Chapter 19

Adjuvant Systemic Therapy in Stage II and III Colon Cancer

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Additional information is available at the end of the chapter

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Abstract

The prognosis of colon cancer is primarily determined through staging of the disease. After curative surgery, clinically occult micrometastases are thought to be the major source of disease recurrence. The main aim of postoperative systemic treatment is to eradicate micrometastases, thereby improving outcomes with an increased cure rate. Adjuvant systemic chemotherapy is indicated for patients with stage III colon cancer, as well as for patients with high-risk stage II colon cancer. Prognostic and predictive markers that identify heterogeneous groups are needed to implement tailored therapeutic strategies. Due to the lack of evidence of predictive value of multigene assays in terms of potential value of adjuvant chemotherapy, multigene assays should not be used to determine adjuvant therapy. The standard treatment for most patients with stage III disease is a combination of oxaliplatin with infusional and bolus 5-fluorouracil (5-FU) or with an oral agent such as capecitabine, which has equivalent results. Adjuvant therapy should not be administered to all patients with stage II colon cancer. High-risk stage II patients may be considered as an eligible group for adjuvant therapy after a complete discussion. There is no high level of evidence to use irinotecan-based combination chemotherapies in the adjuvant setting. The antiangiogenic agent bevacizumab in combination with standard adjuvant chemotherapy regimens also failed to improve outcomes, as did the EGFR agent cetuximab.

Keywords: Adjuvant, Chemotherapy, Colon cancer, Stage II, Stage III

1. Introduction

Colon cancer is heterogeneous in clinical behavior and in the molecular mechanisms underlying its pathogenesis. The prognosis of colon cancer is primarily determined by staging the

disease. TNM is the main staging system in routine clinical practice [1]. In the adjuvant setting, TNM classification remains the only validated prognostic tool.

Nearly a quarter of the 93,090 new diagnoses of colon cancer per annum in the United States are predicted to be stage II disease, which is characterized by the absence of lymph node metastases (i.e., N0 disease), subdivided into IIA (invasion of T3 lesions through the muscularis propria into pericolorectal tissues) and IIB (T4a lesions, with direction invasion or adherence of the tumor to other organs or structures) [1, 2]. Five-year survival rates for stage II patients after surgery alone range from 72 to 85% [3].

Stage III disease includes colon cancer with any T and N1–2 and M0 [1]. According to TNM staging, patients with stage III disease have various long-term outcomes based on T and N stages at initial diagnosis. Tumors with T1–2 and N1 involvements are classified as stage IIIA and they result in 83% 5-year overall survival (OS) rates. Tumors with T3–4 and N1 involvements are staged as stage IIIB with 64% 5-year OS. Patients with stage IIIC colon cancer with any T and N2 involvement have the worst prognosis with 44% 5-year OS. Thus, approximately 40% of patients with stage III colon cancer experience disease recurrence and many lose the chance of cure during the course.

After curative surgery, clinically occult micrometastases are thought to be the major source of disease recurrence. Adjuvant therapy is administered with the fundamental aim of reducing any probability of disease recurrence and to annihilate micrometastases after the potentially curative resection of colon cancer. Despite many studies representing an augmentation of survival in patients with stage III (node-positive) colon cancer as a result of adjuvant systemic chemotherapy, its impact in resected stage II colon cancer still remains unproven in defiance of several related trials.

In this chapter, the principles of adjuvant systemic therapy in stage II and III colon cancers will be discussed with a review of the literature. Chemotherapy options will be discussed by using findings from clinical trials. Prognostic factors and potential predictive markers of possible benefit of adjuvant systemic therapy will be reviewed, and whether current knowledge in genetic expression profiling helps the physician during decision making will be highlighted.

2. Adjuvant systemic treatment in stage III colon cancer

(a) Fluorouracil with levamisole or leucovorin in stage III colon cancer

Up to the late 1980s, the role of systemic chemotherapy in the adjuvant setting was not established in colon cancer. In 1988, a systematic review of randomized controlled trials about adjuvant therapy of colorectal cancer was performed [4]. The findings of trials evaluating radiotherapy or chemotherapy were combined. Fluorouracil-containing regimens were shown to provide a small OS benefit (odds ratio [OR]: 0.83, 95% confidence interval [CI]: [0.70–0.98]). All other combinations of trials failed to demonstrate statistically significant OS benefit between treated and control patients.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has conducted several clinical trials on adjuvant chemotherapy and compared different adjuvant chemotherapy regimens or adjuvant chemotherapy versus surgery alone in patients with stage II and III colon cancer (**Table 1**). NSABP C-01 trial was the first adjuvant chemotherapy trial of NSABP conducted between November 1977 and February 1983 and included 1166 patients with stage II and III carcinomas of the colon [5]. Patients were randomized to one of three therapeutic categories: (1) no further treatment following curative resection (394 patients); (2) postoperative chemotherapy consisting of 5-fluorouracil (5-FU), semustine, and vincristine (379 patients); or (3) postoperative BCG (393 patients). A comparison between patients who received postoperative adjuvant chemotherapy and those treated with surgery alone indicated that there was an overall improvement in disease-free survival (DFS) (P = 0.02) and survival (P = 0.05) in favor of the chemotherapy-treated group. At 5 years of follow-up, patients treated with surgery alone were at 1.29-times the risk of developing a treatment failure and at 1.31-times the likelihood of dying compared with similar patients treated with combination adjuvant chemotherapy. The findings from this study were the first from a randomized prospective clinical trial to demonstrate that a significant DFS and survival benefit can be achieved with postoperative adjuvant chemotherapy in patients with stage II and III carcinomas of the colon who undergo curative resection.

Trial [reference number]	**Stages included**	**Regimens**	**Number of patients**	**DFS**	**OS**
NSABP C-01 [5]	II, III			**5-year DFS**	**5-year OS**
		(1) No adjuvant therapy	394		
		(2) 5-FU/semustine/ vincristine (MOF)	379	P = 0.02	P = 0.05
		(3) BCG	393		
NSABP C-02 [6]	All stages			**4-year DFS**	**4-year OS**
		(1) No adjuvant therapy	581	64%	73%
		(2) Portal vein infusion of 5-FU	577	74%	81%
				P = 0.02	P = 0.07
INT-0035 [7]	III			**3-year DFS**	**3-year OS**
		(1) No adjuvant therapy	315	<60%	47%

Trial [reference number]	Stages included	Regimens	Number of patients	DFS	OS
		(2) Levamisole	310	<60%	49%
		(3) 5-FU plus levamisole	304	>60%	60%
				P < 0.0001	*P* = 0.0007
NCCTG and Mayo Clinic by Laurie et al. [8]	II, III			**3-year DFS**	**3-year OS**
		(1) No adjuvant therapy	135		
		(2) Levamisole	130	*P* = 0.05	*P* = 0.12
		(3) 5-FU plus levamisole	136	*P* = 0.003	*P* = 0.09
NSABP C-03 [9]	II, III			**3-year DFS**	**3-year OS**
		(1) 5-FU/semustine /vincristine (MOF)	524	64%	77%
		(2) 5-FU plus leucovorin (LV) (5-FU/LV)	521	73%	84%
				P = 0.0004	*P* = 0.003
NSABP C-04 [10]	II, III			**5-year DFS**	**5-year OS**
		(1) 5-FU/LV	691	65%	74%
		(2) 5-FU plus levamisole	691	60%	70%
		(3) 5-FU/LV plus levamisole	696	55%	75%
NSABP C-05 [6]	II, III			4-year DFS	4-year OS
		(1) 5-FU/LV	1088	69%	80%
		(2) 5-FU/LV plus alpha-interferon	1088	70%	81%
				P = 0.34	*P* = 0.41
INT-0089 [11]	II, III			5-year DFS	5-year OS
		(1) 5-FU/LV Mayo Clinic	908	60	66
		(2) 5-FU/LV	910	58	66

Trial [reference number]	Stages included	Regimens	Number of patients	DFS	OS
		Roswell Park			
		(3) 5-FU plus levamisole for 6 months	802	55	64
		(4) 5-FU plus levamisole for 12 months	780	49	54
				$P > 0.05$	$P > 0.05$

DFS, disease-free interval; OS, overall survival.

Table 1. The randomized prospective clinical trials comparing adjuvant treatment with fluorouracil, fluorouracil/levamisole, or fluorouracil/leucovorin and surgery alone in patients with resected colon cancer.

In a randomized cooperative trial performed by Lauri et al., 401 eligible patients with resected stage II and III colorectal carcinoma were randomized to no adjuvant therapy or to adjuvant single-agent levamisole or to adjuvant levamisole plus fluorouracil (5-FU/levamisole). 5-FU/levamisole, and to a lesser extent single-agent levamisole, resulted in decreased cancer recurrence compared with no adjuvant therapy [8]. Both single-agent levamisole and 5-FU/levamisole regimens resulted in significant overall improvements in survival. These improvements reached borderline significance only for stage III patients treated with 5-FU/levamisole ($P = 0.03$). Adjuvant chemotherapy was found to be clinically safe.

In the INT-0035 trial, 5-FU/levamisole reduced the recurrence rate by 40% ($P < 0.0001$) and the death rate by 33% ($P = 0.0007$) in patients with stage III colon cancer. The regimen was found to be tolerable and patient compliance was excellent. There was no evidence of late adverse effects [7]. After these findings were reported, 5-FU/levamisole was recommended as adjuvant chemotherapy for patients with resected stage III colon cancer in a consensus meeting held by the National Institute of Health [12].

The results from the NSABP C-03 trial indicated that fluorouracil plus leucovorin (5-FU/LV) was an active treatment regimen for colon cancer in the adjuvant setting, which precipitated a head-to-head comparison between 5-FU/levamisole and 5-FU/LV [9]. In the landmark NSABP C-04 trial, more than 2000 patients with stage II and III colon cancer were randomized between treatment with 5-FU/LV, 5-FU/levamisole, or 5-FU/LV with levamisole [10]. In terms of DFS and OS, 5-FU/LV demonstrated superiority over 5-FU/levamisole as the standard-of-care adjuvant chemotherapy for patients with both stage II and III colon cancers.

In the randomized Intergroup 0089 trial (INT 0089), the efficacy of 5-FU/LV and 5-FU/levamisole as well as the two most common dose/schedules for the administration of 5-FU/LV, the Roswell Park (5-FU and high-dose LV) and the Mayo Clinic (5-FU and low-dose LV) regimens, were compared in patients with stage II and III patients [11]. The four treatment arms were 5-FU/levamisole (12-month protocol), 5-FU/high-dose LV (Roswell Park, 7 months),

5-FU/low-dose LV (Mayo, 6 months), and 5-FU/LV/levamisole (6 months). All treatment arms were found to be equivalent in terms of both 5-year DFS and OS with a median of 10 years. These results provided a choice for patient treatment schedules based on toxicities and other existing factors rather than on maximization of survival outcome [13].

The important messages from all these findings were as follows: (1) adjuvant 5-FU/LV administered for 6 months was equivalent to 5-FU/levamisole administered for 12 months, (2) two schedules of 5-FU/LV (Mayo Clinic for 6 months, Roswell Park for four cycles) showed different toxicity profiles but same efficacy, and (3) the incorporation of levamisole to 5-FU/LV did not improve long-term outcomes [14].

In stage III colon cancer, adjuvant systemic treatment became the standard treatment approach because it results in improvement in DFS and OS with an approximately 30% relative reduction in the risk of disease recurrence and a 20–30% relative reduction in mortality [6, 15].

(b) Oxaliplatin with 5-FU/LV in stage III colon cancer

The demonstration that adjuvant therapy with 5-FU/levamisole reduced the mortality rate among patients with stage III colon cancer prompted several trials, which established 6 months of treatment with 5-FU/LV as the standard adjuvant chemotherapy for stage III colon cancer. Furthermore, several cytotoxic agents investigated in the metastatic colorectal cancer setting were considered to hold promise for the adjuvant setting. Several phase III trials investigated potential roles of oxaliplatin and irinotecan in combination with 5-FU/LV in adjuvant setting after their successes in metastatic colorectal cancer [16–19]. In addition, an orally bioavailable prodrug of 5-FU, capecitabine, was introduced into the adjuvant setting and investigated for noninferiority to bolus 5-FU/LV (the Mayo Clinic regimen) [20]. Results from trials of these three agents helped shape the current treatment approaches (**Table 2**).

The Multicenter International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) was a large-scale randomized controlled trial performed mainly in Europe, which assessed the efficacy and safety of FOLFOX4 as an adjuvant therapy [19]. One arm of study was the de Gramont Schedule [5-FU/LV regimen, which was a 2-h infusion of LV (200 mg/m^2), a 5-FU bolus (400 mg/m^2), and then a 22-h 5-FU infusion (600 mg/m^2) administered on two consecutive days every 14 days, for 12 cycles]. The FOLFOX4 was the other arm and consisted of the same 5-FU/LV regimen plus a 2-h infusion oxaliplatin (85 mg/m^2) on day 1, given simultaneously with LV. A significant improvement in 5-year DFS and 6-year OS was demonstrated in the FOLFOX4 group compared with the 5-FU/LV group. Ten-year follow-up results were recently reported [23]. The survival benefit of FOLFOX4 was maintained in patients with stage III colon cancer (10-year OS 67% in FOLFOX4 versus 59% in 5-FU/LV, hazard ratio [HR], 0.80; $P = 0.016$). Ten-year OS was similar in both treatment arms in stage II colon cancer (78% in FOLFOX4 versus 80% in 5-FU/LV).

In the NSABP C-07 trial, a total of 2409 eligible patients were randomized to either intravenous (iv) bolus 5-FU/LV (FU 500 mg/m^2 performed weekly for 6 weeks; LV 500 mg/m^2 iv weekly for 6 weeks of each 8-week cycle for three cycles) or 5-FU/LV plus oxaliplatin (FLOX, 85 mg/m^2 iv on days 1, 15, and 29 of each cycle) [24]. OS was found to be similar between treatment groups.

With 8-year median follow-up, FLOX remained superior for DFS (HR, 0.82; $P = 0.002$). The NSABP C-08 trial confirmed that modified sixth version of the FOLFOX regimen (mFOLFOX6) therapy was equivalent to FOLFOX4 therapy in terms of efficacy and safety [22]. Either adjuvant FOLFOX4 or mFOLFOX6 is routinely given as 12 courses (2 weeks per course).

Trial [reference number]	Stages included	Regimens	Number of patients		
NSABP C-07 [21]	II, III			**5-year DFS**	**5-year OS**
		(1) 5-FU/LV	1207	64%	78%
		(2) 5-FU/LV plus oxaliplatin (FLOX)	1200	69%	80%
				$P = 0.002$	$P = 0.08$
MOSAIC [15]	II, III			**6-year DFS**	**6-year OS**
		(1) Bolus plus continuous-infusion 5-FU/LV	1123	67%	76%
		(2) FOLFOX4	1123	73%	79%
				$P = 0.003$	$P = 0.046$
XELOXA [22]				5-year DFS	5-year OS
		(1) Bolus FU/FA		60%	74%
		(2) XELOX*		66%	78%
				$P = 0.0045$	$P = 0.148$

DFS, disease-free interval; OS, overall survival.
*XELOX was given as oxaliplatin 130 mg/m^2 on day 1 plus capecitabine 1000 mg/m^2 twice daily on days 1–14 every 3 weeks for 24 weeks). The bolus FU/FA was given as a standard adjuvant regimen (Mayo Clinic for 24 weeks or Roswell Park for 32 weeks).

Table 2. Clinical trials comparing fluoropyrimidines with fluoropyrimidine plus oxaliplatin-based combination regimens as adjuvant therapy in patients with stage III colon cancer.

The results of these randomized controlled phase III trials have led combination chemotherapy with FOLFOX to be the standard of care for resected stage III colon cancer [15, 19, 21, 24].

(c) Oral fluoropyrimidines with or without oxaliplatin in stage III colon cancer

Continuous 5-FU is administered via indwelling iv catheters in an infusion pump and carries the risk of some complications such as thrombosis, embolism, or infection. Thus, oral fluoropyrimidines were developed with the aim to avoid these complications while preserving the improved tolerability of continuous infusion. Capecitabine, uracil/tegafur (UFT), and S-1 are most the commonly investigated oral fluoropyrimidines in colon cancer. Capecitabine is absorbed intact through the intestinal wall. It is converted to FU after three sequential enzymatic reactions. Tumor cells contain higher levels of thymidine phosphorylase, which is

the final requisite enzyme, than normal cells. This allows capecitabine to selectively accumulate in tumor cells and results in less toxicity or better tolerability.

In NSABP C-06 trial, three cycles of Roswell Park regimen (weekly bolus 5-FU/LV) were compared with five cycles of oral UFT/LV (300 mg/m^2/day with LV 90 mg/day for 4 weeks followed by a 1-week rest period) in 1608 patients with stage II and III colon cancer [25]. No difference was found between the two treatment arms in relapse-free survival (RFS), DFS, and OS. The toxicities and quality of life on the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) instrument were not different between the two arms. Greater fatigue was experienced with UFT in one instrument, but three other instruments demonstrated greater convenience and lower prevalence of symptoms with UFT. A Japanese meta-analysis showed a reduced risk of recurrence (15%) and improved survival (11%) for adjuvant oral chemotherapy (usually UFT or carmofur plus mitomycin C) compared with surgery without chemotherapy in patients with resected stage I, II, and III colon cancers.

The efficacy of capecitabine in stage III colon cancer was assessed in the Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial [20]. The 1987 patients with resected stage III colon cancer were randomized to receive either capecitabine (1250 mg/m^2 twice a day on days 1–14 every 3 weeks for a total of eight cycles) or the bolus 5-FU/LV (Mayo Clinic regimen consisted of 5-FU 425 mg/m^2 and LV 20 mg/m^2 given on days 1–5 as iv boluses every 4 weeks, for six cycles). The capecitabine was found to be at least as effective as 5-FU/LV. In fact, RFS was superior to capecitabine (3-year RFS: 65.5% versus 61.9%, HR, 0.86; P = 0.0407) and there was a trend toward better DFS (3-year DFS: 64.2% versus 60.6%; HR, 0.87; P = 0.0528) and OS (81.3% versus 77.6%; HR, 0.84; P = 0.0706). The required dose reductions were similar between the two treatment groups (42% capecitabine, 44% bolus 5-FU/LV). With the exception of hand-foot syndrome, capecitabine was generally better tolerated with fewer patients experiencing nausea and vomiting, mucositis, diarrhea, and leukopenia.

Although the data from the X-ACT study and NSABP C-06 demonstrated that oral fluoropyrimidine regimen was at least as effective as an iv regimen, UFT was not approved for commercial availability in the Unites States.

S-1 is an oral fluoropyrimidine consisting of tegafur, gimeracil, and oteracil. The antitumor effects of S-1 have been demonstrated in treating various gastrointestinal cancers including metastatic colon cancer when administered as monotherapy or in combination chemotherapy. A randomized phase III study from Japan investigated the efficacy of S-1 as adjuvant chemotherapy for curatively resected stage III colon cancer by evaluating its noninferiority to tegafur-uracil plus LV (UFT/LV) [26]. A total of 1518 patients aged 20–80 years were randomized to receive S-1 (80–120 mg/day on days 1–28 every 42 days; four courses) or UFT/LV (UFT, 300–600 mg/day, and LV, 75 mg/day on days 1–28 every 35 days; five courses). The 3-year DFS rate was 75.5% and 72.5% in the S-1 and UFT/LV group, respectively. The stratified HR for DFS in the S-1 group compared with the UFT/LV group was 0.85, demonstrating the noninferiority of S-1 (noninferiority stratified log-rank test, P < 0.001). In the subgroup analysis, no significant interactions were identified between the major baseline characteristics and the treatment groups. Thus, findings of this Japanese phase III trial confirmed noninferiority of S-1 in DFS at adjuvant setting of stage III colon cancer compared with UFT/LV.

In a multicenter, randomized trial NO16968 (XELOX in Adjuvant Colon Cancer Treatment [XELOXA]), capecitabine plus oxaliplatin (XELOX) was compared with bolus 5-FU/LV as an adjuvant therapy in patients with stage III colon cancer [22] (**Table 2**). XELOX was given as oxaliplatin 130 mg/m^2 on day 1 plus capecitabine 1000 mg/m^2 twice daily on days 1–14 every 3 weeks for 24 weeks). The bolus FU/FA was given as a standard adjuvant regimen (Mayo Clinic for 24 weeks or Roswell Park for 32 weeks). XELOX was superior to bolus FU/FA in terms of DFS with a HR of 0.80 (95% CI: [0.69–0.93]; $P = 0.0045$), corresponding to a 20% relative risk reduction. The 3-year DFS rates for XELOX and FU/FA were 70.9 and 66.5%, respectively. The 4-year and 5-year DFS rates in the XELOX group were 68.4 and 66.1%, respectively, compared with 62.3 and 59.8% in the FU/FA group, demonstrating that the superior efficacy of XELOX versus FU/FA was maintained over time, with increasing differences between study arms. The HR for OS for XELOX compared with FU/FA was 0.87 (95% CI: [0.72–1.05]; $P = 0.1486$). The 5-year OS for XELOX and FU/FA were 77.6% and 74.2%, respectively.

Adjuvant capecitabine with or without oxaliplatin versus 5-FU/LV with or without oxaliplatin has been directly compared in a pooled analysis [27]. In total, 8734 patients with resected stage III colon cancer from four randomized controlled trials (NSABP C-08, X-ACT, XELOXA, and AVANT) were evaluated in this pooled analysis. The adjuvant treatment regimens were XELOX (oxaliplatin and capecitabine), 5-FU/LV, capecitabine, FOLFOX-4, and mFOLFOX-6. DFS, RFS, and OS were found to be similar between patients treated with 5-FU/LV versus those treated with capecitabine in adjusted analyses. Multiple Cox regression analysis of OS revealed a significant interaction between oxaliplatin and fluoropyrimidine ($P = 0.014$). Post-relapse survival was similar in adjusted ($P = 0.23$) and unadjusted analyses ($P = 0.33$) for the comparison of XELOX or FOLFOX versus 5-FU/LV and was also similar for capecitabine-based regimens versus 5-FU/LV-based regimens (unadjusted $P = 0.26$). Thus, the combination therapy with oxaliplatin provided consistently improved outcomes without adversely affecting post-relapse survival in the adjuvant treatment of stage III colon cancer, irrespective of whether the fluoropyrimidine backbone was capecitabine or 5-FU/LV.

In another recent pooled analysis, a total of 12,233 patients, treated with adjuvant systemic treatment and enrolled to the randomized trials C-07, C-08, N0147, MOSAIC (Adjuvant Treatment of Colon Cancer), and XELOXA (adjuvant XELOX), were investigated to examine the impact of oxaliplatin and tumor-specific factors on the time course of recurrence and death [28]. The addition of oxaliplatin significantly reduced the risk of recurrence within the first 14 months post treatment for patients with stage II disease and within the first 4 years for patients with stage III disease. Oxaliplatin also significantly reduced the risk of death from 2 to 6 years post treatment for patients with stage III disease, with no differences in timing of outcomes between treatment groups (i.e., oxaliplatin did not simply postpone recurrence or death compared with 5-FU/LV). This pooled analysis also supported the addition of oxaliplatin to fluoropyrimidine-based adjuvant therapy in patients with stage III disease.

These data added to the existing evidence that oxaliplatin plus capecitabine or 5-FU/LV is the standard of care for the adjuvant treatment of stage III colon cancer and offers physicians' flexibility to treat patients according to the patients' overall physical performance and

preference. The preferred oxaliplatin-fluoropyrimidine-based combination regimens are XELOX, FOLFOX4, FOLFOX6, FOLFOX7, XELOX, and FLOX.

(d) Irinotecan-based combination regimens

The efficacy of irinotecan in the adjuvant setting was evaluated in two large trials of patients with resected stage II/III colon cancer. In the trial performed in the United States, a 5-FU/LV bolus plus irinotecan regimen (IFL) was compared with 5-FU/LV bolus alone [18]. The IFL regimen was not shown to have superiority over 5-FU/LV-alone arm in terms of either DFS or OS. Furthermore, IFL resulted in significantly higher toxicity, including lethal toxicity. PETACC-3 was designed to compare 5-FU/LV/irinotecan (FOLFIRI) with 5-FU/LV in the adjuvant setting because IFL was demonstrated to be inferior to FOLFOX in patients with advanced colon cancer [11]. The 5-year DFS rate was found to be 56.7% with FOLFIRI and 54.3% with 5-FU/LV alone ($P = 0.106$). OS was similar between the two arms (5-year OS 73.6% versus 71.3%, respectively; log-rank $P = 0.094$). Thus, irinotecan should not be used in the standard management of stage II/III colon cancer.

3. Adjuvant systemic therapy in stage II colon cancer

It is remarkable that an OS and DFS benefit in the combined population compared with surgery alone could only be identified at a significant rate almost exclusively in patients with stage III disease in several trials of fluoropyrimidine-based chemotherapy that enrolled a mix of patients with stage II and III colon cancers [9, 29–32] (**Table 3**). On the other hand, some large trials that specifically delved into the benefit of fluoropyrimidine-based chemotherapy in patients with stage II disease failed to show a clear benefit for adjuvant chemotherapy [9, 33, 34]. In the INT-0035 trial, stage II and III patients were randomized into either 5-FU/levamisole administration or surgery alone [7]. The 7-year survival rate for the 5-FU/levamisole treatment group was 60.2% versus 47% for the surgery-alone group ($P = 0.0007$) among stage III patients, whereas the 7-year survival rate for stage II patients was 72% for both groups ($P = 0.83$). As a result, the study demonstrated a significant contribution of the adjuvant therapy to stage III patients, regardless of the small number ($n = 318$) of patients with stage II disease [7].

One of the most noteworthy several meta-analyses that assessed the benefit of adjuvant fluoropyrimidine-based chemotherapy in patients with resected stage II colon cancer is the International Multicenter Pooled Analysis of Colon Cancer Trials (IMPACT), which did not support the routine use of 5-FU/LV in all patients with stage II colon cancer [5, 13, 14]. The data pooled from 1016 patients with T3N0 disease enrolled in five similar trials of observation versus 5-FU/LV found a non-statistically significant improvement in EFS that favored chemotherapy (76% versus 73%; HR, 0.83), and 5-year OS was similar (82% versus 80%, HR, 0.86) [29].

The American Society of Clinical Oncology (ASCO) held a panel to provide recommendations through a literature-based meta-analysis conducted by the Ontario group regarding adjuvant therapy for patients with stage II colon cancer [35]. The Ontario group analysis included the

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comparison of 5-FU/LV versus observation for stage II colon cancer, 37 trials and 11 meta-analyses [36]. Chemotherapy was associated with a small but significant absolute improvement in DFS (5–10%) according to the results of this analysis, which failed to translate into a statistically significant difference in OS (risk ratio [RR] 0.87, 95% CI: [0.75–1.10], $P = 0.07$) [36]. These trials failed to support the routine use of adjuvant chemotherapy for stage II colon cancer, and the ASCO panel did not recommend the routine use of adjuvant chemotherapy for patients with stage II colon cancer due to the lack of significant improvement in OS.

	Patients	Regimens		5-year DFS		5-year OS	
Trial	**Stage II/total**	**Control**	**Experimental arm**	**Control**	**Experimental arm**	**Control**	**Experimental arm**
IMPACT 1	841/1493	Surgery alone	Surgery plus 5-FU and folinic acid	76%	79%	90%	88%
IMPACT 2	1016/1016	Surgery alone	Surgery plus 5-FU and leucovorin	73%	76%	80%	82%
INT-0035*	325/1296	Surgery alone	Surgery plus 5-FU and levamisole			72%	72%
NSABP	1565/4006	Surgery alone	Surgery plus combination chemotherapy**	NR	NR	75%	70%
Gill et al.	1440/3302	Surgery alone	Surgery plus 5-FU-based therapy***	72%	76%	80%	81%
ACCENT	6896/20898	Surgery plus FU/LV alone	Surgery plus 5-FU and oxaliplatin	NR	NR	67%	72%

ACCENT, Adjuvant Colon Cancer Endpoints; DFS, disease-free survival; IMPACT, International Multicenter Pooled Analysis of Colon Cancer Trials; INT-0035, intergroup study; NSABP, National Surgical Breast and Bowel Project; NR, not reported; OS, overall survival.
*7-year survival.
**Combination chemotherapy: semustine, vincristine, 5-FU, and perioperative 5-FU portal vein infusion.
***5-FU-based therapy: FU + leucovorin or FU + levamisole.

Table 3. Clinical trials of fluoropyrimidine-based adjuvant therapy for stage II colon cancer.

The ASCO panel further addressed the issue of adjuvant therapy for those stage II patients with high-risk features including inadequately sampled nodes, T4 lesion, perforation, or poorly differentiated histology. Although randomized trials failed to demonstrate an improvement in OS, the number of patients with high-risk stage II disease in these studies was considered inadequate to demonstrate benefit. Moreover, adjuvant therapy is considered reasonable for those patients with suboptimal lymph node examinations.

There are studies that indicated the benefits of adjuvant treatment in resected stage II colon cancer, including the NSABP study of fluorouracil-based adjuvant therapy trials for patients

with stage II and III colon cancer from 1977 to 1990 [13, 34]. The data from these four combined studies, 41% of the patients in which had stage II (1565 patients) disease, indicated a 30% reduction in overall mortality for the stage II patients versus surgery alone [16]. The mortality reduction was 18% for stage II patients, which was greater than that observed for stage III patients regardless of the presence or absence of high-risk features, including the presence of obstruction, perforation, or extension to adjacent organs, having resulted in an absolute survival improvement of 5%; therefore, the NSABP recommended adjuvant chemotherapy for all stage II patients [37–39]. One of the studies that supported the NSABP study was a recent meta-analysis of 12 randomized controlled trials from 1985 to 2010 in which surgery alone was the control group, which found a significant benefit to adjuvant therapy in patients with stage II colon cancer [37]. A significant improvement in 5-year OS was associated with surgery combined with postoperative adjuvant chemotherapy for stage II colon cancer (HR, 0.81; 95% CI: [0.71–0.91]) and the 5-year DFS also favored the group of surgery combined with postoperative adjuvant chemotherapy for stage II colon cancer (HR, 0.86; 95% CI: [0.75–0.98]). An important reduction in risk of recurrence was found for stage II colon cancer in favor of postoperative adjuvant chemotherapy (RR, 0.82; 95% CI: [0.71–0.95]) [40].

The data of 3151 patients with stage II colon cancer who were considered to carry "usual" risk for recurrence were obtained from the Surveillance, Epidemiology, and End Results (SEER) Medicare database and analyzed. Stage II disease with usual risk was defined as tumors with a stage of T3N0 and without obstruction and perforation. The OS rate of the group administered with chemotherapy was 78% compared with 75% of the group not administered with chemotherapy [36]. The analysis confirmed that the findings in randomized studies of adjuvant therapy (e.g., IMPACT) were similar to those encountered in real-world practice with the improvement in OS with adjuvant therapy for patients with stage II colon cancer is at best 2–5%, which is a statistically insignificant improvement in OS with adjuvant therapy [36].

The QUASAR trial randomly assigned 3239 patients (2963 (91%) with stage II (node negative) disease and 2291 (71%) with colon cancer) with an "uncertain indication for adjuvant therapy" to chemotherapy with 5-FU/LV or with or without levamisole or observation following resection of colon or rectal cancer [41], which indicated a small but statistically significant survival benefit for patients with stage II disease treated with 5-FU/LV (HR, 0.86; 95% CI: [0.54–1.19]), 5-year survival 83.9% versus 81.5%). Nevertheless, patients with higher-risk disease may benefit more from adjuvant therapy because approximately 64% of patients had less than 12 lymph nodes sampled (the median number of lymph nodes examined was only six) in this study [42].

The benefit of oxaliplatin for stage II disease remains uncertain due to the scarcity of data available on the benefits of oxaliplatin-based adjuvant chemotherapy for patients with stage II disease. One of the most important trials in this respect is MOSAIC, which compared 6 months of adjuvant 5-FU/LV versus FOLFOX (oxaliplatin plus short-term infusional 5-FU and LV) in patients with resected stage II (40%) or III (60%) colon cancer [15]. Five-year DFS of patients with stage II cancer was slightly but not significantly higher than with FOLFOX (84% versus 80%, HR for recurrence 0.84, $P = 0.26$) [43]. After longer follow-up, no difference in 10-year OS was noted in the stage II subpopulation (79.5% versus 78.4%; HR, 1.00; $P = 0.98$) (21).

Colon cancer with high-risk features was defined as colon cancer with at least one of the following: stage T4, perforation, bowel obstruction, poor differentiation, and venous invasion (<10 lymph nodes examined). The patients with high-risk stage II disease who received FOLFOX did not have improved DFS or OS benefit compared with those who received infusional 5-FU/LV. Similar results were identified in the NSABP C-07 trial, which compared weekly oxaliplatin plus bolus 5-FU/LV (FLOX) to bolus 5-FU/LV in patients with stage II and III colon cancer [21].

Although most of these analyses showed that patients with stage II colon cancer do not have significantly better survival with adjuvant therapy, not all stage II patients are at equal risk. Patient/physician discussions individualized for the patient as well as explanations of the specific characteristics of the disease should be included in decision making for the use of adjuvant therapy in patients with stage II disease; prognosis and evidence related to the efficacy and possible toxicities associated with treatment should be centered on patient choice [38]. The oncologist should help the patient to make an informed decision by estimating the relative risk of recurrence and/or death with and without adjuvant chemotherapy and discussing the expected adverse effects of treatment. The possible benefit of adjuvant therapy is small as patients with average-risk stage II colon cancer have a very good prognosis. Although patients with stage II colon cancer and high-risk features have been considered more likely to benefit from adjuvant chemotherapy, currently it is known that many patients with high-risk features do not have recurrence, whereas some patients with average-risk features do. Thus, the current definition of high-risk stage II colon cancer is accepted as inadequate [39]. Moreover, there are no data points on features that are predictive of benefit from adjuvant chemotherapy and no data correlating risk features and selection of chemotherapy in patients with high-risk stage II disease.

Overall, the National Comprehensive Cancer Network (NCCN) panel found it reasonable to accept the relative benefit of adjuvant therapy in stage III disease as indirect evidence of benefit for stage II disease, particularly for those with high-risk features [39], which initiated efforts to use clinicopathologic and molecular features to select groups of patients with higher-risk stage II disease for a greater risk of recurrence who might benefit more from adjuvant chemotherapy.

Clinicopathologic features associated with a worse prognosis in patients with stage II disease are T4 primary [4, 44]; poorly differentiated histology (including signet ring and mucinous tumors) [45]; lymphovascular invasion (LVI) [40]; perineural invasion [40]; bowel obstruction or perforation [46, 47]; close, indeterminate, or positive margins; inadequately sampled lymph nodes (less than 13 in the surgical specimen) [48]; a high preoperative serum carcinoembryonic antigen (CEA) level [40, 49]; and occult nodal micrometastases as detected by molecular or immunohistochemical methods (**Table 4**). Expert groups such as ASCO [38], NCCN, and the European Society for Medical Oncology (ESMO) [50] have different definitions for high-risk early colon cancer.

Despite the adverse influence of the foregoing features on prognosis, there is subtle evidence to indicate that patients with any of these high-risk features are more prone to benefit from chemotherapy (i.e., factors associated with poorer prognosis are not necessarily predictive of

chemotherapy response). The benefit of chemotherapy in higher-risk subsets of stage II disease has been examined by only a few studies [15, 32, 45, 51]. The next-generation Intergroup trial INT-0089 randomized 3759 patients with high-risk stage II (20% of accrual) and stage III patients to receive one of four combinations of 5-FU with LV and/or levamisole [7]. High-risk stage II disease was defined as those stage II patients with evidence of bowel obstruction, bowel perforation, or adherence to or invasion of adjacent organs or tumor perforation. The four combinations did not result in any difference among the high-risk stage II or the stage III patients. The 5-year OS rate ranged from 75 to 77% in the treated high-risk stage II patients and it was found to be comparable with the survival rate of the general population of stage II patients treated with surgery alone. It concludes an uncertainty as to whether this conventionally described high-risk group would have had a similar survival rate if no adjuvant therapy had been given [12]. While a more recent analysis of more than 24,847 patients with stage II colon cancer (75% had one or more poor prognostic features) from the SEER-Medicare database showed no 5-year survival benefit for adjuvant chemotherapy over observation, even in patients with stage II disease with one or more poor prognostic features (obstruction, perforation, emergency admission for surgery, T4 stage, resection of fewer than 12 lymph nodes, and poorly differentiated or undifferentiated histology) (HR, 1.03; 95% CI: [0.94–1.13]) [52].

1. Obstructed or perforated colon cancer
2. High-risk histology
3. LVI/extramural spread
4. Perineural invasion
5. Poorly differentiated tumor (grades 3–4)
6. T4 primary tumor
7. Inadequate lymph node sampling (<12)
8. Elevated preoperative CEA
9. 18q deletion
10. Indeterminate, close, or positive margin

Table 4. High-risk factors in patients with stage II colon cancer.

In the MOSAIC study, which assessed the effect of oxaliplatin (FOLFOX versus 5-FU/LV), there was a trend toward improved DFS with FOLFOX (82% versus 75%) in the subgroup of stage II patients with high-risk tumors (clinical T4, poorly differentiated, perforation, or obstruction (<10 nodes in the surgical specimen)) (**Table 4**). Although the OS was substantially the same in both groups (85% versus 83%, $P = 0.65$), the lack of a control group treated with surgery alone makes it impossible to identify whether these results are better than surgery alone [15].

The number of lymph nodes extracted is also very important to define high-risk stage II disease. An Intergroup 0089 trial (INT-0089) of high-risk, stage II and III colon cancer patients indicated

the number of lymph nodes analyzed as an independent prognostic variable [53]. Survival increased as the number of the analyzed lymph nodes increased, regardless of whether lymph nodes were found positive or negative ($P = 0.0001$ and $P = 0.0005$, respectively, for stage III and II disease). The American Joint Committee on Cancer and the College of American Pathologists recommended that at least 12 lymph nodes should be examined [32, 44]. The patient should be considered inadequately staged when fewer than 12 nodes are sampled and reported, in which case reexamination of the surgical specimen may be requested.

4. Monotherapy as adjuvant chemotherapy in colon cancer

Whenever any contraindication for combination chemotherapy with fluoropyrimidine and oxaliplatin exists, single-agent fluoropyrimidine could be an option as an adjuvant chemothErapy regimen. In contrast, there is no evidence to support use of oxaliplatin as a single agent in adjuvant setting. Additionally, irinotecan as single agent or irinotecan-based combination regimens should not be recommended for patients with stage III colon cancer as adjuvant systemic therapy.

5. Targeted agents in the adjuvant setting

Bevacizumab: In NSABP C-08 and AVANT, randomized phase III trials, the potential benefit of bevacizumab was evaluated in addition to oxaliplatin-based chemotherapy in patients with stage II and III colon cancer [54, 55]. The bevacizumab group had a significantly higher rate of toxicity including hypertension, wound complications, pain, proteinuria, and hand-foot syndrome, but bevacizumab in combination with chemotherapy did not provide a DFS or OS advantage over chemotherapy alone in the NSABP C-08 trial [54]. Bevacizumab also did not prolong DFS when added to adjuvant chemotherapy in resected stage III colon cancer with AVANT [56]. The DFS HR for bevacizumab-FOLFOX4 versus FOLFOX4 was 1.17 ($P = 0.07$), and for bevacizumab-XELOX versus FOLFOX4, it was 1.07 ($P = 0.44$). After a minimum follow-up of 60 months, the OS HR for bevacizumab-FOLFOX4 versus FOLFOX4 was 1.27 ($P = 0.02$), and for bevacizumab-XELOX versus FOLFOX4, it was 1.15 ($P = 0.21$). Thus, OS data suggested a potential detrimental effect with bevacizumab plus oxaliplatin-based adjuvant therapy in these patients.

Cetuximab: NCCTG NO147 and PETACC-8 trials investigated the possible role of cetuximab in the adjuvant setting [57, 58]. In NCCTG NO147, the potential benefit of cetuximab added to mFOLFOX6 in patients with resected stage III wild-type KRAS colon cancer was assessed. Three-year DFS for mFOLFOX6 alone was 74.6% versus 71.5% with the addition of cetuximab (HR, 1.21; $P = 0.08$) in patients with wild-type KRAS and 67.1% versus 65.0% (HR, 1.12; $P = 0.38$) in patients with mutated KRAS, with no significant benefit in any of the subgroups assessed. Among all patients, grade 3 or higher adverse events (72.5 versus 52.3%; OR, 2.4; $P < 0.001$) and failure to complete 12 cycles (33 versus 23%; OR, 1.6; $P < 0.001$) were significantly higher

with cetuximab. Increased toxicity and greater detrimental differences in all outcomes were observed in patients aged 70 years or more [57]. In PETACC-8, whether the addition of cetuximab to standard adjuvant oxaliplatin, fluorouracil, and leucovorin chemotherapy (FOLFOX4) in patients with stage III colon cancer improved DFS was assessed [58]. In the experimental and control groups, DFS was similar in the intention-to-treat population and in patients with KRAS exon 2/BRAF wild-type (n = 984) or KRAS exon two-mutated tumors (n = 742).

On the basis of the available data, bevacizumab, cetuximab, or panitumumab should not be used in the adjuvant treatment of patients with curatively resected stage III colon cancer.

6. Molecular prognostic and predictive markers

Prognostic and predictive markers that identify heterogeneous groups are needed to implement tailored therapeutic strategies. There are several well-defined prognostic markers related to either patient or tumor, including grade of tumor, LVI, perineural invasion, lymphoid inflammatory response, positive surgical margins, bowel obstruction, and perforation [15]. These are well-defined parameters for patients with stage II colon cancer during decision making; however they are not used in patients with stage III colon cancer. The impact of tumor molecular factors on prognosis and the response to adjuvant chemotherapy in stage II and III disease is a current subject for ongoing studies [59–61].

(a) In stage II colon cancer

Allelic loss of chromosome 18q and microsatellite instability (MSI) in colon tumors are prognostic markers that may be employed to sift stage II patients in terms of risk and decide on who should receive adjuvant chemotherapy.

Allelic loss of chromosome 18q in colon tumors has been demonstrated to be a marker of poor prognosis [59] in an examination of 145 tumor samples for 18q loss. The 5-year survival rate was reported to be lower in patients with 18q loss than in those without 18q loss (54% versus 93%, respectively) [59].

Mismatch repair (MMR) genes may result in MMR protein deficiency and MSI if they are mutated or modified [60]. Approximately 15–20% of colorectal cancers have sporadic or inherited (Lynch syndrome) deficiency of an MMR protein, most commonly MLH1 or MSH2 [61], with tumors characteristically located proximally and a mucinous histology with tumor-infiltrating lymphocytes a better prognosis than do microsatellite-stable (MSS) tumors [62]. MSI (the biological footprint of DNA MMR deficiency) is an important piece of information to consider when deciding whether to use adjuvant chemotherapy in patients with stage II disease. MSI appearance seems to be related with a relative resistance to fluoropyrimidines.

Most (but not all) [63, 64] studies have shown that MSI or deficient mismatch repair (dMMR) is a marker of a more favorable outcome and a predictor of increased benefit from adjuvant therapy with a fluoropyrimidine alone in patients with stage II disease [65–67]. A retrospective

study of 570 patients enrolled in three trials of 5-FU-based adjuvant therapy analyzed retrospectively tumor samples for MSI [65]. The 5-year survival rate was significantly better in patients with tumors that exhibited high-frequency MSI (88 versus 68.4%; $P = 0.004$) than those with tumors exhibiting microsatellite stability or low-frequency instability among patients who did not receive adjuvant therapy. Adjuvant chemotherapy improved the OS of patients with MSS tumors or tumors exhibiting low-frequency MSI ($P = 0.04$) but not those with high-frequency MSI. Even harm in terms of OS was suggested in patients treated with dMMR tumors [65]. In parallel, results from another retrospective study of pooled data from adjuvant trials by Sargent and George suggested that adjuvant 5-FU chemotherapy appeared to be destructive in patients with stage II disease in tumors characterized as dMMR [66]. In contrast to the findings of Sargent and George [66], a recent study of 1913 patients treated in the QUASAR study, a randomized comparison of 5-FU/LV and supportive care in stage II colon cancer, confirmed the prognostic significance of dMMR, but not its predictive capacity [42]. A recent study of patients in the CALGB 9581 and 89803 trials reached a similar conclusion [68]. MMR status was prognostic but not predictive of benefit or detrimental impact of adjuvant therapy in patients with stage II colon cancer.

It is not clear if oxaliplatin supplementation would overcome the lack of benefit from adjuvant 5-FU in patients with dMMR. Adjuvant chemotherapies with and without oxaliplatin have been examined on patients with dMMR tumors in retrospective analyses, among which one report noted a significant benefit from adding oxaliplatin to 5-FU/LV in patients with MSI tumors [69], whereas another suggested a lower rate of disease control with FOLFOX in patients with dMMR tumors compared with those with proficient mismatch repair (pMMR) tumors [70]. A preliminary report of a retrospective analysis of 433 patients with resected dMMR tumors (57% stage II) from several French centers was reported at the 2014 ASCO annual meeting [71]. Seventeen percent of the patients with stage II disease ($n = 41$) received adjuvant chemotherapy. Overall, 3-year RFS was 75% for surgery alone, 66% for FU alone, and 84% with FOLFOX. In the subgroup analysis, the benefit of FOLFOX compared with FU and surgery alone was significant for stage III disease (HR for relapse 0.38, 95% CI: [0.21–0.69]) with a tendency toward better results in patients with stage II disease (HR for relapse 0.14, 95% CI: [0.02–1.04]; $P = 0.05$). Tumor specimens characterized as MSI-high (MSI-H) are more common in stage II disease than in stage III disease according to the data from the PETACC-3 trial (22% versus 12%, respectively; $P < 0.0001$) [72]. The percentage of stage IV tumors characterized as MSI-H was only 3.5% [73] in another large-scale study. These results suggest that MSI-H tumors have a decreased likelihood to metastasize.

BRAF mutation in a patient with dMMR colorectal cancer is considered as a negative prognostic indicator, which is also supported by emerging data with a view that BRAF mutations are a negative prognostic factor among patients with pMMR and stage II colon cancer [72, 74, 75]. BRAF mutations were associated with poor OS in a combined analysis of 2299 patients enrolled in two NSABP trials that tested the value of adjuvant chemotherapy in patients with stage II or III colon cancer [76]. The 5-year survival rate was highest in patients with dMMR, BRAF wild-type tumors (90%) and worst in those with pMMR and BRAF-mutated tumors (69%). In a large population-based study of Samowitz et al., microsatellite-unstable tumors

were associated with an excellent 5-year survival regardless of whether the V600E mutation was present or absent (76 and 75%, respectively), whereas for MSS tumors, the presence of a V600E mutation significantly worsened 5-year survival (17 versus 60%) [77]. Among patients with stage II MSS tumors, death risk was significantly higher in those with a BRAF mutation (four of 17 [24%] compared with 47 of 889 [5.3%], HR for death 4.88, 95% CI: [1.73–13.76]). In a preliminary report of data from the PETACC-3 adjuvant trial, which was conducted in patients with stage II or III colon cancer, a BRAF V600E mutation was a marker of poor RFS and OS in patients with MSS left-sided tumors, but not MSI-unstable or right-sided tumors [75]. Despite all these results, there still is not sufficient evidence to use BRAF mutation status to select patients among those with stage II colon cancer.

(b) In stage III colon cancer

In several studies, a subgroup of stage III disease, which has better prognosis similar with stage II disease, has been tried to be determined. Numerous studies, including a meta-analysis, have demonstrated that patients with dMMR colorectal cancer have better stage-independent survival relative to patients with pMMR [13]. Furthermore, a predictive role for MMR has been revealed by using data from randomized clinical trials of FU-based therapy versus surgery-only control [78]. The treatment benefit differed by MSI status. Patients with MSI-H and treated with FU-based therapy had a trend toward inferior outcomes compared with patients who were treated with surgery alone. In contrast, patients with MSI-H tumors had been reported to have similar outcomes with chemotherapy or appeared to receive a greater benefit from FU-based adjuvant treatment in other studies [63, 79].

A variety of other markers including 18q deletion, KRAS mutations, TP53, TGFBR2, DCC, and thymidylate synthase gene expression have been proposed to refine T- and N-based groups, but their integration into the clinical setting requires extensive validation of their relative value and optimal use [80]. In addition, there is lack of consensus in performing these markers, such as different antibodies used or different scoring methods, which makes their results incomparable. Colon cancer treatment guidelines do not recommend the use of predictive marker information during decision making because there is no strong evidence for a predictive marker regarding the benefit of adjuvant chemotherapy for stage III colon cancer.

7. Gene expression profiling during decision making of adjuvant chemotherapy in stage II and III colon cancer

After the discovery of numerous molecular features of cancer including gene expression profile, several molecular tests that provide important prognostic and predictive information were investigated to aid clinical decision making [39] (**Table 5**). Despite varying design and sample numbers of the validation analyses, all of these tests have been indicated to have prognostic value in independent patient series [81].

Assay	Gene signature
Oncotype DX Colon Cancer Assay (Genomic Health, Inc.)	12 genes (seven recurrence-risk genes and five reference genes)
ColoPrint colon cancer recurrence assay (Agendia)	18-gene expre ssion profile
ColDx microarray-based multigene assay	634 probe

Table 5. Gene expression assays in stage II colon cancer.

Genomic Health Inc. (Redwood City, CA, USA) has conducted four studies involving more than 1800 patients with stage II or stage III colon cancer; genomic profiling was performed to identify genes that predict recurrence in patients with colon cancer who were treated with surgery alone or surgery plus 5-FU/LV chemotherapy. By using the findings of these studies, the 12-gene colon cancer recurrence score (Oncotype DX Colon Cancer Assay) which quantifies the expression of seven recurrence-risk genes and five reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence was designed [82]. This 12-gene assay's ability to predict recurrence rate was independently validated through the analysis of data from the prospective QUASAR trial [83] and through a separate analysis of data from the CALGB 9581 trial [84]. Recurrence at 3 years was, respectively, 12%, 18%, and 22% for the low-, intermediate-, and high-recurrence-risk groups [83].

The 12-gene recurrence score is the best documented and validated tool. In addition three other colon cancer recurrence score assays based upon microarray gene expression including one by Oh et al [85], one by Jiang et al [86], and the Almac microarrays ADXCRC provided added prognostic value. ColoPrint (Agendia, Amsterdam, the Netherlands) is a prognostic 18-gene signature and was identified on the basis of unbiased gene selection by searching the whole genome for genes that had the highest correlation to a tumor relapse event. This prognostic gene signature was validated in an independent set of 206 patients with stage I–III colon cancers and in 135 clinical samples of patients with stage II colon cancer, using a diagnostic microarray platform [87].

How the recurrence score should be integrated with other known prognostic markers for decisions regarding adjuvant chemotherapy is uncertain. Yothers et al. performed an independent, prospectively designed clinical validation study of recurrence score. Archival specimens were obtained from patients with stage II and III colon cancers who were randomized to receive 5-FU or 5-FU plus oxaliplatin in NSABP C-07 [88]. Continuous Recurrence Score predicted recurrence (HR for a 25-unit increase in score, 1.96, $P < 0.001$), as well as DFS (HR for a 25-unit increase in score, 1.60; $P < 0.001$) and OS (HR, 1.89; $P < 0.001$). After adjustment for stage, lymph nodes examined, MMR, grade, and treatment, and recurrence score were shown to predict recurrence risk ($P = 0.001$). Recurrence score did not have significant interaction with stage ($P = 0.90$) or age ($P = 0.76$). Relative benefit of oxaliplatin was found to be similar across the range of recurrence score (interaction $P = 0.48$); accordingly, absolute benefit of oxaliplatin increased with higher scores, most notably in patients with stage II and

IIIA/B diseases [88]. However, the authors underlined that the recurrence score was not predictive of oxaliplatin efficacy and did not directly identify patients who would or would not benefit from oxaliplatin treatment.

These genomic profiling tests may provide information about the level of risk of recurrence over other risk factors; thus they potentially have high prognostic value. Due to the lack of evidence of predictive value of multigene assays in terms of potential value of adjuvant chemotherapy, the NCCN panel does not recommend the use of multigene assays to determine adjuvant therapy [89]. ASCO guidelines do not address the use of this assay.

8. Impact of age and medical comorbidity on adjuvant treatment outcomes for stage III colon cancer

Adjuvant oxaliplatin plus capecitabine or 5-FU/LV (XELOX/FOLFOX) is the standard of care for stage III colon cancer; however, there is disagreement regarding oxaliplatin benefit in patients aged >70 years.

Recently, the efficacy and safety of adjuvant XELOX/FOLFOX versus 5-FU/LV were compared with respect to age and medical comorbidity using pooled data [56]. Individual data from patients with stage III colon cancer in four randomized, controlled trials (NSABP C-08, XELOXA, X-ACT, and AVANT) excluding bevacizumab-treated patients were analyzed. Patients were grouped by treatment, medical comorbidity (low versus high), or age (<70 versus ≥70 years) and compared for DFS, OS, and adverse events. Although benefits were modestly attenuated for patients aged ≥70 years, DFS benefits were demonstrated for XELOX/FOLFOX versus 5-FU/LV regardless of age or medical comorbidity. The OS was found to be improved in all groups. Grade 3/4 serious adverse event rates were comparable across cohorts and medical comorbidity scores and higher in patients aged ≥70 years. Oxaliplatin-relevant grade 3/4 adverse events, including neuropathy, were comparable across ages and medical comorbidity scores. Thus, the findings of this pooled analysis further supported the consideration of XELOX or FOLFOX as standard treatment options for the adjuvant management of stage III colon cancer in all age groups and in patients with comorbidities.

9. Optimal time to start adjuvant systemic therapy

Although no randomized trials have investigated the optimal time to initiate adjuvant systemic treatment, several retrospective studies in which the majority of patients had stage III disease demonstrated that a delay beyond 8 weeks resulted in shorter event-free survival and OS [73, 90, 91]. Starting 5–8 weeks post-surgery has not been shown to lead statistically significant decrease in OS compared with initiation within 4 weeks [73]. However, commencing beyond 8 weeks was associated with decreased OS compared with initiation within 8 weeks. Biagi et al. performed a systemic review and meta-analysis to define the optimal timing from surgery to initiation of adjuvant chemotherapy [92]. Ten eligible studies involving 15,410 patients

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(seven published articles, three abstracts) were identified. A meta-analysis of these demonstrated that a 4-week increase in time to adjuvant chemotherapy was associated with a significant decrease in both OS (HR, 1.14; 95% CI: [1.10–1.17]) and DFS (HR, 1.14; 95% CI: [1.10–1.18]).

The major limitation of this meta-analysis and majority of other studies is to include only studies with fluoropyrimidine-based adjuvant therapy. Currently, oxaliplatin in combination with fluoropyrimidine is preferred adjuvant regimens in stage III colon cancer. A population-based analysis was performed to investigate the effect of delay in initiating oxaliplatin-based chemotherapy on RFS and colon cancer-specific survival for stage III colon cancer [93]. At a median follow-up of 57.9 months, 5-year RFS was 70.9% (95% CI: [65.2–76.5]) for patients who began to receive adjuvant chemotherapy within 8 weeks and 72.1% (95% CI: [67.2–77]) for patients in whom adjuvant chemotherapy was started later than 8 weeks after surgery. Five-year cancer-specific survival was 82% (95% CI: [87.09–76.91]) and 82.8% (95% CI: [78.30–87.30]), respectively. In a multivariate analysis, delayed time to adjuvant chemotherapy was not found to have a prognostic significance on either RFS (HR, 1.08; $P = 0.609$) or cancer-specific survival (HR, 1.02; $P = 0.893$). Therefore, contrary to most existing data, which are primarily based on 5-FU-based adjuvant chemotherapy, delay of oxaliplatin-based adjuvant chemotherapy beyond 8 weeks did not appear to be associated with inferior outcomes.

Although recent evidence obtained from studies with oxaliplatin-based adjuvant chemotherapy and absence of data about the exact time when patients lose adjuvant systemic therapy, it is still concluded in international guidelines that adjuvant chemotherapy should be initiated as soon as it is practically feasible and ideally should not be delayed later than 8 weeks from surgery [94, 95].

10. Factors resulting in delay to start adjuvant chemotherapy

In a retrospective analysis, factors associated with starting treatment after 8 weeks were found to be older age, emergency resection, anastomotic leakage, referral to another hospital for adjuvant chemotherapy, and prolonged postoperative hospital admission [73]. A meta-analysis performed by Malietzis demonstrated that significant predictors of delayed initiation of adjuvant systemic treatment were age >75 years, marital status (single), low socioeconomic status, worse comorbidity status, low tumor grade, prolonged length of stay, and readmission [7]. Laparoscopy compared with open surgery was found to be a significant predictor of earlier initiation of adjuvant therapy.

The practice variation with respect to adherence to the NCCN recommendations within the National Cancer Date Base was evaluated in a recent study performed by Boland et al. [95]. The main purpose of that study was to examine the impact of adherence to guidelines on stage-specific survival outcomes in patients with stage III and high-risk stage II colon cancer, to identify factors associated with survival, and to identify subgroups of patients who may benefit from improved access to or delivery of cancer care. Male sex, insurance status other than private insurance such as Medicaid, other government insurance or lack of insurance, African

American race, lower household income, treatment at a community hospital, and treatment at an institution other than the hospital of diagnosis were found to be the main factors associated with increased risk of death both in patients with stage III disease and those with high-risk stage II disease.

In conclusion, oxaliplatin plus capecitabine or 5-FU/LV is the standard of care for the adjuvant treatment of stage III colon cancer (**Figure 1**). The preferred oxaliplatin-fluoropyrimidine-based combination regimes are XELOX, FOLFOX4, FOLFOX6, FOLFOX7, XELOX, and FLOX (**Table 6**). Whenever any contraindication for combination chemotherapy with fluoropyrimidine and oxaliplatin exists, single-agent fluoropyrimidine can be given as an adjuvant chemotherapy regimen (**Table 6**). During the decision making of adjuvant chemotherapy in stage II colon cancer patients, physicians should take into account the minimal potential improvement in OS of approximately 2–5% and the actual risk of mortality of 0.5–1%. High-risk stage II patients may be considered as an eligible group for adjuvant therapy after a complete discussion. Other factors, including MSI and 18q loss of heterozygosity, require further assessment to determine which combination of these is the most important and correlates best with therapeutic benefit. Making a treatment decision is not yet recommended according to the multigene assay. The new generation of adjuvant trials will help to determine if recently developed therapies will further improve the survival of this particular population. In stage II colon cancer treatment, the potential risks of adjuvant treatment and its benefit should be assessed and decision should be made on an individual patient basis.

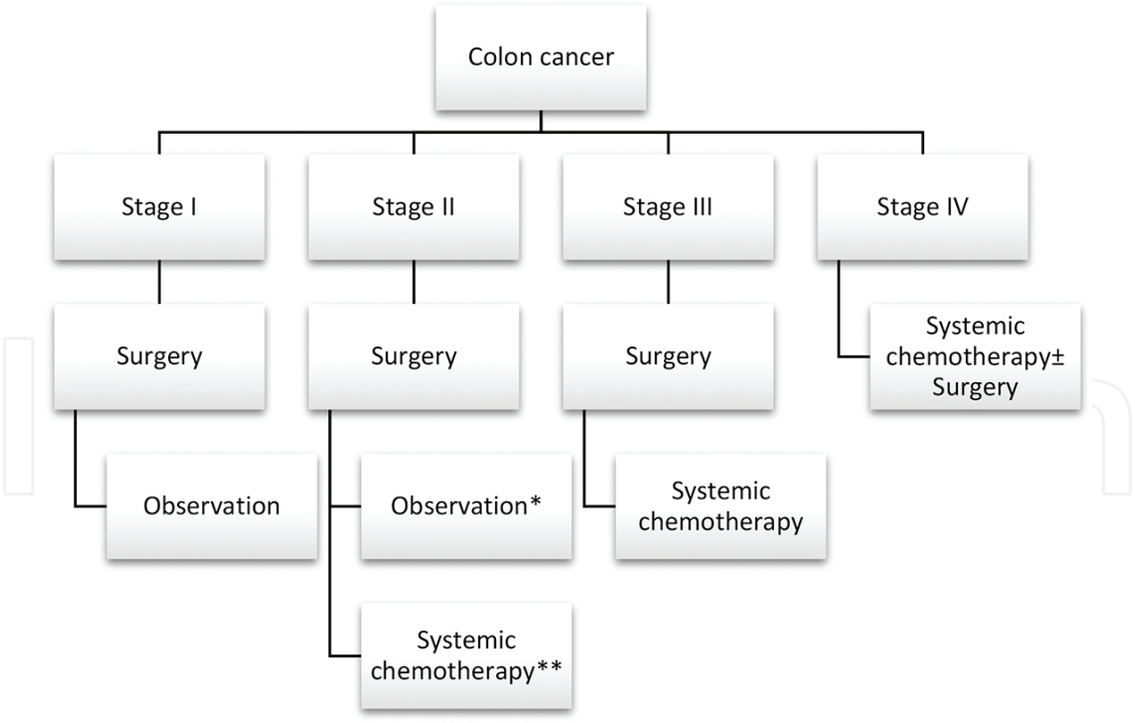

Figure 1 Algorithms for adjuvant systemic chemotherapy in colon cancer. *Observation is recommended to patients with T3N0 and dMMR or MSI-H colon cancer and without high-risk factors for systemic recurrence. **Systemic chemotherapy for 6 months after surgery is recommended for patients with high-risk factors for systemic recurrence.

Regimen	Drug	Route of administration	Dosage	Give on days of each cycle	Repeat every cycle	Total cycle
Fluorouracil-oxaliplatin-based combination regimens – preferred*						
FOLFOX4	Leucovorin	iv infusion	200 mg/m^2	Days 1, 2	14 days	12 cycles
	Oxaliplatin	iv infusion	85 mg/m^2	Day 1		
	5-FU	iv bolus	400 mg/m^2	Days 1, 2		
	5-FU	iv 22 h infusion via pump	600 mg/m^2	Days 1, 2		
FOLFOX6	Leucovorin	iv infusion	400 mg/m^2	Day 1	14 days	12 cycles
	Oxaliplatin	iv infusion	85 mg/m^2	Day 1		
	5-FU	iv bolus	400 mg/m^2	Days 1, 2		
	5-FU	iv 22 h infusi on via pump	1200 mg/m^2	Days 1, 2		
FOLFOX7	Leucovorin	iv infusion	400 mg/m^2	Day 1	14 days	12 cycles
	Oxaliplatin	iv infusion	85 mg/m^2	Day 1		
	5-FU	iv bolus	400 mg/m^2	Day 1		
	5-FU	iv 22 h infu sion via pump	1200 mg/m^2	Days 1, 2		
XELOX	Capec itabine	Oral	850–1000 mg/m^2 twice daily	Days 1–14	21 days	8 cycles
	Oxaliplatin	iv infusion	130 mg/m^2	Day 1		
FLOX	5-FU	iv bolus	500 mg/m^2	Days 1, 8, 15, 22, 29, 35	8 weeks	3 cycles
	Leucovorin	iv bolus	500 mg/m^2		8 weeks	3 cycles
	Oxaliplatin	iv infusion	85 mg/m^2	Days 1, 8, 15, 22, 29, 35		
				Days 1, 15, 29		
Fluoropyrimidines with or without leucovorin**						
Capeci tabine	Capeci tabine	Oral	1250 mg/m^2 twice daily	Days 1–14	21 days	8 cycles
5-FU/LV (Roswell Park regimen)	Leuco vorin	iv infusion	500 mg/m^2	Days 1, 8, 15, 22, 29, 35	8 weeks	4 cycles
	5-FU	iv bolus	500 mg/m^2	Days 1, 8, 15, , 29, 35		
5-FU/LV (Mayo regimen)	Leuco vorin	iv bolus	20 mg/m^2	Days 1–5	4 weeks	6 cycles
		iv bolus	425 mg/m^2	Days 1–5		

Regimen	Drug	Route of administration	Dosage	Give on days of each cycle	Repeat every cycle	Total cycle
	5-FU					
5-FU/LV	Leucovorin	iv bolus	400 mg/m^2	Day 1	14 days	12 cycles
(Modified de Gramont regimen)	5-FU	iv bolus	400 mg/m^2	Day 1		
	5-FU	iv 46 h infusion via pump	2400 mg/m^2	Day 1		

5-FU, 5-fluorouracil; iv, intravenous; LV, leucovorin.
*Fluorouracil-oxaliplatin-based combination regimens are preferred in all patients with stage III colon cancer and in selected patients with stage II colon cancer.
**Fluoropyrimidines with or without leucovorin should be given to patients who have a contraindication to oxaliplatin.

Table 6. Recommended chemotherapy regimens for patients with resected colon cancer.

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