In the “Current Status of Adjuvant Therapy for Colorectal Cancer,” Dr. O’Connell provides important highlights of historical and recent developments in adjuvant treatment for colon and rectal cancer. In addition, he provides insight into the future directions of research for adjuvant therapy of cancer of the colon and rectum. As the review is thorough, we would like to expand upon a couple of areas including lymph node evaluation, changes to the staging system, and the use of molecular prognostic and predictive markers in future studies.

In colon and rectal cancer, lymph node evaluation is of paramount importance. As mentioned by Dr. O’Connell, studies have shown that the number of lymph nodes sampled impacts on survival; this is likely due to more accurate staging of patients.\[1,2\] These studies showed that the overall survival for patients with zero positive nodes was 79% when greater than 20 lymph nodes were evaluated, as compared to 59% to 73% for those patients who had less than 20 lymph nodes evaluated. Optimally greater than 12 lymph nodes should be analyzed as per the recommendations of the College of American Pathologists; however, anything more than six is the minimum requirement.\[3\] If fewer than six lymph nodes are sampled, a request should be made for the pathologist to reexamine the surgical specimen, as lymph node positivity impacts on treatment decisions.

Staging Changes
The American Joint Commission on Cancer revised the definitions of metastatic nodules in 2002.\[4\] Smooth nodules in pericolonic fat are considered metastatic lymph nodes and irregular nodules in peritumoral fat are considered vascular invasion. Again, these subtle changes can make differences in treatment decisions. As much of the therapy for rectal cancer has moved to the neoadjuvant setting, accurate lymph node assessment has become more difficult postoperatively. This highlights the importance of the routine use of endoscopic ultrasound and computerized tomography scanning for adequate pretreatment staging for patients receiving neoadjuvant therapy for rectal cancer. Further changes to the colon cancer staging system in 2002 included subdivisions of stages II and III. Stage II has been subdivided into A (T3, N0, M0) and B (T4, N0, M0). The stage III patients have been subdivided into A (T1-2, N1, M0), B (T3-4, N1, M0), and C (any T, N2, M0). These changes were made in order to reflect the variability of prognosis within these substages of patients. The estimated 5-year disease-free survival with surgery and adjuvant chemotherapy for low-grade colon tumors is 82% for stage IIA, as compared to 74% for stage IIB; for high-grade tumors the rates are 79% (stage IIA) and 70% (stage IIB).\[5\] Even more variability in estimated 5-year disease-free survival is seen within stage III patients who receive surgery and adjuvant chemotherapy for low-grade colon tumors is 82% for stage IIA, as compared to 74% for stage IIB; for high-grade tumors the rates are 79% (stage IIA) and 70% (stage IIB).\[5\] Even more variability in estimated 5-year disease-free survival is seen within stage III patients who receive surgery and adjuvant therapy: 81% for stage IIIA, 53% to 68% for stage IIIB, and 27% to 64% for stage IIIC in patients with low-grade colon tumors. Stage III patients with high-grade lesions also show wide variability in 5-year disease-free survival with stage IIIA at 77%, IIIB at 46% to 61%, and IIIC at 21% to 59%.\[5\] Although there would likely be inadequate numbers of patients in any one subgroup who would participate in separate clinical trials, it will be important for future studies to plan to examine the degree of benefit obtained for patients within each subgroup, and to determine which patients may benefit from more aggressive adjuvant therapies.

Clinical Trial Models
Currently there are at least four models of clinical trials that have the potential to define whether select molecular markers can serve as prognostic markers or predictive markers linked to outcome. The most commonly used method of study has been to retrospectively review tissue blocks banked from large studies for molecular markers and compare the outcomes of patients on the study. An example of such a study is that reported by Watanabe et al.\[6\] Tumor specimens from patients who had been enrolled in two intergroup adjuvant chemotherapy colon cancer trials were analyzed for chromosomal abnormalities, p53, p21, and microsatellite instability to determine if these markers
were predictive of survival. Prospective hypothesis-driven studies are currently in development. In these studies, laboratory correlates are prospectively written into the protocol, yet they are not used to determine the treatment of patients in the study. Stratification studies look at specific markers and use those to risk-stratify patients receiving treatment but do not change the treatment intervention. Finally, intervention assignment studies are designed to prospectively use specific prognostic markers to determine the treatment assignment for patients in the study. The adjuvant stage II colon cancer study referred to by Dr. O'Connell is such a study. **Prognostic and Predictive Markers**

In adjuvant treatment of colon cancer, those patients with stage II disease have a 20% to 30% chance of relapse. Prognostic indicators can help determine which subset of patients has a worse prognosis; however, none of the currently known prognostic markers have yet been proven to demonstrate predictive ability, ie, determine the chance of the patient responding to treatment. With the evolution of microarray technology enabling the identification of thousands of genes, select profiles containing patterns of genes may emerge to serve as both prognostic and predictive markers. Current and future clinical trials with multivariate analyses of manageable numbers of molecular markers offer the best hope of developing individual patient treatment strategies based on tumor biology. In less than 5 years, a host of new agents have produced a near doubling of survival for patients with metastatic colorectal cancer. There is hope that these therapies, including monoclonal antibodies, will also benefit patients who are candidates for adjuvant therapy. With this growing menu of treatment possibilities, it becomes all the more urgent to identify markers that can predict those individuals most likely to achieve the best survival advantage from a particular intervention. **Conclusion**

In conclusion, the article by Dr. O’Connell provides an excellent summary of the past, present, and future directions of adjuvant therapy for colon and rectal cancer. Future study designs will need to incorporate prognostic and predictive molecular markers to determine the subsets of patients who will derive benefit from standard therapy and future therapies.

**Disclosures:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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