Ann Surg Oncol (2011) 18:2711–2713
DOI 10.1245/s10434-011-1821-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL

Clinical Scoring Systems for Stratifying Risk after Resection of Hepatic Colorectal Metastases: Still Relevant?

William R. Jarnagin, MD

Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

Predicting response to therapy remains an area of intensive investigation throughout oncology. The results of these efforts hold promise for identifying subgroups of patients most likely to benefit from treatment. Even more important, however, is the potential to identify patients in whom the likelihood of incurring treatment-related toxicity or complications greatly outweighs any potential therapeutic advantage. For some malignancies, such as breast and colorectal cancer, molecular markers have entered clinical practice to some degree, but their use remains limited.[1,2] Indeed, the era of personalized cancer therapy, where effective treatment is based on individualized assessment of molecular events, is far from a clinical reality for most solid tumors.

In the absence of robust and clearly defined biomarkers, clinical variables, often combined into grading systems, have proven to be useful surrogate predictors of treatment outcome, and this has been particularly true in the area of resectable hepatic colorectal metastases.[3–8] From the time that resection emerged as the most effective treatment for this problem, optimal patient selection has been the subject of ongoing debate. These scoring systems evolved to fill the void by attempting to provide a rational approach to clinical decision making. Several such schemes have been proposed over the past several years, most of which comprise independent predictors of outcome identified on multivariate analyses of hundreds of patients. Although these patients all have stage IV disease by definition, wide variability in outcome after resection is well known. However, by accounting for multiple patient- and disease-related variables, classification systems are able to stratify patients into groups on the basis of risk of disease recurrence and survival.

Such an approach, although useful and clinically relevant, is not perfect. First, most risk scoring systems are based on single-institutional data and are therefore steeped with bias related to local referral patterns and treatment approaches. Also, there is often significant overlap in outcome between adjacent risk groups, and allocation to a high-risk group does not necessarily preclude long-term survival, making it difficult to recommend definitively against resection. Furthermore, in most schemes, the variables are not weighted but rather assigned equivalent magnitude, which almost certainly is inconsistent with tumor biology. Additionally and perhaps most importantly, the clinical data used to develop these scoring systems are derived from patients treated over several years, during which time treatment algorithms and approaches have evolved.

One of the biggest changes, of course, has been the advent of several more effective chemotherapeutic agents and combination therapies. This development has greatly affected the practice of hepatic resectional surgery for colorectal metastases, primarily by extending the indications for operation and increasing the proportion of patients potentially eligible for R0 resections, a result often achieved with neoadjuvant chemotherapy.[9,10] As a consequence, the clinical heterogeneity of this patient population, already wide, has been increased further.

Because most of the information used to establish clinical risk scoring systems either spans or predates the era of more effective chemotherapy, their relevance to contemporary practice has been called into question.[11,12] In this issue of *Annals of Surgical Oncology*, Ayez et al. examine this topic with a detailed analysis of four well-known scoring systems and the effect of neoadjuvant therapy on their prognostic power.[13] The authors confirm that although all four classification systems effectively

Published Online: 3 June 2011

W. R. Jarnagin, MD
e-mail: jarnagiw@mskcc.org

stratify risk and survival in patients taken directly to operation, prior treatment with neoadjuvant therapy greatly diminishes their predictive capacity. When scores were calculated before administering neoadjuvant therapy, only one of the four systems maintained significance for predicting disease-free survival and/or disease-specific survival. By contrast, when risk scores were calculated after neoadjuvant treatment, significance was largely restored. This observation is primarily the result of chemotherapy-induced changes in specific components of individual scoring systems, primarily tumor size, carcinoembryonic antigen (CEA) level, and number of tumors.

On the surface, this would appear to be a fairly simple exercise in arithmetic—change one or more numbers that comprise a sum, and the sum (i.e., the risk score) changes. However, what does this mean biologically? Does a change in clinical risk score after treatment equate to improved outcome after resection, in the same way one might expect after pathologic downstaging?

The current study touches on this issue and indirectly addresses the role of neoadjuvant therapy and its impact on outcome after resection of hepatic colorectal metastases. The authors show clearly that neoadjuvant therapy can result in changes to the clinical risk score, with some degree of migration of patients to lower risk stages, and these reconfigured stage groupings generally had better survival figures after neoadjuvant therapy. Although it is impossible to make any definitive conclusions, the data would suggest that response to neoadjuvant therapy, as measured by the variables that comprise the clinical risk scoring systems, may be associated with better survival.

One problem with the analysis is that the authors used the final histopathological results to recalculate the number of tumors, a variable that figures prominently in all of the scoring systems. In so doing, the authors bring histopathologic response to therapy into the equation, making the results more difficult to interpret. Pathologic response to treatment has been shown to correlate with survival.[14] Using this variable, however, defeats the purpose of a preoperative risk scoring system, because treatment response can only be assessed definitively after the resection trigger has been pulled. The question of whether treatment-induced changes in clinical risk score, as determined by *preoperatively* measured variables, can serve as a surrogate for histopathologic treatment response remains unanswered.

In the end, molecular profiling likely will provide greater insight into the biology of hepatic colorectal metastases and allow a more enlightened stratification of risk and selection of patients for resection. At present, however, molecular biology has yet to deliver on this promise. Despite their shortcomings, clinical scoring systems remain the most effective means of stratifying patients based on risk of recurrence and survival. The study by Ayez et al. identifies a potential source of inaccuracy in these systems, specifically related to neoadjuvant chemotherapy treatment. If recent history is any indicator, the management of colorectal liver metastatic disease will continue to evolve at a rapid pace. The present study highlights the need for periodic reassessment and possible modification to include new patient-, treatment-, and/or tumor-related variables, if warranted, as is done by the American Joint Committee on Cancer for pathologic staging. The utility of clinical risk scoring systems will remain vulnerable to such practice changes and must continue evolve with them in order to maintain clinical relevance.[12]

REFERENCES

1. Kao KJ, Chang KM, Hsu HC, et al. Correlation of microarray-based breast cancer molecular subtypes and clinical outcomes: implications for treatment optimization. *BMC Cancer.* 2011;11:143.
2. Salazar R, Roepman P, Capella G, et al. Gene expression signature to improve prognosis prediction of stage II and III colorectal cancer. *J Clin Oncol.* 2011;29:17
3. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. *Cancer.* 1996;77: 1254–62.
4. 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;230:309–21.
5. Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg.* 1999;189:291–9.
6. Nagashima I, Takada T, Matsuda K, et al. A new scoring system to classify patients with colorectal liver metastases: proposal of criteria to select candidates for hepatic resection. *J Hepatobiliary Pancreat Surg.* 2004;11:79–83.
7. Rees M, Tekkis P, Welsh R, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg.* 2008;247: 125–35.
8. Konopke R, Kersting S, Distler M, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. *Liver Int.* 2009;29:89–102.
9. Adam, R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg.* 2004; 240:644–58.
10. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary respectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomized phase 2 trial. *Lancet Oncol.* 2010;11:38–47.
11. Small RM, Lubezky N, Shmueli E, et al. Response to chemotherapy predicts survival following resection of hepatic colorectal metastases in patients treated with neoadjuvant therapy. *J Surg Oncol.* 2009;99:93–8.
12. Reissfelder C, Rahbari NN, Koch M, et al. Validation of prognostic scoring systems for patients undergoing resection of colorectal cancer liver metastases. *Ann Surg Oncol.* 2009;16:3279–88.

13. Ayez N, Lalmahomed ZS, van der Pool AEM, et al. Is the clinical risk score for patients with colorectal liver metastases still useable in the era of effective neoadjuvant chemotherapy? *Ann Surg Oncol*. In press. doi:10.1245/s10434-011-1819-8.

14. Blazer DG III, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *J Clin Oncol.* 2008;24:5344–51.