Editorial

KRAS Mutation in Patients Undergoing Hepatic Resection for Colorectal Liver Metastasis: A Biomarker of Cancer Biology or a Byproduct of Patient Selection?

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Patients with colorectal cancer (CRC) have experienced remarkable progress in a range of surgical and oncologic management strategies over the past decades, with a corresponding improvement in survival.[1] As a consequence, the course of disease has changed both in terms of recurrence patterns and long-term outcomes, as evidenced from national cohort studies.[2,3] The majority of patients with CRC will develop disease recurrence within the first 2 years, and >50% of these individuals will develop a single-organ recurrence, of whom less than one-third will be offered metastatic surgery. The liver is the most frequent site of disease recurrence. As resectability criteria have changed over the past 20 years, with changes in preoperative techniques (eg, the use of forced liver hypertrophy and staged resection procedures) noted among others,[4] it has both increased the number of surgical resections and also improved outcomes. Indeed, improvements in patient selection and surgical techniques have resulted in improved outcomes after hepatic resection for patients with a colorectal liver metastasis (CRLM), with 5-year and 10-year overall survival rates reported to be as high as 40% and 20%, respectivley.[5] However, the selection of operability and resectability remains a controversial topic and continues to be based largely on subjective judgment with considerable variation noted among clinicians, even those deemed to be leading experts in the field.[6] Furthermore, metastasis detection and patient selection have improved with better imaging modalities, including contrast-enhanced ultrasonography, computed tomography, and positron emission tomography scanning. However, even imaging has its limitations, including the problem of "disappearing liver metastasis," which are increasingly noted after neoadjuvant chemotherapy.[7] Furthermore, the practice of routine perioperative chemotherapy differs between continents and remains an area of debate, with results from preoperative chemotherapy trials demonstrating only a modest increase in survival at the subsequent cost of increased surgical morbidity. Even among patients with a complete pathological response, long-term remission occurs in only 20% to 50% of patients treated with systemic therapy. Consequently, and despite the many advances, the majority of patients who undergo hepatic resection for CRLMs experience disease recurrence and die of the disease. Thus, understanding the underlying biology, both for improved prediction and for defining new therapeutic targets, becomes important.

CRC progression follows distinct pathways of genetic instability with defined clinical outcomes and associated molecular features. Proposed clinical-morphological-genetic classifications for classifying patients into distinct prognostic groups have not replaced TNM staging for prognosis; in patients with primary resectable disease, lymph node status remains the most prognostic feature, despite its controversial standing. However, some genetic features have appeared as potential predictive and prognostic factors, including *KRAS* mutation status. *KRAS* is an oncogene located downstream of the epidermal growth factor receptor (EGFR), which is the target for anti-EGFR treatment, such as cetuximab. It is interesting to note that patients with *KRAS* wild-type status respond best to anti-EGFR treatment. *KRAS* is known as an early mutated event in CRC and is found in approximately 15% of patients with advanced adenomas and in 35% to 45% of patients with primary CRC (TNM stages I-III).[8,9] The frequency of *KRAS* mutations in patients with a CRLM

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corresponds well, but not perfectly, with the status of the primary tumor. Studies have reported the variably of *KRAS* testing in the primary tumor, metastasis, or both, with some mutations noted on formalin-fixed and others on fresh frozen tissue. Despite this similarity with regard to *KRAS* status, it is clear that primary tumors and their corresponding CRLMs are genetically different.[10] In general, *KRAS* mutations are associated with a more aggressive tumor behavior across the spectrum of CRC development, from adenomas to primary tumors, and patients with *KRAS* mutations have a poorer overall survival after liver resection.[11]

In this issue of *Cancer*,[12] investigators from the Memorial Sloan-Kettering Cancer Center studied the predictive role of *KRAS* for patterns of disease recurrence among patients undergoing hepatic resection for CRLMs in addition to hepatic artery infusion (HAI) therapy. The study by Kemeny et al demonstrates that patients with *KRAS* mutations have shorter recurrence-free survival and an increased risk of developing liver and lung metastasis. These findings[12] corroborate previous results demonstrated in other patient cohorts, including the series from Johns Hopkins University,[13] The University of Texas MD Anderson Cancer Center,[14] and Vienna,[15] which all reported reduced recurrence-free and overall survival for patients with *KRAS* mutations. It is thus tempting to suggest *KRAS* as a strong and independent prognostic factor, and one that even overrules current clinical risk scores and other prognostic features in patients undergoing surgery for liver metastases. However, these cohorts are fairly different in size and patient selection and generalizing may not be warranted beyond the reported cohorts. One study[14] was based on 193 patients of a series of 1406 patients consecutively treated for CRLMs (14%), whereas the other studies represented cohorts ranging from 60 to 169 patients, based on several selection criteria as well as variability in available tissue for DNA extraction and mutation analysis. Furthermore, the prevalence of *KRAS* mutations found in the cohorts ranged from 18% (or 14% if the *NRAS* mutations were excluded) in The University of Texas MD Anderson Cancer Center series[14] to 25% in the Vienna series,[15] 29% in the Johns Hopkins series, and 30% in the Memorial Sloan-Kettering Cancer Center study.[12] It is interesting to note that the presence of the *BRAF* mutation, a rare but very strong negative predictor that is reported to occur in 5% to 10% of patients with CRC,[16] was either not found at all[15] or was only present in 0.6%,[12] 1%,[14] and 2%,[13], of patients, respectively, which may point to a somewhat preselected population of patients. All patients had received some form of neoadjuvant chemotherapy (with or without bevacizumab); some included concomitant ablation techniques[13] and only 1 study included patients who received HAI therapy only,[12] a therapeutic option that is clearly not widespread in use and very institution-dependent in terms of the reported benefit and outcomes.

This obvious heterogeneity does not necessarily devaluate or rule out the prognostic information found for *KRAS* in each and every cohort, but it questions the role of *KRAS* as a useful prognostic biomarker in an upfront selection of patients with CRLMs and the proposed relation to prognosis. More importantly, it raises doubts regarding the role of *KRAS* in decision-making prior to surgical resection. For one, we do not know how information regarding a *KRAS* mutation would compare in strictly unselected, all-comer cohorts of patients undergoing hepatic resection. In addition, we do not know whether the *KRAS* status also is mirrored in those patients not undergoing hepatic resection and therefore may instead be a driver of prognosis not influenced by the intervention per se. Indeed, one may envision the true controls to be patients with *KRAS* wild-type who did not undergo hepatic resection, and how mutational status corresponded with biological disease progression and clinical outcome for this group. Because distant metastases is what eventually kills patients, it would be of interest to learn whether it is *KRAS* mutation status or undergoing liver surgery per se that changes the course of the disease.

The presence of the *KRAS* mutation may simply be a byproduct of the selection process, both in terms of cancer biology and disease aggressiveness, as well as clinical criteria and the selection process for various types of treatment in each and every institution. It begs the response to several additional questions that are important in the current and often difficult decision-making process for patients with a CRLM. For example, how well does *KRAS* predict prognosis for patients who are treated with a liver-first (without neoadjuvant chemotherapy) approach? The reported studies included patients who were all given a neoadjuvant chemotherapy regimen of some sort. What is the role of *KRAS* in patients whose CRLMs were removed with a simple wedge resection, in contrast to those patients who require formal hepatectomy (ie, representing either size or the number of tumors in addition to location)? It would be of interest to determine whether *KRAS* has the same predictive value in patients with single-metastasis disease compared with that of patients with multiple CRLMs. Indeed, the multivariable analysis by Kemeny et al[12] demonstrated that having ≥ 3 metastases was an independent prognostic factor for recurrence-free

survival together with *KRAS* status in the patient cohort that received HAI. Furthermore, how does *KRAS* status contribute to our understanding of cancer biology and clinical prediction in synchronous compared with metachronous CRLMs? Would *KRAS* be influential in the choice of strategy for a primary versus liver-first approach or choice of (neo)adjuvant chemotherapy? Does *KRAS* play a predictive and prognostic role in such clinical settings? We cannot tell from the current data, but we would surely like to learn the answers.

The clinical role of *KRAS* status in patients with resectable CRLMs is definitely not settled. The response to anti-EGFR therapy among patients with nonresectable metastatic disease is being explored to further illuminate the potential response factors, many of which include downstream genetic signaling of the EGFR pathway.[17,18] Plausibly, one would believe that patients with a wild-type *KRAS* status (and who therefore are eligible for treatment with cetuximab) would benefit from adjuvant anti-EGFR treatment after liver resection for a CRLM. It is interesting to note that the recent EPOC study[19] found, in contrast to the implied biological response and to the investigators' surprise, that patients with the *KRAS* wild-type mutation who received cetuximab actually fared worse than those who did not receive this treatment. If nothing else, it reveals that cancer biology continues to be poorly understood.

The frequently used and reported clinical risk scores for patients with CRLMs who are undergoing hepatic resection are able to stratify patients into high-risk and low-risk groups. Similarly, *KRAS* mutation status may also point to a certain outcome, whereas neither system allows for the accurate prediction of the individual patient in whom a potential cure is clearly precluded. Furthermore, it remains to be demonstrated how *KRAS* may predict prognosis and disease behavior when compared with other and apparently strong predictors of outcome, ranging from alternative mutations, microRNAs, and circulating tumor cells.

We do agree with the sentiments expressed by Vauthey and Kopetz[20] in a recent editorial published in *Cancer* that under the current multidisciplinary and multistrategic approach to CRLMs, with several strategies currently in use for preoperative assessment and presurgical treatment, the use of clinical risk scores is made unreliable or even useless for the comparison of research results and/or for prognostic purposes. We therefore may have to turn to the underlying biology to better understand the metastatic processes; the molecular mechanisms; and what factors may be of importance for monitoring, prognostication, and even improved targeted therapy. Last, we may find predictors that would make hepatic surgery futile and not necessary for some patients, in particular if it does not alter the disease course or does not provide a chance for cure. The recent prognostic studies on *KRAS*[11-15] have demonstrated that both overall and recurrence-free survival are considerably shortened, and the risk of distant metastasis in the lungs, brain, and other sites may be increased. How to use this information intelligibly for future patient selection is hard to discern because it depends both on an already present image-based and clinical-based patient selection and interacts with related genetic factors and molecular pathways. Whether *KRAS* is truly a biomarker for cancer biology or a byproduct of patient selection therefore remains an open question.

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