Original Article

Point: Treating Stage II Colon Cancer: The Quest for Personalized Adjuvant Care

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Abstract

The development of treatment decision strategies to guide the use of adjuvant chemotherapy in patients with stage II colon cancer continues to challenge many oncologists. Clearly, recurrence risk and prognosis for patients with stage II colon cancer can be variable, with subsets of patients with stage II disease at potentially higher risk than some with stage III. Adjuvant chemotherapy seems to produce a consistent relative risk reduction for recurrence across studies. Using clinical calculators to predict individual recurrence risk based on histopathologic and patient data allows this relative risk reduction to be translated into absolute benefit to the patient. In addition, gene expression assays in combination with these histopathologic data may further improve the accuracy of recurrence risk calculations and allow more accurate absolute benefit estimations. This absolute benefit should be discussed with the patient, taking into account the risk of morbidity from chemotherapy and individual preferences to arrive at a shared medical decision regarding adjuvant chemotherapy. (*JNCCN* 2012;10:1370–1374)

Stage II colon cancer is a biologically heterogeneous entity. Treatment with surgery alone is associated with a 5-year or more disease-free survival (DFS) of approximately 65% to 75% for average-risk clinical trial patients[1–4] and an even larger variation of 58% to 88% for patients from the SEER database with T4b,N0 through T3,N0 disease, respectively.[5] Currently, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)[6] for Colon Cancer separate stage II disease into T3,N0 disease without high-risk features and T3,N0 disease with high-risk features or T4,N0 disease (to view the most recent version of these guidelines, visit NCCN.org). Traditional high-risk features, derived from older studies with small sample sizes, include poorly differentiated histology (grade 3–4), obstruction, perforation, fewer than 12 lymph nodes analyzed, indeterminate or positive margins, and lymphovascular or perineural invasion. Treatment choices include observation, clinical trial, or chemotherapy (5-fluorouracil/leucovorin [5-FU/LV] or capecitabine alone in T3,N0 disease without high-risk features; 5-FU/LV or capecitabine or 5-FU/LV plus oxaliplatin or capecitabine plus oxaliplatin in T3,N0 with high-risk features or T4,N0 disease) after discussion of prognosis, evidence of benefit from treatment, morbidity of treatment, and patient preferences.

Although these clinically and pathologically based risk factors offer helpful guidance for general population-based prognoses and potential benefits of chemotherapy as a whole, unfortunately they lack the ability to personalize an approach based on more patient-specific biologic information. For example, some patients with stage III disease (T1–2,N1b–a) have a markedly improved prognosis compared with those with stage II (T4b–a,N0), with 5-year survivals of 83% to 91% versus 58% to 79%, respectively,[5] and yet are offered adjuvant chemotherapy. Evidence shows that stage II and III disease have very similar gene expression profiles and therefore may be more similar than previously realized.[7] In addition, even in stage III disease, in which adjuvant chemotherapy is standard of care, approximately 11 patients must be treated to observe one positive outcome using traditional clinicopathologic risk factors for treatment decisions.[8] This article argues that use of standard and emerging biomarkers combined with the existing risk factor assessment will allow much more

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patient-specific prognostication compared with the current staging system alone, and leads to more accurate personalized information for the oncologist and patient to consider.

Review of Stage II Adjuvant Trials

For average-risk disease (no high-risk features), conflicting reports exist of a DFS or overall survival (OS) benefit for adjuvant chemotherapy. Moertel et al[1] (INT-0035) randomized 325 patients with stage II disease to bolus 5-FU and levamisole versus observation and found an 8% absolute reduction (32% relative reduction in risk) in 7-year DFS (*P*=.10) but no 7-year OS benefit. A more recent prospective study by Schippinger et al[2] randomized 535 patients with stage II disease to bolus 5-FU/LV versus observation and found 10-year relapse-free survivals of 85% versus 78%, respectively (32% relative risk reduction), which was nonsignificant. Both studies were underpowered to detect an OS benefit, and therefore definitive conclusions about 5-FU–based adjuvant therapy in stage II disease are difficult to draw from these studies.

In contrast, 2 large studies by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and Quick and Simple and Reliable (QUASAR) groups, including 1565 and 3239 patients with Dukes' B/stage II disease, respectively, have shown advantages in OS (5% and 3.6% absolute benefit, respectively) and DFS (30% and 19% relative risk reductions, respectively) after 5-FU–based adjuvant chemotherapy for average-risk patients with stage II disease.[3,9] Furthermore, a large pooled analysis of 7 randomized controlled trials (NCCTG, ECOG-NCCTG/INT, SWOG-INT0035, Siena, NCIC-CTG, FFCD, GIVIO) including 1440 patients with node-negative disease revealed a 4% absolute 5-year DFS benefit (*P*=.049) with an OS advantage. In addition, a statistically significant treatment effect from 5-FU–based adjuvant chemotherapy across all nodal subgroups (0, 1–4, ≥5) was noted, although the magnitude of this benefit varied, with larger benefits in patients with higher N staging.[4] Additionally, the ACCENT data set, including 18 phase III adjuvant therapy trials, confirmed an absolute 8-year OS advantage of 6% (66.8% vs. 72.2%; *P*=.026) for 5-FU–based adjuvant therapy in approximately 6900 patients with stage II disease.[10] The authors estimated the relative risk reductions in these 2 retrospective analyses to be approximately 15%. Lastly, a recent meta-analysis including 12 high-quality randomized controlled trials with 8201 stage II colorectal patients who were randomized to adjuvant chemotherapy or observation, confirmed significant benefit in both OS (5-year hazard ratio [HR], 0.81; 95% CI, 0.71–0.91; *P*=.0005) and DFS (5-year HR, 0.86; 95% CI, 0.75–0.98; *P*=.03) for stage II colon cancer.

No clear data exist for the estimated benefit of 5-FU–based adjuvant therapy in high-risk patients, because only subgroup analyses have been reported and were underpowered as such. MOSAIC, which randomized 2246 patients, including 900 patients with stage II disease, to either 5-FU/LV versus FOLFOX4, found no 5-year DFS or 6-year OS advantage in average- or high-risk patients with stage II disease with the addition of oxaliplatin compared with 5-FU alone. There was, however, a nonsignificant trend toward improved 5-year DFS in high-risk patients with stage II disease with the addition of oxaliplatin (82.3% vs. 74.6%; HR, 0.72; 95% CI, 0.50–1.02) in an unplanned subset analysis.[12] If this represented an underpowered result, then this translates into a relative risk reduction in DFS of 28% with the addition of oxaliplatin to 5-FU–based therapy in high-risk patients.

At the very least, average-risk patients with stage II disease seem to derive a small but measurable risk reduction for recurrence and absolute DFS (15%–32% and 4%–8%, respectively) across all studies, regardless of statistical significance. In addition, high-risk patients with stage II disease may derive an additional 28% risk reduction with the addition of oxaliplatin to 5-FU. It is critical to note that relative risk reduction requires an accurate assessment of a patient's baseline prognosis or recurrence risk to calculate an absolute benefit of adjuvant therapy for that particular patient. Therefore, the focus of this article now shifts to tools used to calculate absolute benefit based on standard risk factors and newer biomarkers that may better predict recurrence risk or prognosis.

Absolute Risk Calculators

Absolute risk calculators are not predictive of response to adjuvant chemotherapy for any given patient. Instead, they use the consistent relative

risk reduction noted from clinical trials for patients with stage II disease to estimate absolute benefit from adjuvant therapy using individual patients' calculated prognosis. The utility of these calculators is that they allow a clinician to quantify the expected benefit associated with adjuvant chemotherapy for a specific patient, which can be contrasted with the potential risk associated with adjuvant chemotherapy. For example, the addition of oxaliplatin to 5-FU has long-term complications, including peripheral sensory neuropathy (40%)[13] and hepatotoxicity with vascular sinusoidal injury (10%–50%).[14] According to NCCN, both the expected benefits and risks must be discussed with the patient, and these calculators may help facilitate these conversations in a meaningful way.[6]

Adjuvant! Online (www.adjuvantonline.com) allows medical professionals to register and have access to a colon cancer calculator, which includes age, sex, comorbidities, depth of invasion, number of positive lymph nodes, number of lymph nodes examined, and histologic grade to calculate 5-year mortality or recurrence from the SEER registry reported outcomes. Bar graphs depict categories, including "alive and without cancer at 5 years," "alive and without cancer at 5 years due to chemotherapy," "relapse," and "die of other causes." Calculations are made using the assumption of a 20% risk reduction for 5-FU–based chemotherapy and a 39% risk reduction for oxaliplatin with 5-FU (although risk reduction can be modified based on which study or data set the user believes is most representative).

Numeracy is another Web-based adjuvant therapy tool for colon cancer (www.mayoclinic.com/calcs/colon/index-ccacalc.cfm). This calculator uses number of positive lymph nodes, T stage, grade, and age of the patient to calculate recurrence and overall survival percentages for patients who receive no therapy, 5-FU–based therapy alone, or combination 5-FU and oxaliplatin therapy. This calculator does not allow modification of the risk reduction factor, and uses 17% and 14% for 5-FU–based therapy and 18% and 18% for combination 5-FU and oxaliplatin therapy in terms of recurrence risk and absolute risk reduction, respectively. Notably, risk reductions are based on abstracts presented in 2003 for the pooled analysis[15] and MOSAIC (3-year follow-up only).[16]

In a recent study, Adjuvant! Online was compared with Numeracy directly using patient datasets from the British Columbia Colorectal Cancer Outcomes Unit and the North Central Cancer Trials Group (NCCTG) 94651 and 914653. Although the authors found similar predictive performance and reliability in patients with stage III disease, they reported an overestimation of survival with the use of adjuvant 5-FU–based therapy in stage II disease using either calculator.[17] These data emphasize the fact that traditional histologic and pathologic staging is not ideal for identifying patients who are at highest risk for recurrence and most likely to gain an absolute benefit from adjuvant chemotherapy.

Emerging Tools and Biomarkers

Microsatellite instability high (MSI-H) has emerged as a new biomarker, with both prognostic and predictive implications for adjuvant therapy. Sargent et al[18] reported a 5-year DFS of 75% for mismatch repair (MMR)–proficient tumors and 90% for MMR-deficient tumors in stage II disease, with a borderline significant (P=.09) finding for a worse 5-year DFS for patients with MMR-deficient tumors treated with 5-FU–based chemotherapy. Therefore, patients with MSI-H stage II tumors have a good prognosis with surgery alone and do not benefit from adjuvant 5-FU chemotherapy.

Multiple gene expression assays have been developed to better prognosticate recurrence risk, and only one is commercially available at the time of this article. Onco*type* DX was tested using tumor tissue from patients from NSABP C-01/C-02, C-04, and C-06 and Cleveland Clinic, validated in the QUASAR population, and confirmed in patients from CALGB 9581.[7,19] Seven recurrence risk genes plus 5 reference genes were selected and used to create an algorithm to calculate a recurrence score. The recurrence score was significantly associated with the risk of recurrence, DFS, and OS. Although recurrence score was predictive of recurrence at 3 years in a continuous fashion, patients were separated into low risk (12%), intermediate risk (18%), and high risk (22%). In addition, Onco*type* DX offers an aid for interpreting the recurrence score (Table 1). Other gene expression assays are being investigated but are not currently commercially available.[20,21] Importantly, no gene expression assay is currently available that predicts response to adjuvant chemotherapy, and therefore the usefulness is limited to a more personalized and accurate recurrence risk prognostication. For example,

Table 1 Aid for Interpreting the Oncotype DX Recurrence Score[a]

Tumor/Patient Characteristic	Aid for Interpreting 3-Year Recurrence Risk
Lymph nodes assessed	≥12 reduces risk by 3%
	<12 increases risk by 2%
5-year recurrence risk	Increases risk by 5%
T4 disease[b]	Increases risk by 10%–15%
MSI-H status (T3 disease)	Decreases risk by 10%–15%

Abbreviation: MSI-H, microsatellite instability-high.
[a]There are insufficient data at this time for NCCN to recommend the use of multigene assay panels to determine adjuvant therapy. This is information posted on the Oncotype DX analysis for guidance of interpretation of results. Further investigation is needed to validate these interpretations.
[b]MMR proficient.

another gene expression assay called ColoPrint was found to be superior compared with the ASCO criteria for predicting risk of recurrence in patients with stage II disease.[20] It is important to note that currently there is insufficient data for NCCN to support the routine clinical use of these multigene assay panels. Further investigation regarding how these panels may change or improve on decision-making and outcomes are needed.

Lastly, another emerging biomarker being investigated includes guanylyl cyclase C expression in histologically negative lymph nodes, which may confer an equivalent recurrence risk as having a histologically positive lymph node, but requires completion of an ongoing validation study.[22]

Conclusions

Traditional histopathologic staging is not ideal for predicting individual recurrence risk for patients with stage II disease. Some of these patients may in fact have worse prognoses than those with stage III disease, in whom the standard treatment is adjuvant chemotherapy. Older studies evaluating the benefit of adjuvant chemotherapy in patients with stage II colon cancer reveal relatively consistent risk reductions for recurrence and DFS (≈20%–30%), but show variable results for OS, potentially related to suboptimal power calculations. Nonetheless, the authors would argue that DFS is a reasonable end point from a patient-centered perspective to justify adjuvant therapy for

Table 2 Treatment Guidance for Clinicians Considering Adjuvant Therapy in Patients With Resected Stage II Colon Cancer

Factors	Treatment Recommendations
MSI-H	No adjuvant therapy
Low or "average" risk	5-FU or capecitabine, but not oxaliplatin (after discussion with patient) because of MOSAIC[10]
High risk	5-FU or capecitabine with the addition of oxaliplatin (after discussion with patient) given reasonable extrapolation from stage III benefit
Gene expression assays	Potential to avoid adjuvant therapy in low-risk patients given good prognosis[a]
Patient discussion[24]	Suggested points of discussion to include: 1. Ask amount of prognostic information preferred and how estimates are conveyed (numbers or words) 2. Discuss whether potential benefits outweigh potential risks - Prognosis with surgery alone using tumor characteristics, other prognostic markers, Numeracy program - Absolute benefit preferred over relative risk reduction for improvement in cure rate with adjuvant therapy - Potential risks during 6 months of therapy with chemotherapy and late toxicities 3. Discuss comorbidities and impact on potential benefit from therapy or risk of adverse effect 4. Elicit patient's perception of how risk and benefits may influence their decision-making

Abbreviations: 5-FU, 5-fluorouracil; MSI-H, microsatellite instability-high.
[a]There are insufficient data at this time for NCCN to recommend the use of multigene assay panels to determine adjuvant therapy. Further investigation is needed into this potential use of multigene assay panels before following this algorithm.

subsets of patients with stage II disease. Many patients perceive that 5 years alive without disease recurrence is better than 5 years alive with disease recurrence. Preventing recurrence if possible is important, because recurrence after surgical resection can dramatically increase levels of anxiety and fear compared with that experienced by patients who are newly diagnosed with metastatic disease.[23]

Although MSI-H is the only predictive marker thus far to identify patients who might experience benefit (or lack thereof) of adjuvant chemotherapy, continued refinement of the ability to more-individually predict recurrence risk is essential to the care of patients with stage II colon cancer. Gene expression assays are promising because they seem to be able to be incorporated with traditional histologic or pathologic defined risk factors to calculate a personalized risk of recurrence for a patient. With this accurate recurrence risk, relative risk reduction data for observation, 5-FU alone, or 5-FU plus oxaliplatin–based therapies can be used to express the absolute benefits patients may expect from adjuvant therapy in their situation. This can be weighed against known long-term adverse effects from receiving adjuvant chemotherapy, optimizing the shared decision-making process between patient and physician. Table 2 provides treatment guidance for clinicians considering adjuvant therapy in patients with stage II disease.

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