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ASCO SPECIAL ARTICLE

# American Society of Clinical Oncology Recommendations on Adjuvant Chemotherapy for Stage II Colon Cancer

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## ABSTRACT

**Purpose**
To address whether all medically fit patients with curatively resected stage II colon cancer should be offered adjuvant chemotherapy as part of routine clinical practice, to identify patients with poor prognosis characteristics, and to describe strategies for oncologists to use to discuss adjuvant chemotherapy in practice.

**Methods**
An American Society of Clinical Oncology Panel, in collaboration with the Cancer Care Ontario Practice Guideline Initiative, reviewed pertinent information from the literature through May 2003.

**Results**
A literature-based meta-analysis found no evidence of a statistically significant survival benefit of adjuvant chemotherapy for stage II patients.

**Recommendations**
The routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer is not recommended. However, there are populations of patients with stage II disease that could be considered for adjuvant therapy, including patients with inadequately sampled nodes, T4 lesions, perforation, or poorly differentiated histology.

**Conclusion**
*Direct* evidence from randomized controlled trials does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer. Patients and oncologists who accept the relative benefit in stage III disease as adequate *indirect* evidence of benefit for stage II disease are justified in considering the use of adjuvant chemotherapy, particularly for those patients with high-risk stage II disease. The ultimate clinical decision should be based on discussions with the patient about the nature of the evidence supporting treatment, the anticipated morbidity of treatment, the presence of high-risk prognostic features on individual prognosis, and patient preferences. Patients with stage II disease should be encouraged to participate in randomized trials.

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## INTRODUCTION

In 2004, approximately 106,000 people living in the United States will be diagnosed with colon cancer.[1,2] Of these patients, just less than one-third will have node-positive disease (stage III), and about one-quarter will have node-negative (stage II) disease. After a complete surgical resection, stage III patients face a 50% to 60% chance of developing recurrent disease. However, randomized trials conducted in the 1980s demonstrated that fluorouracil (FU) -based therapy could decrease the chance of death by approximately 30% (relative risk reduction), which is a greater than 10% absolute improvement in 5-year survival.[3] As a result of these trials, in 1990, the National Institutes of Health (NIH) convened a consensus conference panel that recommended the administration of FU-based adjuvant therapy for all medically fit patients with completely resected stage III colon cancer.[4]

The NIH panel did not recommend any specific adjuvant therapy for stage II patients outside of clinical trials.[4] At that time, clinical trials data did not support adjuvant therapy for stage II colon cancer patients, whose overall prognosis following a curative resection is typically excellent. However, too few stage II patients had been included in the seminal randomized studies to determine whether they derived a small benefit from FU-based postoperative therapy. Controversy surrounding management of stage II colon cancer patients has therefore persisted.

Despite the lack of definitive data about the relative and absolute benefits of adjuvant therapy for the stage II patient population, SEER-Medicare data suggest that a significant percentage of even the elderly stage II colon cancer patient population receives adjuvant therapy in the United States.[5] Given the high incidence of stage II colon cancer (more than 25,000 patients in the US each year) and innovations in both chemotherapy and surgical practice since 1990, the American Society of Clinical Oncology (ASCO) convened an expert panel to develop guidelines to facilitate decision-making in clinical practice. This guideline reviews the evidence base that clinicians and patients have to accurately inform these decisions, and recommends strategies for discussing this controversial topic in clinical practice.

### Questions

This guideline addresses three principal questions: (1) Should all medically fit patients with curatively resected stage II colon cancer be offered adjuvant chemotherapy as part of routine practice? (2) Should patients with curatively resected stage II colon cancer and with identifiable characteristics that predict for a poor prognosis (ie, high-risk patients) be offered adjuvant chemotherapy? (3) What strategies can medical and surgical oncologists use to discuss the issue of adjuvant chemotherapy with their patients in clinical practice?

### Practice Guidelines

Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.[6] Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing its cost. Specifically, utilization of clinical guidelines may provide: (1) improvements in outcomes, (2) improvements in medical practice, (3) a means for minimizing inappropriate practice variation, (4) decision support tools for practitioners, (5) points of reference for medical orientation and education, (6) criteria for self-evaluation, (7) indicators and criteria for external quality review, (8) assistance with reimbursement and coverage decisions, and (9) criteria for use in credentialing decisions.

In formulating recommendations for use of adjuvant chemotherapy for patients with stage II colon cancer, ASCO considered these tenets of guideline development, emphasizing review of data from controlled clinical trials. However, it is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. **Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician, in light of each patient's individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease for which better therapy is sorely needed. In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.**

## METHODS

### Panel Composition

ASCO convened an Expert Panel consisting of experts in clinical medicine, clinical research, health services research, and related disciplines (biostatistics, medical decision making, patient-physician communication) with a focus on expertise in colon cancer. A patient representative was also included on the Panel. The clinical experts represented medical oncology and surgical oncology. Academic and community practitioners, an oncology fellow, and several members of the Cancer Care Ontario (CCO) Practice Guideline Initiative (CCOPGI) Gastrointestinal Cancer Disease Site Group were also part of the Panel. A steering committee under the auspices of the Health Services Committee (HSC) chose Panel participants for the clinical practice development process. The Panel participants are listed in the Appendix.

### Literature Review and Analysis

*CCO systematic review.* The systematic review of the literature on the role of adjuvant therapy in stage II colon cancer conducted by the CCOPGI Gastrointestinal Cancer Disease Site Group served as the primary source of evidence for this guideline. The original CCOPGI systematic review of this topic was published in 1997.[7] After discussions with ASCO, CCOPGI staff undertook an update of the evidence on the use of adjuvant therapy in stage II colon cancer. This process was completed in January 2003, and the updated

systematic review is published in this issue of the *Journal of Clinical Oncology*.[8] Articles were selected for inclusion in the CCO systematic review evidence if they met the following criteria: (1) randomized controlled trials (RCTs) with appropriate control groups, or (2) meta-analyses of RCTs comparing adjuvant therapy with observation in patients with stage II colon cancer who had undergone surgery with curative intent. Additional details of the CCOPGI literature search strategy and meta-analyses can be found in the article by Figueredo et al.[8]

*ASCO Panel literature review and analysis.* The ASCO Panel reviewed all publications identified by the CCO review to select randomized phase III trials pertinent to its deliberations. Based on consultation from the Methodology Subcommittee of ASCO's HSC, the Panel focused attention on randomized trials that included a surgery-alone control arm and at least one FU-based chemotherapy arm. The Panel designed a coding sheet to complete the review of the randomized trials included in the CCOPGI systematic review, and the Co-Chairs assigned each Panel member a subset of articles to review. In addition, authors were contacted by the Panel to facilitate disaggregation of results for stage II and stage III patients in the original reports. Several of the studies identified are only currently available in abstract form. The CCOPGI authors, at the request of the ASCO Expert Panel, completed a literature-based (*v* an individual patient data–based) meta-analysis of trials that included a surgery-alone control arm, and at least one FU–based chemotherapy arm. Results of this analysis are presented here. Finally, an updated MEDLINE search (May 2003 to February 2004) did not identify any studies that have been published since the completion of the formal CCOPGI literature review in May 2003 that would affect the recommendations.

### Consensus Development Based on Evidence

The entire Panel met twice. The purpose of the first meeting was to perform an initial review of the materials provided by CCO and to develop a strategy for developing the guidelines. The purpose of the second meeting was to critically evaluate all of the literature to identify the data relevant to the question and to decide on Panel recommendations. All members of the Panel participated in the preparation of the draft guideline document, which was then disseminated for review by the entire Panel. Feedback from external reviewers was also solicited. The content of the guidelines and the manuscript was reviewed and approved by the HSC and by the ASCO Board of Directors before dissemination. Final text editing was completed by Al B. Benson III, Daniel G. Haller, Deborah Schrag, and Mark R. Somerfield.

### Guidelines and Conflict of Interest

All members of the Expert Panel complied with ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO's disclosure form and were asked to reveal ties to companies developing products that might be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

### Revision Dates

At annual intervals, the Panel Co-Chairs (A.B.B. and D.G.H.) and two Panel members designated by the Co-Chairs will determine the need for revisions to the guidelines based on an examination of current literature. If necessary, the entire Panel will be reconvened every 3 years to discuss potential changes; the Panel will reconvene more frequently if new information suggests that more timely modifications are warranted. When appropriate, the Panel will recommend revised guidelines to the HSC and the ASCO Board for review and approval.

### Definition of Terms

Stage II colon cancer was defined according to the TNM system classification of the American Joint Committee on Cancer as any pT3N0M0 or pT4N0M0 tumor of the colon.[9]

Adjuvant chemotherapy was defined as any FU-based chemotherapy regimen, including portal vein infusion regimens, administered following a curative-intent cancer operation.

### Summary of Outcomes Assessed

Overall survival was the primary outcome of interest. Disease-free survival and treatment toxicity outcomes were also considered as secondary outcomes.

## RESULTS

### Literature Search Results

The CCOPGI systematic review authors identified 37 randomized controlled trials and 11 meta-analyses of adjuvant chemotherapy or immunotherapy for colon cancer. A literature-based meta-analysis of selected data from the trials identified by the CCOPGI authors found no evidence of a significant survival benefit of adjuvant chemotherapy or immunotherapy for stage II patients. At the request of the ASCO Panel, CCOPGI authors completed a literature-based meta-analysis of the subset of 12 trials from the CCOPGI pool of 37 randomized controlled trials. The 12 trials (Table 1) were selected based on the more stringent criteria requiring inclusion of a surgery-alone control arm

**Table 1.** Randomized Trials in Stage II Colon Cancer: FU-Containing Regimen Versus Surgery Alone

| Trial (year) and Treatment Allocation | No. of Months on Therapy | No. of Eligible Patients | | Median Follow-Up (years) | All Trial Patients | | Stage II Patients | |
|---|---|---|---|---|---|---|---|---|
| | | Stage II | Stage III | | DFS (%) | OS (%) | DFS (%) | OS (%) |
| NCCTG (1989)[12] | | | | | | | | |
| Obs | — | 127 | | 7.8 | 45* | 53* | 59*‡ | 76*‡ |
| Lev | 12.0 | 122 | | | 53*† | 59* | 67*‡ | 76*‡ |
| FU + Lev | 12.0 | 124 | | | 57* | 61* | 731*‡ | 76*‡ |
| INT-0035 (1995)[11] | | | | | | | | |
| Obs | — | 159 | — | 7.0 | NA | NA | 71 | 72 |
| FU + Lev | 12.0 | 159 | — | | | | 79 | 72 |
| | | | | | | | ($P$ = .10) | ($P$ = .83) |
| NACCP (2001)[13] | | | | | | | | |
| Obs | — | 365§ | | 4.7 | 51 | 58 | 65 | 70 |
| FU + Lev | 12.0 | 365§ | | | 58† | 68† | 71†‡ | 78†‡ |
| IMPACT 2 (1999)[10] | | | | | | | | |
| Obs | — | 509 | — | 5.8 | NA | NA | 73‖ | 80 |
| FU + FA | 6.0 or 12.0 | 507 | — | | | | 76‖ | 82 |
| | | | | | | | ($P$ = .06) | ($P$ = .06) |
| SWOG (1988)[14] | | | | | | | | |
| Obs | — | 80 | | > 7.0 | 44‖ | 51 | NR | 61‡‖ |
| FU + m-CCNU | 12.0 | 213 | | | 45‖ | 51 | | 57‡‖ |
| FU + m-CCNU + BCG | 12.0 | 190 | | | 40‖ | 47 | | 53‡‖ |
| | | | | | ($P$ = NS) | ($P$ = NS) | | ($P$ = NS) |
| NSABP C-01 (1988)[15] | | | | | | | | |
| Obs | — | 169 | 214 | 6.4 (mean) | 51 | 59 | NR | NR |
| BCG | 20.0 | 154 | 221 | | 56 | 67† | | |
| MOF | 20.0 | 154 | 201 | | 58† | 67† | | |
| CCCSG-Japan, (1995)[16] | | | | | | | | |
| Obs | — | 279# | | NR | 76 | 80 | 88 | 90 |
| MIFU-1 | 6.0 | 327# | | | 81 | 82 | 89 | 88 |
| MIFU-2 | 6.0 | 293# | | | 77 | 80 | 84 | 84 |
| | | | | | ($P$ = NS) | ($P$ = NS) | ($P$ = NS) | ($P$ = NS) |
| Taylor et al (1985)[17] | | | | | | | | |
| Obs | — | 34 | 20 | > 5.0 | NR | 58 | NR | 65 |
| PVI-FU/hep | 7.0 | 38 | 19 | | | 78** | | 95** |
| LBCP-UK (1992)[18] | | | | | | | | |
| Obs | — | 77 | | > 5.0 | NR | 77 | NR | 93‡ |
| PVI-hep | 7.0 | 57 | | | | 73 | | 81‡ |
| PVI-FU/hep | 7.0 | 61 | | | | 82 | | 90‡ |
| ENR | — | 114 | | | | 74 | | 87‡ |
| | | | | | | ($P$ = NS) | | ($P$ = NS) |
| NSABP C-02 (1990)[19] | | | | | | | | |
| Obs | — | 202 | 143 | 3.5 (mean) | 64 | 73 | NR | NR |
| PVI-FU/hep | 7.0 | 189 | 157 | | 74** | 81 | | |
| SAKK (1995)[20] | | | | | | | | |
| Obs | — | 174 | | 8.0 | 48 | 55 | 63‡ | 69‡ |
| PVI-MIFU/hep | 7.0 | 174 | | | 57** | 66** | 68‡ | 77‡ |
| | | | | | | | ($P$ = NS) | ($P$ = NS) |
| NCCTG (1990)[21] | | | | | | | | |
| Obs | — | 106 | | 5.5 | 67 | 68 | NR | 79†† |
| PVI-FU/hep | 7.0 | 103 | | | 73††† | 68 | | 79†† |
| | | | | | ($P$ = .57) | ($P$ = .61) | | ($P$ = 0.73) |

NOTE. Adapted from Figueredo et al,[8] with permission.

Abbreviations: DFS, disease-free survival; FU, fluorouracil; INT, Intergroup of US Clinical Trial Groups; Lev, levamisole; NA, not applicable; NACCP, Netherlands Adjuvant Colorectal Cancer Project; NCCTG, North Central Cancer Treatment Group; NR, not reported; Obs, observation; OS, overall survival; ref, reference number; FA, folinic acid (leucovorin); IMPACT, International Multicentre Pooled Analysis of Colon Cancer Trials; NS, not significant; BCG, bacillus Calmette-Guerin; CCCSG, Colorectal Cancer Chemotherapy Study Group; m-CCNU, methyl-CCNU (semustine); MIFU-1 and MIFU-2, mitomycin C + FU; MOF, semustine + vincristine + FU; NSABP, National Surgical Adjuvant Breast and Bowel Projects; SWOG, Southwest Oncology Group; ENR, eligible patients not randomized; hep, heparin; LCBP-UK, Large Bowel Cancer Project; PVI, portal vein infusion; SAKK, Swiss Group for Clinical Cancer Research.

*Values estimated from survival curves.

†$P$ value < .05 (compared with observation).

‡May include patients with rectal cancer.

§Represents number of patients randomized.

‖These are event-free survival data.

¶Patients in this trial were randomized in two phases. Data marked with this symbol reflect only patients randomized in the second phase of the trail (n = 279 [total]); (n = 56 [stage II]).

#Includes stages I, II, and III colon cancer patients.

**Indicates a statistically significant difference ($P$ < .05 compared with observation).

††Values estimated from survival curves.

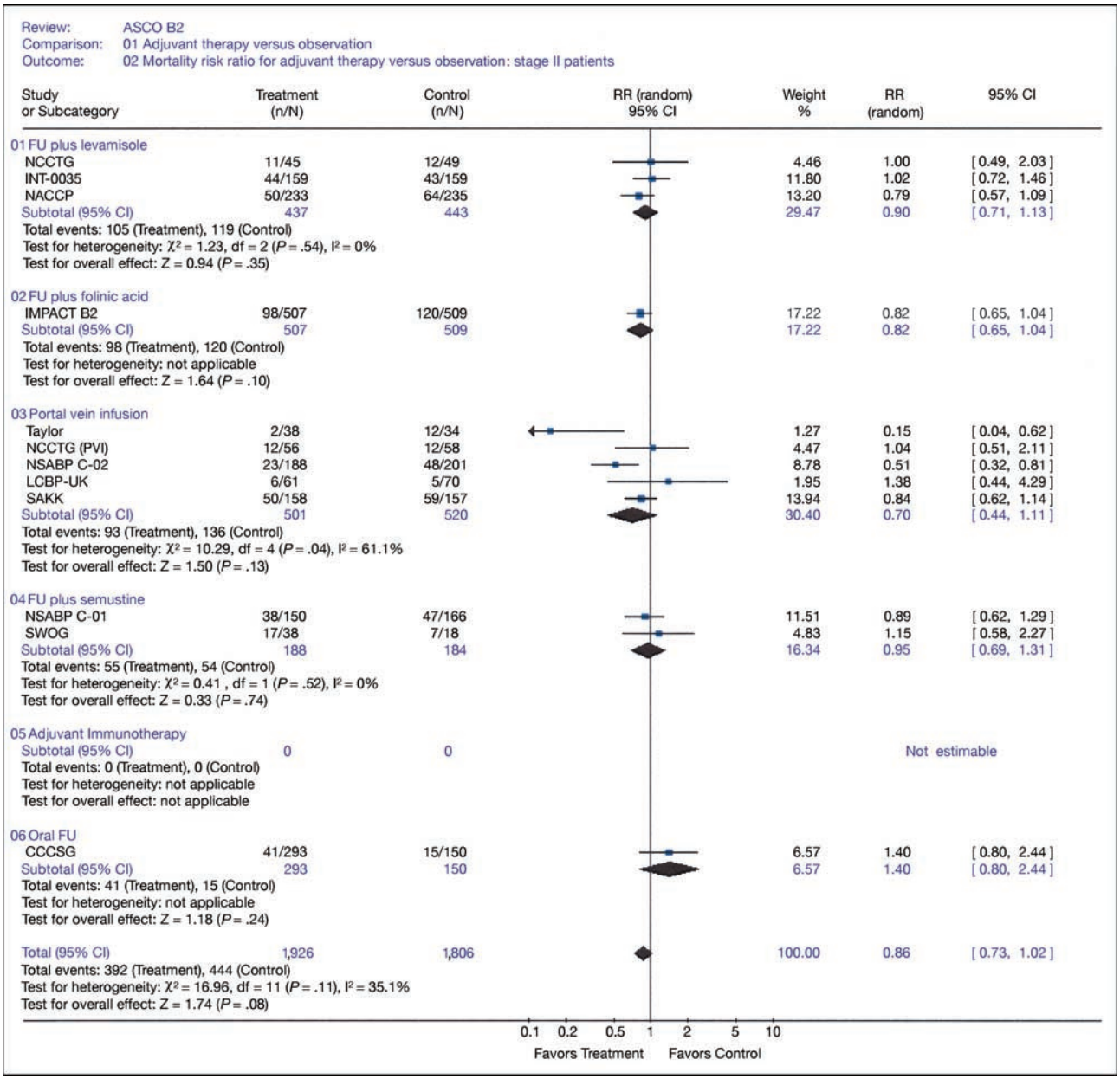


**Fig 1.** Meta-analysis of adjuvant therapy versus observation trials that include at least one fluorouracil-based chemotherapy arm.

and at least one FU-based chemotherapy arm. This second analysis resulted in the same conclusion: adjuvant chemotherapy does not significantly increase the survival for stage II colon cancer patients (Fig 1). Finally, because portal vein infusion is infrequently used in current medical practice, the CCOPGI repeated its meta-analysis excluding trials that administered FU-based adjuvant therapy via this route. The results obtained (data not shown) were similar to the results of the other meta-analyses.

### *Should All Medically Fit Patients With Curatively Resected Stage II Colon Cancer Routinely Receive Adjuvant Chemotherapy?*

*Summary and recommendations.* The routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer is not recommended. Neither the CCOPGI systematic review of 37 RCTs and 11 meta-analyses of adjuvant chemotherapy for colon cancer review, nor the CCOPGI meta-analysis of the 12 ASCO-selected RCTs

found sufficient supporting evidence for the routine use of adjuvant chemotherapy for these patients. Because clinical trials have not demonstrated a significant improvement in survival, inclusion of a surgery-alone control arm in randomized trials for average-risk stage II patients remains justifiable. At the same time, the oncology research community has recently focused efforts on the conduct of trials to better establish the role of molecular prognostic and predictive factors. The motivation behind these trials is the identification of those patients who are most likely to benefit from treatment by virtue of their high risk of recurrence and/or high probability of response to treatment.

*Benefits of adjuvant therapy.* In the late 1980s, benefits from FU-based adjuvant chemotherapy in colon cancer were demonstrated in randomized trials that frequently included both stage II and stage III disease. While the magnitude of the benefits of adjuvant chemotherapy were quite clear in stage III disease, as sample sizes were adequate, no clear benefit could be demonstrated in the stage II patients. The failure to document a statistically and clinically relevant benefit is largely attributable to the relatively good prognosis for stage II patients after surgery alone, and the resulting requirement to randomize thousands of patients to demonstrate a small margin of absolute improvement in survival with adequate statistical power (Table 2).

Because the benefit derived from adjuvant therapy in stage III disease was clear and compelling, the possibility that adjuvant treatment for stage II disease would not confer some degree of benefit seems biologically implausible. Moreover, administration of adjuvant chemotherapy for other good-risk cancers, such as breast cancer, became commonplace during the 1990s. Thus, despite the lack of compelling data from clinical trials, the controversy surrounding the routine use of adjuvant treatment for medically fit patients with stage II disease persisted, while clinicians and patients have made individual decisions on receiving adjuvant treatment.

Attempts have been made to evaluate the probable magnitude of benefit in stage II patients accrued to different studies; to determine whether the relative benefit from adjuvant therapy was similar in both stage II and III patient populations; and to assess whether the absolute benefit in 5-year survival would lead to consensus, and, ultimately, acceptance of treatment in standard practice. Conclusions from such analyses have varied. For example, the Liver Infusion Meta-Analysis Group reported a relative benefit from a FU-based portal vein infusion in both stage II and stage III patients.[22] On the other hand, the International Multicenter Pooled Analysis of Colon Cancer Trials B2 study (IMPACT) combined data from five randomized trials and failed to show a statistically significant benefit of adjuvant FU with leucovorin when compared with surgery alone in the subsets of patients with stage II disease.[10] The 5-year overall survival estimates were not statistically different (80% for surgery compared with 82% for those receiving adjuvant therapy) for the 1,016 stage II patients included in this meta-analysis.

The CCOPGI Gastrointestinal Cancer Disease Site Group, in the development of its guideline on adjuvant therapy in stage II colon cancer, undertook a systematic review of the English-language published literature of randomized clinical trials and meta-analyses evaluating adjuvant therapy compared to observation.[7] In a recent update, the review included 37 randomized trials and 11 meta-analyses.[8] Overall, 20,317 patients were included (7,803 patients with colon cancer and 12,514 with colorectal cancers). The proportion of patients with stage II disease ranged from 23% to 100% (average of 48%) in the trials reviewed. The analysis demonstrated that adjuvant therapy was associated with a small absolute improvement in disease-free survival (ranging from 5% to 10%), but this did not translate into a statistically significant difference in overall survival. The CCOPGI guideline[7] concluded that there was no clear evidence to routinely recommend adjuvant therapy for stage II patients, and encouraged continued inclusion of a surgery-alone treatment arm in randomized trials.

*Risks of adjuvant therapy.* In general, a recommendation to offer cancer therapy to an individual patient recognizes that the potential benefits of treatment outweigh the potential risks. Overall, stage II colon cancer patients who have a complete surgical resection have a good prognosis with surgery alone. Therefore, a recommendation to treat with adjuvant chemotherapy for this group of patients must include a discussion of the projected cure rate with surgery alone, the potential incremental (relative and absolute) improvement in the cure rate with the addition of chemotherapy, and the known risks of administering chemotherapy, as well as the potential late toxicities of treatment. The expected toxicities of standard FU and leucovorin regimens, and the more recent combination chemotherapy schedules that include either irinotecan or oxaliplatin, are well described in the literature.[23-28] For most patients, treatment is well tolerated, and the primary hardship is the $\geq$ 6-month duration of typical adjuvant regimens. Adjuvant therapy typically causes moderate fatigue and gastrointestinal complaints. More severe toxicities of FU-based therapy that may require hospitalization, such as mucositis and myelosuppression, are unusual, but, in rare circumstances, they can be life-threatening. The mortality rates associated with adjuvant treatment are in the 1% range and seem to be higher among elderly people. Although recent data have emerged from the European MOSAIC study that suggest a small benefit in 3-year disease-free survival for oxaliplatin-based chemotherapy in the subset of stage II patients, overall survival data are not yet available, and oxaliplatin-associated neurotoxicity can be prolonged and disabling.[29]

**Table 2.** Number of Patients Needed to Detect Treatment Benefit

| | Stage II | | | Stage III | | |
|---|---|---|---|---|---|---|
| | Survival (%) | ARR (%) | No. of Patients | Survival (%) | ARR (%) | No. of Patients |
| At 3 Years | 85 | 2.5 | 8,000 | 65 | 5.2 | 3,400 |
| At 5 Years | 75 | 4.0 | 4,700 | 50 | 6.6 | 2,400 |

Abbreviation: ARR, absolute risk reduction.

### *Should Patients With Curatively Resected Stage II Colon Cancer and With Identifiable Characteristics That Predict for a Poor Prognosis (ie, high-risk patients) Be Offered Adjuvant Chemotherapy?*

*Summary and recommendations.* The recommendations that follow are based on the Panel's review of the evidence on prognostic and predictive factors in colon cancer, and Panel consensus. The evidence base considered includes the final reports of early stage II and III adjuvant chemotherapy trials that include risk factor data,[11,30] large-scale National Cancer Data Base (NCDB) analyses of nodal status and prognosis,[31,32] a secondary analysis of data from a large Intergroup randomized trial to determine the association between number of nodes recovered and overall survival,[33] a recent pooled analysis of prognostic and predictive factors in colon cancer,[34] a College of American Pathologists consensus statement on prognostic factors in colorectal cancer,[35] and selected studies on emerging molecular markers.[36,37]

Patients for whom the number of sampled lymph nodes was very small can be considered inadequately staged and at greater risk of having microscopic residual disease.[31,33] As a result, patients with inadequately sampled nodes[29] could be offered adjuvant chemotherapy. In general, the greater the number of lymph nodes examined, the easier it is to have confidence that the patient truly lacks micrometastatic disease. The NCDB analyses[30,31] suggest that when 13 or more lymph nodes are analyzed, the probability that the patient has residual disease is lower than when fewer nodes are analyzed. Although there is no absolute number of lymph nodes analyzed that should be considered adequate or inadequate, clinicians should weigh adjuvant treatment recommendations and decision making in the context of the number of nodes analyzed.

Other patients with any of a number of poor prognostic features such as T4 lesion (defined as adherence to or invasion of local organs), perforation, or poorly differentiated histology,[26,34,35] might also be considered as candidates for adjuvant chemotherapy. It should be emphasized that, although these tumor characteristics may be prognostic markers, there are no data to suggest that they serve as predictive markers (ie, tumor characteristics that predict response to adjuvant chemotherapy). Finally, it should be noted that the magnitude of risk conferred by these characteristics, relative to nodal status, cannot be reliably estimated from available data.

The question of whether or not to offer adjuvant chemotherapy to stage II patients at high risk or with inadequately sampled nodes should be considered in light of the available evidence. *Direct* evidence from randomized controlled trials, and from meta-analyses of such trials, does not yet demonstrate a survival benefit for adjuvant chemotherapy in high-risk stage II disease, and, as previously reviewed, there are toxic effects of treatment; it is thus reasonable to recommend against the use of such therapy to a well-informed patient. However, because of the limited numbers of patients with high-risk disease evaluated in trials, the potential benefits of adjuvant therapy have not been adequately tested.

On the other hand, given this uncertainty, it is reasonable in the setting of high-risk disease for oncologists and patients to invoke *indirect* evidence of benefit by generalizing from the positive results of adjuvant chemotherapy in patients with stage III disease. Those who would generalize are prepared to take the risk that the toxicity of treatment is worth the potential, but as yet unproven, benefits of therapy, based on the beneficial results obtained in the stage III population and the assumption of biologic equivalence of stage II and stage III colon cancers.

In summary, *direct* evidence from randomized controlled trials does not support the use of adjuvant chemotherapy, even for patients with high-risk stage II colon cancer. Patients and oncologists might reasonably be reluctant to choose adjuvant therapy because of this lack of direct evidence of benefit. However, patients and oncologists who are prepared to take the risk of accepting the results from stage III disease as adequate *indirect* evidence of benefit are justified in considering the use of adjuvant chemotherapy in stage II disease, provided that they understand that the magnitude of benefit as measured in absolute improvement in survival, is small. Patients who have had a complete resection can be reassured that adjuvant treatment for typical stage II disease does not improve 5-year survival by more than an absolute 5%. Whether smaller incremental improvements in survival can be derived from treatment remains open to question.

In either case, the clinical decision should be based on a discussion with the patient about the nature of the direct evidence supporting treatment, the assumptions inherent in accepting indirect evidence of benefit, the anticipated morbidity of treatment, the presence of high-risk prognostic features, and patient preferences. A subsequent section on "talking points" advises oncologists about how to approach such a discussion. The optimal approach remains to encourage patients with stage II disease who are facing this decision to participate in randomized trials.

*Prognostic and predictive markers of high-risk stage II colon cancer.* Although patients with stage II colon cancer are generally considered to have a good prognosis after surgery alone, approximately one-quarter will experience recurrence within 5 years. More complete knowledge about prognostic and predictive factors will allow clinicians to identify those patients at higher risk of recurrence who are more likely to benefit from adjuvant chemotherapy, and those who are at lower risk for recurrence and death, and who are thus unlikely to derive any benefit.

Both the quality of surgery and lymph node sampling have been extensively evaluated, and the latter has been most often implicated in assessing prognosis for high-risk colon cancer. Inherent in the accurate staging of a patient with a stage II tumor is the retrieval and examination of an adequate number of lymph nodes. In a series of 35,787 cases of stage II colon cancer from the National Cancer Data Base (NCDB), the 5-year survival rate for stage II colon cancer varied from 64%, if only one or two lymph nodes were examined, to 86% if more than 25 lymph nodes were examined.[21] Although the precise number of lymph nodes that should be examined is not known, the NCDB investigators concluded that at least 13 lymph nodes should be retrieved and declared pathologically negative before a patient is labeled or treated as having stage II disease. Another recent report from a large adjuvant trial of high-risk stage II and stage III patients, in which all patients received adjuvant chemotherapy,[33] also showed a strong correlation between survival and the number of lymph nodes examined, independent of other known prognostic factors. The available data do not support a precise cutoff; however, fewer than six lymph nodes in a colon cancer surgical specimen should prompt careful scrutiny of the operative report and pathology report, and careful consideration of adjuvant therapy.[31,33] In this regard, the Panel strongly supports recent calls for increased standardization of lymph node harvesting and processing methodologies.[35,38]

Other clinical and pathologic features have been identified and used to identify node-negative patients who are high risk.[35] These include patients with bowel obstruction at presentation, perforation of the colon at the tumor site, poor histologic grade, and peritumoral lymphovascular involvement.

Additional prognostic and predictive markers for high-risk colorectal cancer have been retrospectively evaluated, but tested prospectively only a limited basis,[36] or not at all. For example, defective mismatch repair mechanisms result in DNA microsatellite instability (MSI), and tumors may be designated as high-frequency MSI (MSI-H) or low-frequency MSI (MSI-L or MSS). It has been suggested that MSI-H patients seem to have a better prognosis, and may, therefore, not benefit from adjuvant therapy, both because of a higher cure rate with surgery alone, as well as intrinsic resistance to FU.[27] Although there are markers for high-risk stage II colon cancer, it should be cautioned that the identification of such markers may simply indicate a patient at higher risk for recurrence or death, without necessarily leading to the conclusion that adjuvant therapy will be of significant clinical benefit. Until more complete information about predictive factors is available, decisions must continue to be made based on our current knowledge of prognosis and the risks of therapy. Clinicians should carefully review the pathologic report to identify poor prognostic factors such as poor tumor differentiation, a questionable surgical margin, or few sampled nodes, but there is inadequate evidence to support analysis of molecular markers to facilitate adjuvant treatment decision-making.

### What Strategies Can Medical and Surgical Oncologists Use to Discuss the Issue of Adjuvant Chemotherapy With Their Patients in Clinical Practice?

*Summary and recommendations.* The Panel emphasizes that the treatment decision-making process in stage II colon cancer must incorporate patient choice. The responsibility of the oncologist is to estimate the risk of recurrence and cancer-related death with and without chemotherapy and to help the patient make an informed decision. Discussion should center on whether the potential benefits of treatment outweigh the potential risks.

For patients with well-developed numeracy skills, these discussions may incorporate elicitation of the particular threshold of treatment benefit required to accept therapy. For example, after describing the toxicities of adjuvant treatment, the clinician might say, "after hearing what I have explained about this treatment, would you be interested in completing this therapy program if the chances of your being alive in 5 years could be increased by 2% to 4%?" If the answer to this question is "yes," the clinician must indicate that, to date, clinical trials have not been large enough to rule out the possibility of such a small improvement. For patients with less sophisticated numeracy skills, the qualitative descriptors of "small" or "very small" may need to be substituted. Patients who opt for adjuvant treatment must understand that, if there is a benefit to be derived from treatment, the order of magnitude is likely to be a single digit ($< 5\%$)

**Table 3.** Points of Discussion Between the Patient and Physician: The Value of Adjuvant Chemotherapy for Stage II Colon Cancer

| |
|---|
| Ask the patient how much prognostic information he/she wishes to hear during the discussion about whether or not to receive adjuvant chemotherapy for stage II colon cancer[40,41] and whether he/she prefers to hear estimates conveyed as numbers (eg, 3%) or as words (eg, "very small"). |
| It is important to understand the patient's perceptions of risks and benefits and individual patient and tumor factors that might influence decision-making. |
| Discussion should center around whether the potential benefits of treatment outweigh the potential risks. |
| Surgically resected stage II colon cancer patients have a good prognosis with surgery alone (overall 75% to 80% 5-year survival). There are differences in survival for patients with stage IIa (T3N0) versus IIb (T4N0) disease. |
| The potential incremental (relative and absolute) improvement in the cure rate with the addition of chemotherapy is limited, as described in the literature. Patients should be informed that, for typical stage II patients, clinical trials have been adequately large to determine that fluorouracil-based treatment does not improve survival at 5 years by more than 5%. However, smaller incremental improvement in survival at 5 years in the range of 2% to 4%, may be derived from treatment. Clinical trials conducted to date have not been large enough to prove or disprove this possibility. The individual patient needs to consider what magnitude of potential survival benefit is worth the risk of toxicity and commitment to 6 to 8 months of chemotherapy. Patients understand risks and benefits presented in absolute terms more easily than in relative terms.[42,43] |
| Potential risks include the administration of chemotherapy over 6 to 8 months and the potential of late toxicities of newer chemotherapeutic and biologic agents. Toxicity should be discussed in detail, including risk of treatment-related death ($< 1\%$). |
| Definition of risk includes tumor characteristics: T and N stage, tumor differentiation, tumor perforation, vascular invasion, lymphatic invasion, neuroinvasion, and number of lymph nodes analyzed (eg, 5-year survival: 64% for a one– to two–lymph node sample,[21] 86% for $> 25$ lymph nodes[21]; $< 13$ lymph nodes retrieved suggests inadequate staging). It should be emphasized that although these tumor characteristics may be prognostic markers, there are no data to suggest that they serve as predictive markers (ie, tumor characteristics that predict response to adjuvant chemotherapy). |
| Additional potential prognostic and predictive markers can be discussed, including 18q status, microsattelite instability, S phase, TS, etc; however, only retrospective data are available, and, in general, "high-risk" characteristics of a tumor defined by either pathology descriptions or molecular profiling, cannot be used to predict benefit from chemotherapy at this time, even if they appear to suggest poor prognosis. |
| Any comorbidities should be discussed in detail and placed in perspective as to their effect on potential benefit of therapy versus potential risk. |
| A numeracy program, which is a model estimate of survival and is stratified by age, tumor grade, nodal status, and T stage (http://www.mayoclinic.com/calcs), is available. Although this tool does not contain all of the discussion points mentioned above, it may assist the patient and physician in analyzing the individual patient's risk. |

improvement in overall survival at 5 years; and that overall prognosis exceeds 75% survival at 5 years.

Treatment decision making with all stage II patients should include an assessment of other medical problems and anticipated life expectancy. When life expectancy is limited by comorbid illness or very old age, adjuvant treatment offers less potential benefit. To further refine the individual risk for a patient, tools incorporating T and N stage with age and tumor differentiation may also be one way for patients and their physicians to begin discussions about the individual's risk of recurrence and death.[39] Table 3 provides a summary of suggested points of discussion between physicians and patients on the value of adjuvant chemotherapy for stage II colon cancer.

### *Limitations of the Literature*

Why has adjuvant chemotherapy for patients with stage II colon cancer remained a subject of considerable controversy? Buyse and Piedbois[44] have provided a statistical perspective on the benefit of adjuvant therapy in these patients. They attribute the lack of a demonstrable survival benefit to the insufficient number of patients in previously reported trials, to the relatively good prognosis of patients with stage II disease, and to the competing non–cancer related deaths in this population. They further described different approaches to evaluate the benefits of adjuvant therapy in stage II disease. The first approach is to consider the overall effect of therapy regardless of stage, as there are no known a priori biologic reasons for stage II tumors to be different from stage III tumors, or to respond differently to adjuvant treatment. The second approach, which the CCOPGI systematic review followed,[8] was to estimate the benefit in a meta-analysis of only stage II patients. One problem with this approach is the lack of consistent information provided on the stage II subsets in the trials analyzed; furthermore, the percentage of patients with stage II disease in each trial has been relatively small. The third approach is to perform tests of interaction between treatment effect and stage. Although this is the most sensitive approach, it requires adequate information and requires a high number of patients to demonstrate the benefit of therapy.

In conclusion, although it seems likely that the same relative benefit results from adjuvant therapy in both stage II and stage III patients, the number of patients assessed in most individual studies is too small to detect and quantify absolute survival benefits from adjuvant therapy in

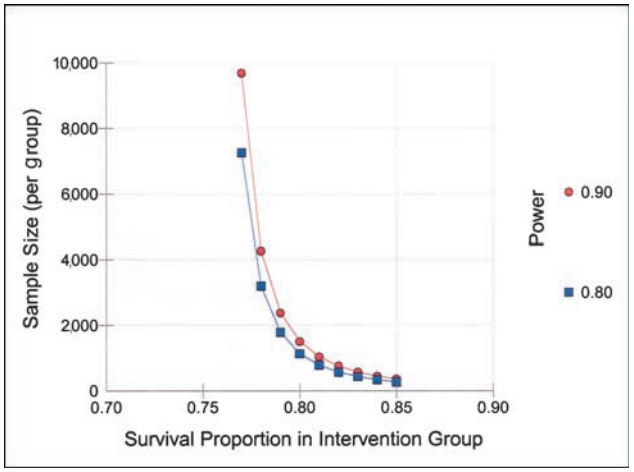


**Fig 2.** Sample size requirements for trial of adjuvant chemotherapy for colon cancer.

stage II disease. Indeed, as shown in Figure 2, a sample size of 9,680 *per group* would be needed to detect a survival difference of 2% between treatment and control arms of a trial (90% power with a significance level of .05). Buyse and Piedbois have calculated that the number of stage II patients required to reliably detect benefit from therapy was twice the number of stage III patients (Table 2).

### Ongoing and Future Clinical Trials

If analyses of past trials have failed to show convincing evidence of a clinically relevant and statistically significant benefit for average risk stage II patients, are there studies that could lead to agreement among clinicians and clinical trialists as to an optimal and standard management strategy? The current lack of agreement has led to variability in trial designs. In Europe, a trial has been developed specifically for stage II colon cancer patients, comparing irinotecan and infusional FU (FOLFIRI) to surgery alone. Patients are stratified on MSI status in this trial. The National Surgical Adjuvant Breast and Bowel Project (NSABP) has included both stage II and stage III colon cancer patients in the statistical design of all of its adjuvant trials. This design strategy will be continued in the newest NSABP colon adjuvant trial, C-08, that will evaluate the combination of oxaliplatin and FU (FOLFOX), with or without bevacizumab. The United States Intergroup stage II colon cancer trial will incorporate promising biologic prognostic variables, evaluating 18q and MSI status on tumor specimens obtained immediately after surgery for stage II patients. High-risk and low-risk profiles will be determined by molecular analysis, with the low-risk patients assigned to observation, and the high-risk patients randomized to FOLFOX or to FOLFOX plus bevacizumab.

### Interpretive Summary

Randomized controlled trials and meta-analyses of randomized controlled trials have failed to detect a survival benefit for adjuvant chemotherapy in stage II colon cancer. Clinical trials conducted to date have accrued adequate numbers of patients to demonstrate that adjuvant FU-containing regimens do not provide a survival benefit that exceeds an absolute 5% improvement in survival at 5 years. However, insufficient numbers of patients have been accrued to determine whether there is a smaller benefit ($< 5\%$).

For the subset of patients with "high-risk" or poor prognosis stage II disease, or in those with inadequate sampling of nodes, the *direct* evidence does not yet support the use of adjuvant therapy outside of clinical trials. However, concern about adequate power from the studies done thus far, and *indirect* evidence based on the experience with stage III disease, might cause some oncologists and patients to explore the use of adjuvant chemotherapy in patients with high-risk stage II disease. In making decisions about the use of adjuvant chemotherapy in stage II high-risk disease, both oncologists and patients need to discuss the implicit assumptions inherent in generalizing from the results of trials in stage III disease, and be aware of the potential, yet uncertain, benefits of treatment and the accompanying side effects. Decisions about appropriate care for an individual patient must always depend on other factors, including patient and physician perceptions of risks and benefits, and individual patient and tumor factors that might influence decision-making.

The Panel emphasizes that the treatment decision-making process in stage II colon cancer must incorporate patient choice, and that the responsibility of both surgical and medical oncologists is to ensure that the patient has adequate information to make a well-informed decision that incorporates personal preferences. The best estimate of the magnitude of survival benefit from adjuvant chemotherapy, if it exists, is an absolute improvement in the 5-year survival rate of 2% to 4%.[10] While this magnitude of benefit might merit FU-based therapy for some patients, it does not for many others.[45] The decision-making process should incorporate information about the individual patient's tumor characteristics, comorbid illnesses, and natural remaining life expectancy (based on estimates of physiologic age), as well as the risks and benefits of treatment (Table 3).

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**Appendix:** ASCO Stage II Adjuvant Chemotherapy Expert Panel

| Investigator | Institution |
|---|---|
| Al B. Benson III, MD, Co-Chair | Northwestern University Feinberg School of Medicine |
| Daniel G. Haller, MD, Co-Chair | University of Pennsylvania Cancer Center |
| Alfred M. Cohen, MD | Lucille P. Markey Cancer Center |
| Alvaro Tell Figueredo, MD | Hamilton Regional Cancer Centre |
| Patrick J. Flynn, MD | Minnesota Oncology Hematology P.A. |
| Monika K. Krzyzanowska, MD | Dana-Farber Cancer Institute |
| Jean Maroun, MD | Ottawa Regional Cancer Center |
| Pamela McAllister, PhD | Marti Nelson Cancer Foundation |
| Deborah Schrag, MD | Memorial Sloan-Kettering Cancer Center |
| Eric Van Cutsem, MD, PhD | University Hospital Gasthuisberg, Belgium |
| Melissa Brouwers, PhD, Ex-Officio | McMaster University |
| Manya Charette, Ex-Officio | McMaster University |

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