Review Article

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

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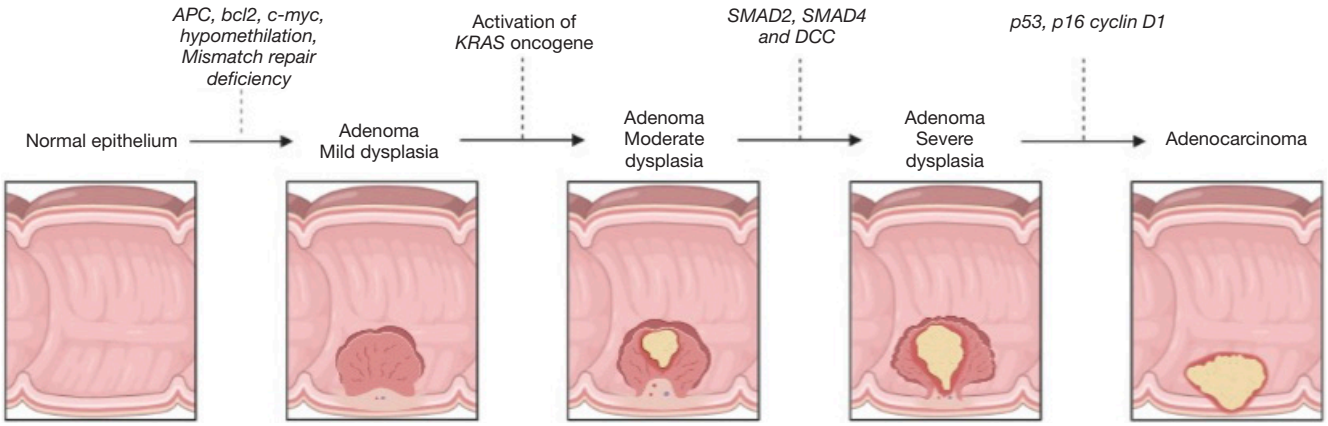

Figure 1 Gene amplifications, fusions, deletions, and DNA methylation involved in the carcinogenesis of colorectal cancer. Created with BioRender.com.

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

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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

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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

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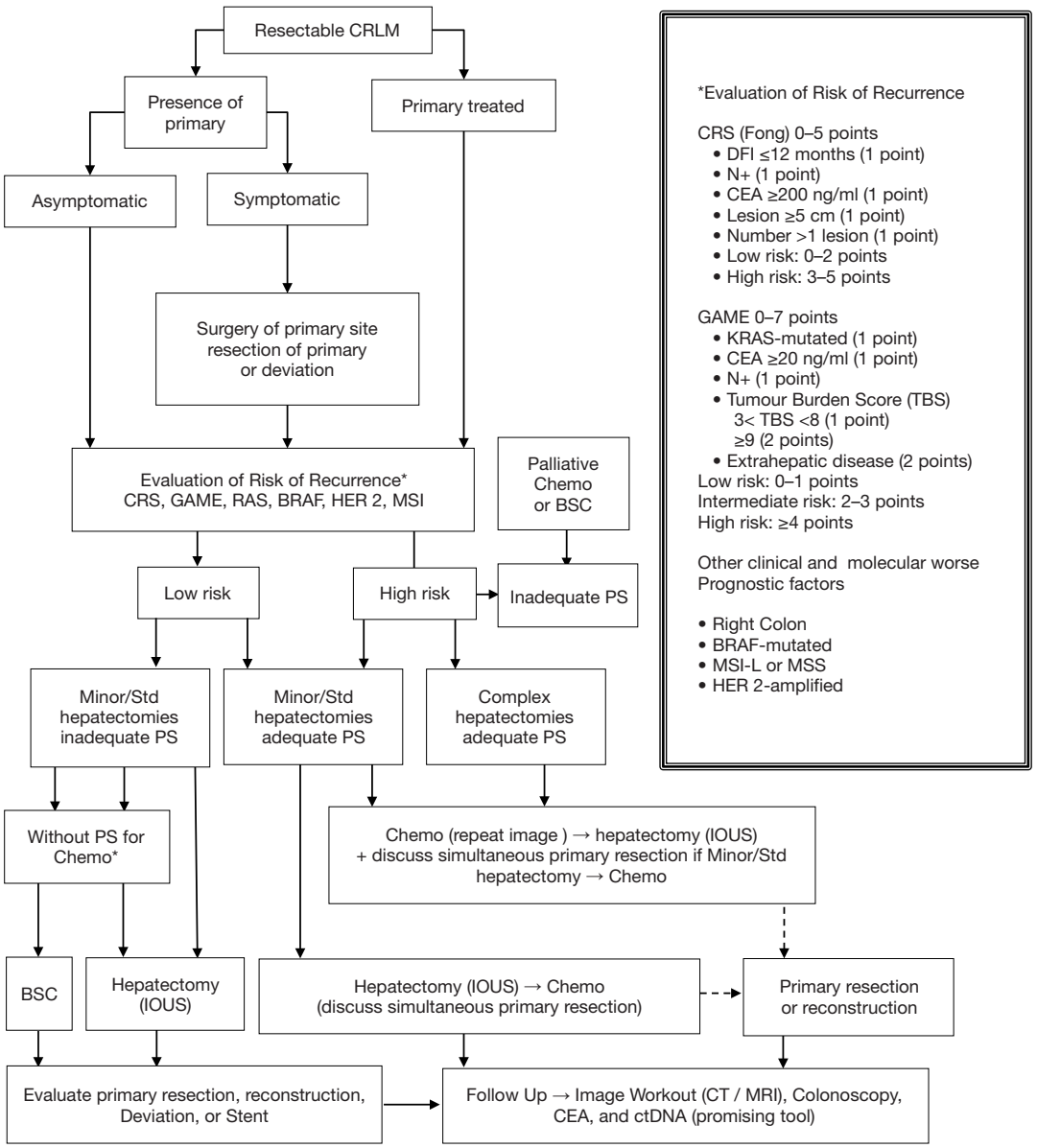

Figure 2 Flowchart summarizing the decision-making process for the management of cases of patients with initially resectable CRLM. CRLM, colorectal liver metastases; CRS, Clinical Risk Score; Chemo, chemotherapy (systemic treatment); DFI, disease-free interval; CT, computerized tomography; IOUS, intraoperative 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

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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

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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

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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

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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

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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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