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Molecular Determinants and Other Factors to Guide Selection of Patients for Hepatic Resection of Metastatic Colorectal Cancer

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide and the fourth most common cancer in the USA, responsible for over 50,000 American deaths in 2020 alone [1, 2]. Metastatic disease is a major driver of colon cancer deaths, and the liver is the most common site for metastatic lesions. In fact, colorectal liver metastases (CRLM) are found in 15–25% of patients at the time of cancer diagnosis, and up to half of colorectal cancer patients will eventually develop liver metastases [3, 4].

Years ago, when fluorouracil and leucovorin were introduced as the only chemotherapeutic options for metastatic CRC, median overall survival (OS) improved from six months to 8–12 months [5••, 6]. Now cytotoxic chemotherapy with FOLFOX/FOLFIRI and targeted therapies (e.g., irinotecan, oxaliplatin, bevacizumab, and cetuximab) have improved survival outcomes and expanded the range of treatment possibilities for CRLM. As for surgical treatment, resection of colorectal liver metastases, when feasible, has evolved as the standard of care over the last 20 years. Resection and/or ablation offers the only potentially curative treatment for patients with CRLM, offering 5- and 10-year OS rates up to 55 and 25%, respectively, for patients with pathologically negative margins (R0 resection) [7, 8]. Unfortunately, only a minority of patients (15–20%) with hepatic metastases are eligible for surgical resection [9], though advances in chemotherapy (downstaging or conversion chemotherapy) and strategies to grow the FLR (portal vein embolization, selective internal radiation therapy, and ALPPS) continue to increase the number of patients considered eligible for CRLM resection.

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Conflict of Interest

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Patient selection for CRLM resection has historically been based largely on clinical risk scores. One of the most widely used scores is the Fong clinical risk score, which assigns one point to each of the following clinical markers: disease-free interval less than 12 months, node-positive primary, more than one solitary liver metastasis, largest liver metastasis greater than 5 cm in diameter, and serum carcinoembryonic antigen (CEA) level above 200 μg/L [10]. Many other scores have been presented to prognosticate outcomes after CRLM resection [11]; however, their utility remains uncertain, as none have proven accuracy in predicting long-term survival [12, 13]. Currently, for those who do undergo CRLM resection, close to two thirds develop a recurrence and 15% die within one year of surgery [14–16].

The rapid growth in our understanding of genetic profiles on tumor behavior has been helpful for prognostication and treatment decisions. CRCs expressing common oncogene mutations, such as KRAS and BRAF mutations, are known to exhibit more aggressive behavior with increased rates of extrahepatic disease, specific chemotherapy resistance patterns, and worse disease-free survival (DFS) and OS [3, 17, 18]. Such advances in our understanding of key CRC biomarkers and increasing focus on molecular profiling for risk stratification have helped shared decision-making regarding the utility of chemotherapy for CRLM. How to incorporate this rapid expansion of knowledge concerning genetic and molecular markers into decisions regarding patient selection for CRLM resection is the next frontier in surgical decision-making for this patient population. This article offers a brief review of recent developments in key genetic and molecular considerations for resection of CRLM.

Treatment

In this section, we will summarize the recent literature regarding the impact of several oncogene mutations and other molecular markers on DFS and OS following resection of CRLM.

KRAS mutations

Kirsten rat sarcoma viral oncogene homolog (KRAS) is an oncogene in the RAS pathway that has been shown to be negatively associated with DFS and OS in patients undergoing resection of CRLM [19, 20]. KRAS-mutated cells, found in 25–52% of CRLMs, exhibit more aggressive, invasive behavior, demonstrated by an increased likelihood of presenting with bone, brain, and lung metastases [21, 22•].

In a large systematic review and meta-analysis including 1833 patients undergoing R0/R1 resection of CRLM, Tosi et al. reported KRAS mutations were found in 34% of CRLMs and were associated with decreased DFS (HR, 1.529; 95% CI, 1.287–1.817; $P < 0.001$) and OS (HR, 3.055; 95% CI, 1.794–5.204; $P < 0.0001$) in patients undergoing liver resection [5••]. These findings were corroborated by another large systematic review in which Tsilimigras et al. sought to clarify the clinical significance and prognostic relevance of KRAS, BRAF, PI3K, and TP53 genetic mutations for resectable and unresectable colorectal liver metastases. Their analysis concluded that KRAS mutations predicted worse OS, ranging

from 19.6 to 50.9 months in KRAS-mutated CRLM, versus >70 months in wild-type KRAS CRLM patients [3]. Importantly, the authors also noted that while 1–4-mm surgical margins were sufficient for most CRLMs, wider resection (including anatomic hepatectomy) was associated with improved DFS and OS for KRAS-mutated CRLM [3, 23••].

In an effort to further delineate which KRAS mutation locations have the greatest impact on survival outcomes in metastatic CRC, Saadat et al. conducted a retrospective, single-center study of 938 patients undergoing resection of CRLM and linked KRAS mutation location with DFS and OS [22•]. In their report, KRAS mutations were found in 47% of patients, equally distributed between men and women. The vast majority (91.5%) of KRAS mutations were in exon 2. The next most common KRAS mutation locations were exon 4 (5%) and exon 3 (3%). As expected, patients with KRAS-mutated CRLMs had worse OS (55.5 months vs. 91.3 months). Patients with KRAS-mutated CRLMs were also more likely to have right-sided primary tumors and a higher rate of extrahepatic disease at the time of liver resection, but there is no difference in tumor size or number of metastases compared to wild-type KRAS CRLMs. Importantly, the authors did not identify any difference in OS based on the location of exon mutation; however, this evidence is not conclusive as the sample size for exon 3 and exon 4 mutations was relatively small [22•].

Metastasectomy is associated with improved OS regardless of KRAS status for well-selected CRC patients [18, 24••]. Median OS for patients with metastatic colorectal cancer, according to multiple randomized clinical trials (FIRE-3, CALGB/SWOG 80405, TRIBE1, and TRIBE 2), is between 22.5 and 30 months [25–28]. In comparison to the overall metastatic CRC population, OS is worse for patients with unresectable KRAS-mutated CRLM [3, 29]. In patients undergoing CRLM resection, median DFS has most recently been reported as 10.8 vs. 15.8 months in KRAS-mutated vs. wild-type KRAS CRLM [22•]. OS ranges between 19.6 and 55.5 months in patients with KRAS-mutated tumors, compared to 70–90+ months in wild-type KRAS CRLMs [3, 22•].

However, for patients with KRAS-mutated CRLM and multiple high-risk factors (node-positive primary, individual CRLM > 3 cm, and more than 7 cycles of systemic chemotherapy given), the benefits of aggressive surgical treatment may not outweigh the risks [24••]. Patients with all three risk factors listed above are reported to have median OS of 22 months and five-year survival of 0%; hepatectomy may not provide any survival benefit, when added to administration of systemic chemotherapy, for such patients [7, 24••]. While the data are overall in favor of hepatectomy for KRAS-mutated CRLM, further research is required to better identify high-risk patients who may not receive any survival benefit from surgery.

Current first-line options for chemotherapy in metastatic colorectal cancer include systemic oxaliplatin- or irinotecan-based chemotherapy (FOLFOX, FOLFIRI), often with the addition of bevacizumab (antivascular endothelial growth factor (VEGF) agent) or cetuximab (epidermal growth factor inhibitor (EGFR)) [27, 30, 31]. Importantly, anti-EGFR therapies (e.g., cetuximab and panitumumab) while demonstrating improved resection rates, DFS, and OS for wild-type RAS CRLMs are less helpful in KRAS-, NRAS- and BRAF-mutated CRLMs, as these oncogene mutations are known to predict resistance to anti-EGFR

therapies [5•, 32]. Regardless of RAS mutation status, bevacizumab has been demonstrated to improve DFS and OS when added to irinotecan-based therapies (and DFS when added to oxaliplatin-based therapies) [33].

In the recent TRIBE study [30], a triple-drug combination of fluorouracil (plus leucovorin), oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab was compared to FOLFIRI plus bevacizumab in metastatic CRC patients and demonstrated improved OS in FOLFOXIRI-treated patients (29.8 months, 95% CI 26.0–34.3 vs. 25.8 months, 22.5–29.1; $P = 0.03$). Specifically, for RAS- and BRAF-mutated CRLM, the TRIBE study did not demonstrate any difference in OS between treatment arms [27]. The CHARISMA trial, which is currently underway, will help determine whether neoadjuvant capecitabine and oxaliplatin (XELOX) improve OS in high-risk patients with primary resectable CRLM, without extrahepatic disease [6].

Key takeaways

- KRAS-mutated tumors are found in 25-52% of patients with CRLM and exhibit more aggressive behavior, including higher rates of bone, brain, and lung metastases [3, 21, 22•].
- KRAS-mutated tumors are associated with worse DFS and OS, compared to wild-type KRAS tumors, in patients undergoing resection of CRLM [3, 17, 18].
- The significance of KRAS mutation locations is unclear. KRAS exon 2 mutations are most prevalent, while exon 3 and 4 mutations are found in a minority of patients with resectable CRLM. KRAS exon 4-mutant tumors may have a less aggressive phenotype; however, the evidence is mixed [22•, 34].
- Wider resections (>1 cm), even anatomic hepatectomy, may provide additional survival benefit for KRAS-mutated CRLMs [3, 23••].
- Metastasectomy for KRAS-mutated CRLM is associated with improved OS for appropriately selected patients; however, high-risk patients may not benefit from surgery [24••].

BRAF mutations

The b-viral oncogene homolog B1 (BRAF) oncogene, like KRAS, is a component of the RAS pathway and associated with more aggressive tumor biology [5••]. While the overall incidence of BRAF mutations is 8–12% in the metastatic CRC population, BRAF-mutated tumors are only found in 1–4% of CRC patients undergoing metastasectomy [35••, 36]. Such disparate prevalence of BRAF-mutated cancers likely suggests that BRAF-mutated tumors are underrepresented in studies evaluating hepatectomy for CRLM, due to their more invasive nature, often presenting with unresectable disease and multiorgan involvement [5••, 35••, 37].

BRAF mutations confer decreased DFS, OS, and cancer-specific survival in metastatic CRC patients, as BRAF-mutated tumors are more likely to be poorly differentiated with mucinous histology and microsatellite instability [36–39]. BRAF-mutated tumors were

initially thought to have similar phenotypic characteristics to KRAS-mutated CRLM, since BRAF is downstream from KRAS in the same signaling pathway; however, more recent studies have elucidated differences in BRAF-mutated CRLM, especially the BRAF V600E mutation [35••, 40].

BRAF V600E mutations are the most common BRAF mutations in CRC and identify a subgroup of metastatic CRCs with a worse prognosis [35••, 41]. Multiple studies have established BRAF V600E mutations as an indicator for shorter DFS and OS after metastasectomy compared to wild-type BRAF patients [5••, 42–44]. A recent large, international study which sought to delineate the impact of BRAF V600E on OS and recurrence after resection of CRLM included 853 patients who underwent metastasectomy with curative intent between 2000 and 2016 [35••]. In their study population, 5.3% (43/849) possessed a mutated BRAF genotype and 38.4% (326/849) a mutated KRAS genotype. The authors reported BRAF mutations to be associated with female sex (62.8%), 65 and older age group, right-sided tumors (62.8% vs. 17.4%), more advanced T stage, and metachronous liver metastases. Patients with any BRAF-mutated genotypes demonstrated median DFS of 9.9 months and median OS of 26 months after CRLM resection. Stratified within the BRAF-mutated group, V600E mutations were found in 76.7% of patients (33/43 patients), versus non-V600E BRAF mutations in <14% (6/43) (and nonspecific BRAF mutations in 9.3% (4/43)). This report concluded that BRAF V600E mutations were associated with worse DFS (HR, 2.04; 95% CI, 1.30–3.20; $P = 0.002$) and OS (HR, 2.76; 95% CI, 1.74–4.37; $P < 0.001$), whereas non-V600E BRAF mutations were similar to the wild-type BRAF group in all outcome measures [35••].

Is surgical resection advisable for patients with BRAF V600E-mutated CRLM? According to Johnson et al., hepatectomy for BRAF V600E-mutated tumors does improve DFS and OS [45•]. In their single-center study, 52 patients were identified with BRAF V600E-mutated CRLM, of which 71% had right-sided primary tumors and 28% had liver-limited metastases. Median DFS for all 52 patients was 9.3 months, and median OS was 25 months. The subset of patients ($n = 21$) who underwent metastasectomy had longer DFS (13.6 months vs. 6.2 months, HR 0.53, CI, 0.28–0.97; $P = 0.03$) and OS (29.1 months vs. 22.7 months, HR 0.33; CI, 0.12–0.78; $P = 0.01$) compared with the nonmetastasectomy cohort [45•].

There are, however, conflicting data emerging regarding the impact of BRAF V600E mutations on survival in patients undergoing CRLM resection. In a multicenter study of 1497 patients undergoing hepatectomy for metastatic colorectal cancer, there was no difference in survival or recurrence outcomes between BRAF V600E and non-V600E BRAF mutations [41], At a median follow-up of 57 months, the authors reported median OS of 40 months for BRAF-mutated tumors overall and 31 months (range 5 to 104, $P = 0.16$) specifically for BRAF V600E mutations. To further confound the issue, some data suggest that non-V600E BRAF mutations may even confer a survival benefit compared to wild-type BRAF CRLM. According to a 2017 report of nearly 10,000 patients with metastatic CRC and next-generation sequencing data, median OS was significantly longer in patients with non-V600E BRAF-mutant metastatic CRC compared with those with either BRAF V600E-mutant or wild-type BRAF metastatic CRC (60.7 vs. 11.4 vs. 43.0 months, respectively; $P < 0.001$) [46].

Key takeaways

- BRAF mutations are relatively rare in patients with resectable CRLM (1–4%) [35••, 36].
- To date, most literature agrees that BRAF mutations are associated with worse DFS and OS following metastasectomy for CRLM and that BRAF V600E mutation is the most common and most aggressive subtype [35••, 37–39, 41].
- Metastasectomy improves DFS and OS in BRAF V600E-mutated CRLM [45•].

NRAS mutations

Neuroblastoma RAS viral oncogene homolog (NRAS), another member of the RAS oncogene family, may also predict worse OS in metastatic CRC patients. In a retrospective, single-center study of 938 patients undergoing CRLM resection, NRAS mutations were found in 4.2% of patients and predicted worse OS (50.9 months vs. 73.3 months in the wild-type NRAS group; $P = 0.03$), but there is no difference in DFS [22•]. Evidence concerning NRAS mutations in metastatic CRC is slowly emerging, and to date, multiple studies have corroborated these findings of decreased OS in NRAS-mutant CRLM patients [47, 48]. NRAS is known to be associated with left-sided primary CRC tumors, female gender, and African American race [47].

SMAD4 inactivation

SMAD4 is a protein coding gene and mediator of TGF-β signaling that is altered in 15–20% of sporadic CRC cases [49]. SMAD4 inactivation is correlated with worse patient outcomes for any stage colon cancer, perhaps especially when found in patients with RAS-mutated metastatic CRC [50]; however, SMAD4 alterations may not predict any difference in outcomes when observed in wild-type RAS/BRAF patients [50].

Microsatellite instability (MSI-H)

Microsatellite instability (MSI-H) is found in 4–8% of metastatic CRC tumors [51]. When compared to patients with microsatellite stability (MSS), the MSI-H phenotypes have been shown to predict worse DFS and OS (HR 1.33; 95% CI, 1.12–1.57; $P = 0.001$ and HR 1.35; 95% CI, 1.13–1.61, $P = 0.001$, respectively) [52]. Right-sided primary CRC tumors, which often exhibit MSI-H, are associated with resistance to anti-EGFR and 5-fluorouracil therapies and confer worse OS [53, 54], One report suggests that right-sided CRC tumors are associated with worse five-year OS, compared to left-sided tumors (39.4% vs. 50.8%, $P = 0.03$). Interestingly, the effect of primary tumor laterality on OS disappears when considering only patients with KRAS-mutated CRLM [55]. Further research is required to determine the prognostic impact of primary tumor laterality for other common genetic profiles in CRLM.

Immunotherapies, encouragingly, have improved the response rate and progression-free survival (PFS) in patients with stage IV MSI-H CRC [56]. In an ongoing phase III clinical trial, the impact of pembrolizumab versus standard of care chemotherapy (one of six

regimens) on DFS and OS in stage IV CRC is being investigated [57]. Studies concerning *neoadjuvant* immunotherapy for MSI-H CRLM are limited, but early data are promising [58].

TP53 mutations

TP53 gene mutations are common in metastatic CRC, with a prevalence between 36 and 66% in resected liver metastases [3]. There is no consensus on TP53's impact on DFS and OS for patients undergoing resection of CRLM; however, recent data have emerged demonstrating potentially worse OS following CRLM resection for patients with concomitant RAS and TP53 mutations.

Datta et al. sought to determine which genomic profiles were found in patients at the extremes of survivorship in metastatic colon cancer postmetastasectomy. They reported KRAS exon 2 mutations and TP53 variants were more frequently found in patients surviving less than 2 years after metastasectomy, compared with patients surviving more than 10 years [16]. Median DFS and OS were worse in patients with cooccurrent KRAS and TP53 mutations and significantly worse than those in patients with either individual mutation. The authors outlined three prognostic subgroups, which were, in descending order of OS: (1) TP53 alterations alone (median OS, 132 months), (2) RAS/BRAF alterations alone (median OS, 64.7 months) and pan-wild-type tumors (median OS, 59.9 months), and lastly (3) coaltered TP53 and RAS/BRAF tumors (median OS, 40 months) [16]. The negative impact of concomitant RAS and TP53 mutations on OS following CRLM has been supported by other studies [59•].

CD8+ T cells and stromal cell-derived factor-1

High densities of infiltrating CD8+ T cells are associated with improved DFS and OS in colorectal cancer [60, 61]. Immunoscore, an internationally validated prognostic tool in stage I–III CRC, considers the density of T lymphocytes in the center and periphery of tumors and has improved prognostication in colorectal cancers [60, 62]. There are limited data published to support Immunoscore as a prognostic tool in patients undergoing CRLM resection [63]; however, further research is required to fully understand the utility of Immunoscore in stage IV CRCs.

More recently, stromal cell-derived factor 1's (SDF-1) role has been explored in conjunction with CD8+T cells. SDF-1 (CXCL12) is a chemokine produced by several cell types (e.g., tumor cells, T lymphocytes, bone marrow cells, and mucosal epithelial cells) that plays an important role in tumor-stromal communication for cancer growth—angiogenesis and metastasis; SDF-1 has been linked to reduced OS in multiple cancers [64, 65]. In a study specifically examining CD8+ T cells and SDF-1 in colorectal cancer, high SDF-1 expression and CD8+ T cell infiltration predicted improved five-year survival compared to patients with high CD8+ T cell infiltration alone (66%, 95% CI 48–79% vs. 55%, 95% CI 45–64%; $P = 0.0004$) [61]. High SDF-1 expression has also been shown to represent a favorable prognostic factor for DFS in CRC [66]. Our understanding of CD8+ T cells and SDF-1 as it pertains to CRC and more specifically to metastatic CRC remains superficial. Still, CD8+

T cells and SDF-1 are new molecular markers that may convey prognostic information in colorectal cancer patients.

PTEN and PIK3CA mutations

PTEN (phosphatase and tensin homolog) is a tumor suppressor that deactivates the phosphatidylinositide-3-kinase (PI3K) signaling pathway, a kinase in the PI3K/AKT1/MTOR pathway [67]. Mutations in the PI3K subunit PIK3CA contribute to carcinogenesis and survival of multiple solid tumors and are found in 15–20% of CRCs [68, 69]. Recent literature suggests that PIK3CA mutations result in resistance to first-line chemotherapies, including FOLFOX and cetuximab [70]; however, evidence is mixed regarding the prognostic role of PIK3CA mutations in CRC [68, 69]. A single-center study analyzing 396 metastatic CRC patients who underwent hepatectomy between 2005 and 2015 demonstrated that concurrent mutations in APC and PIK3CA were associated with worse DFS and OS after hepatectomy (three-year DFS, 3.1% vs. 20%; $P < 0.001$; three-year OS, 44% vs. 84%; $P < 0.001$) [71•]. This double mutation (APC and PIK3CA) also predicted worse OS in a separate cohort of patients with CRLM receiving chemotherapy alone (without hepatectomy) [71•].

Future directions

Genetic/molecular risk scores

Patient selection for CRLM resection based on clinicopathological variables alone is insufficient to predict long-term outcomes but may be enhanced by inclusion of genetic data in risk stratification scores [72, 73]. As an example, a 20-gene molecular risk score (MRS) recently developed at the Memorial Sloan Kettering Cancer Center was independently prognostic of OS for CRLM resection [74]. Cell-free DNA and microRNA tests may also provide less invasive methods of characterizing tumor biology [75–77]. Ongoing research concerning the prognostic value of mutation locations and subtypes (e.g., KRAS exon 2 and BRAF V600E) will inform future risk scores and continue to improve our ability to optimize patient selection for CLRM resection.

Consensus molecular subtypes

In 2015, the Colorectal Cancer Subtyping Consortium published the consensus molecular subtypes (CMS classification) in an effort to resolve inconsistencies in reporting genetic signatures in CRC. Four distinct gene expression subtypes were identified—CMS1 (immune), CMS2 (canonical), CMS3 (metabolic), and CMS4 (mesenchymal)—using multiple microarray or RNA sequencing datasets of primary tumor samples [78]. The CMS classification was developed using primarily early-stage colon cancers (92% of samples), and therefore, metastatic colon cancer was underrepresented in the initial classification system [78]. In recent years, retrospective and exploratory analyses of large clinical trials concerning chemotherapy selection in metastatic CRC (FIRE-3, CALGB/SWOG 80405) have bolstered the CMS classification as an independent prognostic tool in metastatic CRC [79, 80]. CMS may offer a framework for selection of chemotherapeutic agents and targeted

therapies in stage IV CRC and should be prospectively evaluated as a stratification factor in future clinical trials.

Circulating tumor DNA

Analyzing circulating tumor DNA (ctDNA) is a noninvasive method of detecting somatic mutations in many cancer types, including colorectal cancer. ctDNA is typically analyzed from blood samples but can be isolated from several other body fluids (e.g., saliva, pleural effusions, urine, stool, and CSF) [81]. Recent studies indicate that ctDNA analysis has a 87.2% sensitivity and 99.2% specificity for clinically relevant KRAS mutations in metastatic colorectal cancers [82]. The sensitivity of ctDNA, however, depends on tumor burden and may only be detectable in approximately 50% of patients with nonmetastatic CRC. As evidence matures, ctDNA may be beneficial for early CRC diagnosis, residual disease detection, and monitoring for disease progression, resistance, and recurrence [81–83].

Hepatic artery infusion pumps

Hepatic artery infusion pumps (HAIP) deserve mention as a useful treatment for metastatic colorectal cancer, especially for initially unresectable disease [84]. HAIP involves delivery of floxuridine (FUDR) directly to liver metastases via a surgically implanted pump attached to a catheter in the gastroduodenal artery [85]. This therapy is used at select high-volume centers and has demonstrated impressive response rates in patients with initially unresectable CRLM when used in combination with systemic chemotherapy (up to 92% in chemotherapy naïve patients and 85% in pretreated patients with unresectable CRLM) [86]. Conversion to resectable CRLM has been reported as high as 52% in pretreated patients [87]. A recent multicenter retrospective cohort study demonstrated that HAIP could safely and feasibly be implemented in specialized centers to treat unresectable CRLM; however, to date, its use is largely limited to few high-volume, specialized centers in North America [88].

Conclusions

Our understanding of key genetic profiles and molecular markers in metastatic CRC is rapidly expanding and will continue to guide decisions concerning patient selection for CRLM resection. KRAS and BRAF mutations are known to confer worse DFS, reduced OS, and specific chemotherapy resistance patterns and therefore should be considered in multidisciplinary discussions about the applicability and timing of surgical intervention. This article highlights the complexity of interpreting genetic data for patient selection in CRLM resection, as emerging evidence points to differing biologic activity and prognostic value of even particular oncogene mutation subtypes and exon locations. Further research is needed to clarify the impact of more specific genetic profiles on survival and recurrence outcomes following CRLM resection.

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Opinion statement

Treatment for metastatic colorectal cancer (CRC) has changed significantly over the last few decades as cytotoxic and targeted chemotherapies have evolved and resection of (technically feasible) colorectal liver metastases (CRLM) has become standard of care for eligible patients. Overall, survival for metastatic CRC has considerably improved, but recurrences are common. Numerous clinical risk scores have been suggested to guide patient selection for CRLM resection, but none perfectly predict outcomes; therefore, a personalized approach to metastatic CRC treatment using genetic profiles for risk stratification and prognostication is a critically important advancement. All patients with suspected metastatic CRC should undergo genetic testing for common oncogene mutations (e.g., KRAS, BRAF, and NRAS) in addition to a triphasic CT scan of the chest, abdomen, and pelvis; if hepatectomy may be entertained and there is concern about the future liver remnant (FLR), liver volumetrics should also be performed. MRI and PET are useful adjuncts for cases in which diagnosis or extent of disease is unclear. The decision to operate should be individualized and based on each patient's condition, tumor biology, and technical resectability. Genetic profiles should be used to inform multidisciplinary meetings surrounding topics of chemotherapy and surgical resection, as well as patient discussions concerning the risks and benefits of surgery. In the end, most patients with technically resectable colorectal cancers and adequate cardiopulmonary fitness benefit from surgical resection, as it remains the only chance of long-term survival.