Received: 12 January 2022 | Accepted: 5 June 2022

DOI: 10.1002/ags3.12591

AGSurg Annals of Gastroenterological Surgery Open Access WILEY

REVIEW ARTICLE

Precision surgery for colorectal liver metastases: Current knowledge and future perspectives

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Funding information
NIH/NCI Cancer Center, Grant/Award Number: Support Grant P30 CA008748; MD Anderson Cancer Center

Abstract

Precision surgery for colorectal liver metastases (CRLM) includes optimal selection of both the patient and surgery. Initial attempts of using clinical risk scores to identify patients for whom technically feasible surgery is oncologically futile failed. Since then, patient selection for single-stage hepatectomy followed three distinct approaches, all of which incorporated biomarkers. The *BRAF* V600E mutation, the G12V *KRAS* variant, and the triple mutation of *RAS*, *TP53*, and *SMAD4* appear to be the most promising, but none can be used in isolation to deny surgery in otherwise resectable cases. Combining biomarkers with clinicopathologic factors that predict poor prognosis may be used to select patients for surgery, but external validation and matched analyses with medically treated counterparts are needed. Patient selection for special surgical procedures (two-stage hepatectomy [TSH], Associating Liver Partition and Portal vein Ligation for staged hepatectomy [ALPPS], and liver transplant [LT]) has been recently refined. Specifically, *BRAF* mutations and right-sided laterality have been proposed as separate contraindications to LT. A similar association of right-sided laterality, particularly when combined with *RAS* mutations, with very poor outcomes has been observed for ALPPS and has been suggested as a biologic contraindication. Data are scarce for TSH but *RAS* mutations may portend very poor survival following TSH completion. The selection of the best single-stage hepatectomy (optimal margin and type of resection) based on biomarkers remains debated, although there is some evidence that *RAS* may play a significant role. Lastly, although there are currently no criteria to select among the three special techniques based on their efficacy or appropriateness in different settings, *RAS* mutational status may be used to select patients for TSH, while right-sided tumor in conjunction with a *RAS* mutation may be a contraindication to LT and ALPPS.

KEYWORDS
colorectal liver metastases, mutations, precision surgery

1 | INTRODUCTION

The United States National Cancer Institute defines oncologic precision medicine as the "[use of] specific information about a person's tumor to help make a diagnosis, plan treatment, find out how well treatment is working, or make a prognosis." The term is relatively new, but in the case of surgical treatment of colorectal liver metastases (CRLM), precision medicine has been pursued for a long time, although the "specific information about a person's tumor" used to be clinicopathologic and not molecular. Precision surgery for CRLM includes both optimal patient selection and selection of the best surgery for a specific patient.

2 | PATIENT SELECTION FOR SURGERY

2.1 | Patient selection for single-stage hepatectomy in the premolecular era

The two philosophies surrounding patient selection for single-stage hepatectomy seem to work in opposition; one expands the technical indications for surgery and the other aims to identify "biological" contraindications to surgery.

Advances in surgery and systemic therapy have increased the proportion of patients with CRLM whose disease is technically resectable. The strict selection criteria of fewer than four liver metastases, no extrahepatic disease, and a resection margin of at least 10 mm reported by Ekberg et al in 1986[1] have been supplanted by the current selection criteria of any tumor burden as long as the liver remnant is sufficient to maintain adequate liver function.[2–4] In addition, cytotoxic chemotherapeutics and biologic agents convert unresectable CRLM to resectable disease in around 15% of cases, further expanding the pool of patients who are eligible to undergo surgery.[5,6]

As the proportion of technically resectable cases was increasing, surgeons recognized the importance of tumor biology beyond technical resectability alone. In 1987, Adson from the Mayo Clinic wrote, "As more surgeons are now able to remove large portions of the liver with little risk, it is time to ask not how such surgery can be done safely, but when it should be done—or when is it worthwhile?"[7] At that time, the alternative to surgery was 5-fluorouracil monotherapy, which conferred a median overall survival (OS) of only 9 months; thus, even little benefit from surgery sufficed to justify it. After 2000, the introduction of more potent chemotherapeutics and biologic agents improved the median OS of patients treated with systemic therapies to more than 2 years.[8] This fueled the search for biomarkers to identify patients who most likely would not benefit more from surgery than from systemic therapies alone. The lack of appropriate biomarkers led investigators to search for clinicopathologic factors that portend poor prognosis as surrogates of aggressive tumor biology. Since no single clinicopathologic factor has been identified that reliably predicts poor prognosis, multiple factors were combined to create clinical risk scores to predict patients with particularly poor survival for whom technically feasible surgery might be oncologically futile.[9–13] The most popular of these clinical risk scores (CRS) is the Fong score.[14] The main limitation of the clinical risk scores is the poor reproducibility of their predictions in external cohorts.[15] Attempts to improve the performance of the clinical risk scores by adjusting cutoffs for each variable (eg, tumor size) and using different combinations of clinicopathologic factors have been exhausted; thus, the production of clinical risk scores has decreased in the last 5 years.[16]

2.2 | Patient selection for single-stage hepatectomy in the molecular era

2.2.1. Mutational status of RAS

Although the molecular era started in the 2000s, a study by Vauthey et al published in 2013 solidified the prognostic role of molecular data (*RAS* mutation) in CRLM.[17] At the time of that study, *RAS* mutational status was routinely tested by medical oncologists to determine the eligibility of patients for anti-EGFR agents and thus was widely available. This allowed a group from Johns Hopkins Hospital (JHH)[18] and a group from The University of Texas MD Anderson Cancer Center[19] to combine *RAS* status with some important clinicopathologic factors to develop the first two hybrid clinical and genetic risk scores, published in 2017. Both scores outperformed the most popular clinical risk score (the Fong score), largely retained their discriminatory capacity on external validation, and were able to identify patients with particularly poor survival. Interestingly, on external validation the highest-risk subgroups were found to have considerably better median OS than what was reported in the original cohorts: around 22 months (vs 16 months) for the Johns Hopkins score and 30 months (vs 16 months) for the MD Anderson score. Furthermore, there were 5-year survivors in both highest-risk groups.

These outcomes were superior to what had been reported for modern chemotherapy (without biologic agents) alone, suggesting that patients should not be denied surgery based on these scores. However, one must note that the reported outcomes for the best medical treatment apply to the average patient with unresectable disease and may overestimate outcomes for high-risk patients. A possible solution would be to conduct a study matching high-risk patients identified by clinical and genetic risk scores and treated with single-stage hepatectomy to their medically treated counterparts, although only a small portion of patients fall into these high-risk groups, potentially limiting their clinical relevance. It is also possible that *RAS* mutation is not powerful enough to identify patients who have such aggressive tumor biology that surgery does not benefit them. Indeed, a recent meta-analysis of patients who underwent curative-intent resection of CRLM showed that the hazard ratio for OS for *RAS* mutations vs wild-type *RAS* is not larger than 1.5.[20] Thus, it may not be surprising that the incorporation of *KRAS* mutation status into the Johns Hopkins and MD Anderson scores led to only modest gains in discriminatory ability, as shown by two independent

external validations in international cohorts.[21,22] Of note, the negative effect of *RAS* mutations persists in patients who undergo a repeat hepatectomy for recurrent CRLM, and thus may impact patient selection for a second hepatectomy. Specifically, among patients who underwent repeat hepatectomy, the MD Anderson group reported median OS of 27 months for the patients with *RAS*-mutated tumors vs 42 months for the patients with *RAS* wild-type tumors.[23]

2.2.2 | *Mutational status of other genes or **RAS** variants*

To find more powerful prognostic biomarkers than *RAS* status, groups have applied three distinct approaches. The first was pioneered by the Vauthey and the D'Angelica groups, which extended genetic analysis by testing for less frequent but deleterious somatic mutations, the most notable being mutations in *TP53* and *SMAD4*.[24–27] Although these biomarkers refined prognostication and considerably improved our knowledge, they are unlikely to be used for patient selection.[28] For example, comutation of *RAS* and either *TP53* or *SMAD4* was associated with a median OS of 52 months after resection of CRLM, but while this was shorter than the survival of patients with *RAS* mutations alone, the survival period was too long to support the concept that patients with these comutations may not benefit from surgery.[25] The Vauthey group also demonstrated that information about alterations in signaling pathways (eg, *TP53*, *APC*, *RAS/BRAF*, and *SMAD4*) improves prognostic stratification.[29] This pathway-centric approach was successful in stratifying patients into four groups with distinct prognoses. However, it cannot be used in isolation to deny surgery to patients, as the median OS of the highest risk group was as high as 48 months. The Vauthey group also published on triple mutation of *RAS*, *TP53*, and *SMAD4*, which was more promising, as it was associated with a median OS of 28 months after resection of CRLM.[25] However, this extended mutation testing is not routinely performed, and only a few centers have data to externally validate the outcomes of these patients. Of note, Lange et al published a hybrid score that uses *RAS* and *SMAD4* data and reported a median OS of 12 months and no 5-year survivors among patients undergoing hepatectomy for CRLM who had double mutation in the presence of certain clinicopathologic factors.[30] However, this group had only six patients, and this score has not been externally validated.

The second approach has been to focus on *BRAF* mutation, which is associated with multifocal, aggressive disease that is often not amenable to surgery and has long been suggested to be a biological contraindication to surgery.[31–33] Of note, the poor outcomes of patients with *BRAF* mutated mCRC, whose disease has progressed after one or two prior regimens can be improved by the combination of the *BRAF* inhibitor encorafenib and the anti-EGFR monoclonal antibody cetuximab.[34,35] The low incidence of *BRAF* in resected CRLM precluded meaningful analyses until 2018, when groups from Johns Hopkins,[36] Memorial Sloan Kettering Cancer Center (MSKCC),[37] and France performed studies.[38] The Johns Hopkins study showed that patients with *BRAF*-mutated CRLM had a median OS of only 26 months, although this was driven by the V600E variant specifically as the non-V600E mutation was associated with a good prognosis.[36] This finding is consistent with reports on patients with mCRC of any site and highlights the importance of differentiating the variants of somatic mutations.[39] These results were recently confirmed by a multi-institutional study from Margonis et al that found a median OS of 30 months in patients with *BRAF* V600E-mutated tumors.[40] Importantly, *BRAF* V600E is the only somatic mutation that has been used to match surgically and medically treated patients with CRLM and examine if surgery confers any benefit. Specifically, Margonis et al showed that, among patients with *BRAF* V600E-mutated tumors, those who were treated with systemic therapies alone fared worse than those who underwent surgery (median OS, 20 months vs 25 months).[41] Similarly, a study from the Mayo Clinic that compared outcomes in patients with *BRAF* mutated mCRC who were treated with metastesectomy vs systemic treatment alone reported a superior median OS for surgically vs medically treated patients (29.1 vs 22.7 months, respectively).[42] Bachet et al not only support surgical treatment of *BRAF*-mutated CRLM, but they even questioned whether *BRAF* mutation truly increases the risk of relapse after resection.[38] These studies have been contradicted by a study by Kobayashi et al that suggested that even technically resectable CRLM should be considered oncologically unresectable.[31] Although, in our opinion, *BRAF* mutation alone cannot be used as a biological contraindication to surgery, a group from MSKCC showed that the combination of *BRAF* mutation and at least two of several clinicopathologic factors (node-positive primary tumor, carcinoembryonic antigen [CEA] level >200 μg/L, and clinical risk score ≥4) was associated with a median OS of only 13 months.[37] A subsequent study by Margonis et al showed an even poorer OS among patients with *BRAF* mutations and concurrently resected extrahepatic disease.[40] These patients had a median OS of 9 months, with no patients surviving beyond 36 months, and the subset with *BRAF* V600E mutations fared abysmally, with a median OS of 6.5 months and an 18-month OS rate of zero. Even though these estimates were limited by a small sample size of 13, the dramatically poor OS certainly warrants reconsideration of surgery for these patients. The unique prognostic importance of *BRAF* mutations in patients with extrahepatic disease is highlighted by the fact that patients with extrahepatic disease and *RAS/TP53* comutation had a considerably higher median OS of 39 months.[43]

The third approach to identifying molecular prognostic biomarkers for patients with CRLM was to analyze *KRAS* mutations by nucleotide-specific variants, which seem to have distinct biology. Margonis et al at Johns Hopkins were the first to report prognostic differences among tumors with different codon- and point-specific mutations.[44] Interestingly, a French group has validated the finding that codon 12 mutations are associated with worse outcomes than codon 13 mutations, although their study focused on patients who underwent lung metastasectomy for mCRC.[45] In contrast, Passot et al later reported that no prognostic differences exist across tumors with different codon-specific variants.[46] Most recently, the

Margonis group completed a large cohort study and also found that patients with CRLM with *KRAS* codon 12 and codon 13 mutations fared similarly.[47] However, Amini et al demonstrated that this only applied to patients with right-sided colon cancer; survival of patients with codon 12 vs codon 13 *KRAS* mutations differed significantly in patients with left-sided disease.[48] Importantly, in a new study, Margonis et al reported that prognostic differences persisted on the point mutation level. For example, they found that G12V mutations were associated with a poor OS of 31 months, which was remarkably consistent with what they had found in their original study (median OS of around 28 months).[47] It is also consistent with a study by Jones et al that evaluated a mixed cohort of surgically and medically treated patients with mCRC.[49] Importantly, the G12V mutation was relatively common, found in one-fifth (n = 118) of the *KRAS*-mutated tumors in that study. Thus, it would be worthwhile to investigate whether triple mutation of G12V, *TP53*, and *SMAD4* is associated with even worse outcomes than the previously investigated any *RAS*, *TP53*, and *SMAD4* triple mutation. The long-term outcomes of patients with the G12V mutation and clinicopathologic factors related to poor outcomes have not been investigated.

The *BRAF* V600E mutation, the *KRAS* G12V mutation, and triple mutation of *RAS*, *TP53*, and *SMAD4* are all associated with a poor median OS of 26–31 months, but 5-year survivors are observed in all three groups. Thus, mutational status in isolation should not be used to deny surgery to patients with otherwise resectable disease. However, the combination of these mutations with clinicopathologic factors that predict poor prognosis (eg, positive nodal status, high CEA level) has been shown to result in a very poor median OS of 6.5–13 months.[37] As mentioned above, the most striking example is in patients with *BRAF* V600E mutations and concurrently resected extrahepatic disease. However, also as mentioned above, the small sample size and the lack of external validation preclude their use in clinical practice. Furthermore, no matter how poor the surgical outcomes are, it is possible the outcomes of patients with somatic mutations and clinicopathologic factors related to poor outcomes might be even worse if these patients were treated with systemic therapy alone. This was the case in patients who had resected *BRAF*-mutated CRLM and advanced baseline disease (CRS higher than 3). In fact, the difference in OS in favor of surgery increased when the analysis was restricted from any medically treated patient to medically treated patients with a clinical risk score of 3 or greater (from 25 vs 20 months to 25 vs 15 months).[41]

2.3 | Patient selection for special surgical procedures

Some patients with CRLM have extensive, bilobar disease that cannot be resected in one stage even when resection is combined with other techniques, such as portal vein embolization, local ablation therapy, or vascular reconstruction. Special procedures intended for such patients include conventional two-stage hepatectomy (TSH), associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), and liver transplant (LT). The main advantages of ALPPS over conventional TSH include a shorter interval between the two stages and a greater increase in the future liver remnant (FLR). In turn, the dropout rates are much lower, the R0 rate approaches 100%, and Portal vein embolization (PVE) or portal vein ligation (PVL) failure can be better tolerated. Although the Paul Brousse team introduced the concept of TSH in 1992, the technique was not published until 2000.[50] ALPPS was formally introduced in 2012,[51] and LT has undergone a revival in the last 15 years.[50] Thus, the premolecular era distinction does not apply for these techniques.

The selection of patients expected to complete TSH is particularly important, as patients in whom the procedure cannot be successfully completed not only have a significantly lower 5-year OS rate, but may even fare worse than patients with similar baseline disease who are treated with chemotherapy only.[52,53] The reasons for this are unclear, but likely do not relate to post-stage-I complications.[54] Selecting patients for TSH requires predicting who can undergo both stages of the procedure and, among those patients, identifying the patients who will derive oncologic benefit. Several clinicopathologic factors that predict dropout after the first stage of the procedure have been identified. These can be divided into factors that indicate high tumor burden, including large tumor size, high tumor number, and high CEA level, and factors indicating an inability to control the disease, including disease progression during chemotherapy and a large number of chemotherapy cycles.[55–58] Imai et al used some of these factors (CEA, tumor size, disease progression during chemotherapy, and chemotherapy cycles) to assemble a predictive score that calculates the probability of dropout.[54]

Although no biomarkers have been assessed for predicting dropout after the first stage of TSH, biomarkers have been used with clinicopathologic factors to predict long-term outcomes following successful completion of TSH. In a study by Passot et al, all patients with *RAS* mutation had recurrence within 18 months after the first-stage resection, and only one patient with *RAS* mutation was alive 5 years after the first stage.[55] The prognostic impact of *RAS* mutations appears much more pronounced in TSH than in single-stage hepatectomy. A possible explanation is that patients with extensive bilobar disease (ie, TSH candidates) and *RAS* mutations have a higher frequency of concomitant deleterious mutations such as *TP53* and *SMAD4* mutations than do patients with less extensive disease and *RAS* mutations. Of note, the Passot study was published in 2016, before the role of double and triple mutations was appreciated, and thus the tumors were not tested for these mutations.

RAS mutations seem to also have a more pronounced effect in ALPPS than in single-stage hepatectomy. For example, Serenari et al reported that patients with *KRAS*-mutated tumors who underwent ALPPS had a median OS of only 15.3 months, compared to 38.3 months for those with wild-type tumors.[59] A study that assembled a cohort of 510 patients from 22 ALPPS centers corroborated these findings and suggested that progression during neoadjuvant chemotherapy and *KRAS* or *NRAS* mutation should be considered exclusion criteria for ALPPS.[60] This study also showed even worse survival for patients with *KRAS*-mutated CRLM that originated from

right-sided primary tumors. These patients had a median OS of ~18 months, and there were no survivors 4 years after ALPPS.

Interestingly, a similar association of right-sided tumors and very poor outcomes has been observed in patients who undergo LT for CRLM. Specifically, it was reported that all patients with CRLM originating from right-sided primary tumors who underwent LT had a relapse within 16 months of LT.[61] Their median OS was 12 months, and only one patient was alive after 23 months, but with multiple unresectable lung metastases.[61] Similarly, in the SECA-I study, none of the patients with right-sided tumors survived for 5 years after LT. Thus, right-sided tumor has been proposed as a contraindication for LT.[62] *BRAF* has also been proposed as an absolute contraindication to LT, although only two patients with *BRAF*-mutated CRLM have been reported to have undergone LT.[61] Thus, this recommendation is not based on studies of *BRAF* mutations in patients undergoing transplantation. Interestingly, *RAS* mutation was not found to be prognostic in patient selection for LT, although the studies were limited by small sample sizes. Clinicopathologic factors are also used in patient selection for LT, including the presence of extrahepatic disease, progression during chemotherapy, and undifferentiated adenocarcinomas/signet ring primary tumor.[62] The Oslo criteria,[63] which represented the first attempt to define selection criteria for LT, used clinicopathologic variables as surrogates for tumor biology; unsurprisingly, the Oslo criteria resemble the Fong criteria and include a tumor size above 5.5 cm, disease progression during chemotherapy, interval from resection of the primary tumor to transplant less than 24 months, and a pretransplant CEA level greater than 80 μg/mL. Lastly, it is worth noting that there are nine ongoing clinical trials of LT for CRLM and that these may better define patient selection criteria as most of them include an arm of chemotherapy alone.[64] The selection of patients for LT is particularly important, given the shortage of organ donors, which mandates the optimal allocation of available organs.

3 | SELECTION OF SURGICAL TECHNIQUE

3.1 | Selection of technique for single-stage hepatectomy in the premolecular era

In the surgical treatment of CRLM, the type of resection (anatomical (AR) vs nonanatomical (NAR)) and resection margin width are the only variables that are, to an extent, under the surgeon's direct control and may influence oncologic outcomes. Thus, it is not surprising that several studies have tried to find the optimal type of resection and the optimal surgical margin. Of note, none were randomized trials, and thus causality cannot be determined. As a result, several authors have considered positive margins to be merely a marker of advanced disease.[65] In addition, the Vauthey group has suggested that recurrence and prognosis are likely driven by individual tumor biology rather than surgical margins.[66] Specifically, they showed that an R1 resection had no association with any pattern of recurrence (including local recurrences) and OS. In contrast, *RAS/TP53* comutation was associated with a higher incidence of recurrence and was an independent predictor of poor OS.

The debate regarding optimal margin width is ongoing and was sparked in 1986 when Ekberg et al suggested that a resection margin of at least 1 cm should be obtained.[1] Subsequently, other groups proposed ideal margin widths ranging from 1 mm to 1 cm; some even suggested that an R1 resection may not hurt long-term outcomes.[67,68] One possible explanation for the opposing recommendations is that different optimal margins apply to different patient subgroups. A study from the Vauthey group showed that the impact of positive margins depends on the response to prehepatectomy chemotherapy. Specifically, an R1 margin was detrimental in patients with a minor pathologic response to systemic therapy, but had negligible impact in patients with a major response.[69] Of note, that study did not recommend a target margin width for patients with a minor response to chemotherapy.

A parallel debate regarding AR vs NAR was fueled by a study from MSKCC that showed a superior 5-year OS rate for patients who underwent an AR vs NAR (49% vs 37%, respectively).[70] Another study, by Lahlalomed et al, showed similar findings.[71] However, several studies, including a meta-analysis,[71] showed that NAR had long-term outcomes equivalent to those of anatomical resection, while also leaving behind sufficient liver to allow for a repeat hepatectomy if needed. Thus, nonanatomical resections became widely accepted. Of note, no explanation was offered regarding the contradictory findings of these studies.

3.2 | Selection of technique for single-stage hepatectomy in the molecular era

The debate regarding optimal margin width took a sudden turn in 2016 when groups from Johns Hopkins and MD Anderson suggested that different resection margins apply to patients with different underlying disease biology. The Johns Hopkins group reported that "the group of patients [with *KRAS*-mutated CRLM] with a margin width of 5–9 mm tended to have a better OS compared to patients who had an R1 resection."[72] However, this difference was not statistically significant, and the authors ultimately suggested that aggressive tumor biology implied by the presence of a *KRAS* mutation could not be counterbalanced by extensive resection, and that even an R1 resection might not seriously impact outcomes in patients with *KRAS*-mutated CRLM. A subsequent collaboration among JHH, MSKCC, the International Genetic Consortium for Liver Metastases (IGCLM), and the Massachusetts Institute of Technology reassessed optimal margin width in patient with *KRAS*-mutated tumors via artificial intelligence–based techniques.[73] The study authors proposed an optimal margin width of 7 mm for *KRAS*-mutated tumors. This cutoff was successfully validated in an external cohort.[73]

The debate regarding anatomical vs nonanatomical resection took a sudden turn in 2017, when a group from JHH suggested that AR may be preferable for *KRAS*-mutated tumors while AR and NAR had equivalent outcomes for wild-type tumors.[74] Of note, this

finding does not call into question the parenchymal-sparing dogma, as both NAR and limited AR (such as segmentectomies) are considered parenchymal-sparing. Interestingly, a French group indirectly validated these results by showing that AR is associated with significantly improved survival and a longer time to pulmonary recurrence in patients with *KRAS*-mutated colorectal cancer lung metastases, but not in those with wild-type lung metastases.[75] The association of AR and favorable outcomes in *KRAS*-mutated CRLM has been contested by Joechle et al,[76] and it is hoped that more definitive answers will be provided by the ongoing ARMANI (Anatomical Resection of Liver Metastases in patients with *RAS*-mutated colorectal cancer) trial, a randomized trial that aims to compare the intrahepatic disease-free survival (iDFS) of patients with *KRAS*-mutated tumors who undergo AR vs NAR. The rationale for anatomical resection in *KRAS*-mutated tumors relates to the propensity of these tumors to migrate into intrahepatic portal branches and form secondary intrahepatic metastases, as reported by Tanaka et al.[77] Anatomical resection includes removal of the portal branches and, in theory, would prevent intrahepatic recurrences. The choice of iDFS as the endpoint of the ARMANI trial is wise, as intrahepatic metastases are commonly amenable to repeat hepatectomy. Thus, OS may be equivalent between patients with anatomically and those with nonanatomically resected *KRAS*-mutated CRLM if patients with nonanatomical resection undergo repeat hepatectomy. However, more evidence is needed to explain the mechanism through which an AR benefits only patients with *KRAS*-mutated CRLM. To date, it has not been possible to study *KRAS* status in conjunction with vascular invasion, tumor growth patterns, and micrometastatic disease, as only part of the liver is resected. Interestingly, LT may answer these questions through examination of the explants of patients with *KRAS*-mutated vs wild-type tumors (or even those with triple mutations, *KRAS* variants, etc.) given that the *KRAS* mutation is not a contraindication to LT, as discussed above.

3.3 | Selection of special surgical procedures

The selection of TSH, ALPPS, or LT for CRLM not amenable to single-stage hepatectomy could in theory begin with comparing their oncological efficacy. However, the necessary data are lacking. Few studies have compared the long-term outcomes of TSH vs ALPPS, and no studies have compared the outcomes of TSH vs LT.[78,79] The most notable study that compared long-term outcomes of TSH vs ALPPS was prospective and showed superior outcomes for ALPPS.[80] However, it has been heavily criticized, since the superiority of ALPPS stemmed from an unusually short survival of patients who underwent TSH.[81] In fact, it is more likely that the long-term outcomes of completed TSH and ALPPS were similar, as the groups were similar in terms of relevant factors such as postoperative mortality and morbidity, recurrence rates, and recurrences amenable to repeat surgery.

Aside from efficacy, it is also possible that specific procedures are more appropriate for different subsets of patients. For example, the main difference between conventional TSH and ALPPS is the lower rate of dropouts in ALPPS; thus, patients with a high risk of dropping out after the first stage of TSH may benefit from ALPPS instead. This is particularly important, as patients who complete the first stage of TSH but fail to proceed to the second stage may actually fare worse than those with similar baseline disease who are treated with chemotherapy only and no surgery.[54] An alternative is rescue ALPPS, but this approach has not been validated. In most cases, patients drop out from TSH because of disease progression and not because the liver remnant fails to regenerate.[54] As such, factors that increase the chances of disease progression following the first stage of TSH could be the selection criteria for ALPPS over TSH. The most consistent of such factors has been a large number of chemotherapy cycles and high tumor burden (as indicated by tumor size, tumor number, and CEA level).[54–58] On a more pessimistic note, one may reason that disease progression may not be halted by an earlier second-stage resection and will merely manifest later, rendering ALPPS futile.

The main deficiency of the previous studies that assessed predictors of TSH dropout was the lack of biomarkers in the regression analyses. Interestingly, neither tumor side nor *RAS* mutational status has ever been tested. Specifically, *RAS* has only been tested in patients who underwent second-stage resection, and thus is irrelevant for selecting between TSH and ALPPS.[55] We believe that future studies should include dedicated regression analyses of the factors that predict disease progression following the first stage of TSH, including tumor side, *RAS* status, and other somatic mutations.

4 | CONCLUSION

The two markers that are best supported in guiding precision surgery for CRLM are *RAS* mutational status and primary tumor side. Specifically, *RAS* mutational status may be used to tailor surgical techniques in patients who undergo single-stage hepatectomy and is also used to select patients for TSH, while right-sided tumor might be a contraindication to LT and ALPPS (when combined with an *RAS* mutation). Interestingly, *RAS* mutational status and primary tumor side are also the two markers of tumor biology that are used to guide the selection of biologic agents in metastatic colon cancer. Specifically, *RAS* mutation is a contraindication to anti-EGFR agents, while tumor side determines the use of anti-VEGF agents (for right-sided tumors) or anti-EGFR agents (for left-sided, wild-type tumors).[82]

Although single-stage hepatectomy cannot currently be denied on the sole basis of biomarkers, future studies should validate the recent finding that *BRAF* V600E mutation with concurrently resectable extrahepatic disease leads to very poor survival. Future studies should also assess whether multiple mutations and the subset of *KRAS* G12V variant and a right-sided primary tumor are associated, either alone or in combination with other clinicopathologic factors, with extremely poor survival. Next, liquid biopsies can be used in these patient groups to examine whether these individual

patient characteristics are associated with residual disease after hepatectomy reflected by the detection of posthepatectomy circulating tumor DNA (ctDNA). If so, liquid biopsies can also determine whether certain local (eg, surgical technique) or systemic therapies can eliminate residual disease and improve outcomes. Although one of these characteristics (ie, *RAS*/*TP53* comutations) has already been associated with an increased risk for postoperative ctDNA detection and early recurrence after CRLM resection, no studies to date have assessed whether the other aforementioned individual patient characteristics, including tumor mutational profiles, are associated with postoperative ctDNA detection.[83] We also propose the investigation of a large number of genes of potential prognostic and/or predictive relevance through next-generation sequencing (NGS), in particular for patients who are candidates for TSH, ALPPS, and LT because the stakes are high for these patients and this information might impact treatment decisions. Finally, randomized controlled trials may not be ethical for defining the selection criteria for surgery vs systemic therapy alone. In that case, the use of real-world data (RWD) to make causal inferences may be the best option. Data science can use RWD to make counterfactual predictions (ie, what *would* have happened if we *had* given a different treatment such as surgery vs systemic therapy alone), which can be used to make patient selection recommendations.

ACKNOWLEDGMENT

We thank Stephanie Deming, Research Medical Library, MD Anderson Cancer Center, for editing the article.

DISCLOSURE

Funding: Georgios Antonios Margonis was supported by NIH/NCI Cancer Center Support Grant P30 CA008748. The funding source had no role in the design, practice or analysis of this study.

Conflict of interest: The authors declare no conflicts of interest for this article.

AUTHOR CONTRIBUTION

None.

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REFERENCES

1. Ekberg H, Tranberg KG, Andersson R, Lundstedt C, Hägerstrand I, Ranstam J, et al. Determinants of survival in liver resection for colorectal secondaries. Br J Surg. 1986;73(9):727–31.
2. Charnsangavej C, Clary B, Fong Y, Grothey A, Pawlik TM, Choti MA. Selection of patients for resection of hepatic colorectal metastases: Expert consensus statement. Ann Surg Oncol. 2006;13(10):1261–8.
3. Adams RB, Aloia TA, Loyer E, Pawlik TM, Taouli B, Vauthey JN, et al. Selection for hepatic resection of colorectal liver metastases: Expert consensus statement. HPB (Oxford). 2013;15(2):91–103.
4. Adam R, de Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: A multidisciplinary international consensus. Oncologist. 2012;17(10):1225–39.
5. Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg. 1996 Oct;224(4):509–20. discussion 20-2.
6. Lam VW, Spiro C, Laurence JM, Johnston E, Hollands MJ, Pleass HC, et al. A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases. Ann Surg Oncol. 2012;19(4):1292–301.
7. Adson MA. Resection of liver metastases--when is it worthwhile? World J Surg. 1987;11(4):511–20.
8. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, al-Batran SE, et al. Folfiri plus cetuximab versus folfiri plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (fire-3): A randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(10):1065–75.
9. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association francaise de chirurgie. Cancer. 1996;77(7):1254–62.
10. Nagashima I, Takada T, Matsuda K, Adachi M, Nagawa H, Muto T, et al. A new scoring system to classify patients with colorectal liver metastases: Proposal of criteria to select candidates for hepatic resection. J Hepato-Biliary-Pancreat Surg. 2004;11(2):79–83.
11. Iwatsuki S, Dvorchik I, Madariaga JR, Marsh JW, Dodson F, Bonham AC, et al. Hepatic resection for metastatic colorectal adenocarcinoma: A proposal of a prognostic scoring system. J Am Coll Surg. 1999;189(3):291–9.
12. Aldrighetti L, Castoldi R, di Palo S, Arru M, Stella M, Orsenigo E, et al. prognostic factors for long-term outcome of hepatic resection for colorectal liver metastases. Chir Ital. 2005;57(5):555–70.
13. Konopke R, Kersting S, Distler M, Dietrich J, Gastmeier J, Heller A, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. Liver Int. 2009;29(1):89–102.
14. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. Ann Surg. 1999 Sep;230(3):309–18. discussion 18–21.
15. Mahar AL, Compton C, Halabi S, Hess KR, Weiser MR, Groome PA. Personalizing prognosis in colorectal cancer: A systematic review of the quality and nature of clinical prognostic tools for survival outcomes. J Surg Oncol. 2017;116(8):969–82.
16. Fruhling P, Urdzik J, Stromberg C, Isaksson B. Composite score: Prognostic tool to predict survival in patients undergoing surgery for colorectal liver metastases. BJS Open. 2021;5(5):5.
17. Vauthey JN, Zimmitti G, Kopetz SE, Shindoh J, Chen SS, Andreou A, et al. Ras mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. Ann Surg. 2013;258(4):619–26. discussion 26-7.
18. Margonis GA, Sasaki K, Gholami S, Kim Y, Andreatos N, Rezaee N, et al. Genetic and morphological evaluation (game) score for patients with colorectal liver metastases. Br J Surg. 2018;105(9):1210–20.
19. Brudvik KW, Jones RP, Giuliante F, Shindoh J, Passot G, Chung MH, et al. Ras mutation clinical risk score to predict survival after resection of colorectal liver metastases. Ann Surg. 2019;269(1):120–6.
20. Pikoulis E, Papaconstantinou D, Pikouli A, Wang J, Theodoridis C, Margonis GA. Reevaluating the prognostic value of ras mutation status in patients with resected liver metastases from colorectal cancer: A systematic review and meta-analysis. J Hepatobiliary Pancreat Sci. 2021;28(8):637–47.
21. Wong GYM, Bhimani N, Mol B, Diakos C, de Reuver P, Molloy MP, et al. Performance of prognostic models incorporating kras

mutation status to predict survival after resection of colorectal liver metastases. HPB (Oxford). 2022. doi:10.1016/j.hpb.2022.01.003. Online ahead of print.
22. Sasaki K, Gagnière J, Dupré A, Ardiles V, O'Connor JM, Wang J, et al. Performance of two prognostic scores that incorporate genetic information to predict long-term outcomes following resection of colorectal cancer liver metastases: An external validation of the md anderson and jhh-msk scores. J Hepatobiliary Pancreat Sci. 2021;28(7):581–92.
23. Denbo JW, Yamashita S, Passot G, Egger M, Chun YS, Kopetz SE, et al. Ras mutation is associated with decreased survival in patients undergoing repeat hepatectomy for colorectal liver metastases. J Gastrointest Surg. 2017;21(1):68–77.
24. Datta J, Smith JJ, Chatila WK, McAuliffe JC, Kandoth C, Vakiani E, et al. Coaltered ras/b-raf and tp53 is associated with extremes of survivorship and distinct patterns of metastasis in patients with metastatic colorectal cancer. Clin Cancer Res. 2020;26(5):1077–85.
25. Kawaguchi Y, Kopetz S, Newhook TE, de Bellis M, Chun YS, Tzeng CWD, et al. Mutation status of ras, tp53, and smad4 is superior to mutation status of ras alone for predicting prognosis after resection of colorectal liver metastases. Clin Cancer Res. 2019;25(19):5843–51.
26. Mizuno T, Cloyd JM, Vicente D, Omichi K, Chun YS, Kopetz SE, et al. Smad4 gene mutation predicts poor prognosis in patients undergoing resection for colorectal liver metastases. Eur J Surg Oncol. 2018;44(5):684–92.
27. Chun YS, Passot G, Yamashita S, Nusrat M, Katsonis P, Loree JM, et al. Deleterious effect of ras and evolutionary high-risk tp53 double mutation in colorectal liver metastases. Ann Surg. 2019;269(5):917–23.
28. Kawaguchi Y, Kopetz S, Panettieri E, Hwang H, Wang X, Cao HST, et al. Improved survival over time after resection of colorectal liver metastases and clinical impact of multigene alteration testing in patients with metastatic colorectal cancer. J Gastrointest Surg. 2021;26(3):583–93.
29. Kawaguchi Y, Kopetz S, Kwong L, Xiao L, Morris JS, Tran Cao HS, et al. Genomic sequencing and insight into clinical heterogeneity and prognostic pathway genes in patients with metastatic colorectal cancer. J Am Coll Surg. 2021;233(2):272–84. e13.
30. Lang H, Baumgart J, Heinrich S, Tripke V, Passalaqua M, Maderer A, et al. Extended molecular profiling improves stratification and prediction of survival after resection of colorectal liver metastases. Ann Surg. 2019;270(5):799–805.
31. Kobayashi S, Takahashi S, Nomura S, Kojima M, Kudo M, Sugimoto M, et al. Braf v600e potentially determines "oncological resectability" for "technically resectable" colorectal liver metastases. Cancer Med. 2021;10(20):6998–7011.
32. Karagkounis G, Torbenson MS, Daniel HD, Azad NS, Diaz LA Jr, Donehower RC, et al. Incidence and prognostic impact of kras and braf mutation in patients undergoing liver surgery for colorectal metastases. Cancer. 2013;119(23):4137–44.
33. Lipsyc M, Yaeger R. Impact of somatic mutations on patterns of metastasis in colorectal cancer. J Gastrointest Oncol. 2015;6(6):645–9.
34. Kopetz S, Grothey A, Yaeger R, van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, binimetinib, and cetuximab in braf v600e-mutated colorectal cancer. N Engl J Med. 2019;381(17):1632–43.
35. Tabernero J, Grothey A, van Cutsem E, Yaeger R, Wasan H, Yoshino T, et al. Encorafenib plus cetuximab as a new standard of care for previously treated braf v600e-mutant metastatic colorectal cancer: Updated survival results and subgroup analyses from the beacon study. J Clin Oncol. 2021;39(4):273–84.
36. Margonis GA, Buettner S, Andreatos N, Kim Y, Wagner D, Sasaki K, et al. Association of braf mutations with survival and recurrence in surgically treated patients with metastatic colorectal liver cancer. JAMA Surg. 2018;153(7):e180996.
37. Gagnière J, Dupré A, Gholami SS, Pezet D, Boerner T, Gönen M, et al. Is hepatectomy justified for braf mutant colorectal liver metastases?: A multi-institutional analysis of 1497 patients. Ann Surg. 2020;271(1):147–54.
38. Bachet JB, Moreno-Lopez N, Vigano L, Marchese U, Gelli M, Raoux L, et al. Braf mutation is not associated with an increased risk of recurrence in patients undergoing resection of colorectal liver metastases. Br J Surg. 2019;106(9):1237–47.
39. Jones JC, Renfro LA, al-Shamsi HO, Schrock AB, Rankin A, Zhang BY, et al. (non-v600) braf mutations define a clinically distinct molecular subtype of metastatic colorectal cancer. J Clin Oncol. 2017;35(23):2624–30.
40. Margonis GA, Buettner S, Andreatos N, Sasaki K, Poultsides G, Imai K, Morioka D, Cameron JL, Endo I, Baba H, Kreis M, Benoist S, Bachet JB, Wolfgang CL, D'Angelica M. Demystifying BRAF mutation status in colorectal lover metastases: a multi-institutional, collaborative approach to 7 open clinical questions. Paper presented at: The 121st Annual Congress of Japan Surgical Society; April 8, 2021–10; Chiba, Japan.
41. Margonis G, Boerner T, Andreatos N, Buettner S, Sasaki K, Poultsides G, Cameron JL, Misiakos E, Pikoulis E, Moretto R, Cremolini C, Wolfgang CL, D'Angelica M. Is hepatectomy for BRAF V600E-mutated colorectal liver metastases justified? A comparative analysis of long-term outcomes among patients treated with surgery vs systemic therapy alone. Paper presented at: 32nd Panhellenic Surgery Conference & International Surgical Forum; June 9, 2021–12; Thessaloniki, Greece.
42. Johnson B, Jin Z, Truty MJ, Smoot RL, Nagorney DM, Kendrick ML, et al. Impact of metastasectomy in the multimodality approach for braf v600e metastatic colorectal cancer: The mayo clinic experience. Oncologist. 2018;23(1):128–34.
43. Lillemoe HA, Passot G, Kawaguchi Y, et al. Ras/tp53 comutation is associated with worse survival after concurrent resection of colorectal liver metastases and extrahepatic disease. Ann Surg. 2020. doi:10.1097/SLA.0000000000004672. Online ahead of print
44. Margonis GA, Kim Y, Spolverato G, Ejaz A, Gupta R, Cosgrove D, et al. Association between specific mutations in kras codon 12 and colorectal liver metastasis. JAMA Surg. 2015;150(8):722–9.
45. Renaud S, Guerrera F, Seitlinger J, Costardi L, Schaeffer M, Romain B, et al. Kras exon 2 codon 13 mutation is associated with a better prognosis than codon 12 mutation following lung metastasectomy in colorectal cancer. Oncotarget. 2017;8(2):2514–24.
46. Passot G, Denbo JW, Yamashita S, Kopetz SE, Chun YS, Maru D, et al. Is hepatectomy justified for patients with ras mutant colorectal liver metastases? An analysis of 524 patients undergoing curative liver resection. Surgery. 2017;161(2):332–40.
47. Olthof PB, Buettner S, Andreatos N, Wang J, Løes IM, Wagner D, et al. KRAS alterations in colorectal liver metastases: shifting to exon, codon, and point mutations. British Journal of Surgery. 2022. doi: 10.1093/bjs/znac147. Online ahead of print.
48. Amini N, Andreatos N, Margonis GA, et al. Mutant kras as a prognostic biomarker after hepatectomy for rectal cancer metastases: Does the primary disease site matter? J Hepatobiliary Pancreat Sci. 2021;29(4):417–27.
49. Jones RP, Sutton PA, Evans JP, Clifford R, McAvoy A, Lewis J, et al. Specific mutations in kras codon 12 are associated with worse overall survival in patients with advanced and recurrent colorectal cancer. Br J Cancer. 2017;116(7):923–9.
50. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg. 2000;232(6):777–85.

51. Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;255(3):405–14.
52. Wicherts DA, Miller R, de Haas RJ, Bitsakou G, Vibert E, Veilhan LA, et al. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. Ann Surg. 2008;248(6):994–1005.
53. Lam VW, Laurence JM, Johnston E, Hollands MJ, Pleass HC, Richardson AJ. A systematic review of two-stage hepatectomy in patients with initially unresectable colorectal liver metastases. HPB (Oxford). 2013;15(7):483–91.
54. Imai K, Benitez CC, Allard MA, Vibert E, Cunha AS, Cherqui D, et al. Failure to achieve a 2-stage hepatectomy for colorectal liver metastases: How to prevent it? Ann Surg. 2015;262(5):772–8. discussion 78–9, 779.
55. Passot G, Chun YS, Kopetz SE, Zorzi D, Brudvik KW, Kim BJ, et al. Predictors of safety and efficacy of 2-stage hepatectomy for bilateral colorectal liver metastases. J Am Coll Surg. 2016;223(1):99–108.
56. Narita M, Oussoultzoglou E, Jaeck D, Fuchschuber P, Rosso E, Pessaux P, et al. Two-stage hepatectomy for multiple bilobar colorectal liver metastases. Br J Surg. 2011;98(10):1463–75.
57. Quénet F, Pissas MH, Gil H, Roca L, Carrère S, Sgarbura O, et al. Two-stage hepatectomy for colorectal liver metastases: Pathologic response to preoperative chemotherapy is associated with second-stage completion and longer survival. Surgery. 2019;165(4):703–11.
58. Giuliante F, Ardito F, Ferrero A, Aldrighetti L, Ercolani G, Grande G, et al. Tumor progression during preoperative chemotherapy predicts failure to complete 2-stage hepatectomy for colorectal liver metastases: Results of an italian multicenter analysis of 130 patients. J Am Coll Surg. 2014;219(2):285–94.
59. Serenari M, Alvarez FA, Ardiles V, de Santibanes M, Pekolj J, de Santibanes E. The alpps approach for colorectal liver metastases: Impact of kras mutation status in survival. Dig Surg. 2018;35(4):303–10.
60. Petrowsky H, Linecker M, Raptis DA, Kuemmerli C, Fritsch R, Kirimker OE, et al. First long-term oncologic results of the alpps procedure in a large cohort of patients with colorectal liver metastases. Ann Surg. 2020;272(5):793–800.
61. Smedman TM, Line PD, Hagness M, Syversveen T, Grut H, Dueland S. Liver transplantation for unresectable colorectal liver metastases in patients and donors with extended criteria (seca-ii arm d study). BJS Open. 2020;4(3):467–77.
62. Line PD, Dueland S. Liver transplantation for secondary liver tumours: The difficult balance between survival and recurrence. J Hepatol. 2020;73(6):1557–62.
63. Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257(5):800–6.
64. Finotti M, Vitale A, Gringeri E, D'Amico FE, Boetto R, Bertacco A, et al. Colon rectal liver metastases: The role of the liver transplantation in the era of the transplant oncology and precision medicine. Front Surg. 2021;8:693387.
65. Sadot E, Groot Koerkamp B, Leal JN, et al. Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer: Surgical technique or biologic surrogate? Ann Surg. 2015;262(3):476–85. discussion 83–5, 485.
66. Nishioka Y, Paez-Arango N, Boettcher FO, Kawaguchi Y, Newhook TE, Chun YS, et al. Neither surgical margin status nor somatic mutation predicts local recurrence after r0-intent resection for colorectal liver metastases. J Gastrointest Surg. 2021;26(4):791–801.
67. de Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: Is it still a contraindication to surgery? Ann Surg. 2008;248(4):626–37.
68. Margonis GA, Sergentanis TN, Ntanasis-Stathopoulos I, Andreatos N, Tzanninis IG, Sasaki K, et al. Impact of surgical margin width on recurrence and overall survival following r0 hepatic resection of colorectal metastases: A systematic review and meta-analysis. Ann Surg. 2018;267(6):1047–55.
69. Andreou A, Aloia TA, Brouquet A, Dickson PV, Zimmitti G, Maru DM, et al. Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy. Ann Surg. 2013;257(6):1079–88.
70. DeMatteo RP, Palese C, Jarnagin WR, Sun RL, Blumgart LH, Fong Y. Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. J Gastrointest Surg. 2000;4(2):178–84.
71. Deng G, Li H, Jia GQ, Fang D, Tang YY, Xie J, et al. Parenchymal-sparing versus extended hepatectomy for colorectal liver metastases: A systematic review and meta-analysis. Cancer Med. 2019;8(14):6165–75.
72. Margonis GA, Sasaki K, Andreatos N, Kim Y, Merath K, Wagner D, et al. Kras mutation status dictates optimal surgical margin width in patients undergoing resection of colorectal liver metastases. Ann Surg Oncol. 2017;24(1):264–71.
73. Margonis GA, Bertsimas D, Sujichantararat S, et al. Using artificial intelligence to find the optimal margin width in hepatectomy for colorectal cancer liver metastases. JAMA Surg. 2022:e221819. doi:10.1001/jamasurg.2022.1819. Online ahead of print.
74. Margonis GA, Buettner S, Andreatos N, Sasaki K, Ijzermans JNM, van Vugt JLA, et al. Anatomical resections improve disease-free survival in patients with kras-mutated colorectal liver metastases. Ann Surg. 2017;266(4):641–9.
75. Renaud S, Seitlinger J, Lawati YA, Guerrera F, Falcoz PE, Massard G, et al. Anatomical resections improve survival following lung metastasectomy of colorectal cancer harboring kras mutations. Ann Surg. 2019;270(6):1170–7.
76. Joechle K, Vreeland TJ, Vega EA, Okuno M, Newhook TE, Panettieri E, et al. Anatomic resection is not required for colorectal liver metastases with ras mutation. J Gastrointest Surg. 2020;24(5):1033–9.
77. Tanaka M, Omura K, Watanabe Y, Oda Y, Nakanishi I. Prognostic factors of colorectal cancer: K-ras mutation, overexpression of the p53 protein, and cell proliferative activity. J Surg Oncol. 1994;57(1):57–64.
78. Ratti F, Schadde E, Masetti M, Massani M, Zanello M, Serenari M, et al. Strategies to increase the resectability of patients with colorectal liver metastases: A multi-center case-match analysis of alpps and conventional two-stage hepatectomy. Ann Surg Oncol. 2015;22(6):1933–42.
79. Adam R, Imai K, Castro Benitez C, Allard MA, Vibert E, Sa Cunha A, et al. Outcome after associating liver partition and portal vein ligation for staged hepatectomy and conventional two-stage hepatectomy for colorectal liver metastases. Br J Surg. 2016;103(11):1521–9.
80. Hasselgren K, Røsok BI, Larsen PN, Sparrelid E, Lindell G, Schultz NA, et al. Alpps improves survival compared with tsh in patients affected of crlm: Survival analysis from the randomized controlled trial ligro. Ann Surg. 2021;273(3):442–8.
81. Allard MA, Kitano Y, Imai K, Baba H, Vauthey JN, Adam R. Comment on "alpps improves survival compared with tsh in patients affected of crlm: Survival analysis from the randomized controlled trial ligro" survival benefit of alpps versus tsh: A proof of concept or a concept to be proved? Ann Surg. 2021;274(6):e764–e65.

82. Yin J, Cohen R, Jin Z, et al. Prognostic and predictive impact of primary tumor sidedness for previously untreated advanced colorectal cancer. J Natl Cancer Inst. 2021 Jun;1.
83. Nishioka Y, Chun YS, Overman MJ, Cao HST, Tzeng CWD, Mason MC, et al. Effect of comutation of ras and tp53 on postoperative ctdna detection and early recurrence after hepatectomy for colorectal liver metastases. J Am Coll Surg. 2022;234(4):474–83.

How to cite this article: Margonis GA, Vauthey J-N. Precision surgery for colorectal liver metastases: Current knowledge and future perspectives. Ann Gastroenterol Surg. 2022;6:606–615. doi:10.1002/ags3.12591