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Challenges in the management of stage II colon cancer

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Abstract

Approximately one-third of patients diagnosed with early stage colorectal cancer (CRC) will present with lymph node involvement (stage III) and about one-quarter with transmural bowel wall invasion but negative lymph nodes (stage II). Adjuvant chemotherapy targets micrometastatic disease to improve disease-free and overall survival. While beneficial for stage III patients, the role of adjuvant chemotherapy is unestablished in Stage II. This likely relates to the improved outcome of these patients, and the difficulties in developing studies with sufficient power to document benefit in this patient population. However, recent investigation also suggests that molecular differences may exist between stage II and III cancers and within stage II patients. Validated pathologic prognostic markers are useful at identifying stage II patients at high risk for recurrence for whom the benefit from adjuvant chemotherapy may be greater. Such high risk features include higher T stage (T4 versus T3), suboptimal lymph node retrieval, presence of lymphovascular invasion, bowel obstruction or bowel perforation, and poorly differentiated histology. However, for the majority of patients who do not carry any of these adverse features and are classified as “average risk” stage II patients, the benefit of adjuvant chemotherapy remains unproven. Emerging understanding of the underlying biology of stage II colon cancer has identified molecular markers which may change this paradigm and improve our risk assessment and treatment choices for stage II disease. Assessment of microsatellite stability which serves as a marker for DNA mismatch repair system function has emerged as a useful tool for risk stratification of patients with Stage II CRC. Patients with high frequency of microsatellite instability (MSI-H) have been shown to have increased overall survival and limited benefit from 5FU based chemotherapy. Additional research is necessary to clearly define the most appropriate way to use this marker and others in routine clinical practice.

Introduction

Several studies have conclusively demonstrated the benefit of adjuvant infusional and bolus 5-FU plus oxaliplatin (FOLFOX) in patients with stage III colon cancer with improvement in disease free survival (DFS) to nearly 75% [1–7]. For stage II disease, where the typical patient with “average risk” has a 70–80% chance of cure with surgery alone, the benefit of adjuvant chemotherapy remains controversial [8, 9]. The presence of traditional “high-risk” pathologic factors in stage II colon cancer can identify a subgroup of patients with a

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recurrence risk approximating stage III disease. Newer molecular markers can further define patient subsets with stage II disease that may benefit from adjuvant therapy. While discussing adjuvant chemotherapy for stage II colon cancer, we must consider both prognostic and predictive markers. Prognostic markers predict survival independent of treatment effect, while predictive markers predict benefit from a particular therapy. While prognostic markers have been validated in stage II disease, limited data exist for predictive markers.

Pathologic markers

T stage

The American Joint Committee of Cancer (AJCC) 7th edition staging manual classifies stage II tumors as T3 with invasion through the muscularis propria or into pericolic tissue, and T4 with invasion into adherent organs [10]. T4 tumors are subclassified into T4a (penetrating visceral peritoneum) and T4b (penetrating other organs/structures). A SEER database analysis supported the revised staging by demonstrating significant differences in 5 year relative survival rates between T3 and T4 tumors within stage II disease (T3N0 87.5% $\pm$ 0.4%; T4N0 71.5% $\pm$ 0.8%) and between T4a and T4b disease (T4a 79.6% $\pm$ 1%; T4b 58.4% $\pm$ 1.3%) [11].

The prognostic significance of T stage was demonstrated by a pooled analysis of >3,000 stage II/III patients treated with surgery alone versus surgery plus adjuvant 5-FU based therapy [12]. A univariate analysis of prognostic factors for disease free survival (DFS) demonstrated a correlation between deeply penetrating tumors and inferior survival (hazard ratio (HR) of 1.21 for T3 and 1.81 for T4 tumors).

Early retrospective studies suggested a potential role for adjuvant external beam radiotherapy for T4 tumors with nodal involvement or penetrance into adjacent tissue [13–16]. Willett et al reported improved local control and recurrence free survival in patients with T4 tumors receiving adjuvant radiotherapy [17]. Based on these findings, Intergroup 0130 evaluated adjuvant radiotherapy (45–50.4 Gy) in T4 or T3 node positive tumors following adjuvant 5-FU chemotherapy [18]. Although closed early due to slow accrual, radiotherapy appeared to increase toxicity without improving DFS or OS. Although this study had limited power to detect meaningful differences, the routine use of radiotherapy is not recommended. For T4 tumors that extend to fixed structures such as the pelvic side wall, radiotherapy may still have a role.

Lymph Node Retrieval

An additional validated prognostic marker is the number of lymph nodes resected during curative surgery. Intergroup 0089 study was a large randomized controlled trial comparing three different 5FU based chemotherapy regimens for stage II and III CRC. A secondary analysis demonstrated a clear prognostic impact for retrieval of a greater number of lymph nodes in stage II and III colon cancer, with a greater effect in stage II disease [19, 20]. Among patients with node negative disease, OS and cancer specific survival (CSS) were improved with increased number of lymph nodes removed ($p=0.005$ and 0.007 respectively). A SEER database analysis demonstrated a strong correlation between increasing number of examined lymph nodes and improved survival, particularly for T3 tumors. These observations resulted in broad adoption of a minimum of 12 examined lymph nodes for proper staging of colon cancer [19, 21–27]. Bilimoria et al. evaluated the rate of adequate lymph node retrieval among stage II colon cancer patients [28]. More lymph nodes were removed during right versus left colectomies and in high versus low volume centers. A recent analysis confirmed higher percentages of adequate lymph node retrieval in NCCN centers versus SEER database centers (92 versus 58%) [29]. This prognostic marker can be

improved with greater awareness by surgeons and pathologists. Our group demonstrated increased lymph node retrieval in a large community cancer network following a targeted educational initiative [30].

Additional high-risk pathologic features

Other pathologic factors associated with increased risk of recurrence in stage II disease include lymphatic and/or vascular invasion, poorly differentiated histology, and evidence of obstruction and/or perforation at presentation [12, 31–33]. Most of these factors were analyzed in series combining stage II and III tumors with the aim to draw conclusions regarding their prognostic role. Gill et al. identified histologic grade (high versus low) as an independent prognostic marker associated with worse DFS (HR=1.34; $p=0.0017$) [12]. An important cautionary note is that tumors with high microsatellite instability may frequently demonstrate a high grade phenotype and would be considered low risk.

The prognostic significance of bowel obstruction was demonstrated in a pooled analysis of over 1,000 patients from two NSABP studies [33]. Patients presenting with bowel obstruction had shorter DFS ($p=0.0007$), with the highest incidence of bowel obstruction noted for descending colon tumors (21%). This impact was maintained when controlling for nodal involvement, age, sex, and tumor location.

Lymphatic and/or vascular invasion have been shown to correlate with increased incidence of nodal involvement and liver metastases and thus are included as a high risk feature of stage II tumors [34–38]. Ouchi and colleagues reported an increasing incidence of vascular invasion when comparing tumor samples from patients with early stage tumors, metachronous liver metastases, and synchronous liver metastases (15.4%, 75%, and 89.5%, respectively; $p<0.001$) [35]. Wasif et al. reported occult nodal involvement by cytokeratin stain in 23.4% of early stage colon cancers, which correlated with high histologic grade ($p=0.022$) and lymphovascular invasion ($p<0.001$) [39]. All these studies point out the high risk of lymph node involvement and development of distant metastases for tumors with lymphovascular invasion. Patients with tumors with this characteristic should be considered for adjuvant therapy.

In general, traditional pathologic features such as T4 tumors, obstruction, perforation, high grade histology, and lymphovascular invasion are poor prognostic features. However, they cannot predict for chemotherapy benefit. Molecular markers may ultimately provide prognostic and predictive information.

Molecular markers

Increasing understanding of colon cancer biology has identified potential molecular markers to risk-stratify early stage colon cancer patients. This may be most useful for patients with stage II colon cancer where adjuvant chemotherapy is debated. However, tests utilizing immunohistochemistry or gene expression analysis are costly. In addition, proper validation of markers, techniques, and cutoff values is critical.

Microsatellite instability

Microsatellites are short, tandemly repeated DNA sequences present throughout the genome. They are easily susceptible to errors of DNA replication, particularly in the presence of a defective mismatch repair (MMR) system. Thus, microsatellite stability can serve as a surrogate for normally functioning DNA MMR. In colon cancer, mutations in the MMR system lead to a high frequency of microsatellite instability (MSI). Inherited germ line mutations in MMR and the presence of MSI are found in approximately 50% of patients with a family history that fulfills the Amsterdam criteria [40–46]. These defects result most

commonly from alterations of the MLH1, MSH2 or MSH6 mismatch repair genes [43, 45, 47, 48]. Loss of MLH1 expression due to methylation of its promoter has also been described in up to 15% of sporadic colon cancer [49, 50].

Tumors are classified according to the percentage of abnormal microsatellite regions present as MSI-high (MSI-H) (>30–40%), MSI-low (<30–40%) or microsatellite stable (MSS – no abnormalities) [51]. MSI-H status is present in 22% of stage II and 12% of stage III colon cancers and associated with younger age, higher T stage, lower N stage, right-sided lesions, and poorly differentiated histology [51–54]. Testing for microsatellite instability as a marker for MMR can be performed at the gene level (gold standard) or the protein level using immunohistochemistry (IHC). At the protein level, IHC is typically performed for the most common protein alterations hMLH1 and hMSH2 and due to its low cost and rapidity of the results is the recommended initial screening test [53, 55–57].

The improved prognosis of patients with MSI-H tumors was initially demonstrated by Gryfe et al [41]. Ribic et al subsequently reported improved 5 year survival among patients with stage II/III colon cancer and MSI-H tumors compared to MSI-low/MSS tumors (HR for death 0.31, $p=0.004$) [58]. In a multivariate analysis, MSI-H tumors were associated with improved OS (HR for death 0.61, $p=0.03$). Similar findings were later reported in a pooled analysis of over 7,000 early stage colon cancer patients treated with adjuvant 5-FU (HR for OS 0.65) [59]. This survival benefit was similar for stage II and III tumors and independent of treatment setting. Data from the PETACC III, EORTC 40993, and SAKK 60-00 studies similarly demonstrated improved recurrence free survival (RFS) and OS among patients with MSI-H compared with MSS tumors (HR for OS 0.45, $p=0.0003$). A subgroup analysis revealed a stronger effect among stage II patients (RFS: HR=0.26, $p=0.004$; OS: HR= 0.153, $p=0.009$) compared with stage III patients (RFS: HR= 0.69, $p=0.06$; OS: HR= 0.674, $p=0.09$) [52, 60]. Similar observations of improved outcome among patients with MSI-H tumors regardless of other pathologic markers have been reported [41, 58, 61].

While stage II patients with MSI-H tumors have improved outcome, the role of MSI as a predictive marker is less clear. Popat et al. reported a lack of benefit from adjuvant 5-FU among patients with MSI-H tumors (HR for OS 1.24) [59]. In the analysis by Ribic et al., patients with MSI-H tumors did not benefit from adjuvant 5-FU (HR for death 2.17, $p=0.10$) while those with MSI-low/MSS tumors did (HR for death 0.69, $p=0.02$). Sargent et al. similarly reported a DFS and OS benefit for adjuvant 5-FU for patients with proficient MMR (OS: HR=0.69, $p=0.047$; DFS: HR=0.59, $p=0.004$) but not deficient MMR (OS: HR=1.26, $p=0.68$; DFS: HR=1.41, $p=0.53$) in a pooled analysis of 341 tumors from intergroup trials [62]. *In vitro* models also demonstrate resistance to 5-FU in MSI-H tumor samples [63, 64]. In contrast, a retrospective analysis of NSABP trials did not identify any interaction between MSI status and adjuvant chemotherapy benefit, suggesting biology rather than therapy might define outcome [65]. MSI status has also been examined as a predictor of irinotecan adjuvant therapy in stage 3 patients, with conflicting results [52, 66].

In summary, MSI status can be used in the clinic as a prognostic tool to identify a subgroup of stage II patients with improved prognosis. ECOG 5202 was a recently closed study that may provide prospective validation of MSI as a prognostic marker (Figure 1). Patients with stage 2 colon cancer underwent MSI and 18q LOH evaluation (see below) and were classified into low or high risk. High risk patients were randomized to FOLFOX or FOLFOX plus bevacizumab while low risk patients were observed. Although this design limits any predictive evaluation of MSI, the prognostic impact of MSI-H status can be assessed. However, recent reports demonstrating no benefit for the addition of bevacizumab to FOLFOX adjuvant treatment forced premature closure of ECOG 5202 [67–70]. Regarding the predictive impact of MSI status, the NCCN guidelines were recently updated

to recommend MSI testing for patients with stage II colon cancer if considering fluoropyrimidine therapy only [26]. Based on the above data, patients with MSI-H stage II colon cancer without any additional high risk features would fall into the “low risk” category and may be observed without any chemotherapy. Patients with MSI-H tumors but with traditional high-risk pathologic features (i.e. lymphovascular invasion) represent a challenging subset without a clear standard of care.

18qLOH – 18q Loss of heterozygosity

Loss of heterozygosity (LOH) of chromosome 18 is another molecular event which can risk stratify patients with early stage colon cancer. The 18q loci contains several genes with roles in apoptosis and carcinogenesis which may be affected by LOH: *DCC* (Deleted in Colon Cancer), *Smad4*, *Smad2*, and *Smad7* [51, 60, 71–73]. Watanabe and colleagues found 18qLOH in 49% of high risk stage II and stage III CRC samples, with significantly shorter DFS and OS compared to retained 18q (DFS 44% versus 64%, $p=0.002$; OS 50% versus 69%, $p=0.005$) [71]. Among patients with MSS tumors, 18qLOH conferred the worst prognosis. Jen et al. similarly found significantly worse 5 year survival among stage II/III patients with 18qLOH compared to those with normal chromosome 18 (HR: 2.83; $p=0.008$) [74]. Similar findings for a deleterious impact of 18qLOH on overall survival were reported in a large meta-analysis of 27 studies comprising over 2,000 patients with stage I-IV disease (HR=2.0) and numerous other studies [74–81].

A stage specific analysis of the PETACC 3-EORTC 40993-SAKK 60-00 trial found 18qLOH to be of greater prognostic significance in stage II compared to stage III patients and suggested *Smad4* as a potential independent prognostic marker [60]. The frequency of 18q alterations among stage II and III patients was 63% and 70% respectively ($p=0.04$). Alazzouzi et al. examined early stage colon cancer samples for IHC expression and mutation analysis of *Smad4* [82]. Tumors with high expression of *Smad4* had improved OS ($p<0.025$) and DFS ($p<0.013$) compared to low-expressing tumors. Low *Smad4* expression among patients receiving 5-FU based adjuvant chemotherapy was also associated with a shorter median survival (1.4 years versus >9 years) [83]. Similar reports are available from a small series by Boulay and colleagues linking *Smad7* overexpression to inferior outcomes (OS HR=2.1, $p=0.02$) [84].

Data evaluating the predictive role of 18qLOH are limited. The analysis by Watanabe et al included 460 patients with stage III and high risk stage II colon cancer treated with adjuvant 5-FU based chemotherapy [71]. However, the lack of a control group and the small number of stage II patients limits predictive conclusions. In the UK AXIS trial, in which patients with early stage colon cancer were randomized between adjuvant 5FU via portal vein infusion and observation, tumor samples were analyzed for 18qLOH [85]. This analysis tested 18qLOH at two loci: D18S61 and D18S851. While patients with LOH at both loci or at the D18S61 locus had limited benefit from adjuvant therapy, LOH at the D18S851 locus did not influence treatment outcome [85]. This study emphasizes the need for better understanding of the significance of 18qLOH at the various loci.

Gene expression profiling

Gene expression profiling was pioneered in breast cancer, where the commercial assay Oncotype DX® serves as a prognostic and predictive tool for patients with early stage node negative estrogen receptor positive breast cancer [86–88]. The initial analysis in colon cancer was performed by Wang and colleagues who analyzed RNA transcripts from 74 patients with stage II colon cancer and identified a 23-gene signature with 72% sensitivity and 83% specificity to predict recurrence. A scale was developed where patients with a high risk score had a 13-fold increased risk of recurrence within 3 years compared to those with a

low risk score [89]. Barrier et al. reported on a 30 gene prognostic set in stage II colon cancer with 85.1% sensitivity and 67.5% specificity for recurrence prediction [90].

The most extensive evaluation of this technique was done by O'Connell et al. on 1,851 stage II/III tumor samples obtained from patients enrolled on NSABP studies (C01, C02, C04, C06) and the Cleveland Clinic [91]. The group developed a recurrence scale classifying patients into low, intermediate, and high recurrence risk and a treatment score predicting response to adjuvant 5-FU chemotherapy. The use of paraffin embedded tissue rather than fresh frozen tissue makes it easier to incorporate this assay into clinical practice. Kerr and colleagues performed an independent clinical validation of this scale in stage II colon cancer patients enrolled into the QUASAR trial where patients were randomized to receive 5FU or observation after surgical resection. The recurrence score (RS) was a strong predictor of recurrence risk ($p=0.004$), shorter DFS ($p=0.01$) and OS ($p=0.04$), with a linear correlation between risk of recurrence and increasing RS [92]. In a multivariate analysis, RS retained its prognostic significance ($p=0.008$). T stage ($p=0.005$) and MSI status ($p<0.001$) were two other independent prognostic markers identified in this analysis. In contrast, the treatment score did not predict for benefit from 5-FU ($p=0.19$). The reported risk of recurrence was 12% at 3 years for the low RS patients, 18% for the intermediate RS patients, and 22% for the high RS patients. Given that the cure rate for stage II patients is commonly cited as 70–80%, the clinical utility of a RS with cure ranges from 78–88% is unclear. Furthermore, since MSI and T stage were identified as independent prognostic makers, this assay may be of greater utility for patients with uninformative T stage or MSI status. Gene expression profiling is not currently recommended for routine use [26].

Guanylyl Cyclase C (GCC)

Expression of guanylyl cyclase C (GCC) in resected lymph nodes is under investigation as another prognostic marker. GCC is an interstitial tumor suppressor which is selectively expressed in normal intestinal epithelium and overexpressed in malignant gastrointestinal cells [93]. Dysregulation of GCC promotes tumorigenesis. A recent study evaluated 257 samples from patients with resected N0 colon cancer and demonstrated that the presence of GCC messenger RNA in lymph nodes was an independent negative prognostic marker (HR for recurrence= 4.66, $p=0.04$; HR for DFS=3.27, $p=0.03$) [94]. However, this initial study found GCC expression in the majority of resected lymph nodes, a fact clearly at odds with the known risk of recurrence in this patient population. Further studies are ongoing.

Selecting therapy for stage II colon cancer – practical considerations

Addition of oxaliplatin

While the role of adjuvant combination chemotherapy is well established in stage III colon cancer, the benefit in stage II patients remains controversial. The MOSAIC study demonstrated improved DFS and OS for stage III patients treated with FOLFOX compared with those treated with 5FU alone (DFS HR=0.80, $P = 0.003$; OS HR = 0.84, $P = .046$ for OS), and established FOLFOX as the current standard of care for adjuvant treatment of stage III [4]. No improvement in DFS or OS was noted in 899 patients with stage II disease (DFS HR=0.84, $p= 0.258$; OS HR=1.00, $p=0.986$). A trend toward improved outcome with oxaliplatin was noted among high risk stage II patients with T4 tumors, bowel obstruction, poorly differentiated tumors, venous invasion, or less than 10 examined lymph nodes (DFS HR=0.72; OS HR=0.91, $P =0.648$). A 6 year update of MOSAIC stratified patients with stage II disease into high risk (T4 or <12 lymph node examined, $n=503$) and low risk categories ($n=396$) and reported no benefit for FOLFOX in the low risk group [95]. Among high risk patients the HR for DFS was 0.76 (95% CI- 0.49–1.06) and for OS 0.81 (95%: 0.52–1.26). NSABP C-07 randomized stage II/III patients to either receive bolus 5-FU/LV

alone or with oxaliplatin. Similar to the MOSAIC trial, while a clear benefit for the addition of oxaliplatin was noted in stage III patients, no benefit was noted in stage II. [7]. It is clear from these data that “average risk” stage II patients (without any high risk features) do not derive additional benefit from adding oxaliplatin to 5-FU. For “high risk” stage II patients (T4 tumors, presence of lymphovascular invasion, obstruction, perforation, or limited lymph node retrieval) it is reasonable to consider FOLFOX in the adjuvant setting due to the strong trend demonstrated in the above studies (Figure 2).

Single agent fluoropyrimidine vs. no treatment

Whether or not fluoropyrimidine monotherapy improves outcome in “average-risk” stage II colon cancer remains unproven. The QUASAR study was the largest study to evaluate the role of adjuvant 5-FU compared with observation alone in 2,963 stage II patients with colon and rectal cancer (71% and 29% respectively). Adjuvant 5-FU decreased the risk of recurrence compared to observation alone (relative risk (RR) for colon cancer=0.78, $p=0.004$; RR for rectal cancer =0.68, $p=0.004$) [96]. The relative risk of death from any cause was improved for treated patients with stage II colon cancer (0.84; $p=0.046$), which translated into an absolute survival improvement of 3.6%. Other studies evaluating 5-FU based therapy in stage II colon cancer have had smaller sample sizes, necessitating subgroup analyses with limited power (Table 2) [4, 5, 11, 83–85]. Thus, meta-analyses have been conducted [4, 15, 86, 87]. The IMPACT B2 analysis pooled 5 randomized clinical trials evaluating 5-FU based therapy to observation in the adjuvant setting [1]. The analysis included 1,016 stage II patients followed for a median of 5.75 years. No significant improvement in event free survival (EFS) (HR=0.83, 90%CI 0.72 to 1.07) or OS (HR=0.86, 90% CI 0.68 to 1.07) was noted in treated patients compared with controls. Similarly, the Cochrane Collaboration analysis evaluated 18 studies comparing various adjuvant chemotherapy regimens to observation in over 8,000 patients with stage II colon cancer and detected no survival improvement with treatment (HR=0.96; 95% CI 0.87–1.05) but a small improvement in DFS (HR of 0.83, 95% CI: 0.75–0.91) [97].

Average-Risk Patients

For patients without any high-risk pathologic features (i.e. T4 tumors, lymphovascular invasion, obstruction, perforation, <12 lymph nodes examined), observation or single agent fluoropyrimidine is appropriate. Oxaliplatin only increases toxicity in this patient population and is not recommended [26]. The survival benefit of single agent fluoropyrimidine in this setting is at most 5%. A sample size of over 9,000 patients would be required to reliably detect this difference in a clinical trial [98]. Physicians should discuss with patients disease natural history, life expectancy, and benefit from adjuvant therapy (Figure 2).

MSI-H tumors

Current data support avoiding adjuvant chemotherapy in stage II patients with MSI-H tumors without high risk pathologic features. No data exist regarding the role of FOLFOX in this patient population, and conflicting data exist regarding the utility of irinotecan. Further study is warranted. Whether or not to recommend adjuvant therapy for stage II patients with MSI-H tumors and other high-risk features (i.e. lymphovascular invasion) remains a subject of debate.

The elderly

Despite a median age of 71 for colon cancer, the elderly are underrepresented in clinical trials [99]. Schrag et al performed a SEER database pooled analysis of 3,151 Medicare stage II colon cancer patients (aged 65–75) [9]. There was no difference in five year survival between treated and untreated patients (78% versus 75% respectively). A subgroup analysis

by age of the QUASAR study included approximately 20% of patients (663) 70 years and older and did not show any decreased recurrence rate with adjuvant chemotherapy in this group (HR=1.13) [96]. The ACCENT database included patient information from six international adjuvant chemotherapy trials combining 5FU with oxaliplatin or irinotecan. A pooled analysis also did not demonstrate any benefit for adjuvant chemotherapy in older individuals (HR for OS: 1.14; HR for DFS: 1.11) [100]. A similar trend was noted in the MOSAIC study which reported limited benefit from adjuvant FOLFOX in patients >65 years of age with stage II and III colon cancer [4, 101]. In contrast, in a pooled analysis of over 3,000 stage II/III, Sargent et al. noted similar benefit in elderly patients and the group as a whole without significant differences in toxicity [102]. Similar findings were later reported by Fata and colleagues [103].

Treatment decision-making for elderly patients with stage II colon cancer must be individualized with careful attention to the patient's functional status, life expectancy and risk of treatment related morbidity. It is clear that combination chemotherapy provides less benefit in this group of patients, although for the fit elderly with reasonable life expectancy, combination therapy could be considered.

Summary

Adjuvant therapy for stage II colon cancer remains a topic of debate, primarily for “average-risk” patients without clear pathologic risk factors. As our knowledge of underlying biology expands, molecular markers will play a more prominent role in our decision-making. To date, MSI-H status has emerged as the marker most closely linked to improved outcome and limited benefit from adjuvant fluoropyrimidine therapy. Much work still remains to be done to improve our ability to risk-stratify patients and improve outcomes while limiting toxicity. Ongoing prospective studies and enhanced participation in clinical trials is critical for continued progress in this field.

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Figure 1. Schema of ECOG 5202

Figure 2. Treatment algorithm for patients with stage II colon cancer

5FU/LV-5 - fluorouracil and leucovorin; FOLFOX- 5FU, leucovorin and oxaliplatin; MSI – microsatellite instability; 18qLOH – loss of heterozygosity of chromosome 18q.

Table 1

Major prospective studies and meta-analyses evaluating 5-FU based adjuvant therapy for stage II colon cancer

Study	Number of patients with stage II colon	Treatments	Recurrence	Overall survival (OS)
Quasar [96]	2963	5FU/leucovorin observation	RR for recurrence of colon = 0.78 (p=0.004)* RR for recurrence of rectal =0.68 (p=0.004)*	RR for death for colon cancer=0.84 (0.046) RR for death for rectal cancer=0.77 (p=0.05)
NCCTG (1989) [104]	36 35 33	Surgery alone (control) Levamisole alone 5FU+Levamisole	Control vs Levamisole: p=0.43 Control vs. Levamisole +5FU: p=0.26	Control vs Levamisole: p=0.43 Control vs. Levamisole +5FU:p=0.26
INT-0035 [8]	159 159	Observation 5FU+Levamisole	RR for recurrence=0.69 (p=0.10)	No significant difference
NACCP (2001) [105]	235 233	Observation 5FU+Levamisole	RFS=65% RFS=71%	OS=70% OS=78%
Francini et al. [106]	60 59	Observation 5FU+folic acid	DFS=77% DFS=83%	OS=86% OS=89%
Glimelius et al **. [107]	1135	Observation 5FU±folic acid±Levamisole	No difference	No difference
IMPACT B2 **. [1]	509 507	Observation 5FU+Leucovorin	EFS=73% EFS=76%	OS=80% OS=82%
Cochrane Review **. [97]	8,642	Observation Adjuvant chemotherapy	Relative risk for recurrence=0.83	Relative risk= 0.96

* achieving statistical significance p<0.05.

** Meta-analyses.

RR-relative risk; 5FU- 5 fluorouracil; RFS- recurrence free survival; EFS- event free survival; OS- overall survival.