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Colon Cancer: What's New for Stage Two?

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Colon cancer is traditionally 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 prior to 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 (Stage I and II), all of the tumor is contained within the wall of the colon. Recurrences occur in <10% of patients with Stage I disease, and adjuvant chemotherapy is not administered as it provides no benefit. In Stage II colon cancers, there are recurrences in about 20% of cases and adjuvant chemotherapy provides a minimal benefit¹, which is usually considered not worth the toxic effects of the drugs. Furthermore, there is quite a range of five-year survival (as low as 60%) within the Stage II group depending upon the incremental depth of invasion². Stage III colon cancers have regional lymph node metastases, cancer recurs in >50% of cases, and multiple clinical studies have demonstrated significant increases in survival with the administration of adjuvant chemotherapy². Patients with distant metastases (Stage IV) receive a variety of more intensive regimens, which are not usually curative. Rectal tumors are *sui generis*, and not part of this discussion.

The use of adjuvant chemotherapy in Stage II patients remains controversial as the vast majority of patients never develop recurrences¹. Treating all Stage II patients is “overtreatment”³, as a small subset derives any therapeutic benefit, whereas others experience harm, a poorer quality of life, and no net benefit⁴. Prior attempts at identifying the subset of high-risk Stage II colon cancer patients have not been robust⁵, underscoring the need to discover prognostic and predictive biomarkers that can facilitate the selection of patients for additional treatment.

In this issue of the *Journal*, Dalerba and colleagues report a novel approach to the problem of identifying colon cancer patients who might benefit from adjuvant chemotherapy⁶. They reasoned that the presence of a stem cell-like state would be associated with more aggressive tumors, and performed a bioinformatics search for a gene-expression signature that would reflect this. By mining a large pre-existing database of colon cancers, they found sixteen

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genes in which expression was inversely related to the stem-like state. The CDX2 gene was the most clinically actionable of these, since it is suitable for immunohistochemistry. A series of validations was performed on multiple independent datasets—a necessary approach for data-mining research. The first confirmed an inverse relationship between CDX2 expression and patient outcome in which CDX2^{neg} colon tumors (6.9% in the discovery dataset) were associated with significantly worse five-year disease-free survivals than CDX2^{pos} tumors (41% versus 74%). A validation set using immunohistochemistry (13% CDX2^{neg}) confirmed survivals of 48% versus 71% for colon cancers based upon CDX2-expression. However, this was not sufficient to prove that the subset with a worse natural history would benefit from adjuvant chemotherapy; they could be less responsive to treatment. The investigators focused upon Stage II patients and confirmed that CDX2^{neg} cancers showed significantly worse survival than the CDX2^{pos} cancers (48–51% versus 80–87%), and finally used an expanded database to demonstrate that the administration of chemotherapy improved disease-free survival from 56% to 91% in the Stage II group and from 37% to 74% in the Stage III group.

This was not a perfect or definitive study. In spite of the rigorous bioinformatics, the number of Stage II patients with CDX2^{neg} tumors was small. This was a retrospective study, and requires prospective confirmation with uniform interventions, which was not necessarily the case in the different cohorts. The immunohistochemistry was performed on tissue microarrays, which 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, which could lead to the discovery of novel approaches to treating the fundamental problem.

This work provides an opportunity for oncologists to move beyond what has been an inadequate method of selecting Stage II colon cancer patients for adjuvant chemotherapy. In addition to genetic targets, hypermethylation of the TFAP2E gene promoter⁷ and altered expression of specific miRNAs⁸ are among the growing list of DNA-based and epigenetic biomarkers that have shown prognostic and predictive promise in Stage II colon cancer (reviewed in^{9,10}). It is likely that a combination of genetic and epigenetic biomarker panels will soon help refine and advance the field of predictive oncology.

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References

1. Marshall JL. Risk assessment in Stage II colorectal cancer. *Oncology* (Williston Park). 2010; 24:9–13. [PubMed: 20225606]
2. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med*. 2005; 352:476–87. [PubMed: 15689586]

3. Kneuert PJ, Chang GJ, Hu CY, et al. Overtreatment of young adults with colon cancer: more intense treatments with unmatched survival gains. *JAMA Surg.* 2015; 150:402–9. [PubMed: 25806815]
4. Lewis C, Xun P, He K. Effects of adjuvant chemotherapy on recurrence, survival, and quality of life in stage II colon cancer patients: a 24-month follow-up. *Support Care Cancer.* 2015
5. Benson AB 3rd, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol.* 2004; 22:3408–19. [PubMed: 15199089]
6. Dalerba P, Sahoo D, Paik S, et al. CDX2 as a Prognostic and Predictive Biomarker in Stage-II/III Colon Cancer. *N Engl J Med.* 2015 xx:xx.
7. Ebert MP, Tanzer M, Balluff B, et al. TFAP2E-DKK4 and chemoresistance in colorectal cancer. *N Engl J Med.* 2012; 366:44–53. [PubMed: 22216841]
8. Zhang JX, Song W, Chen ZH, et al. Prognostic and predictive value of a microRNA signature in stage II colon cancer: a microRNA expression analysis. *Lancet Oncol.* 2013; 14:1295–306. [PubMed: 24239208]
9. Carethers JM, Jung BH. Genetics and Genetic Biomarkers in Sporadic Colorectal Cancer. *Gastroenterology.* 2015; 149:1177–90. e3. [PubMed: 26216840]
10. Okugawa Y, Grady WM, Goel A. Epigenetic Alterations in Colorectal Cancer: Emerging Biomarkers. *Gastroenterology.* 2015; 149:1204–25. e12. [PubMed: 26216839]