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

Georgios Antonios Margonis1,2 | Jean-Nicolas Vauthey3

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 $\text{BRAF}^{V600E}$ mutation, the $\text{G12V KRAS}$ variant, and the triple mutation of $\text{RAS}$, $\text{TP53}$, and $\text{SMAD4}$ 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, $\text{BRAF}$ 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 10mm reported by Ekberg et al in 1986 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. 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.

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?” 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 make a diagnosis. 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. 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

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. 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) and a group from The University of Texas MD Anderson Cancer Center 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.
external validations in international cohorts.\textsuperscript{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.\textsuperscript{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.\textsuperscript{24-27} Although these biomarkers refined prognostication and considerably improved our knowledge, they are unlikely to be used for patient selection.\textsuperscript{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.\textsuperscript{29} The Vauthey group also demonstrated that information about alterations in signaling pathways (eg, TP53, APC, RAS/BRAF, and SMAD4) improves prognostic stratification.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{34,35} The low incidence of BRAF in resected CRLM precluded meaningful analyses until 2018, when groups from Johns Hopkins, Memorial Sloan Kettering Cancer Center (MSKCC),\textsuperscript{36} and France performed studies.\textsuperscript{37} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{41} Similarly, a study from the Mayo Clinic that compared outcomes in patients with BRAF mutated mCRC who were treated with metastectomy vs systemic treatment alone reported a superior median OS for surgically vs medically treated patients (29.1 vs 22.7 months, respectively).\textsuperscript{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.\textsuperscript{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.\textsuperscript{35} 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.\textsuperscript{37} A subsequent study by Margonis et al showed an even poorer OS among patients with BRAF mutations and concurrently resected extrahepatic disease.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{45} In contrast, Passot et al later reported that no prognostic differences exist across tumors with different codon-specific variants.\textsuperscript{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. 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. 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). It is also consistent with a study by Jones et al that evaluated a mixed cohort of surgically and medically treated patients with mCRC. 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. 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).

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 Broussse team introduced the concept of TSH in 1992, the technique was not published until 2000. ALPPS was formally introduced in 2012, and LT has undergone a revival in the last 15 years. 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. The reasons for this are unclear, but likely do not relate to post-stage-I complications. 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. 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.

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. 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. 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. 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. Their median OS was 12 months, and only one patient was alive after 23 months, but with multiple unresectable lung metastases. 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. 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. 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 tumors. The Oslo criteria, 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. 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. 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. In addition, the Vauthey group has suggested that recurrence and prognosis are likely driven by individual tumor biology rather than surgical margins. Specifically, they showed that an R1 resection had no association with any pattern of recurrence (including local recurrences) and OS. In contrast, RAS/TP53 mutation 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. 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. 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. 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). Another study, by Lahalamed et al, showed similar findings. However, several studies, including a meta-analysis, 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.” 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. The study authors proposed an optimal margin width of 7 mm for KRAS-mutated tumors. This cutoff was successfully validated in an external cohort.

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. Of note, this
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. 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. 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). 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. 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).

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.33 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.

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ORCID
Georgios Antonios Margonis https://orcid.org/0000-0003-4894-5743

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