

Reply to D.J. Sargent et al

We appreciate the response from Sargent et al¹ to our correspondence² and the opportunity to further discuss how to optimize the use of adjuvant chemotherapy after colon cancer surgery. Sargent et al agree with our comments for stage II, but disagree with our comments for stage III cancer. What we stated was not that adjuvant therapy should be omitted in stage III, but that it could be omitted for some patients. It is no longer appropriate to simply group patients into stage II or stage III, as we noted in our correspondence. Treatment has advanced and we must consider the individual's risk of recurrence and define the need for adjuvant therapy on the basis of pathology factors such as tumor stage, nodal stage, tumor-node substages, degree of differentiation, vessel and nerve infiltration, extramural depth of invasion, number of nodes sampled, and quality of the surgical specimen. Patient and clinical factors such as age, quality of care provided, elective and emergency surgery, pre- and postoperative carcinoembryonic antigen levels, and microsatellite instability are required. In the near future, molecular and immune markers will also be required. The relative importance of each of these factors is not precisely known, and some vary considerably between hospitals; however, by using them, we can better stratify patients according to their individual risk. Some patients with stage II will have a much higher risk of recurrence than some patients with favorable stage III. The need for treatment will thus be greater in some stage II patients than in some stage III patients. For example, patients with a stage II pT4bN0 tumor (zero of eight nodes) and extramural vascular invasion–positive microsatellite stable have a much higher risk of recurrence than patients with a stage III pT3aN1 tumor (one of 29 nodes) and extramural vascular invasion–negative MSS. Because knowledge of response predictors is limited, the indication for providing adjuvant therapy is the risk of recurrence.

Knowledge about how much lower the recurrence risk is today compared with when the trials were run is limited for any particular stage. A systematic overview could not find such patient series.³ A report by Tsikitis et al⁴ gives results in a large series with lower recurrence rates than seen before; however, as stressed by Sargent et al,¹ results can be confounded by adjuvant therapy some patients received. The Adjuvant Colon Cancer End Points (ACCENT) database, of great value for many research questions, does not provide any information on results that are reached today. Even if the hospitals were considered to be among the best, the quality of their details about care, and thus outcome during the 1990s, is inferior to that of current standards. Recurrence risks overall and by stage are much lower today than they were in the past when trials showing improvements in recurrence risk were run. In the Shi et al⁵ article from the ACCENT database, a tendency toward fewer recurrences was seen in patients in trials between 1995 and 2002, which supports our notion, but patients still did not have the standard of care they would have today. The focus on improved

colon cancer care on a national level in Sweden since about 2004,⁶ including better preoperative workup, improved surgery with the concept of complete mesocolic excision, and better pathology, might at least partly explain why relative survival was significantly superior to that in six other European countries.⁷ Even without that specific focus, survival has clearly improved since 2001 in one of the other countries (Denmark) that participated in the comparison.⁸

It is also important that we discuss absolute gains and not relative gains at multidisciplinary team conferences and with patients. This precision medicine is tailored to individual risk and uses all of the patient's information, not simply stage II or stage III. In the near future, we will have access to a wide range of additional factors that affect the risk of recurrence, so we must rigorously and effectively assess their value with respect to current patient information to help us accurately predict risk and site of recurrence in an individual patient.

For the record, from the 2,031 patients in the QUASAR (Leucovorin and Fluorouracil Compared With Observation in Treating Patients With Colorectal Cancer That Has Been Surgically Removed) study, in which information was available on lymph node numbers, the median yield was 9 and the mean was 10.7 lymph nodes (Hutchins G, personal communication), and not 6 as stated in the correspondence. However, this information is insufficient according to present standards.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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