the benefit from adjuvant treatment was within the biomarker-negative group, the patients with the most primitive tumors. The findings have generated a new hypothesis that is now ready for testing in a prospective randomized clinical trial.

If the hypothesis that nearly all the benefit from adjuvant chemotherapy is in the biomarker-negative group is confirmed, over 90% of patients with stage II colon cancer will be reassured that avoiding the unpleasantness of standard adjuvant therapy is unlikely to affect their outcome adversely. No one expected that.

How would data sharing work best? We think it should happen symbiotically, not parasitically. Start with a novel idea, one that is not an obvious extension of the reported work. Second, identify potential collaborators whose collected data may be useful in assessing the hypothesis and propose a collaboration. Third, work together to test the new hypothesis. Fourth, report the new findings with relevant coauthorship to acknowledge both the group that proposed the new idea and the investigative group that accrued the data that allowed it to be tested. What is learned may be beautiful even when seen from close up.

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Prognostic Subgroups among Patients with Stage II Colon Cancer

C. Richard Boland, M.D., and Ajay Goel, Ph.D.

Colon cancer has traditionally been treated surgically. However, many cases of colon cancer are systemic at the time of diagnosis, and apparently curative surgery is followed at a later date by tumor recurrence as a consequence of circulating tumor cells before the surgery. Adjuvant medical therapies are designed to prevent recurrences after surgical resection.

The current standard for clinical prognostication relies principally on pathological staging. In early-stage colon cancers (stages I and II), all the tumor is contained within the wall of the colon. Less than 10% of patients with stage I disease have a recurrence, and adjuvant chemotherapy is not administered because it provides no benefit. Approximately 20% of patients with stage II colon cancers have a recurrence, and adjuvant chemotherapy provides a minimal benefit that is usually considered to be not worth the toxic effects of the drugs. Furthermore, among patients with stage II disease, there is quite a range of rates of 5-year survival (as low as 60%), depending on the incremental depth of tumor invasion. Stage III colon cancers have regional lymph-node metastases; cancer recurs in more than 50% of patients, and multiple clinical studies have shown significant increases in survival with the administration of adjuvant chemotherapy. Patients with distant metastases (stage IV colon cancer) receive a variety of more intensive regimens that are not usually curative. Rectal tumors are different and are not part of this discussion.

The use of adjuvant chemotherapy in patients with stage II colon cancer remains controversial because recurrence never develops in the vast majority of these patients. Treatment of all patients with stage II colon cancer is “overtreatment,” since only a small subgroup of patients derives any therapeutic benefit, whereas in others there is harm, a poorer quality of life, and no net benefit. Prior studies to identify the subgroup of patients with high-risk stage II colon cancer have not been robust, and the lack of prognostic and predictive criteria underscores the need to discover biomarkers that can facilitate the selection of patients for additional treatment.

In this issue of the Journal, Dalerba and colleagues report on a novel approach to the problem of identifying patients with colon cancer who might benefit from adjuvant chemotherapy. They reasoned that the presence of a stem-cell-like state would be associated with more aggressive tumors, and they performed a bioinformatics search for a gene-expression signature obtained from populations of stem cells and progenitor cells. By mining a large preexisting
database of colon cancers, they found 16 genes in which expression was inversely related to the stem-cell–like state. The CDX2 gene product was the most clinically actionable of these genes, since it is suitable for detection by means of immunohistochemical analysis.

The investigators performed a series of validation analyses involving multiple independent data sets; this is a necessary approach for data-mining research. The first analysis confirmed an inverse relationship between CDX2 expression and patient outcome in which CDX2-negative colon tumors (in 6.9% of the patients in the discovery data set), as compared with CDX2-positive tumors, were associated with significantly lower rates of 5-year disease-free survival (41% vs. 74%). Immunohistochemical analysis was performed to evaluate CDX2 protein expression in colon cancers. This analysis of a validation data set in which 13% of the patients had CDX2-negative tumors confirmed 5-year survival rates of 48% among patients with CDX2-negative tumors, as compared with 71% among patients with CDX2-positive tumors. However, this finding was not sufficient to prove that the subgroup of patients with a worse natural history would benefit from adjuvant chemotherapy; they could be less responsive to treatment.

The investigators focused on patients with stage II colon cancer and confirmed that CDX2-negative cancers, as compared with CDX2-positive cancers, were associated with significantly lower rates of survival (48 to 51% vs. 80 to 87%). Finally, they used an expanded database to show that the administration of chemotherapy increased rates of disease-free survival from 56% to 91% among patients with stage II colon cancer and from 37% to 74% among patients with stage III colon cancer.

This was not a perfect or definitive study. In spite of the rigorous bioinformatics analysis, the number of patients who had stage II colon cancer and CDX2-negative tumors was small. This retrospective study requires prospective confirmation with uniform interventions, which was not necessarily the case in the different cohorts. The immunohistochemical analysis was performed on tissue microarrays that facilitated rapid throughput but may have underestimated the heterogeneity of CDX2 expression throughout the tumor. Furthermore, these findings raise the important question of what mechanism might be at work in silencing CDX2; the answer to this question could lead to the discovery of new approaches to treating the fundamental problem.

This study provides an opportunity for oncologists to move beyond what has been an inadequate method of selecting patients with stage II colon cancer for adjuvant chemotherapy. In addition to genetic targets, hypermethylation of the gene encoding transcription factor AP-2 epsilon (TFAP2E) and altered expression of specific micro-RNAs are among the growing list of DNA-based and epigenetic biomarkers that have shown prognostic and predictive promise in stage II colon cancer. A combination of genetic and epigenetic marker panels will be assessed for their ability to enhance the prediction of disease course in oncology.

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