Molecular profiling and patient selection for the multimodal approaches for patients with resectable colorectal liver metastases

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Abstract: Colorectal cancer represents the third most common cancer and about 20% are diagnosed with synchronous metastatic disease. From a historical point of view, surgery remains the mainstream treatment for resectable colorectal liver metastases (CRLM). Furthermore, disease outcomes are improving due significant advances in systemic treatments and diagnostic methods. However, the optimal timing for neoadjuvant chemotherapy or upfront surgery for CRLM has not yet been established and remains an open question. Thus, patient selection combining image workouts, time of recurrence, positive lymph nodes, and molecular biomarkers can improve the decision-making process. Nevertheless, molecular profiling is rising as a promising field to be incorporated in the multimodal approach and guide patient selection and sequencing of treatment. Tumor biomakers, genetic profiling, and circulating tumor DNA have been used to offer as much personalized treatment as possible, based on the precision oncology concept of tailored care rather than a guideline-based therapy. This review article discusses the role of molecular pathology and biomarkers as prognostic and predictor factors in the diagnosis and treatment of resectable CRLM.

Keywords: Colorectal liver metastases (CRLM); surgery; chemotherapy; molecular pathology; circulating tumor DNA; tumor markers

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Introduction

Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer-related deaths in the United States (US) in 2022 for both men and women. Globally, CRC represents the third most diagnosed malignancy and the second cause of cancer-related deaths (1,2). Although the estimated 5-year relative survival for localized disease achieves 91%, it drops to 15% in patients with metastatic disease (1). Moreover, the impact of the advanced disease is magnified considering that metastatic CRC (mCRC) represents 21% of the incident CRC cases in the US (1).

The historical and well-established curative-intent treatment for potentially resectable colorectal liver metastases (CRLM) is complete surgical resection (3). Surgical and oncologic outcomes have been improving over time not only because of refinements in imaging and surgical techniques, anesthesiology, and critical care management, but also due to the incorporation of effective systemic chemotherapy that provided better outcomes, increased response rates, and supporting the selection of the suitable candidates for CRLM surgery (4).

Since patient selection has been mandatory for the treatment of CRC, from patients to early detection to patients who need conversion therapy (treating unresectable CRLM until became resectable for surgical treatment), decision-making goes beyond tumor burden on imaging assessments. Tumor makers and genetic profiles have been used to offer as much personalized treatment as possible, based on the precision oncology concept of *tailor-made* care instead of a "one size fits all" therapy. This review article aims to explore the relevance of molecular pathology and biomarkers as prognostic and predictor factors, covering staging, systemic therapy, minimal residual disease assessment, and follow-up for potentially resectable CRLM.

Tumor biology

Basis of molecular approach for CRC

The main molecular events that drive CRC are well-described, but it is still an evolving field with potential therapeutic implications in the management of liver metastasis. Both inherited and acquired genetic alterations are responsible for driving the transformation from normal colonic epithelium to adenocarcinoma through the adenoma-carcinoma pathway. This CRC oncogenic pathway arising from precancerous precursors is based on pathologic and clinical data since carcinomas are frequently found within adenomatous polyps (5). In addition, the incidence of CRC is reduced through the removal of adenomatous polyps according to prospective trials (5). Another alternative pathway through serrated polyps is also described (6).

The accumulation and sequence of mutations in the adenomatous polyposis coli (*APC*) gene occur in the early phase of the transformation of the CRC, whereas the *TP53* mutation is a late event. Besides, gene amplifications, fusions, deletions, and DNA methylation are also involved in the carcinogenesis of CRC as depicted in *Figure 1*.

Concerning molecular pathways in the CRC onset, the most well-established are: (I) the DNA mismatch repair pathway, which is related to the Lynch syndrome as well as to sporadic CRC cases with loss of DNA mismatch repair (MMR) protein activity; (II) the chromosomal instability (CIN) pathway, that is exemplified by the familial adenomatous polyposis syndrome and presents gross chromosomal abnormalities such as deletions, insertions and loss of heterozygosity; and (III) the hypermethylation phenotype, which presents a high frequency of CpG island methylation (7,8).

The molecular landmark of the DNA mismatch pathway results from germline mutations in one of the MMR genes, most commonly *MLH1* or *MSH2*. Tumors with this characteristic accumulate DNA errors throughout the genome. Microsatellites, which are repeated short sequences of nucleotide bases, also accumulate abnormalities that are captured by sequencing tests and typify microsatellite instability (MSI). This genetic pathway is found in 15% of sporadic CRC and is associated with a higher response to immunotherapy (9).

A proportion of CRCs has a high prevalence of methylation. This feature may result in methylation of the promoter region of the repair enzymes such as *MLH1*. As an example, *BRAF* mutations occur particularly in tumors with MSI and hypermethylation phenotypes that do not carry *KRAS* mutations (10). On the other hand, CRC related to inherited Lynch syndrome can present only with *KRAS*, but eventually not *BRAF* mutations (11). Interestingly, patients with MSI and *BRAF* mutations present an unfavorable prognosis compared to patients without it, but a better prognosis compared to patients with only *BRAF* mutations
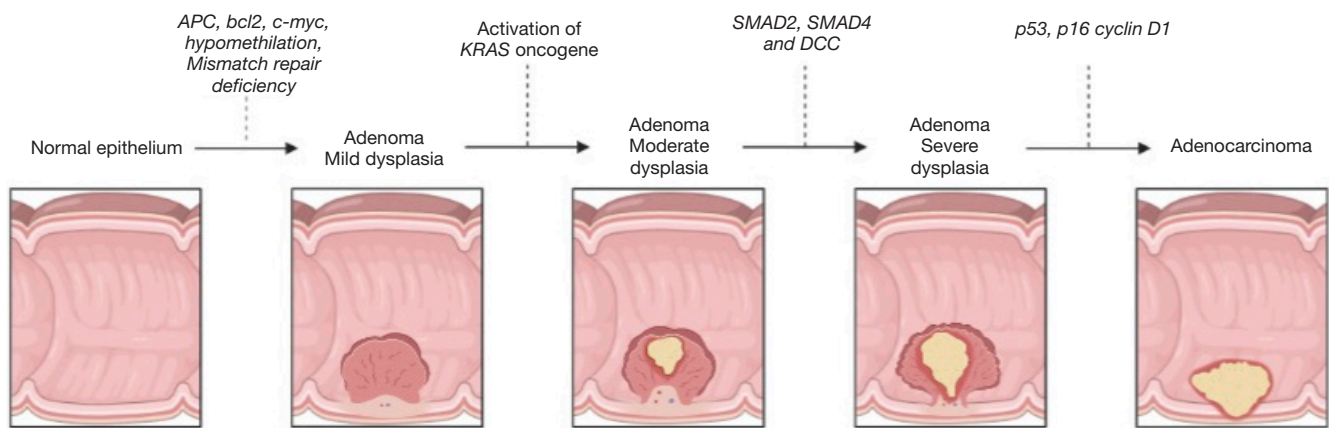
Figure 1 Gene amplifications, fusions, deletions, and DNA methylation involved in the carcinogenesis of colorectal cancer. Created with BioRender.com.

without MSI (12).

RAS oncogene presents three variants, named *HRAS*, *KRAS*, and *NRAS*. Mutations in all of them can trigger malignant transformations, but *KRAS* is the most frequent (13). *RAS* proteins normally cycle between an inactive guanosine diphosphate (GDP)-bound form and an active guanosine triphosphate (GTP)-bound state. *RAS* mutations induce resistance to GTP hydrolysis by GTPase, resulting in a constitutively active growth stimulus. *RAS* mutations are described in 50% of sporadic CRCs (14). *RAS* mutation detection in fecal material is a potential screening method for the early diagnosis of CRC (15). Besides, in the metastatic context, *RAS* mutations are associated with the absence of response to agents targeting the epidermal growth factor receptor (*EGFR*) such as panitumumab and cetuximab (16).

Losses of heterozygosity for chromosomes 5q, 8p, 17p, or 18q are detected in 36%, 50%, 73%, and 75% of cases, respectively (17). Tumor suppressor genes were subsequently identified on 5q (*APC*), 18q (*DCC*, *SMAD4*, and *SMAD2*), and 17p (*TP53*). *APC* is critical in the early development of CRC with somatic mutations in both alleles of *APC* present in 80% of sporadic CRCs, and a single germline mutation in this gene is responsible for familial adenomatous polyposis. The majority of mutations in *APC* lead to premature truncation of the APC protein and loss of its beta-catenin regulation which binds and activates the transcription factor Tcf-4 (17).

TP53 is mutated in approximately 50% to 70% of CRCs,

but it is rarely altered in adenomas. This suggests that the loss of the p53 function represents a relatively late event in CRC transformation (18). *SMAD4* encodes a protein integrating the signaling pathway of the transforming growth factor-beta (TGF-β). The TGF-β suppresses the growth of most normal cells, but CRC cells are resistant to this growth-suppressive effect (19,20). Based on clinical and molecular data generated during the past decades of research, a classification named consensus molecular subtypes (CMS) of CCR was created and addresses biologically and clinically distinct subgroups with potential therapeutic implications, as demonstrated in *Table 1* (21).

The understanding of the molecular alterations that drive CRC are to key to develop potential tools to be applied in the management metastatic disease, especially in the multidisciplinary approach of CRLM. Some of these alterations may serve as a background to assays designed to detect micrometastatic or minimal residual disease (MRD), as detailed in the section "Molecular profile, prognostic and predictor factors".

The biological process of CRLM

Approximately 50% of CRC patients develop liver metastasis during the disease course, being that 10–15% have synchronous liver spread. Liver metastasis represents a major cause of CRC-related deaths (20). The molecular background of liver metastasis from CRC is complex and involves multiple factors and biological processes. A better

Table 1 CMS: molecular and clinical features of colorectal cancer

Characteristics	CMS1 Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
Frequency	14%	37%	13%	23%
Potential precursor lesion	Serrated adenoma	Tubular adenoma	Tubular adenoma	Serrated adenoma
Molecular pathways	JAK/STAT immune evasion	WNT/MYC	Metabolic deregulation	TGF-B–EMT
Molecular features	MSI high	CIN	KRAS	CIN
	CIMP		CIMP low	
	BRAF			
Microenvironment	Immune infiltration			Stromal, angiogenesis
Clinical features	Good prognosis			Dismal prognosis
	Poor prognosis after recurrence			

Based on Guinney *et al.* (21). WNT, a group of signaling pathways; MYC, a group of proto-oncogenes; BRAF, a proto-oncogene. CMS, consensus molecular subtypes; CIMP, CpG island methylator phenotype; CIN, chromosomal instability; EMT, epithelial-mesenchymal transition; JAK/STAT, Janus kinase/signal transducers and activators of transcription; MSI, microsatellite instability; TGF, transforming growth factor.

understanding of these processes is critical for developing therapeutic strategies, and patient selection to achieve better long-term outcomes.

The process of CRLM is triggered by a subset of CRC cells that acquired the capacity to evade from the primary site, drive-by steps of epithelial-mesenchymal transition (EMT), migration through the extracellular matrix, tissue invasion, overcoming circulation and colonization to liver parenchyma (22). EMT can be facilitated by the binding of *STAT3* and miR-34A, which are induced by active interleukin receptor-6 in CRC metastasis (23). Other studies showed that miRNAs are involved in EMT, such as the miR-200 family, which regulates the epithelial phenotype through repression of *ZEB1* and EB2 mRNA translation. It has been shown that CRC without liver metastasis has a lower level of mIR-200c compared to metastatic sites of CRC (24,25). Several genomic abnormalities appear to be implicated in the development of liver metastasis, such as non-coding RNAs, *NOTCH* pathway, TGF-β signaling, *c-MET* signaling, L1 cell adhesions molecule, and phosphatase of regenerating liver (PRL3) (26).

Mutations in *BRAF*, *RAS*, *PI3KCA*, and *TP53* seem to increase the risk of liver metastasis. *BRAF* mutations in the presence of CRLM are associated with worse prognoses (27). Moreover, *NOTCH1* and *PIK3C2B* mutations are suggested to be associated with higher cure rates, whereas *SMAD3* mutations are associated with lower rates of cure of liver metastasis from CRC (28).

In the process of the CRLM, both liver immunology and tumor microenvironment are contributors to the CRLM seeding process. The liver has physiological immunosuppressive features due to the constant influx of mesenteric antigens and self-antigens. This process is mediated by regulatory T cells (TREGs) and the overexpression of immunosuppressive molecules such as programmed death ligand 1 (*PDL1*), *PDL2*, and interleukin 10 (29). In the tumor microenvironment, tumor-associated macrophages (TAM) also express immunosuppressive molecules and activate TREGs by secreting interleukin-10 and TGF-β (29). Moreover, TAMs also secrete other several extracellular matrix (ECM) factors such as metalloproteinases and plasminogen activation systems that model the EMC and enhance the migration of tumor cells (30). In animal models, when targeting chemotactic proteins such as *CCL2/CCR2*, TAMs are reduced in metastasis and promote a more effective anti-tumor activity of cytotoxic lymphocytes (31). It has been reported that chemotactic and chemokine ligands receptors (such as CXCL5/CXCR2) are dysregulated and promote a pro-tumoral microenvironment in CRC (32). In parallel, the TREGs inhibit adaptative immune responses against tumor cells, which is associated with clinical outcomes in CRLM (33). Targeting TREGs and TAMs activity, as well as the tumoral immune environment, could be a valuable therapeutic approach to be explored in future studies.

Currently, the biological processes associated with

CRLM are not definitive for therapeutic proposes, although the prognostic implication of some molecular alterations may help in the selection of the therapeutic strategy. In the setting of local treatment for CRLM, tumors that harbor *RAS* mutations are associated with an earlier and higher rate of tumor progression after percutaneous ablation (34). Shady *et al.* observed that patients submitted to radiofrequency ablation for liver metastasis with *KRAS* mutated CRC had worse survival and higher rate of liver and peritoneal spread (35). In a retrospective study with 136 patients submitted to percutaneous ablation of CRLM, minimal ablation margin ≤10 mm and *RAS* mutation were associated with worse progression-free survival, with only 29% of 3-year local progression-free survival for tumors with mutated *RAS* and ablation margins ≤10 mm (36).

Pre-operative staging

The mainstream staging procedures for CRLM are based on preoperative imaging workouts based on computerized tomography (CT) scan of the chest, abdomen, and pelvis in searching for any extra-hepatic disease and the determination of the carcinoembryonic antigen (CEA) baseline. For best planning a liver resection, an MRI should also be done to study the liver and the anatomical relations of the lesion for a putative hepatic resection (4). The detection rate can also be enhanced by using the liver-specific contrast-enhancing agent (gadoxate disodium) and diffusion-weighted evaluations (37). Macera *et al.* compared MRI methods, finding significant differences in accuracy between contrasting-enhance plus diffusion, contrasting-enhancing, and diffusion-weighted MRI, 89.2%, 76.5%, and 65.1%, respectively (38). Nevertheless, patients who received preoperative fluoropyrimidines or irinotecan can develop steatosis, which decreases the contrast between liver parenchyma and metastases (37,39). MRI represents the best imaging modality in scenarios where steatosis has developed, especially considering disappearing liver metastases by chemotoxicity.

The use of positron emission tomography (PET)/CT is not routinely recommended for staging purposes only. However, in patients with significant allergies or chronic kidney failure that are not on dialysis, a PET /CT can be used for staging (4). When a surgically curable M1 disease scenario is found on CT or MRI, then a PET/CT scan should be done, because it may exclude an unrecognized metastatic site of disease, which would change the indication for a surgery in about 8% to 24% of the patients (40,41). For patients who are candidates for image-guided therapy, such as ablation or radioembolization, fusion pre-acquired PET-CT images can be fusion with a real-time ultrasound (42) or in a follow-up after radiofrequency ablation (RFA), since PET/CT is superior to CT for demonstrating recurrence after RFA in about 25% of the patients, mainly the patients with multiple and bilobar lesions (43). Moreover, a previous study has found a correlation in *KRAS* mutations with 2-[18F]FDG uptake in PET images (44).

Intraoperative ultrasound (IOUS) is another imaging tool that helps to find tiny liver tumors that have been missed in preoperative imaging, and nowadays is considered indispensable in surgery for CRLM, because an IOUS can change the surgical plan in about 24% of the cases even in the era of the liver-specific MRI era (45,46). Indirect signs to identify new liver metastases by IOUS are the presence of bile duct dilatation, distortion, interruption of the venous wall, and a hypoechogenic lesion (46). It can be optimized using image fusion systems to allow IOUS navigations with CT or MRI, which increases the rate of finding occult lesions (39).

Patient selection and timing for surgery of resectable CRLM

Historically, the ordinary curative-intent treatment of initially resectable CRLM is complete surgical resection. Even though it has never been tested in a randomized controlled trial, a previous study has demonstrated long-term survival and cure rates of 17–25% with surgery (47). More recently, Creasy *et al.* reported a 10-year survival after resection of CRLM is 24% with an observed 20% cure rate (48). Additionally, Buisman *et al.*, in a multicentric study with 4,112 patients who underwent complete resection of CRLM, reported a 10-year OS of 30% (49).

Although complete resection is considered the only potentially curative treatment for CRLM, with 5-year survival rates ranging from 35% to 58%, patients with initially resectable CRLM with a high tumor burden or poor prognosis typically undergo neoadjuvant chemotherapy followed by surgery (50), with the aim to achieve complete macroscopic resection with negative margins (R0 resection). More recently, in multi-nodular cases, complete removal of the macroscopic tumor without safe margins in vascular

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structures (R1 resection) seems to be acceptable, and it is braced by the increasingly effective chemotherapy on long-term outcomes after R1 resection, with survival similar to R0 resection (50).

Although the straight definitions of resectability can diverge from guidelines, in general, metastases are considered resectable if their removal can be planned by pre- or intraoperative image workout pursuing R0 resection, while an adequate functional parenchyma volume is spared. According to the Americas Hepato-Pancreato-Biliary Association, the resectable CRLM are those that can be completely removed with a remnant liver representing at least two contiguous segments, with patency of inflow and outflow structures, and preserving minimally 20% of total liver volume, for healthy and unexposed livers to chemotherapy, or at least 30% for patients who underwent previous chemotherapy (51). Nevertheless, only 20–30% of patients with CRLM are initially considered for hepatic resection (52). Considering local treatment options for patients with neither adequate remnant liver volume nor function, but amenable to complete resection, they can be candidates for local therapy or even in combination with a resection, such as ablative techniques like radiofrequency ablation (RFA), electro-coagulation or microwave coagulation can be used (4). For lesions smaller than 3 cm, both overall survival (OS) and recurrence free survival (RFS) may be similar to surgery in select cases (53). Moreover, a 5 mm minimal margin after RFA ablation seems to be a positive predictor for satisfactory local tumor control (54).

Regarding patient selection based on clinical and image findings, Fong *et al.* described the most used Clinical Risk Score (CRS) to predict recurrence after hepatic resection for metastatic CRLM (55). It was based on five independent prognostic factors: positive nodal status of the primary tumor, the disease-free interval from identification of the primary tumor to the discovery of liver metastases of <12 months, number of metastatic tumors >1, preoperative carcinoembryonic antigen (CEA) level >200 ng/mL, and size of the largest tumor >5 cm. Patients with scores of 0, 1, or 2 had more favorable outcomes compared with scores of 3, 4, or 5 (55). This CRS works as a practical clinical tool helping to select patients for upfront surgery or systemic therapy according to the estimated risks, as shown in *Figure 2*. More Recently, the GAME (Genetic And Morphological Evaluation) score for CRLM has shown the use of *KRAS* status also adds value in clinical patient selection, especially preoperatively assessing the *KRAS* status of CRLM assuming the high concordance between primary and metastatic sites (34-36,56).

Moreover, GAME score a composite variable (TBS; tumor burden score) as a surrogate of tumor morphology, instead of isolating the size of the largest lesion and the total number of lesions, the TBS adjust some discrepancies among patient presentations, and the calculation is based on the Pythagoras theorem: TBS^2 = [maximum tumor diameter]^2 + [number of liver lesions]^2 (56).

Several strategies have been introduced to guide the clinical practice to increase the number of patients eligible for curative hepatic resection, including neoadjuvant chemotherapy, two-stage hepatectomies, and portal vein embolization. In 2004, Adam *et al.* reported postoperative 5-year survival of patients submitted to conversion therapy is 33% after rescue surgery (57). This outcome remains a work in progress and has been increasing with the advent of more modern regimens such as triplet therapies and monoclonal antibodies (37).

The EPOC trial randomized patients with initially resectable CRLM into preoperative chemotherapy (FOLFOX4) or surgery alone. While no benefit in OS was demonstrated, preoperative chemotherapy significantly increased progression-free survival (PFS) in eligible patients and those with resected CRLM (58,59). Based on those findings, the addition of systemic chemotherapy to surgical resection has become the standard of care for CRLM in many centers.

We previously reported a comparison between perioperative and postoperative chemotherapy after potentially curative hepatic resection for metastatic CRC that was conducted at the Memorial Sloan-Kettering Cancer Center in retrospective 10-y practice (60). The groups were different at baseline, with the perioperative group presenting smaller but more numerous liver metastases, shorter disease-free interval (DFI), and more bilateral disease. Consequently, RFS rates were significantly better for those who received adjuvant chemotherapy than for patients in the perioperative regimen group (5-year RFS of 38% and 31%, respectively, P=0.036). However, once the RFS was adjusted for CRS (high and low risk of recurrence according to Fong's CRS), the differences between the groups were no longer statistically significant, and differences in OS were neither detected before nor after CRS split (60). Therefore, we concluded that the timing of additional
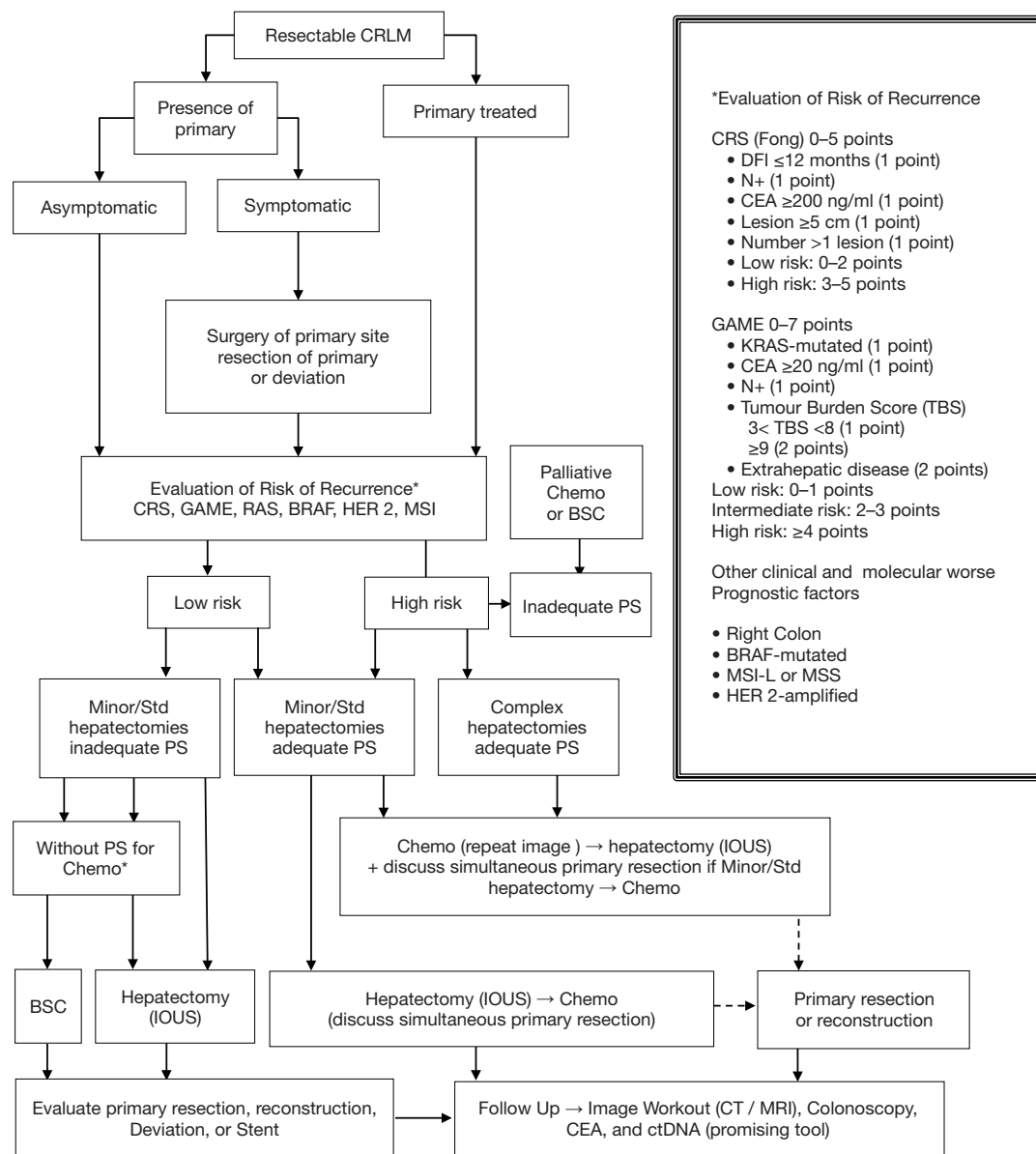
Figure 2 Flowchart summarizing the decision-making process for the management of cases of patients with initially resectable CRLM. CRLM, colorectal liver metastases; CRS, Clinical Risk Score; Chemo, chemotherapy (systemic treatment); DFI, disease-free interval; CT, computerized tomography; IOUS, intraoperative ultrasound; MRI, magnetic resonance image; N+, positive node in the primary tumor site; CEA, carcinoembryonic antigen; GAME, Genetic And Morphological Evaluation score; MSI-L, microsatellite instability-low; MSS, microsatellite stability; std, standard; BSC, best support of care; TBS, tumor burden score; ctDNA, circulating tumor deoxyribonucleic acid.

chemotherapy for resected CRLM was not associated with outcomes (60). Corroborating those findings, a systematic review, and meta-analysis, based on nonrandomized and randomized data, suggested that patients with CRLM who underwent curative hepatic resection showed that regardless of timing and, patients submitted to hepatic resection for

CRLM should receive additional chemotherapy, given that this strategy relative increases RFS, and perhaps OS (61). Recently, a randomized controlled trial examining the use of adjuvant chemotherapy (modified infusional fluorouracil, leucovorin, and oxaliplatin-mFOLFOX6) in patients with liver-only metastatic CRC was published (62). Kanemitsu

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Table 2 Comparison of randomized clinical trials with patients who underwent surgery and additional chemotherapy for initially resectable colorectal liver metastases

Studies	Initial design	Number of patients		Chemotherapy			Median FU		RFS					OS				
									Median mo		Treatment effect			Median mo		Treatment effect		
		ITT	PP	Regimen	Std Arm	Exp Arm	Std Arm	Exp Arm	Std Arm	Exp Arm	HR	95% CI	P	Std Arm	Exp Arm	HR	95% CI	P
Langer (65)	OS	129	107	Adj	0	5-FUx6	NR	NR	20	39	0.78	0.46, 1.31	0.35	43	53	0.77	0.42, 1.40	0.39
Portier (66)	RFS	171	171	Adj	0	5-FUx6	87.4	87.4	17.6	24.4	0.66	0.46, 0.96	0.028	46.4	62.1	0.73	0.48, 1.10	0.13
Nordlinger (58,59)	RFS	364	342	Periop	0	FOLFOX x12	8.5 y	8.5 y	20	12.5	0.78	0.61, 0.99	0.041	54.3	61.3	0.87	0.66, 1.14	0.3
Ychou (67)	RFS	321	306	Adj	5-FU	FOLFIRI x6	42.4	41.7	21.6	24.7	0.89	0.66, 1.19	0.35	72% 3 y	73% 3 y	1.09	0.72, 1.64	0.69
Primrose (64)	RFS	257	236	Periop	FOLFOX	Cetux + FOLFOX	21.1	19.8	20.5	14.1	1.48	1.04, 2.12	0.03	NR	39.1	1.49	0.86, 2.60	0.16
Kanemitsu (62)	RFS	300	283	Adj	0	mFOLFOX6 x12	59.2	59.2	38.% 5 y	49.% 5 y	0.67	0.5, 0.92	0.006	83.% 5 y	71.% 5 y	1.25	0.78, 2	0.42
Snoeren (68)	RFS	79	77	Adj	CAPOX x8	CAPOXx8 + Beva x8	36	36	54% 2 y	55% 2 y	0.96	0.53, 1.75	0.88	94% 2 y	94% 2 y	NR	NR, NR	0.43

OS, overall survival; RFS, recurrence free survival; HR, hazard ratio; ITT, intention to treat; PP, per protocol; FU, follow up; Std, standard; Exp, exposed; Adj, adjuvant; mo, months; Periop, perioperative; 5-FU, 5-fluorouracil; FOLFOX, 5-FU + Leucovorin + Oxaliplatin; mFOLFOX, modified FOLFOX; FOLFIRI, 5-FU + Leucovorin + Irirnotecan; CAPOX, Capecitabina + Oxilaliplatin; Cetux, Cetuximab; Beva, Bevacizumab; NR, non-reported; y, year.

et al., after a median follow-up of 59.2 months, demonstrated that adjuvant chemotherapy improved 5-years disease-free survival when compared to hepatectomy alone (49.8% *vs.* 38.7%, CI: 0.41–0.92; P=0.006). No significant differences in 5-year OS were detected, 71.2% (95% CI: 61.7–78.8%) with adjuvant chemotherapy and 83.1% (95% CI: 74.9–88.9%) with hepatectomy alone (62). Recently, Sonbol *et al.* reported in a systematic review and network meta-analysis of 7 RCTs found that the addition of perioperative systemic treatment for resectable CRLM could improve RFS but not OS (63). Based on the findings, the addition of perioperative treatment in resectable CRLM should be individualized weighing the risks and benefits (63). Nonetheless, neither randomized clinical trials using a systemic treatment for resectable CRLM nor meta-analyses detect differences in OS.

The New EPOC trial included patients with resectable exon-2 *RAS* wild-type CRLM who were randomly assigned to receive perioperative chemotherapy, doublet oxaliplatin-based therapy, with or without cetuximab (64). The addition of cetuximab was associated with significantly lower RFS and a trend toward decreased OS. Although the addition of cetuximab to chemotherapy may improve outcomes in patients with initially inoperable metastatic disease, based on the results of this trial, it has a significant disadvantage in resectable patients and should not be used routinely (64). It seems that chemotherapy should be incorporated into the treatment of resectable CRLM, increasing PFS, and possibly OS (48). Nevertheless, no published randomized clinical trial detected significant benefits in OS, as demonstrated in *Table 2* (58,59,62,64-68).

Conversely, the best timing for additional chemotherapy remains unclear. Preoperative chemotherapy may be used to test tumor biology *in vivo* and identify patients who will benefit the most from surgery, and those who would not, and perhaps avoid a futile and morbid surgery. Response to neoadjuvant chemotherapy has been established as a major prognostic factor, as patients with disease stabilization or progression while on chemotherapy appear to have poorer outcomes than good pathologic responders (69,70). Other advantages include earlier treatment of micro metastatic disease, and probable tumor shrinkage, in favor of parenchymal sparing which increases the remnant liver volume and increases the chances of an occasional hepatectomy with similar long-term outcomes of the

first resection accordingly to the patient selection (71). Moreover, part of the patients who underwent hepatectomy will lose a minimal performance status to receive systemic therapy, thus, delivering chemotherapy in a preoperative fashion increases the chance to treat micro metastatic disease and offer surgery as a local treatment. On the other hand, oxaliplatin or irinotecan-based neoadjuvant chemotherapy can increase the rates of perioperative morbidity and cause liver toxicity (72). The toxicity profile of prolonged cytotoxic chemotherapy, including liver toxicity, is one of its major drawbacks (73,74). The enthusiasm for systemic chemotherapy before hepatic resection has been dampened by reports of steatosis, steatohepatitis, vascular injury, noncirrhotic portal hypertension, and sinusoidal dilation in the livers of patients who received irinotecan or oxaliplatin preoperatively (75-78).

In the presence of synchronous lesions, CRC plus CRLM, the decision is usually based on the presence of symptoms. For symptomatic CRC, it means obstructed and bleeding bowels, the treatment of the primary tumor should be firstly done, with resection and/or deviation, followed by systemic chemotherapy. Considering asymptomatic patients with synchronous tumors and those with metachronous hepatic disease, the timing of additional chemotherapy should be guided by the CRS, clinical performance status, and the risk of progression of CRLM (60). For potentially resectable patients with a low risk of recurrence [0–2], initial surgery rather than preoperative chemotherapy, in the perioperative regimen, could be chosen, followed by postoperative chemotherapy. For patients with a high risk of recurrence, perioperative chemotherapy is the preferred approach [2–5]. Instead, pre-operative chemotherapy is an important resource for liver parenchyma sparing in patients who require extended hepatectomy, regardless of whether they have a high or low CRS, as suggested in *Figure 2*. This action may help to prevent postoperative liver dysfunction and increase the chances of clinical performance preservation when undergoing postoperative chemotherapy or re-hepatectomy as indicated (71).

Considering patients with borderline resectable lesions or critically located colorectal liver metastases, upfront chemotherapy represents an appropriate option as conversion therapy to achieve large tumor shrinkage is recommended. For patients with *RAS* wild-type disease, it appears that a cytotoxic doublet in combination with an anti-EGFR offers the best benefit-risk/ratio. A cytotoxic doublet plus bevacizumab or FOLFOXIRI plus bevacizumab is preferred for patients with *RAS*-mutant disease, or tumors arising from the right side of the colon (79). Additionally, caution is necessary for patients in the setting of preoperative use of bevacizumab since they have a higher risk of treatment-related complications such as hemorrhage, hypertension, neutropenia, stroke, intestinal perforation, fistula formation and wound healing complications (80). Thus, an interval of at least 6 weeks between the last dose of bevacizumab and elective surgery has been recommended to mitigate the risk of complications. Nevertheless, its postoperative use should be delayed at least 6 to 8 weeks after surgery (68).

The use of percutaneous ablative methods in combination with chemotherapy in CRLM was explored in the CLOCC trial, which was a multicentric phase II trial including patients with unresectable liver metastasis. Patients were randomized to radiofrequency ablation (with or without resection) plus adjuvant chemotherapy (FOLFOX with or without bevacizumab) versus systemic treatment. Patients that received the combined modality had a significantly longer overall survival with a 5-year survival rate of 43.1% versus 30.3% in the control group. However, the study findings are limited by a smaller sample size than what was preplanned in the original design (81).

Molecular profile, prognostic, and predictor factors

Around 50% of metastatic CRC have mutations on the *RAS-MAPK* pathway and it is well established that tumors harboring mutations in *KRAS*, *NRAS*, *HRAS* or *BRAF* are resistant to anti-EGFR therapies (82,83). Considering the new advances in the molecular understanding of metastatic CRC, and recent data showing that the addition of the anti-EGFR antibody panitumumab to the first-line systemic treatment for advanced disease improves overall survival, efforts have been made to incorporate upfront molecular profiling in all CRC patients (84). In the PARADIGM trial patients with metastatic CRC and molecular ALL-*RAS* wild-type status, were randomized to chemotherapy with mFOLFOX and panitumumab or bevacizumab. The objective response rate (ORR) in patients treated with panitumumab reached an impressive 80%. Furthermore, improvements in overall survival (OS) were also obtained with the anti-EGFR therapy compared to anti-VEGF

therapy bevacizumab, 37.9 versus 34.3 months, HR 0.82 (0.68–0.99), P=0.03 (80).

In the setting of CRLM, anti-*EGFR* therapies were evaluated previously in the above-mentioned New-EPOC trial (64). In the trial, patients with resectable CRLM were randomized to chemotherapy with or without the anti-*EGFR* cetuximab before and after liver resection. The study did not meet the primary outcomes of PFS or OS. The PFS was significantly inferior to anti-*EGFR* therapy, HR 1.48, 95% CI: 1.04–2.12, P=0.03, suggesting a deleterious effect (64). However, in modern times, this study should be evaluated with extreme caution, considering that the evaluated molecular status of the study was only *KRAS* Exon 2 wildtype, instead of the currently recommended full molecular profiling.

Combinations of three drugs associated with anti-*EGFR* therapies were also investigated to improve objective response rates (ORR) in patients with metastatic disease and CRLM. The VOLFI trial evaluated the combination of mFOLFOXIRI with or without panitumumab in advanced *RAS* wild-type CRC patients (85). A total of 96 patients were randomized, with 63 receiving the combination and 33 receiving only chemotherapy. The ORR with the combination was 87.3% versus 60.6% with just chemotherapy. Resection of metastasis occurred in 33% versus 12.1% in the chemotherapy group alone (85). Whether three instead of two drugs are necessary for this subgroup of patients was recently evaluated in the TRIPLETE trial (86). In the trial, 435 patients with advanced CRC, *RAS*, and *BRAF* wild type were treated with mFOLFOXIRI or mFOLFOX both with panitumumab. This trial showed that the intensification of the upfront chemotherapy backbone in combination with panitumumab in molecularly selected and left-sided advanced CRC patients did not improve outcomes including response rate (87).

The laterality of the tumors in CRC has been evaluated. It is well known that patients with advanced left-sided CRC have higher responses with anti-*EGFR* therapies (88). In an analysis of the FIRE-3 trial, *RAS* wild type CRC patients treated with FOLFIRI plus cetuximab had higher median OS than patients treated with bevacizumab, 31 *vs.* 26 months, respectively (HR 0.76, P=0.012). This benefit occurred only in patients with left-sided primary tumors.

Based on these results and considering the high response rate of chemotherapy plus anti-*EGFR* (80%), two-drugs chemotherapy regimens plus anti-EGFR can be used and considered standard of care for systemic treatment in patients with advanced CRC RAS wild-type, particularly left-sided CRC. Also, these regimens can be used as neoadjuvant treatment for patients that would undergo resection with initially unresectable CRLM (79). Patients with *BRAF* mutations comprehend around 5% of metastatic CRC, and have a worse prognosis (89). More intensive regimens, such as mFOLFOXIRI plus bevacizumab, are considered standard of care for metastatic patients with *BRAF* mutations (90).

In patients with advanced but potentially resectable CRLM with *KRAS* or *BRAF* mutations, a more intensive regimen as mFOLFOXIRI plus bevacizumab is considered based on their higher response rates. In the OLIVIA trial, patients with unresectable liver metastasis were randomized to two or three drugs plus bevacizumab (91). In the group of patients treated with bevacizumab plus FOLFOXIRI, the overall resection rate was 61%, and 49% with mFOLFOX plus bevacizumab. R0 resection rates were 49% and 23%, respectively. Overall tumor response rates were also higher with three drugs, 81% versus 62% (91).

More potent combinations are being explored in *BRAF* mutated CRC including combinations with *BRAF* inhibitors on the front-line systemic treatment (92). Currently, *BRAF* directed therapy is approved only for second-line treatment for advanced disease (79).

Another important driver identified in CRC is genomic alterations in *HER-2* (93). It is estimated that *HER-2* genomic aberrations are detected in around 5% of advanced CRC, including mutations and amplifications, and like *BRAF* mutations, are genomic alterations not associated with mutations in *KRAS* (83). Sartore-Bianchi *et al.* reported data with advanced CRC patients treated with *HER-2* directed therapy with monoclonal antibodies and tyrosine kinase inhibitors (TKI) shows that objective responses around 20–40% can be achieved (94). Moreover, in the Phase II study MOUNTAINEER trial, the combination of the TKI tucatinib with trastuzumab in 26 pre-treated CRC patients showed an ORR of 52%, with a median OS of 18.7 months (95). Another combination with effective results is trastuzumab and pertuzumab, from the My Pathway trial (96). The combination was tested in a group of *HER-2* amplified CRC patients who had already been heavily pre-treated. The median OS was 14 months, and the ORR was 40%. However, anti-HER-2 therapies have yet to

be evaluated prospectively in the perioperative treatment of CRLM.

One of the most important agnostic therapies approved to date for the treatment of solid tumors is immune checkpoint inhibitors (ICI) for microsatellite instability-high tumors (MSI-H) (97). In advanced CRC, pembrolizumab was evaluated in MSI-H advanced CRC in the KEYNOTE 177 trial, for upfront treatment in stage IV disease. Compared to chemotherapy, pembrolizumab increased responses (43.8% versus 33.1%) and progression-free survival (16.5 versus 8.2 months, P=0.0002) (98). More potent combinations of ICI like nivolumab and ipilimumab are also being evaluated. The combination in pre-treated MSI-H advanced CRC reached an impressive ORR of around 70–80% in the Checkmate 142 trial (99).

After complete responses for advanced stages, some patients probably are cured. However, the radiological response does not mean the pathological response, thus, a longer follow-up of these patients is necessary in order to either evaluate the correct time to stop therapy or to detect recurrence, most trials consider ICI stopping therapy after 1–2 years of complete response (100). Patients that do not reach a complete response to ICI could be considered for local treatments on oligometastatic disease, however, larger prospective data on this subject is not currently available.

Another agnostic therapy approved is NTRK inhibition for patients with solid tumors harboring NTRK fusions (101). Larotrectinib was evaluated in a multi-tumor cohort of solid tumors harboring NTRK fusions, and an ORR of 75% was reached. The drug is relatively well tolerated as well. Based on the results of the high efficacy of these agents, NTRK inhibitors are an agnostic approval in most countries for these cases. Although very rare, with less than 1–3% of gastrointestinal (GI) cancer patients harboring NTRK fusions, a phase II study with larotrectinib in these patients was presented. In the NAVIGATE trial, a total of 34 metastatic GI cancers harboring NTRK fusions were treated with larotrectinib. Overall, the ORR was 33%, and in the CRC cohort, the ORR was 47% (102). Finally, the combination of ablative methods as explored in the CLOCC trial may induce changes in inflammatory features of the tumor microenvironment. This serves as a background for exploring the use of systemic treatment, such as immune-oncology agents, in combination with local therapies for liver metastasis (81).

Follow-up and silent recurrence

For patients submitted to resection of CRLM, a subject of debate is the follow-up, and strategies to diagnose early recurrence because almost 90% of relapses occur in the first 5 years (103). The NCCN, ASCO, and ESMO guidelines recommend a follow-up guided by an image, with a few differences between them. The NCCN recommends performing a CT scan of the chest, abdomen, and pelvis every 3–6 months in the first 2 years after curative resection, then every 6–12 months for a total of 5 years is sufficient (4). The ESMO advocates more intense image monitoring with a radiological assessment with CT (or MRI) every 3 months during the first 2 years and every 6 months thereafter (104), and ASCO suggests image workout every 3–6 months for 2 years, then every 6 months for a total of the first 5 years after diagnosis (105). The use of PET/CT for surveillance is not routinely supported by the three guidelines, and its use is according to the medical assistance discretion facing equivocal images to confirm or not recurrence or confronting biological signs of silent recurrence.

The CEA is a tumor marker that is consistently evaluated as a prognostic and predictive factor for resections of metastatic disease. Patients with normal CEA levels before resection of CRLM trends to have a better prognosis (106). In an analysis of more than 500 patients who underwent CRLM resections, preoperative CEA levels above 5 ng/mL were statistically associated with worse recurrence-free survival (P=0.003) and overall survival (P=0.023) (94). The association of CEA levels with outcomes is also shown in surgery for localized disease (107,108).

Furthermore, patients who present with elevated CEA levels after CRLM resections have a higher risk of early recurrence and a worse prognosis (109). We previously published a study assessing the value of the postoperative CEA as a prognostic and predictor tool for recurrence in 2 years for patients with CRLM, without extra-hepatic disease, who underwent curative-intent treatment for CRLM (110). This study demonstrates a postoperative CEA of 15 ng/mL and higher as an independent prognostic factor for recurrence (HR 1.87; 95% CI: 1.09–3.2; P=0.023), being a predictive test for recurrence with a specificity of 96% and positive predictive value of 82% for recurrence (110). Thus, CEA testing should be performed at baseline and every 3 to 6 months for 2 years, then every 6 months, for a total of 5 years (111). When

an increasing CEA happens during the follow-up, a full investigation should be done, that include a colonoscopy; CT scan of the chest, abdomen, and pelvis (112). In this scenario, a PET/CT may also be considered (113).

Circulating tumor deoxyribonucleic acid (ctDNA) is also being investigated in CRC management. The ctDNA are fragments of tumoral DNA that can be detected in the blood of the patient, or other fluids like saliva. These fragments are derived for multiple metabolic processes, including necrosis, apoptosis, or other cell death or degradation types. The ctDNA can be analyzed in a platform that through next-generating sequencing (NGS) detects actionable targets, lately used in multiple types of gastrointestinal cancers (114). These platforms also are extremely useful in cases of patients treated with targeted therapies, and aid to detect mechanisms of resistance. As an example, in the CHRONOS trial, dynamic ctDNA assessment in advanced CRC patients treated with anti-EGFR therapy enable to identify arising of *KRAS* mutations during treatment, which confers secondary resistance to the therapy (115).

The other ctDNA platform commonly used is the tumor informed. In that case, the detection of personalized ctDNA based on the sequencing of the primary tumor has been used for detecting MRD (116). In patients with stage II CRC, the detection of ctDNA MRD can be used to guide adjuvant chemotherapy (117). In the trial, a ctDNA-guided approach, in not using chemotherapy in stage II resected CRC that have a negative MRD assessment, reduced the use of adjuvant chemotherapy without compromising RFS (117).

The combination of CEA and ctDNA can be used to stratify patients with CRLM. In a study with 71 patients submitted to CRLM resections, patients with detected preoperative high levels of ctDNA KRAS had worse outcomes than those with low levels of ctDNA. The combination of high CEA levels and ctDNA levels conferred the worse prognosis (118). A retrospective study of 76 patients submitted to resection of CRLM evaluated the prognostic impact of ctDNA MRD assessment (119). In the study, tumor tissue was sequenced, and one somatic mutation was then assessed by digital droplet polymerase chain reaction (ddPCR) in plasma samples collected after surgery to identify the persistence of ctDNA. A total of 39 patients from 76 (51%) had ctDNA detected after surgery. At more than 6 years of median follow-up, 33 of 39 ctDNA-positive patients and 20 of 37 ctDNA-negative patients experienced disease relapse (P=0.008). Furthermore, patients with positive ctDNA had shorter RFS, median RFS 12.7 versus 27.4 months, HR 2.09, P=0.008 (101). In another ctDNA study, 91 patients with CRLM were evaluated after metastasectomy (120). In the study, patients with detectable post-operative and post-ACT ctDNA were associated with significantly shorter recurrence-free survival, furthermore, patients that had decreased ctDNA variant allele fraction (VAF) during adjuvant therapy had a recurrence rate of 63.6%, compared to 92.3% in patients with increased ctDNA VAF. More recently, a prospective cohort of 96 patients undergoing CRLM resections were submitted to serial ctDNA collection (121). Patients with ctDNA detected at any time had worse outcomes, also ctDNA was a strong predictor of recurrence. More interestingly, ctDNA predicted radiological progression in 55.6% of the ctDNA positive cases, with up to 10 months lead-time. More studies are ongoing evaluating ctDNA assessment in CRC; this technology will probably be incorporated into the treatment landscape of the disease and management of CRLM (122,123).

Discussion

No area of liver surgery has undergone as much change as the surgical management of CRLM. Liver surgeons have used a variety of treatments for the surgical treatment of CRLM, including advancements in surgical techniques and the development of new surgical devices, as well as undeniable advancements in radiology, anesthesiology, and intensive care treatments. The old paradigms have given way to more precise methods for the current principles of surgical treatment of CRLM, with only two requirements remaining as necessities for curative-intent treatment: the achievement of free margins with no residual disease (via R0 resection) and the preservation of an adequate remnant liver with preserved inflow and outflow (124). Even though some data in multi-nodular cases suggest that complete removal of the macroscopic tumor, without safe margins in vascular structures (R1 resection), seems to be acceptable, without jeopardizing long-term outcomes when compared to R0 survival rates, and it supposedly by the increasing effective chemotherapy (50).

Advances in surgery and systemic treatment have transformed the oncologic approach to the treatment of

CRLM since the systemic treatment has been used also as an instrument of patient selection for curative-intent resection. Moreover, patients with initially unresectable liver metastases could undergo preoperative chemotherapy and occasionally curative-intent liver surgery that would increase long-term outcomes, since the surgery is the main treatment modifier of the disease in selected patients. Although molecular profiling has gained increasing attention, patient selection is still defined by image workouts, the timing of CRLM has arisen, positive nodes in the primary tumor, CEA level, and surrogates of tumor burden. This rationale follows the idea that only patients with a more limited disease burden would benefit from upfront surgery instead the systemic chemotherapy. For those patients who presented a disease with more systemic than limited presentation (with a higher risk of recurrence), and who would require larger hepatectomies for higher tumor burden, the rationale favors systemic treatment tailored by molecular profile, to either treat micro metastatic disease or obtain an ultimate tumor downsizing and parenchyma-sparing techniques. Patients at either high risk of recurrence or postoperative liver failure due to putative small remnant liver volume should not be operated on upfront. In these cases, tumor biology and chemotherapy response can be tested to optimize patient selection, resulting in CRLM downsizing for "good responders" or occasionally avoiding futile procedures in "non-responders" who presented disease progression during systemic treatment.

Thus, it seems that chemotherapy should always be offered as an additional treatment for liver resections with curative intent, increasing RFS, and a likely survival benefit based on extrapolated results from retrospective series and RCTs in patients with stage IV disease who underwent combined chemotherapy compared with surgery alone has been used in the treatment decision-making process for CRLM patients (3,60,63). Nevertheless, the optimal timing for either chemotherapy regimen or surgery has not yet been ascertained, with an important scarcity of literature for prospective data on this opening question (4,60,79).

The concept of precision medicine, as molecular profiling to identify genotypic and phenotypic alterations and their role as prognostic and predictive factors of treatment, has been progressively applied in clinical practice. The tests are important to guide the optimal therapy according to their molecular profile for either maximizing long-term outcomes or avoiding futile toxicity from inadequate treatment. The application of ctDNA to detect MRD in CRC has revealed benefits in guiding adjuvant therapy decisions. Additionally, it forecasts how the disease will respond to treatment and perhaps how quickly it will advance, preventing both overtreatment and unnecessary exposure to chemotherapy. Thus, it would also aid in patient follow-up after resection of the primary and occasionally detect early and silent recurrences and some trials are investigating these opening questions (125-129).

Nevertheless, randomized clinical trials looking for the value of ctDNA for MRD and recurrence in CRC are still in progress. Conversely, Fakih *et al.* compared surveillance strategies of ctDNA, Imaging, and CEA in CRC who underwent resection of CRC (stage II–IV). In this cohort study of 48 patients with resected CRC, 15 had confirmed disease recurrence by imaging, of whom only 8 had a concurrent positive ctDNA finding (130). Instead, the combination of imaging and CEA level had better sensitivity compared with ctDNA alone in identifying recurrence (73.3% *vs.* 53.3%), suggesting that the ctDNA assay offers no clear advantage over standard imaging and CEA measurement in the surveillance of patients with resected colorectal cancer. We previously indicated that the first CEA after hepatectomy is a very good test for risk stratification, and an inexpensive test, we do believe that it should be used as a basis of comparison for any other new test being proposed since it has a reasonable cost, usefulness, and virtually worldwide available (110).

Conclusions

Patient selection is crucial for ensuring that the best patient outcomes are obtained, and we favor the use of the CRS and molecular profiling, as suggested in *Figure 2*, for decision-making in clinical practice also including the presence of the primary tumor, the extension of the hepatectomy and performance clinical status of the patient. It seems that a better understanding of the genetic and molecular profiles of CRC will lead to more personalized approaches to surgery and systemic treatment for patients with resectable CRLM.

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
3. Araujo RL, Riechelmann RP, Fong Y. Patient selection for the surgical treatment of resectable colorectal liver metastases. J Surg Oncol 2017;115:213-20.
4. Benson AB, Venook AP, Al-Hawary MM, et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:329-59.
5. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687-96.
6. Jass JR, Baker K, Zlobec I, et al. Advanced colorectal polyps with the molecular and morphological features of serrated polyps and adenomas: concept of a 'fusion' pathway to colorectal cancer. Histopathology 2006;49:121-31.
7. Goel A, Nagasaka T, Arnold CN, et al. The CpG island methylator phenotype and chromosomal instability are inversely correlated in sporadic colorectal cancer. Gastroenterology 2007;132:127-38.
8. van Engeland M, Derks S, Smits KM, et al. Colorectal cancer epigenetics: complex simplicity. J Clin Oncol 2011;29:1382-91.
9. Weisenberger DJ, Siegmund KD, Campan M, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. Nat Genet 2006;38:787-93.
10. Domingo E, Niessen RC, Oliveira C, et al. BRAF-V600E is not involved in the colorectal tumorigenesis of HNPCC in patients with functional MLH1 and MSH2 genes. Oncogene 2005;24:3995-8.
11. Rajagopalan H, Bardelli A, Lengauer C, et al. Tumorigenesis: RAF/RAS oncogenes and mismatch-repair status. Nature 2002;418:934.
12. Ogino S, Nosho K, Kirkner GJ, et al. CpG island methylator phenotype, microsatellite instability, BRAF mutation and clinical outcome in colon cancer. Gut 2009;58:90-6.
13. Harada K, Hiraoka S, Kato J, et al. Genetic and epigenetic alterations of Ras signalling pathway in colorectal neoplasia: analysis based on tumour clinicopathological features. Br J Cancer 2007;97:1425-31.
14. Takayama T, Ohi M, Hayashi T, et al. Analysis of K-ras, APC, and beta-catenin in aberrant crypt foci in sporadic adenoma, cancer, and familial adenomatous polyposis. Gastroenterology 2001;121:599-611.
15. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 2004;351:2704-14.
16. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 2014;25:1346-55.
17. Goss KH, Groden J. Biology of the adenomatous polyposis coli tumor suppressor. J Clin Oncol 2000;18:1967-79.
18. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic

alterations during colorectal-tumor development. N Engl J Med 1988;319:525-32.

19. Lin LH, Chang KW, Cheng HW, et al. SMAD4 Somatic Mutations in Head and Neck Carcinoma Are Associated With Tumor Progression. Front Oncol 2019;9:1379.

20. Goyette MC, Cho K, Fasching CL, et al. Progression of colorectal cancer is associated with multiple tumor suppressor gene defects but inhibition of tumorigenicity is accomplished by correction of any single defect via chromosome transfer. Mol Cell Biol 1992;12:1387-95.

21. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350-6.

22. Yu X, Zhu L, Liu J, et al. Emerging Role of Immunotherapy for Colorectal Cancer with Liver Metastasis. Onco Targets Ther 2020;13:11645-58.

23. Rokavec M, Öner MG, Li H, et al. IL-6R/STAT3/miR-34a feedback loop promotes EMT-mediated colorectal cancer invasion and metastasis. J Clin Invest 2014;124:1853-67.

24. Hur K, Toiyama Y, Takahashi M, et al. MicroRNA-200c modulates epithelial-to-mesenchymal transition (EMT) in human colorectal cancer metastasis. Gut 2013;62:1315-26.

25. Paterson EL, Kazenwadel J, Bert AG, et al. Down-regulation of the miRNA-200 family at the invasive front of colorectal cancers with degraded basement membrane indicates EMT is involved in cancer progression. Neoplasia 2013;15:180-91.

26. Yang L, Lin PC. Mechanisms that drive inflammatory tumor microenvironment, tumor heterogeneity, and metastatic progression. Semin Cancer Biol 2017;47:185-95.

27. Tsilimigras DI, Ntanasis-Stathopoulos I, Bagante F, et al. Clinical significance and prognostic relevance of KRAS, BRAF, PI3K and TP53 genetic mutation analysis for resectable and unresectable colorectal liver metastases: A systematic review of the current evidence. Surg Oncol 2018;27:280-8.

28. Pitroda SP, Khodarev NN, Huang L, et al. Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. Nat Commun 2018;9:1793.

29. Mantovani A, Marchesi F, Malesci A, et al. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 2017;14:399-416.

30. Murray PJ, Allen JE, Biswas SK, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity 2014;41:14-20.

31. Grossman JG, Nywening TM, Belt BA, et al. Recruitment of CCR2+ tumor associated macrophage to sites of liver metastasis confers a poor prognosis in human colorectal cancer. Oncoimmunology 2018;7:e1470729.

32. Zhang W, Wang H, Sun M, et al. CXCL5/CXCR2 axis in tumor microenvironment as potential diagnostic biomarker and therapeutic target. Cancer Commun (Lond) 2020;40:69-80.

33. Brudvik KW, Henjum K, Aandahl EM, et al. Regulatory T-cell-mediated inhibition of antitumor immune responses is associated with clinical outcome in patients with liver metastasis from colorectal cancer. Cancer Immunol Immunother 2012;61:1045-53.

34. Odisio BC, Yamashita S, Huang SY, et al. Local tumour progression after percutaneous ablation of colorectal liver metastases according to RAS mutation status. Br J Surg 2017;104:760-8.

35. Shady W, Petre EN, Vakiani E, et al. Kras mutation is a marker of worse oncologic outcomes after percutaneous radiofrequency ablation of colorectal liver metastases. Oncotarget 2017;8:66117-27.

36. Calandri M, Yamashita S, Gazzera C, et al. Ablation of colorectal liver metastasis: Interaction of ablation margins and RAS mutation profiling on local tumour progression-free survival. Eur Radiol 2018;28:2727-34.

37. Araujo RLC, Milani JM, Armentano DP, et al. Disappearing colorectal liver metastases: Strategies for the management of patients achieving a radiographic complete response after systemic chemotherapy. J Surg Oncol 2020;121:848-56.

38. Macera A, Lario C, Petracchini M, et al. Staging of colorectal liver metastases after preoperative chemotherapy. Diffusion-weighted imaging in combination with Gd-EOB-DTPA MRI sequences increases sensitivity and diagnostic accuracy. Eur Radiol 2013;23:739-47.

39. Carpenter S, Fong Y. Management of disappearing colorectal hepatic metastases. Adv Surg 2010;44:269-79.

40. Maffione AM, Lopci E, Bluemel C, et al. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. Eur J Nucl Med Mol Imaging 2015;42:152-63.

41. Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. JAMA 2014;311:1863-9.

42. Mauri G, Gennaro N, De Beni S, et al. Real-Time US-18FDG-PET/CT Image Fusion for Guidance of Thermal Ablation of 18FDG-PET-Positive Liver Metastases: The Added Value of Contrast Enhancement. Cardiovasc

Intervent Radiol 2019;42:60-8.

43. Sahin DA, Agcaoglu O, Chretien C, et al. The utility of PET/CT in the management of patients with colorectal liver metastases undergoing laparascopic radiofrequency thermal ablation. Ann Surg Oncol 2012;19:850-5.

44. Popovic M, Talarico O, van den Hoff J, et al. KRAS mutation effects on the 2-[18F]FDG PET uptake of colorectal adenocarcinoma metastases in the liver. EJNMMI Res 2020;10:142.

45. Arita J, Ono Y, Takahashi M, et al. Routine Preoperative Liver-specific Magnetic Resonance Imaging Does Not Exclude the Necessity of Contrast-enhanced Intraoperative Ultrasound in Hepatic Resection for Colorectal Liver Metastasis. Ann Surg 2015;262:1086-91.

46. Langella S, Ardito F, Russolillo N, et al. Intraoperative Ultrasound Staging for Colorectal Liver Metastases in the Era of Liver-Specific Magnetic Resonance Imaging: Is It Still Worthwhile? J Oncol 2019;2019:1369274.

47. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol 2007;25:4575-80.

48. Creasy JM, Sadot E, Koerkamp BG, et al. Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure? Surgery 2018;163:1238-44.

49. Buisman FE, Giardiello D, Kemeny NE, et al. Predicting 10-year survival after resection of colorectal liver metastases; an international study including biomarkers and perioperative treatment. Eur J Cancer 2022;168:25-33.

50. de Haas RJ, Wicherts DA, Flores E, et al. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? Ann Surg 2008;248:626-37.

51. Charnsangavej C, Clary B, Fong Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1261-8.

52. Adam R, Yi B, Innominato PF, et al. Resection of colorectal liver metastases after second-line chemotherapy: is it worthwhile? A LiverMetSurvey analysis of 6415 patients. Eur J Cancer 2017;78:7-15.

53. Hur H, Ko YT, Min BS, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastasis. Am J Surg 2009;197:728-36.

54. Shady W, Petre EN, Gonen M, et al. Percutaneous Radiofrequency Ablation of Colorectal Cancer Liver Metastases: Factors Affecting Outcomes--A 10-year

Experience at a Single Center. Radiology 2016;278:601-11.

55. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309-18; discussion 318-21.

56. Margonis GA, Sasaki K, Gholami S, et al. Genetic And Morphological Evaluation (GAME) score for patients with colorectal liver metastases. Br J Surg 2018;105:1210-20.

57. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644-57; discussion 657-8.

58. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-16.

59. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:1208-15.

60. Araujo R, Gonen M, Allen P, et al. Comparison between perioperative and postoperative chemotherapy after potentially curative hepatic resection for metastatic colorectal cancer. Ann Surg Oncol 2013;20:4312-21.

61. Araujo RL, Gönen M, Herman P. Chemotherapy for patients with colorectal liver metastases who underwent curative resection improves long-term outcomes: systematic review and meta-analysis. Ann Surg Oncol 2015;22:3070-8.

62. Kanemitsu Y, Shimizu Y, Mizusawa J, et al. Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial. J Clin Oncol 2021;39:3789-99.

63. Sonbol MB, Siddiqi R, Uson PLS, et al. The Role of Systemic Therapy in Resectable Colorectal Liver Metastases: Systematic Review and Network Meta-Analysis [Internet]. 20221014th ed. Oncologist. 2022. Available online: https://www.ncbi.nlm.nih.gov/pubmed/36239399

64. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol 2014;15:601-11.

65. Langer BB H, Shepard L, Nitti D, et al. Fluorouracil (FU)

plus l-leucovorin (l-LV) versus observation after potentially curative resection of liver or lung metastases from colorectal cancer (CRC): Results of the ENG (EORTC/NCIC CTG/GIVIO) randomized trial | Request PDF [Internet]. roc Am Soc Clin Oncol. 2002. Available online: https://www.researchgate.net/publication/313099090_Fluorouracil_FU_plus_l-leucovorin_l-LV_versus_observation_after_potentially_curative_resection_of_liver_or_lung_metastases_from_colorectal_cancer_CRC_Results_of_the_ENG_EORTCNCIC_CTGGIVIO_randomized_t

66. Portier G, Elias D, Bouche O, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. J Clin Oncol 2006;24:4976-82.

67. Ychou M, Hohenberger W, Thezenas S, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. Ann Oncol 2009;20:1964-70.

68. Snoeren N, van Hillegersberg R, Schouten SB, et al. Randomized Phase III Study to Assess Efficacy and Safety of Adjuvant CAPOX with or without Bevacizumab in Patients after Resection of Colorectal Liver Metastases: HEPATICA study. Neoplasia 2017;19:93-9.

69. Tamandl D, Gruenberger B, Herberger B, et al. Surgery after neoadjuvant chemotherapy for colorectal liver metastases is safe and feasible in elderly patients. J Surg Oncol 2009;100:364-71.

70. Sebagh M, Allard MA, Cunha AS, et al. A proposed new method for assessing the pathological response to chemotherapy in resected colorectal liver metastases. Br J Cancer 2014;111:470-6.

71. Hallet J, Cunha AS, Adam R, et al. Outcomes of Rehepatectomy for Colorectal Liver Metastases: A Contemporary Multi-Institutional Analysis from the French Surgical Association Database. Ann Surg Oncol 2016;23:894-903.

72. Fernandez FG, Ritter J, Goodwin JW, et al. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. J Am Coll Surg 2005;200:845-53.

73. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065-72.

74. Kooby DA, Fong Y, Suriawinata A, et al. Impact of steatosis on perioperative outcome following hepatic resection. J Gastrointest Surg 2003;7:1034-44.

75. Zorzi D, Laurent A, Pawlik TM, et al. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 2007;94:274-86.

76. Robinson SM, Wilson CH, Burt AD, et al. Chemotherapy-associated liver injury in patients with colorectal liver metastases: a systematic review and meta-analysis. Ann Surg Oncol 2012;19:4287-99.

77. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15:460-6.

78. Hubert C, Sempoux C, Horsmans Y, et al. Nodular regenerative hyperplasia: a deleterious consequence of chemotherapy for colorectal liver metastases? Liver Int 2007;27:938-43.

79. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-422.

80. Meyerhardt JA, Li L, Sanoff HK, et al. Effectiveness of bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV colorectal cancer. J Clin Oncol 2012;30:608-15.

81. Ruers T, Van Coevorden F, Punt CJ, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst 2017;109:djx015.

82. Usón PLS Jr, Bugano DDG, Moura F, et al. Worst outcomes according to RAS mutation variants: an analysis in patients with metastatic colorectal adenocarcinoma. J BUON 2018;23:925-35.

83. Elez E, Argilés G, Tabernero J. First-Line Treatment of Metastatic Colorectal Cancer: Interpreting FIRE-3, PEAK, and CALGB/SWOG 80405. Curr Treat Options Oncol 2015;16:52.

84. Yoshino T, Watanabe J, Shitara K, et al. Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial. [Internet]. https://doi.org/10.1200/JCO.2022.40.17_suppl.LBA1. 2022. Available online: https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.17_suppl.LBA1

85. Geissler M, Riera-Knorrenschild J, Martens UM, et al. Final results and OS of the randomized phase II VOLFI trial (AIO- KRK0109): mFOLFOXIRI + panitumumab

versus FOLFOXIRI as first-line treatment in patients with RAS wild- type metastatic colorectal cancer (mCRC). [Internet]. https://doi.org/10.1200/JCO.2019.37.15_suppl.3511. 2019. Available online: https://ascopubs.org/doi/10.1200/JCO.2019.37.15_suppl.3511

86. Cremolini C, Rossini D, Lonardi S, et al. Modified FOLFOXIRI plus panitumumab (mFOLFOXIRI/PAN) versus mFOLFOX6/PAN as initial treatment of patients with unresectable RAS and BRAF wild-type metastatic colorectal cancer (mCRC): Results of the phase III randomized TRIPLETE study by GONO. [Internet]. https://doi.org/10.1200/JCO.2022.40.17_suppl.LBA3505. 2022. Available online: https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.17_suppl.LBA3505

87. Rossini D, Antoniotti C, Lonardi S, et al. Upfront Modified Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan Plus Panitumumab Versus Fluorouracil, Leucovorin, and Oxaliplatin Plus Panitumumab for Patients With RAS/BRAF Wild-Type Metastatic Colorectal Cancer: The Phase III TRIPLETE Study by GONO. J Clin Oncol 2022;40:2878-88.

88. Venook AP, Ou FS, Lenz HJ, et al. Primary (1°) tumor location as an independent prognostic marker from molecular features for overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). [Internet]. https://doi.org/10.1200/JCO.2017.35.15_suppl.3503. 2017. Available online: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.3503

89. Kopetz S, Grothey A, Tabernero J. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. Reply. N Engl J Med 2020;382:877-8.

90. Cremolini C, Antoniotti C, Lonardi S, et al. Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer. Retrospective analysis of the TRIBE trial by GONO. Ann Oncol 2018;29:1528-34.

91. Gruenberger T, Bridgewater J, Chau I, et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. Ann Oncol 2015;26:702-8.

92. Kopetz S, Grothey A, Yaeger R, et al. BREAKWATER: Randomized phase 3 study of encorafenib (enco) + cetuximab (cetux) ± chemotherapy for first-line (1L) treatment (tx) of BRAF V600E-mutant (BRAFV600E) metastatic colorectal cancer (mCRC). [Internet]. https://doi.org/10.1200/JCO.2021.39.15_suppl.TPS3619. 2021.

Available online: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.TPS3619

93. Ahcene Djaballah S, Daniel F, Milani A, et al. HER2 in Colorectal Cancer: The Long and Winding Road From Negative Predictive Factor to Positive Actionable Target. Am Soc Clin Oncol Educ Book 2022;42:1-14.

94. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17:738-46.

95. Strickler JH, Ng K, Cercek A, et al. MOUNTAINEER:open-label, phase II study of tucatinib combined with trastuzumab for HER2-positive metastatic colorectal cancer (SGNTUC-017, trial in progress). [Internet]. https://doi.org/10.1200/JCO.2021.39.3_suppl.TPS153. 2021. Available online: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.3_suppl.TPS153

96. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol 2019;20:518-30.

97. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372:2509-20.

98. André T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med 2020;383:2207-18.

99. Lenz HJ, Van Cutsem E, Luisa Limon M, et al. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. J Clin Oncol 2022;40:161-70.

100. Cohen R, Meurisse A, Pudlarz T, et al. One-year duration of nivolumab plus ipilimumab in patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI/dMMR) metastatic colorectal cancer (mCRC): Long-term follow-up of the GERCOR NIPICOL phase II study. [Internet]. https://doi.org/10.1200/JCO.2022.40.4_suppl.013. 2022. Available online: https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.4_suppl.013

101. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med 2018;378:731-9.

102. Garralda E, Hong D, Xu R, et al. SO-31 Long-term efficacy and safety of larotrectinib in patients with

tropomyosin receptor kinase (TRK) fusion gastrointestinal (GI) cancer: An expanded dataset. Ann Oncol 2022;33:S370.

103. Figueredo A, Rumble RB, Maroun J, et al. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. BMC Cancer 2003;3:26.

104. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:10-32.

105. Chiorean EG, Nandakumar G, Fadelu T, et al. Treatment of Patients With Late-Stage Colorectal Cancer: ASCO Resource-Stratified Guideline. JCO Glob Oncol 2020;6:414-38.

106. Takamizawa Y, Inoue M, Moritani K, et al. Prognostic impact of conversion hepatectomy for initially unresectable colorectal liver metastasis. Langenbecks Arch Surg 2022;407:2893-903.

107. Konishi T, Shimada Y, Hsu M, et al. Association of Preoperative and Postoperative Serum Carcinoembryonic Antigen and Colon Cancer Outcome. JAMA Oncol 2018;4:309-15.

108. Nakamura Y, Shida D, Tanabe T, et al. Prognostic impact of preoperatively elevated and postoperatively normalized carcinoembryonic antigen levels following curative resection of stage I-III rectal cancer. Cancer Med 2020;9:653-62.

109. Kataoka K, Kanazawa A, Iwamoto S, et al. Does "conversion chemotherapy" really improve survival in metastatic colorectal cancer patients with liver-limited disease?. World J Surg 2014;38:936-46.

110. Araujo RL, Gönen M, Allen P, et al. Positive postoperative CEA is a strong predictor of recurrence for patients after resection for colorectal liver metastases. Ann Surg Oncol 2015;22:3087-93.

111. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol 2006;24:5313-27.

112. Araujo RLC, Carvalho CGCY, Maeda CT, et al. Oncologic aspects of the decision-making process for surgical approach for colorectal liver metastases progressing during chemotherapy. World J Gastrointest Surg 2022;14:877-86.

113. Lu YY, Chen JH, Chien CR, et al. Use of FDG-PET or PET/CT to detect recurrent colorectal cancer in patients with elevated CEA: a systematic review and meta-analysis. Int J Colorectal Dis 2013;28:1039-47.

114. Berchuck JE, Facchinetti F, DiToro DF, et al. The clinical landscape of cell-free DNA alterations in 1671 patients with advanced biliary tract cancer. Ann Oncol 2022;33:1269-83.

115. Sartore-Bianchi A, Pietrantonio F, Lonardi S, et al. Phase II study of anti-EGFR rechallenge therapy with panitumumab driven by circulating tumor DNA molecular selection in metastatic colorectal cancer: The CHRONOS trial. [Internet]. https://doi.org/10.1200/JCO.2021.39.15_suppl.3506. 2021. Available online: https://ascopubs.org/doi/10.1200/JCO.2021.39.15_suppl.3506

116. Tarazona N, Gimeno-Valiente F, Gambardella V, et al. Targeted next-generation sequencing of circulating-tumor DNA for tracking minimal residual disease in localized colon cancer. Ann Oncol 2019;30:1804-12.

117. Tie J, Cohen JD, Lahouel K, et al. Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer. N Engl J Med 2022;386:2261-72.

118. Polivka J, Windrichova J, Pesta M, et al. The Level of Preoperative Plasma KRAS Mutations and CEA Predict Survival of Patients Undergoing Surgery for Colorectal Cancer Liver Metastases. Cancers (Basel) 2020;12:2434.

119. Marmorino F, Prisciandaro M, Giordano M, Ortolan E, Crucitta S, Manca P, et al. Circulating Tumor DNA as a Marker of Minimal Residual Disease After Radical Resection of Colorectal Liver Metastases [Internet]. https://doi.org/10.1200/PO.22.00244. 2022. Available online: https://ascopubs.org/doi/abs/10.1200/PO.22.00244

120. Wang DS, Yang H, Liu XY, et al. Dynamic monitoring of circulating tumor DNA to predict prognosis and efficacy of adjuvant chemotherapy after resection of colorectal liver metastases. Theranostics 2021;11:7018-28.

121. Øgaard N, Reinert T, Henriksen TV, et al. Tumour-agnostic circulating tumour DNA analysis for improved recurrence surveillance after resection of colorectal liver metastases: A prospective cohort study. Eur J Cancer 2022;163:163-76.

122. Spindler KLG. Optimization of treatment selection and follow up in oligometastatic colorectal cancer [Internet]. NCT04680269; Available online: https://clinicaltrials.gov

123. Newhook T. ctDNA-directed post-hepatectomy chemotherapy for patients with resectable colorectal liver metastasis [Internet]. NCT05062317; Available online: https://clinicaltrials.gov

124. Araujo RL, Linhares MM. Pushing the limits of liver surgery for colorectal liver metastases: Current state and future directions. World J Gastrointest Surg 2019;11:34-40.

125. Folprecht G, Reinacher-Schick A, Weitz J, et al. The CIRCULATE Trial: Circulating Tumor DNA Based

Decision for Adjuvant Treatment in Colon Cancer Stage II Evaluation (AIO-KRK-0217). Clin Colorectal Cancer 2022;21:170-4.

126. Nors J, Henriksen TV, Gotschalck KA, et al. IMPROVE-IT2: implementing noninvasive circulating tumor DNA analysis to optimize the operative and postoperative treatment for patients with colorectal cancer - intervention trial 2. Study protocol. Acta Oncol 2020;59:336-41.

127. Kasi PM, Sawyer S, Guilford J, et al. BESPOKE study protocol: a multicentre, prospective observational study to evaluate the impact of circulating tumour DNA guided therapy on patients with colorectal cancer. BMJ Open 2021;11:e047831.

128. Anandappa G, Starling N, Peckitt C, et al. TRACC: Tracking mutations in cell-free DNA to predict relapse in early colorectal cancer—A randomized study of circulating tumour DNA (ctDNA) guided adjuvant chemotherapy versus standard of care chemotherapy after curative surgery in patients with high risk stage II or stage III colorectal cancer (CRC). [Internet]. https://doi.org/10.1200/JCO.2020.38.15_suppl.TPS4120. 2020. Available online: https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.TPS4120

129. Kotaka M, Shirasu H, Watanabe J, et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. [Internet]. https://doi.org/10.1200/JCO.2022.40.4_suppl.009. 2022. Available online: https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.4_suppl.009

130. Fakih M, Sandhu J, Wang C, et al. Evaluation of Comparative Surveillance Strategies of Circulating Tumor DNA, Imaging, and Carcinoembryonic Antigen Levels in Patients With Resected Colorectal Cancer. JAMA Netw Open 2022;5:e221093.