New Developments in the Adjuvant Therapy of Stage II Colon Cancer

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Colon cancer is estimated to have accounted for 106,100 new cancer cases and 49,920 cancer-related deaths in 2009. Over half of these new diagnoses and deaths occur in individuals age 70 and older. The probability of developing colon cancer increases with advancing age from less than 1% in the first 4 decades of life to nearly 5% in the seventh decade of life. Nearly 40% of these older individuals are diagnosed with stage II disease. While the overall 5-year survival rate for individuals 75 and older is 67% for all stages of colon cancer, survival of those aged 70 to 79 diagnosed with stage II (T3 or T4, N0, M0) colon cancer is 77% (low-grade disease) or 70% (high-grade disease).

The benefit of adjuvant chemotherapy after surgery for stage III colon cancer is well established. However, the role of chemotherapy in patients with stage II disease not as well established and has been a source of debate over the past 2 decades. While the percentage of stage II colon cancer patients of any age that receive adjuvant therapy after surgery is unknown, one study found that 27% of 65- to 75-year-old Medicare beneficiaries received chemotherapy for stage II disease. This article will outline the evidence for chemotherapy in stage II colon cancer and review risk assessments for colon cancer recurrence, with a focus on older patients.

Treatment Efficacy—Fluoropyrimidine Monotherapy

Early studies in adjuvant colon cancer enrolled patients with stage II and III disease. The North Central Cancer Treatment Group (NCCTG) and subsequently the Eastern Cooperative Oncology Group (ECOG) compared the administration of fluorouracil (5-FU) and levamisole with observation in the adjuvant setting. The NCCTG trial enrolled 401 patients with stage II or III colon cancer and demonstrated a 31% reduction in recurrence rate for patients with stage III disease who received fluorouracil and levamisole. In the larger ECOG trial of 1,296 patients, adjuvant fluorouracil and levamisole reduced the risk of recurrence by 41% (P = .0001) and the risk of death by 33% (P = .006) compared with surgery alone in patients with stage III disease. In contrast, no meaningful benefit was noted in the subset of patients with stage II disease.

Multiple pooled analyses that included these and other studies have led to mixed findings regarding the benefit of adjuvant therapy in stage II patients (see Table 1). The International Multicenter Pooled Analysis of Colon Cancer Trials (IMPACT) group conducted two pooled analyses evaluating the impact of fluorouracil and high-dose leucovorin compared to observation following resection of colon cancer that failed to show a survival benefit for patients with stage II disease. Both analyses failed to show a statistically significant benefit in disease-free survival for stage II patients. The National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted pooled analysis of individual patient data of the effect of adjuvant fluoropyrimidine-based regimens for stage II and III disease in NSABP studies C-01, C-02, C-03, and C-04. Of the 3,820 patients enrolled, 41% had stage II (26% of those with high-risk features) and 56% were ≥ 60 years old. Cumulative odds of
death demonstrated survival benefit for both stage II (0.70) and stage III (0.82) patients. Treatment effect was similar for stage II patients regardless of presence of high-risk features (low-risk:
cumulative odds of death = 0.68; 95% confidence interval [CI] = 0.50–0.92; \(P = .01\); high risk:
cumulative odds of death = 0.80; 95% CI = 0.55–1.17; \(P = .26\)).
Gill and colleagues conducted a pooled analysis of 3,302 patients from seven randomized adjuvant trials, including 1,440 patients with stage II disease and 1,864 patients ≥ 60 years old.[3] Adjuvant therapy led to a 4% absolute 5-year disease-free survival (DFS) benefit (76% vs 72%; \(P = .05\)) and no overall survival (OS) benefit (81% vs 80%; \(P = .11\)). For patients 70 to 79 years old, both DFS and OS appeared to be increased among those receiving adjuvant therapy, although the statistical significance of the apparent absolute difference is not described.[3]
In a systematic review of stage II colon cancer patients in 37 clinical trials and 11 meta-analyses on behalf of the Cancer Care Ontario Program in Evidence-Based Care, no OS benefit was noted for adjuvant therapy (\(N = 4,187\), relative risk [RR] of death 0.87, 95% CI = 0.75–1.01; \(P = .07\).[15] An updated pooled analysis of data from 1980 until 2007 noted a 17% reduction in risk of recurrence or death with the use of adjuvant therapy in stage II disease (pooled relative risk ratio = 0.83; 95% CI = 0.75–0.92) without a significant difference in OS (RR = 0.96; 95% CI = 0.88–1.05).[16]
The Adjuvant Colon Cancer Endpoints (ACCENT) Group reported on a collection of individual patient data from 18 trials (20,898 patients with 33% stage II) testing fluorouracil-based adjuvant therapy in stage II or III colon cancer.[17] At 8 years, the OS among stage II colon cancer patients receiving adjuvant chemotherapy was 72.2% compared to 66.8% in those who had surgery alone (\(P = .026\)). The largest randomized clinical trial evaluating treatment of individuals with stage II colon cancer was conducted in the United Kingdom by the Quick And Simple And Reliable (QUASAR) Collaborative Group.[18] In one of the two cohorts of the study, patients who were deemed by their oncologist to have a low risk of cancer recurrence and in whom the indication for chemotherapy was uncertain (ie, mainly stage II cancers) were randomized to a fluoropyrimidine regimen or placebo.[19] The baseline characteristics of the 3,239 patients enrolled were as follows: 71% colon cancer, 29% rectal cancer, 91% stage II disease with 8% stage III, and < 1% stage I. Individuals 70 and older accounted for 20% of each treatment arm. All patients enrolled were included in intention-to-treat analyses with the primary endpoint of overall survival. The relative risk of dying from any cause with chemotherapy vs observation was 0.82 (95% CI = 0.70–0.95). When considering cancer recurrences, the relative risk of recurrence with chemotherapy vs observation was 0.78 (95% CI = 0.67–0.91). When limited to stage II colon cancer patients only, the relative risks for overall mortality (0.86, 95% CI = 0.66–1.12) and recurrence (0.82, 95% CI = 0.63–1.08) are similar to the overall population but not statistically significant.
In QUASAR, while limited by sample size, the point estimates for overall mortality (relative risk 1.02, 95% CI = 0.70–1.48) and recurrence (relative risk 1.13, 95% CI = 0.74–1.75) in patients greater than 70 years old suggests a lack of benefit in elderly patients. This is in contrast to a pooled analysis of seven randomized adjuvant trials (40% with stage II disease) by Sargent et al demonstrating similar OS benefit and decreased time to cancer recurrence for patients ≥ 70 receiving adjuvant chemotherapy compared to their younger counterparts.[20] This pooled analysis, however, included patients with stage II and stage III colon cancer.

**Treatment Efficacy—Combination Therapy**

| TABLE 2 |

| Randomized Clinical Trials of Adjuvant Therapy for Stage II Colon Cancer: Combination Therapy |

Two clinical trials have been initiated to evaluate oxaliplatin (Eloxatin) and a fluoropyrimidine in the adjuvant treatment of colon cancer, both enrolling stage II and III patients[21,22]. Both trials demonstrated statistically significant DFS benefit with the addition of oxaliplatin to a fluoropyrimidine in the overall cohort, with one reaching statistical significance in OS (see Table 2 for trial details).
In the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC), a phase III study of 2,246 patients with stage II or III colon
cancer randomized to receive infusional fluorouracil and leucovorin (LV5FU2) plus or minus oxaliplatin, 40% of patients had stage II disease. The latest report from MOSAIC was published when the last enrolled patient had 5 years of follow-up for DFS and 6 years of OS.[21] While DFS was statistically significant for the overall cohort and stage III subset, the 5-year DFS among stage II patients was 83.7% and 79.9% in the FOLFOX4 and LV5FU2 groups, respectively (hazard ratio [HR] = 0.84, 95% CI = 0.62–1.14; \( P = .26 \)). Similarly, 6-year OS was 86.9% and 86.8%, respectively (HR = 1.00, 95% CI = 0.70–1.41; \( P = .99 \)). While the investigators did not report results of the stage II patients by age, the DFS benefit appeared limited to those under the age of 65 in exploratory analyses of those with stage III disease.

The NSABP randomized 2,407 patients (one-third were ≥ 65 and nearly one-third had stage II disease) to a weekly fluorouracil and leucovorin regimen with or without every-other-week oxaliplatin.[22] While the overall cohort achieved a statistically significant DFS benefit, with a 34-month follow-up and dose intensity of at least 85%, no statistically significant DFS benefit was shown for older patients or those with stage II disease.

**Measuring Risk of Recurrence**

When considering all patients with stage II colon cancer, 5-year overall survival is 82.5%. When this is delineated by substage of disease based on the American Joint Committee on Cancer’s AJCC Cancer Staging Manual (6th edition), overall survival is 85% for those with stage IIa (T3) and 72% for those with stage IIb (T4) disease.[23] However, as with all solid tumors, AJCC staging alone does not fully predict recurrence rates and outcomes. Other factors impact on the cancer recurrence and mortality outcomes of patients. Oncologists often consider these other factors in guiding patients on the use of adjuvant therapy for stage II colon cancer.

Risk assessment depends largely on pathologic characteristics of the tumor, as well as clinical presentation, which indicate underlying tumor biology and potential for recurrence. Poor-risk pathologic factors include depth of invasion (T4 stage), less than 12 lymph nodes sampled at the time of resection, clinical bowel obstruction, clinical bowel perforation, poor histologic tumor grade, and lymphatic or vessel invasion.[24-29] In a single-center study of 448 patients with stage II colon cancer prospectively evaluated from 1990 to 2001, presence of T4 disease, preoperative carcinoemryonic antigen (CEA) level of 5 ng/mL, and lymphovascular or perineural invasion were identified as poor prognostic factors for disease-specific survival. Five-year disease-specific survival was greatly diminished for patients with two or more of these factors at 57%, compared to those with one factor (85%) or none (95%). These results indicate a need for further evaluation of this high-risk subset in clinical trials.

In a combined analysis of two early fluoropyrimidine adjuvant therapy trials (NCCTG and ECOG INT 0035), investigators have reported on subset analyses of stage II patients based on clinical prognostic features.[9] In a cohort of 403 stage II patients, there was a 38% reduction in the rate of recurrence for treatment when compared with observation (\( P = .02 \), adjusting for perforation and location of primary tumor), but no improvement in survival (\( P = .91 \), adjusting for location of primary tumor and age). However, 5-year DFS was appreciably improved with adjuvant chemotherapy compared to observation in patients whose tumors adhered to another organ (87% vs 55%), invaded another organ (79% vs 45%), obstructed (76% vs 56%), or perforated (67% vs 43%). In exploratory analyses of MOSAIC, 5-year DFS in high-risk stage II patients (defined as at least one of the following: T4, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion, or fewer than 10 lymph nodes examined) were 82.3% and 74.6% in the oxaliplatin arm compared to fluorouracil and leucovorin alone (HR = 0.72; 95% CI = 0.50–1.02).

Molecular markers have been studied as tools for risk assessment in all stages of colon cancer, particularly stage II disease. While most studies have shown that microsatellite instability bodes a more favorable prognosis, the presence of tumoral 18q loss of heterozygosity has been associated with an inferior survival in some,[30-32] but not all,[33] studies. Recently, Kerr and colleagues presented data on the value of a panel of markers in formulating a recurrence risk score as a predictive marker for stage II colon cancer.[34] John Marshall further discusses molecular markers later in this supplement to ONCOLOGY.

**Risk Assessment in Older Patients**

Although some data are emerging regarding treatment effect of chemotherapy for stage III colon cancer in older patients,[35-38] there is a paucity of such data in the same population with stage II disease. In a review of Surveillance Epidemiology and End Results (SEER) and Medicare registries
during 1991 to 1996, 62% of 3,151 Medicare patients diagnosed with stage II disease were 70 to 75 years old.[6] Of those patients, 24% received chemotherapy. Ten percent of the cohort had two or more comorbid conditions. Older patients had a 23% increase risk of death compared to those 65 to 69 years old. Those with an increased number of comorbid conditions had a threefold higher increased risk of death. Data on patients ≥ 75 were not collected given prior evidence of low chemotherapy rates among those with stage III disease.[39] While treatment was not predictive of survival, 5-year OS for the cohort was 78% in the treated group compared to 75% in the untreated group.[6]

A key limitation of evidence to date is the relatively small number of elderly patients with stage II colon cancer enrolled in clinical trials. Whereas 70% to 75% of colorectal cancers are diagnosed in patients older than 65, only 40% to 48% of patients enrolled in National Cancer Institute (NCI)-sponsored or cooperative group trials are drawn from this age group [40]. This underrepresentation of elderly patients with colorectal cancer has not improved in the past several years. From 2000 through 2002, only 0.5% of colorectal cancer patients ≥ 75 years enrolled in NCI-sponsored trials, substantially less than the 4% enrollment recorded for patients 30 to 64 years old.[40] A possible explanation for this discrepancy may be financial, although a similarly low rate of enrollment for older patients has been documented in Canada, where the national health care program provides reimbursement for all health care costs.[41] More plausible explanations for the lack of participation of elderly patients in clinical trials may include lack of social support, physician reluctance to offer research protocols, difficulties with access to clinics and hospitals, potential noncoverage of investigational treatments by Medicare, patient refusal, increasing concomitant medication usage and comorbidities with advancing age, and fewer trials specifically aimed at elderly patients.[41-45]

Prediction tools may be useful in guiding treatment decisions for stage II colon cancer. Weiser and colleagues developed a recurrence nomogram based on a cohort of 1,320 patients diagnosed with AJCC stage I to III colon cancer during January 1990 to December 2000 at the Memorial Sloan-Kettering Cancer Center.[46] Nearly 40% of these patients had stage II disease. Of note, the age distribution of the cohort was not provided. Using prognostic factors of age, preoperative CEA, number of negative nodes, tumor location, T stage, tumor differentiation, lymphovascular invasion, and perineural invasion, the nomogram correctly predicted likelihood of colon cancer recurrence 77% of the time, a 3% improvement over that of the AJCC Cancer Staging Manual (6th edition).

Caveats to this approach include the need for validation in other populations. Additionally, this nomogram as well as the recently proposed recurrence score[34] may not account for the impact of comorbid medical conditions or functional status that impact life expectancy and consequently decrease the opportunity for cancer recurrence in older patients.[47-49] Furthermore, the presence of two or more comorbid medical conditions predicted for worse outcome among a SEER/Medicare cohort of older patients with stage II disease.[6]

Cancer-Specific Geriatric Assessment Tool

Patient selection may be further improved by identifying those older patients vulnerable to toxicity and functional decline from chemotherapy. Geriatric assessment has been shown to predict for tolerance and survival in other cancers.[50-52] The Cancer Specific Geriatric Assessment developed by Hurria et al, a brief tool developed specifically for older cancer patients, is currently undergoing validation in large clinical trials (see Table 3).[53-55] It includes independently validated measures of functional status, comorbid medical conditions, cognition, mental health, social functioning and support, medication usage, and nutritional status.
Guidelines on Adjuvant Therapy in Stage II Disease

In 2004, the American Society of Clinical Oncology (ASCO) published guidelines on the use of adjuvant chemotherapy in stage II colon cancer. Following a systematic review of the evidence on the use of adjuvant therapy in stage II colon cancer by the Cancer Care Ontario Practice Guideline Initiative in 2004, ASCO released its recommendations based on data from 37 randomized clinical trials and 11 meta-analyses.[56] ASCO’s expert panel concluded that there is no direct evidence to support the use of adjuvant therapy in stage II colon cancer, even for those with high-risk features, estimating an absolute improvement in 5-year survival of 2% to 4% based on findings from IMPACT B2. A large number of subjects would need to be enrolled to detect a small difference in overall survival for a group with a high rate of survival at baseline.[56,57] No specific recommendations were made regarding the subset of older patients with stage II disease. The authors did recommend incorporating informed patient preferences and considering the impact of comorbid medical conditions and life expectancy in addition to potential treatment effect and toxicity when making treatment decisions.

Similarly, the International Society of Gastrointestinal Oncology recommended against the routine use of chemotherapy for stage II disease but made allowances for patients interested in receiving it.[24] Citing data from the QUASAR study, the National Cancer Comprehensive Network guidelines support the use of adjuvant chemotherapy in high-risk stage II colon cancer.[58]

Conclusion

Current evidence does not support the widespread use of adjuvant therapy in stage II colon cancer. Subsets of patients with stage II disease that have a higher risk of cancer recurrence may derive a survival benefit similar to that seen in stage III disease. Risk-stratified treatment approaches may identify this high-risk subset. Given the large portion of patients who are older, such strategies should include assessments of comorbid medical conditions and functional status to increase delivery of appropriate therapy to this growing population.

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References:
Breast and Bowel Project adjuvant studies (C-01, C-02, C-03, and C-04). *J Clin Oncol* 17:1349-1355, 1999.


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