

Adjuvant Therapy for Stage II Colon Cancer: A Review of Clinical Practice Guidelines

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For oncologists who treat patients with colon cancer, the issue of whether to use adjuvant therapy in patients with resected node-negative (stage II) disease is an important consideration. The recently published recommendations from the American Society of Clinical Oncology (ASCO) on this subject^[1] provide a very thorough discussion of the evidence-based data bearing upon this subject, which almost universally provides no convincing evidence that therapy with adjuvant cytotoxic chemotherapy benefits patients with stage II disease. However, perhaps more importantly than evaluating these data from phase 3 trials, Benson and colleagues provide a thorough discussion of the clinical nuances seen in individual cases, which in the real world are the factors that impel physicians and patients to decide for or against adjuvant chemotherapy.

I suspect that many patients with stage II colon cancer who see a medical oncologist receive treatment. There are a variety of reasons, aside from my personal experience, for this view. First, the referring surgeon has obviously made a decision that adjuvant therapy is a consideration in his/her mind by referring the patient. Also, the typical well-informed patient may be aware that therapy with adjuvant chemotherapy is controversial in stage II colon cancer, but has made a decision to proceed with a full medical oncology consultation. (Presumably, if the patient were not interested in adjuvant therapy, he/she would not have seen the medical oncologist.) The conscious and unconscious decisions made by the patient and referring physician before consultation may well predispose toward the use of adjuvant chemotherapy.

Given the probability that a patient with stage II colon cancer who has consulted with a medical oncologist may well be predisposed toward chemotherapy, what should the oncologist tell such a patient? First, it is important that the patient be made aware that the great majority of clinical trial data shows that there is no statistically significant survival benefit for adjuvant chemotherapy. One should also share with the patient that even when there is a statistically significant level of benefit in the occasional clinical trial or meta-analysis, the benefit is small (typically less than 5%), and this level of improvement could be argued to be clinically of, at most, marginal benefit. For example, at the 2004 ASCO meeting, data from the QUASAR study,^[2] a phase 3 trial of approximately 3300 resected stage II cases randomized to adjuvant 5-fluorouracil plus leucovorin vs follow-up only, demonstrated a survival benefit with therapy of less than 5%. Whether this minimal statistically significant benefit is clinically significant is open to interpretation.

A second factor that should be discussed with stage II disease is that the treatment-related death rate is approximately 1% in adjuvant therapy trials. Therefore, the decision to treat must be made with the understanding that a less than 5% benefit rate is being balanced against a 1% toxic death rate.

Looking at the preceding data, it is clear that a decision to treat patients with stage II cancer with adjuvant therapy would certainly not be based upon an expectation of overwhelming patient benefit. However, are there individual clinical situations that would compel physicians to recommend therapy? We know that there are clinical and pathologic findings associated with poor prognosis in stage II colon cancer, including tumors producing high-grade obstruction, T4 tumor stage, perforation through a tumor, and poorly differentiated tumors. Although these factors are unquestionably associated with a poorer prognosis, whether adjuvant therapy improves that outcome is not clear.

One adverse prognostic factor, which I believe should be weighed heavily in the decision to treat patients with stage II disease, is the number of nodes removed.^[3] Swanson and colleagues demonstrated that in patients with T3N0 disease and only 1 to 2 nodes identified, the 5-year survival rate is 64%, but when more than 25 negative nodes were identified, the 5-year survival rate increases to 80%. These data clearly suggest that without adequate node sampling, patients may be understaged. The authors recommend that the minimum number of nodes for adequate staging is 13. Therefore, if a stage II patient has fewer than 13 negative nodes identified, the clinician is well justified in recommending adjuvant chemotherapy because such a case may be understaged.

Another issue that is now frequently under consideration deals with molecular genetic prognostic and/or predictive factors. These include deletion of the long arm of chromosome 18 (resulting in the loss of the *DCC* gene)^[4] and the presence or absence of microsatellite instability.^[5] The ASCO recommendations discuss the current status of molecular predictive/prognostic markers very well. The major points to be made are: (1) there are no prospective studies completed to

demonstrate clinical usefulness of these techniques; and (2) we have no data demonstrating whether a patient without negative prognostic markers will or will not benefit from the current adjuvant therapies available. This latter point is particularly important as patients may assume that if they have an adverse molecular genetic prognostic marker, they definitely should receive postoperative chemotherapy because such treatment will decrease the likelihood of relapse. However, factors that predict disease do not necessarily predict response to treatment.

In summary, the ASCO recommendation on adjuvant chemotherapy for stage II colon cancer is a useful document covering all of the salient issues in this area of clinical oncology. However, for clinicians dealing with individual patients, the reason to treat or not treat is based upon a panoply of factors, most of which are not associated with hard evidence-based data. These include individual patient and tumor characteristics, the understanding of risk assessment by patients and physicians, and, in my experience, the desire of the patient in many instances to "do something," even if the benefit is small.

References

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