artery infusion (HAI) pump and orthotopic liver transplantation.

Hepatic artery infusion therapy

Early series on HAI for CRLM and trials on adjuvant HAI after complete resection by Kemeny and colleagues paved the way for expanded treatment opportunities using this modality.[86,87] The rationale for HAI includes the fact that liver metastases are almost exclusively perfused by the hepatic artery (whereas normal parenchyma receives dual blood supply by the portal vein and hepatic artery), and that some drugs, such as floxuridine (FUDR), are extracted by the liver during first pass metabolism with minimal systemic spillover and 100-400-fold estimated increase in hepatic exposure.[88] In one phase II trial, HAIP was used to convert unresectable liver-only disease to resectable disease in 64 patients with a median of 13 metastases, of whom 67 % had previously seen systemic therapy and 52 % were converted to resection.[89] Impressively, 23 patients (47 %) were able to undergo complete resection after response, with 4 complete responses, and with an overall response rate of 76 %. Resection translated to a 3-year overall survival (OS) rates of

80 % compared with 26 % in patients who were not resected. A subsequent retrospective analysis confirmed an association with improved median survival among all patients who underwent adjuvant HAI therapy, including among node-positive and node-negative patients, patients with solitary and multiple hepatic metastases, and patients with all clinical risk scores, with the maximum benefit in patients with node-negative disease and low clinical risk scores.[90] These findings have resulted in wider implementation of HAI, including minimally-invasive placement, across the United States and globally at dedicated centers utilizing HAI in the adjuvant and unresectable settings.[91]

Despite the many advantages and survival benefits noted with HAI pumps, their use remains limited to high volume, tertiary centers due to the extensive infrastructure needs with their insertion and management. The insertion of HAI pumps continues to be associated with a 19 % operative morbidity (much improved from the initial reported 35 %), with concerns for pump pocket seroma, hematoma, surgical site infections, as well as extra-hepatic perfusion.[92,93] An important long term complication with HAI pumps includes biliary sclerosis that may be seen in up to a quarter of the patients.[94]

Orthotopic liver transplantation

Given that 40 % of patients with colorectal cancer develop liver metastases and the majority of these patients having unresectable disease a theoretical treatment modality could be with orthotopic liver transplantation. However, given limited organs, potential post-transplant complications, requirement of immunosuppression and its effects on cancer, expectations for equitable graft and patient survival tumor biology and patient selection are extremely critical in selecting patients whom are the most appropriate candidates and will derive benefit from transplantation.

Interest in transplantation for colorectal liver metastases was reported as early as the 1980s however due to poor selection criteria, ineffective chemotherapy, immunosuppression considerations and high perioperative mortality, this was abandoned due to dismal results characterized by high rates of early recurrence and a 5 year overall survival of 0–18 %.[95–97]

In 2013, the first prospective report of the use of liver transplantation for unresectable liver metastases from colorectal cancer emerged from Oslo, Norway.[98] The SECA-I trial was a prospective pilot study that assessed the safety and effectiveness of liver transplantation (LT) for patients with unresectable CRLM. Among 25 patients who were listed for LT, 21 underwent LT, for whom OS at 1, 3, and 5-year was 95 %, 68 %, and 60 %, respectively. However, disease-free survival (DFS) was notably 0 % at 2 years with a median follow up of 27 months. Importantly, many of these disease "recurrences" represented sites that were amenable to further treatment such as resection/ablation for pulmonary metastases. Although overall survival was acceptable, the high rates of recurrence led to criticism. However, this study allowed delineation of key determinants of poor outcomes, which included tumor size, CEA level, disease-free interval from resection of the primary tumor, and response to chemotherapy. The SECA-II trial was then published which employed more strict selection criteria. These criteria included 10 % response to systemic therapy, at least 1 year between the primary tumor diagnosis and listing for LT, lower CEA levels and lower disease burden. The study included 15 patients and showed 1, 3, and 5-year OS rates of 100 %, 83 %, and 83 %, respectively, and DFS rates of 53 %, 44 %, and 35 % at 1, 2, and 3 years, respectively).[99] The SECA-II trial demonstrated that restrictive selection criteria in this group of patients led to improved overall and disease free survival thereby increasing data for justification of use of LT in these patients. However a criticism of the study is the short follow up time of 36 months. Another contribution from the SECA II trial is the utility of PET CT in these patients and its usefulness in detecting extrahepatic disease. While organ availability remains critically different in Norway where these studies originated, these data have encouraged other centers to begin evaluating patients with liver-only metastatic colorectal cancer for both living-donor and extended-criteria deceased donor liver transplant.

Hernandez *et al.*[100] reported on 10 out of 91 patients assessed for LT for unresectable CRLM with stable disease on systemic therapy across 3 centers (2 in the US and 1 in Canada). The authors showed a 62 % recurrence free survival and 100 % overall survival at 1.5 years following living donor liver transplantation with acceptable morbidity for recipients and donors based on established standards.

In order to address clinical expansion in this area, the International Hepato-Pancreato-Biliary Association (IHPBA) published consensus guidelines to help address areas of uncertainty. Notably, and unlike hepatocellular carcinoma where criteria for transplantation remain primarily structural in nature, patients with metastatic colorectal cancer are best selected for transplantation using surrogates of tumor biology, including tumoral genetics, radiographic and serologic responsiveness to chemotherapy, and the natural history of the disease in each patient such that oncologically appropriate patients are selected to justify use of a cadaveric or living donor allograft.[101,102]

The first randomized controlled trial TRANSMET, (NCT02597348) looked at liver transplantation and chemotherapy (CT + LT) versus chemotherapy alone (CT) for patients with unresectable colorectal liver metastases. Results of this trial was recently reviewed at ASCO 2024. Total number of patients included were 94 and 5 year overall survival was 57 % in CT + LT vs 135 in the CT arm (HR: 037, $p = 00003$). The authors showed that patients who underwent LT and CT had improved overall survival and progression free survival compared to CT alone This was based on rigorous patient selection Of note, these survival results are comparable to other indications for liver transplantation 73 % at 5 years justifying use of organs for this indication. Two parallel studies (COLT, NCT03803436 and MELODIC, NCT 04870879) comparing liver transplantation to palliative chemotherapy will provide useful information in patients who are comparable to one

another based on the proposed inclusion criteria and randomization. The primary endpoint in these ongoing trials are overall survival rather than recurrence free survival which has been the focus of existing studies to date.

Although much remains to be learned in this area, including the relative comparison of transplant to other treatment strategies, it seems likely that liver transplantation will be included in the broad range of treatment options available to a highly selected group of patients with liver only unresectable metastatic colorectal cancer.

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Conflicts of interest

None declared.

Appendix 1

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