Editorial Commentary

Modernizing the clinical risk score to more accurately predict survival following resection of colorectal liver metastases

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To date, the National Cancer Institute, NIH estimates 140,250 new colorectal cancer cases for 2018 (1). Out of this population, 20% will present with synchronous metastatic disease and up to 50% will develop metastatic disease. Moreover, in those who develop metastases, the liver is involved 80% of the time. Although historical controls found rare survivors to be noted at 3 years and a median overall survival of 6–12 months in untreated but potentially resectable patients; modern data has found that a multidisciplinary approach incorporating surgical extirpation may allow for up to 55% and 24% actual 5- and 10-year survivors (2,3).

However, it is well recognized that outcomes widely vary, for up to 80% of patients will eventually recur following tumor extirpation and 40% of patients will develop a recurrence within 12 months (4). Therefore, it is clear that heightened prognostic information is needed to risk stratify patients prior to surgery in an attempt to improve "personalized care".

In the July edition of the *Annals of Surgery*, Drs. Brudvik and Vauthey retrospectively evaluated prospectively collected data to determine the impact of RAS mutation as a predictor of oncologic outcomes following resection of metastatic colorectal cancer to the liver. The authors sought to update the traditional clinical risk score (Memorial Sloan Kettering (MSKCC), Fong score) through the addition of RAS mutation status. Since 1999, the traditional clinical risk score has been the most widely utilized predictive tool for providers caring for patients with CRLM. This traditional score includes primary tumor nodal status, disease free interval, number and size of colorectal liver metastases (CRLM) and carcinoembryonic antigen level. However, more recently, this scoring system has drawn scrutiny and has been labeled by some as antiquated since it was developed in an era prior to modern systemic therapy (1985–1998). More importantly, it does not include any biological or genetic tumoral data. In short, the traditional score may not represent modern patient management and outcomes.

The rat sarcoma viral oncogene homolog (RAS) mutation is found in up to 35% of patients with CRLM and has found to be a poor prognostic indicator with associations to inferior overall and recurrence free survivals after liver resection (5). The authors therefore hypothesized that a RAS mutation, which is a direct measure of tumor biology, would be a powerful predictor of oncologic outcome and if added to a scoring system would outperform the traditional clinical risk score. The authors first assessed their internal data (n=524) and then validated their results with an international multicenter cohort of 608 patients. Specifically, on multivariate analysis of the traditional risk score factors and RAS mutation status, the only factors significantly associated with overall survival were primary-tumor positive lymph node status, diameter of the largest

liver metastasis more than 50 mm, and RAS mutation. The other traditional prognostic factors of: Disease-free interval less than 12 months, more than one liver metastasis and CEA level more than 200 ng/mL were not significantly associated with overall survival. The traditional risk score was then modified by replacing the nonsignificant factors (disease-free interval, number of CLM, CEA level) with RAS mutation status.

The resulting modified clinical score was then based on 3 factors: (I) primary tumor lymph node status (1 point assigned for positive nodes), (II) diameter of the largest liver metastasis (1 point for diameter >50 mm), and (III) RAS mutation status (1 point for mutation). Using this modified scoring system, significant differences in overall survival were identified and appeared more clinically relevant than the predictions made by the traditional score. Specifically, there were no significant overall survival differences between patients with traditional scores of 0 and 1, 1 and 2, 2 and 3, 3 and 4, or 4 and 5. However, when the modification was used, there were significant overall survival differences between patients with m-CS scores of 0 and 1, 1 and 2, and 2 and 3. Moreover, there were no significant recurrence-free survival differences between patients with traditional scores of 0 and 1, 1 and 2, and 3 and 4, whereas there were significant recurrence-free survival differences between patients with modified scores of 0 and 1, 1 and 2, and 2 and 3. Of note, the international multicenter validation did in fact corroborate the modified score outperformance of the traditional score at stratifying patients by overall survival.

Of course, this suggested paradigm shift requires close scrutiny. Numerous factors have been suggested to have an association with survival after resection of CRLM however their individual impact in clinical practice has been varied and these factors may not remain significant predictors in modern practice. However, more recent analysis has confirmed that a RAS mutation is associated with overall and recurrence free survival following resection of CRLM (6). Moreover, RAS mutation status has been associated with a negative pathologic response to systemic therapy, surgical margin status and survival following initial as well as repeat hepatectomy for CRLM (7-10). Similarly, recently published in the *British Journal of Surgery*, a Genetic and Morphological Evaluation (GAME) score was suggested to be a modern predictive scoring system to inform treatment selection in patients with CRLM and also includes RAS mutation (11). Of note, this data matches what our group has found in clinical practice. Anecdotally, we have identified and discussed often in multidisciplinary meetings the negative prognostic impact of a RAS mutation on hepatic recurrence free survival and subsequently overall survival. Therefore, in brief, RAS appears to be a modern, valid and highly predictive factor of oncologic outcome.

That said, certain limitations of this manuscript must be addressed. Although intriguing, we must keep in mind that this is retrospective data and therefore biased since only patient who had undergone RAS mutation typing pre-operatively were included. In short, the authors noted that RAS typing varied between centers and countries and was a limitation. Additionally, complete data on the use of perioperative chemotherapy and targeted therapy was not available from the different validation centers. Thirdly, the lymph node status of the primary tumor and RAS mutation status may not be available in patients with synchronously presenting liver metastases. Finally, the importance of KRAS codon 64 or 161 and NRAS mutations (now identified as poor prognostic indicators) were not recognized at the start of this study. Therefore, patients with these specific mutations may have been included in the wild-type cohort and may lead to an underestimation of the impact of mutation on outcome.

In brief, this insightful manuscript attempts to "modernize" the traditional clinical risk score. Albeit with limitations, it is certainly hypothesis generating and raises the poignant topic of surgical resection of CRLM in the RAS population. Although this novel modified score outperformed the traditional score, the concordance index for overall survival and recurrence free survival was relatively low. However, we believe there is truth in the weight of RAS mutation to be a functional method of prognostication. Additionally, the modified score may provide a better stratification for the potential benefit of perioperative chemotherapy, although this would need validation in a prospective setting. Although some have advocated against surgical resection in this patient population, we believe that the data is still naïve. That said, we certainly need novel therapies or treatment approaches, such as immune modulation, for the RAS mutation patient population.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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