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REVIEW ARTICLE

Adjuvant therapy for stages II and III colon cancer: risk stratification, treatment duration, and future directions

U. Bender MDCM,* Y.S. Rho MDCM,† I. Barrera MD,* S. Aghajanyan,* J. Acoba MD,†‡ and P. Kavan MD PhD*

ABSTRACT

Background To date, the role of adjuvant systemic therapy in stages II and III colon cancer remains a topic of interest and debate. The objective of the present review was to assess the most recent data, specifically addressing methods of risk stratification, duration of therapy, and future directions.

Methods PubMed and MEDLINE were searched for literature pertinent to adjuvant chemotherapy in either stage II or stage III colorectal cancer.

Summary Locoregional disease, histopathology, age, laterality, and a number of other biologic and molecular markers appear to have a role in disease risk stratification. The duration of adjuvant therapy for stage III disease can vary based on risk factors, but use of adjuvant therapy and duration of therapy in stage II disease remain controversial. Future directions should include genomic assays and improved study design to provide concrete evidence about the duration of adjuvant FOLFOX or CAPOX and about other types of chemotherapy and immunotherapy.

Key Words Adjuvant chemotherapy, treatment duration, risk stratification, colorectal cancer

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INTRODUCTION

Colorectal cancer (CRC) is the 2nd most frequently diagnosed cancer in Canada, representing 13% of estimated new cancer cases and 12% of cancer-related deaths when both sexes are combined[1]. Comparably, as reported by the Surveillance, Epidemiology, and End Results program in the United States, CRC was estimated to represent 8.3% of all cancer cases and 8.4% of all cancer-related deaths in 2019[2]. Although improvements in screening methods and treatment modalities have resulted in decreased overall rates of incidence and death, CRC remains burdensome and is expected to rise by 60% worldwide by 2030[3].

Currently, per the staging manual published by the American Joint Committee on Cancer (8th edition), surgical resection remains the only curative approach for stages I–III locoregional cancers[4]. Although stage I colon cancer clearly represents a patient population without nodal involvement, stage II and III colon cancers affect a heterogeneous group of patients who might have micrometastases or regional lymph node involvement, or both. Therefore, for the latter two stage groups, adjuvant systemic therapy remains a viable option—most frequently adjuvant therapy that uses 5-fluorouracil (5FU)–based or oxaliplatin-based chemotherapy, or both.

Previous reviews have thoroughly assessed the trials that led to those treatment options[5,6]. Assessing each individual trial was not the main goal of the present review, but a summary table (Table I) is available to help the reader understand the various benefits of adjuvant chemotherapy in locoregional colon cancer. Here, we explore the data available at June 2019 to assess methods of patient risk stratification, methods for determining the optimal duration of adjuvant therapy, and the potential future directions for research and clinical practice. Notably, although our review focuses strictly on locoregional colon cancer, it is important to be aware that most of the available data pertain to colon and rectal cancers alike.

Correspondence to: Petr Kavan, E-783.2 Segal Cancer Centre, Sir Mortimer B. Davis Jewish General Hospital, 3755 Côte-Sainte-Catherine Road, Montreal, Quebec H3T 1E2.
E-mail: petr.kavan@mcgill.ca **DOI:** https://doi.org/10.3747/co.26.5605

RISK STRATIFICATION

Multiple histopathologic, clinical, and molecular or genomic factors have been demonstrated to have prognostic or predictive value (or both) in adjuvant therapy for locoregional colon cancer. Histopathology is routinely used in clinical practice, but other methods that can help in establishing a prognosis are discussed here.

TABLE I Adjuvant chemotherapy in colorectal cancer, the past and the present

Reference (trial name)	Pts (*n*)	Primary endpoints	Disease stages included	Trial conclusions
Moertel *et al.*, 1995[7] (INT-0035)	929	OS	III	5-Fluorouracil–levamisole superior to observation
Wolmark *et al.*, 1999[8] (NSABP C-04)	2078	DFS, OS	Dukes B–C	5-Fluorouracil–leucovorin slightly superior to 5-fluorouracil–levamisole
Andre *et al.*, 2004[9] (MOSAIC)	2246	DFS	II or III	Superiority of FOLFOX4 compared with leucovorin–5-fluorouracil (improves DFS by 3 percentage points for all stage II cases, and by 5 percentage points for high-risk stage II cases)
Saltz *et al.*, 2004[10] (CALGB 89803)	1264	OS	III	No bolus irinotecan–fluorouracil–leucovorin in adjuvant therapy for stage III CRC
Wolmark *et al.*, 2004[11] (NSABP C-06)	1533	DFS	II or III	Equivalency of uracil/tegafur–leucovorin and 5-fluorouracil–leucovorin (uracil/tegafur not approved in the United States and Canada)
Alberts *et al.*, 2005[12] (N0147)	2686	DFS	III	mFOLFOX6–cetuximab not superior to mFOLFOX6 in adjuvant therapy for *KRAS* exon 2 wild-type stage III CRC
Andre *et al.*, 2005[13] (GERCOR C96)	905	DFS	Dukes B2–C	Equivalency of leucovorin–5-fluorouracil and monthly 5-fluorouracil–leucovorin
Haller *et al.*, 2005[14] (INT-0089)	3759	DFS	II or III	Equivalency of 6- and 12-month treatment cycles and of high-dose compared with low-dose leucovorin
Twelves *et al.*, 2005[15] (X-ACT)	1987	DFS	III	Capecitabine equivalency with leucovorin–5-fluorouracil bolus; less toxic
van Cutsem *et al.*, 2005[16] (PETACC-3)	3278	DFS	II or III	Leucovorin–5-fluorouracil plus irinotecan not superior to leucovorin–5-fluorouracil (statistically insignificant)
Kuebler *et al.*, 2007[17] (NSABP C-07)	1407	DFS	II or III	Bolus 5-fluorouracil–leucovorin plus oxaliplatin (FLOX) superior to 5-fluorouracil–leucovorin
Allegra *et al.*, 2011[18] (NSABP C08)	2673	DFS	II or III	mFOLOFOX6 plus bevacizumab not superior to FOLFOX6
de Gramont *et al.*, 2012[19] (AVANT)	2867	DFS	II or III	FOLFOX4 or CAPOX plus bevacizumab not superior to FOLFOX4; detrimental effect with bevacizumab in adjuvant therapy for CRC
Pectasides *et al.*, 2014[20] (ACTRN 12610)	439	DFS	III	Equivalency of FOLFOX6 and CAPOX in adjuvant therapy for stage III CRC
Taieb *et al.*, 2014[21] (PETACC-8)	1602	DFS	III	FOLFOX4 plus cetuximab not superior to FOLFOX4 in adjuvant therapy for *KRAS* exon 2 wild-type stage III CRC
Schmoll *et al.*, 2015[22] (NO16968)	1886	OS	III	Superiority of CAPOX to fluorouracil–folinic acid (improves OS: 73% vs. 67%)
Grothey *et al.*, 2018[23] (IDEA)	12,834	DFS	III	Noninferiority for DFS of 3 months compared with 6 months FOLFOX or CAPOX; treatment depended on risk group and regime; 3 months as effective as 6 months of CAPOX in the low-risk subgroup

Pts = patients; OS = overall survival; NSABP = National Surgical Adjuvant Breast and Bowel Project; DFS = disease-free survival; FOLFOX = 5-fluorouracil–leucovorin–oxaliplatin; CALGB = Cancer and Leukemia Group B; CRC = colorectal cancer; GERCOR = Groupes Coopérateur Multidisciplinaire en Oncologie; CAPOX = capecitabine–oxaliplatin.

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Histopathology

Currently, the major professional societies—including the American Society of Clinical Oncology (ASCO)[24], the European Society for Medical Oncology[25], and the U.S. National Comprehensive Cancer Network[26]—have designated "high-risk" stage II colon cancer as cases having any one or more of these characteristics: stage pT4; a poorly differentiated tumour; perforation; lymphovascular invasion; perineural invasion; a high number of lymph nodes examined (ASCO: <13; European Society for Medical Oncology and U.S. National Comprehensive Cancer Network: <12); and close, indeterminate, or positive margins after surgery (U.S. National Comprehensive Cancer Network). Those features have been extensively studied, and the results have been implemented into clinical practice.

Age

For elderly patients, adjuvant chemotherapy poses unique questions concerning the efficacy and tolerability of treatment. A large study pooled seven randomized controlled clinical trials that explored the administration of adjuvant chemotherapy (5FU–leucovorin or 5FU–levamisole) in stage II and III CRCs and found that benefits in overall survival (OS) and disease-free survival (DFS), and rates of adverse events, in patients 70 years of age and older were similar to those in other age groups[27]. Moreover, analysis of prospective data from 85,934 patients with stage III CRC demonstrated that OS benefits in elderly patients were similar to those in their younger counterparts[28].

Although CRC is commonly viewed as a disease of older age, a notable subset of patients (49 years of age or less) has experienced an annual 2% rise in CRC incidence since 1994[29]. The patient population experiencing young-onset colon cancer poses inherent challenges in the adjuvant setting because the efficacy and long-term implications of adjuvant therapy for those patients are poorly understood. A recent study demonstrated that, at all stages, such patients were 2–8 times more likely to receive adjuvant chemotherapy after resection, with no significant difference in OS when their survival was compared with survival in patients who received concomitant postoperative chemotherapy[30]. That observation is similar to findings reported by our group in the setting of metastatic CRC, where, in patients who received first-line noncurative therapy, progression-free survival was greater in patients with late-onset CRC than in those with young-onset CRC [hazard ratio (HR): 1.96; 95% CI: 1.04 to 3.68][31].

Left Compared with Right Side

The laterality of CRC—that is, right-sidedness or left-sidedness—has become an important topic of discussion as a method of risk stratification. Anatomically, right-sided colon cancer consists of tumours at the cecum, appendix, ascending colon, hepatic flexure, and proximal two thirds of the transverse colon; left-sided colon cancer consists of tumours at the distal one third of the transverse colon, the splenic flexure, sigmoid colon, descending colon, and rectum[32]. The distinction is thought to be secondary to the difference in the embryologic origin of the colon tissue (and therefore the cancerous tissue), because the right is derived from the midgut and the left is derived from the hindgut. Symptoms of right-sided tumours are known to appear later than those of left-sided tumours, often leading to advanced right-sided disease at presentation[33]. A number of studies have demonstrated a lack of association between laterality and outcomes in locoregional disease[34]; others have demonstrated a laterality-dependent difference in outcomes[35,36]. In the metastatic setting, at least, right-sided tumours are associated with worse prognosis[37,38]. Insights into the molecular and genetic components of right-sided and left-sided cancers are needed and could deepen the understanding of their differences in the context of adjuvant therapy for locoregional colon cancer.

Genomic Profiling

The data from the National Surgical Adjuvant Breast and Bowel Project C-07 study suggest that genomic profiling using the Oncotype DX assay (Genomic Health, Redwood City, CA, U.S.A.) might improve risk prognostication in high-risk resected stage II and III colon cancers[39]. A recent study demonstrated that Oncotype DX results altered the decision about adjuvant chemotherapy use in 27% of patients with stages II and IIIA–B CRCs and that its results might be applicable in decision-making for adjuvant therapy in elderly patients[40].

ColoPrint (Agendia, Amsterdam, Netherlands), a gene expression classifier similar to Oncotype DX, has been shown to significantly improve prognostic accuracy in stage II CRC independent of other clinical factors, making it potentially useful for identifying high-risk stage II disease that would benefit from adjuvant therapy[41]. Another similar genomic test that is used for risk stratification in stage II CRC is GeneFx (Med BioGene, Vancouver, BC). Additionally, a tumour cell detection test known as Veridex (Johnson and Johnson, New Brunswick, NJ, U.S.A.) has been approved by the U.S. Food and Drug Administration and has been implemented into metastatic disease surveillance and treatment guidance. Finally, in a study from the MD Anderson Cancer Center, a specific gene expression pattern was identified as an independent predictor of response to chemotherapy and clinical outcomes in patients with CRC[42].

Those advances offer promising insights into the role that genomics will play in clinical guidance for adjuvant therapy in patients. For instance, in 2017, ASCO made recommendations about biomarker testing to improve targeted therapy for colon cancer. They supported testing for genes in the EGFR pathway, given that the information can be used in a clinical setting to predict a negative response to anti-EGFR monoclonal antibodies and to identify individuals who will not benefit from that targeted therapy.

Loss of Heterozygosity at Chromosome 18q

Jen *et al.*[43] evaluated the prognostic value of chromosome 18q in patients with stage II or III CRC, finding that loss of heterozygosity at chromosome 18q was independently prognostic for 5-year survival in stage II, but not stage III, colon cancer. However, those authors also found that, in stage II and stage III colon cancers alike, adjuvant therapy had no prognostic value (HR: 0.74; 95% CI: 0.40 to 1.38).

Carcinoembryonic Antigen

The specificity of carcinoembryonic antigen (CEA) for identifying occult CRC is high, but the sensitivity is low, and so CEA is not recommended as a screening tool. The ASCO Tumor Marker Panel recommends that, preoperatively, CEA be used to provide prognostic information and, postoperatively, to continue surveillance. Postoperative serum CEA testing should therefore be performed every 3 months in patients with stage III disease for at least 3 years[44,45]. Values that persistently rise above baseline should prompt restaging, but they also suggest progressive disease. Data are insufficient to support the use of CEA to determine whether to treat a patient with adjuvant therapy. Caution must be exercised when interpreting a rising CEA level during the first 4–6 weeks of adjuvant treatment, because early rises can occur, especially after the start of oxaliplatin chemotherapy.

Microsatellite Instability and Deficient Mismatch Repair

A number of studies have confirmed the prognostic effect of the high microsatellite instability (MSI-H) phenotype (h*MSH2* or h*MLH1)* in CRC. In a multivariable analysis of 2141 patients with stage II and III CRCs from randomized adjuvant trials, Sinicrope *et al.*[46] observed that, compared with patients having microsatellite-stable (MSS) tumours, patients with tumours showing MSI experienced statistically significant improvements in DFS (HR: 0.73; 95% CI: 0.59 to 0.91; $p = 0.004$) and OS (HR: 0.73; 95% CI: 0.59 to 090; $p = 0.004$). The association of MSI status with improved outcomes was observed in patients with stage II and III disease, but was statistically significant only in stage III when MSI CRCs were compared with MSS CRCs (HR for DFS: 0.76; 95% CI: 0.58 to 1.00; $p = 0.047$; HR for OS: 0.76; 95% CI: 0.59 to 0.99; $p = 0.041$); the association was nonsignificant in stage II (HR for DFS: 0.83; 95% CI: 0.57 to 1.21; $p = 0.339$; HR for OS: 0.81; 95% CI: 0.55 to 1.18; $p = 0.266$)[46]. The PETACC-3 study further demonstrated the stronger prognostic impact of MSI in stage II disease ($p = 0.004$) than in stage III disease ($p = 0.06$)[47].

With respect to mismatch repair (MMR) status as an effective prognostic marker, an association of deficient MMR (dMMR) with improved DFS was observed in patients with stages II and III CRC who did not receive 5FU-based adjuvant chemotherapy (HR: 0.51; 95% CI: 0.29 to 0.89; $p = 0.009$); OS was also improved in those patients (HR: 0.47; 95% CI: 0.26 to 0.83; $p = 0.004$). Patients who received a 5FU-based therapy did not experience a difference in benefit associated with MMR status (HR for DFS: 0.79; 95% CI: 0.49 to 1.25; $p = 0.30$; HR for OS: 0.78; 95% CI: 0.49 to 1.24; $p = 0.28$).

With respect to the predictive potential of MMR status in stage II survival, no difference in benefit seems to accrue from 5FU-based adjuvant chemotherapy for patients with either proficient MMR (pMMR—HR: 0.84; 95% CI: 0.57 to 1.24; $p = 0.38$) or dMMR (HR: 2.30; 95% CI: 0.85 to 6.24; $p = 0.09$). That observation signifies that, for stage II disease, MMR status does not appear to be a useful predictive marker for the effectiveness of a 5FU-based adjuvant regimen because neither dMMR nor pMMR has been associated with any improvement or difference in benefit.

Concerning prediction of the effectiveness of adjuvant therapy in stage III disease, dMMR status shows no association with benefit from treatment (HR: 1.01; 95% CI: 0.41 to 2.51; $p = 0.98$). In contrast, patients having tumours with pMMR experience a benefit from 5FU-based adjuvant chemotherapy (HR: 0.64; $p = 0.001$). Patients with stage III pMMR tumours will therefore likely experience an increase in benefit when given 5FU-based adjuvant chemotherapy.

BRAF

The *BRAF* proto-oncogene on chromosome 7 encodes a protein in the RAS/MAPK pathway that induces neoplastic proliferation. Mutations in the *BRAF* gene are present in 11% of all patients with CRC. A study of 533 patients with high-risk stages II and III CRCs, conducted with the aim of establishing the roles of *BRAF* and MMR status in CRC prognosis, demonstrated significantly improved OS in the *BRAF* wild-type and dMMR groups (5-year survival: 100% vs. 73%, $p = 0.002$)[48]. In 2015, Seppälä *et al.*[49] showed that, compared with patients who were *BRAF* wild-type, those with *BRAF* mutations had an increased risk of poor OS unless the mutation occurred in concert with MSI, and across all stages of disease, mutated *BRAF* or MSS was associated with poor DFS. *BRAF* mutations are therefore assumed to be an isolated risk factor for poor prognosis, especially in conjunction with MSS; however, all data in support of that assumption are derived from retrospective analyses. Prospective research is required to understand and validate the role of *BRAF* in CRC.

Homeobox Protein CDX2

The transcription factor CDX2 is expressed in the epithelia of intestinal cells and is overexpressed in adenocarcinoma of the colon. Overexpression of CDX2 within tumour cells in stages II and III disease has been reported to be correlated with worse 5-year survival. In addition, elevated CDX2 expression predicts tumour response to adjuvant chemotherapy. Interestingly, in a subset of patients with stage II CDX2-negative disease, a survival benefit from adjuvant chemotherapy compared with no adjuvant therapy was observed, thus identifying a population with high-risk CDX2-negative CRC[50].

DURATION OF THERAPY

The phase III randomized MOSAIC trial demonstrated that combination chemotherapy for a standard 6-month duration in stage III resected colon cancer was associated with significant improvements in DFS and OS. However, administration of oxaliplatin was associated with dose-dependent peripheral sensory neurotoxicity[51]. Previous studies of 5FU monotherapy have suggested a potential for similar efficacy with shorter-duration as with longer-duration chemotherapy; shortening the duration of oxaliplatin administration should reduce the incidence of neuropathy and other adverse events that worsen with increasing exposure. Thus, the data from six concurrent phase III trials spanning 12 countries were pooled as part of the IDEA collaboration to determine whether 3 months or 6 months of therapy altered DFS 3 years after therapy with either FOLFOX (5FU–leucovorin–oxaliplatin) or CAPOX (the 5FU pro-drug capecitabine plus oxaliplatin). The analysis included 12,834 patients who met the criteria for modified intention-to-treat and who had comparable tumour characteristics. Overall, about 40% of the patients received CAPOX and 60% received FOLFOX (Table II)[23,57]. The noninferiority of 3 months compared with

TABLE II IDEA trial summary

Variable	Trial name						
	SCOT[52] (U.K., NZ, Denmark, Spain, Australia, Sweden)	**IDEA France[53] (France)**	**TOSCA[54] (Italy)**	**ACHIEVE[55] (Japan)**	**CALGB/SWOG[23] (U.S.A., Canada)**	**HORG[56] (Greece)**	**Overall**
Stage III cases (*n*)	3983	2010	2402	1291	2440	708	12,834
Risk group (%)							
T1–3/N1	51.0	62.0	65.5	55.6	63.6	59.1	58.7
T4, N2, or both	49.0	38.0	34.5	44.4	36.4	40.9	41.3
Chemotherapy regimen (%)							
CAPOX	66.5	10.0	34.0	75.1	0	58.2	39.5
FOLFOX	33.5	90.0	66.0	24.9	100	41.8	60.5
	CAPOX vs. mFOLFOX6	CAPOX vs. mFOLFOX6	CAPOX vs. mFOLFOX4	CAPOX vs. mFOLFOX6	mFOLFOX6	CAPOX vs. mFOLFOX4	
3-Year disease-free survival							
With 3 months' therapy (%)	76.7	72	78.8	79.5			74.6
With 6 months' therapy (%)	77.1	76	78.7	77.9	34.9 Months	47.5 Months	75.5
Median follow-up (months)	36.8	51.3	61.7	36.7			41.8
Grade 2 or greater neuropathy (%)							FOLFOX CAPOX
With 3 months' therapy	25	36	9	14			16.6 14.2
With 6 months' therapy	58	66	31	36			47.7 44.9

CALGB = Cancer and Leukemia Group B; SWOG = Southwest Oncology Group; HORG = Hellenic Oncology Research Group; CAPOX = capecitabine–oxaliplatin; FOLFOX = infusional 5-fluorouracil–leucovorin–oxaliplatin; mFOLFOX = modified FOLFOX.

6 months of treatment was not confirmed in the overall study population [HR: 1.07; 95% CI: 1.00 to 1.15 (the upper limit CI cut-off being 1.12)], but was seen for CAPOX (HR: 0.95; 95% CI: 0.85 to 1.06) and not for FOLFOX (HR: 1.16; 95% CI: 1.06 to 1.26). In patients at a low risk of recurrence (T1–3 and N1), 3 months of therapy was noninferior to 6 months for both regimens, with the 3-year DFS being 83.1% and 83.3% respectively (HR: 1.12; 95% CI: 0.90 to 1.12). Conversely, in patients at high risk of recurrence, the 6-month duration of therapy was superior to the 3-month duration (64.4% vs. 62.7% for the treatments combined; HR: 1.12; 95% CI: 1.03 to 1.23; $p = 0.01$ for superiority)[23].

Based on the aforementioned results, ASCO recommended a 6-month duration of oxaliplatin-containing adjuvant therapy for patients with stage III CRC at high risk of recurrence (T4 or N2, or both). For patients at low risk of recurrence (T1–3 and N1), either 6 months or 3 months of adjuvant chemotherapy can be offered, based on a potential reduction in adverse events and no significant difference in DFS with the 3-month regimen[58]. The ASCO Expert Panel advises a shared decision-making approach, taking into account patient characteristics, values, and preferences, and having a discussion of the potential benefits and risks of harm associated with treatment duration. The guideline did not recommend one oxaliplatin-containing regimen over the other for patients who choose 3 months of adjuvant therapy, but they noted that 3 months of treatment was inferior to 6 months of treatment among patients receiving FOLFOX, and conversely, 3 months of CAPOX was found to be noninferior to 6 months of CAPOX[57].

In contrast to the situation with stage III CRC, no guidelines for the duration of adjuvant chemotherapy in stage II CRC are universally accepted, reflecting a lack of clinical trials designed and powered to study adjuvant chemotherapy in patients with stage II disease. All existing evidence is derived from pooled analyses of stage II and III CRC in clinical trials, often leading clinicians to approach the decision to treat patients with stage II CRC from the perspective of stage III disease.

If a decision to treat stage II CRC with 5FU is made, the standard duration of treatment is 6 months. The INT-0089 clinical trial found no significant difference in DFS or OS between 6-month and 12-month 5FU treatment regimens[14]. In the MOSAIC trial, a significant increase in DFS was observed in the patients with stage III CRC, but not in those with stage II CRC (HR: 0.80; 95% CI: 0.56 to 1.15). Nevertheless, the DFS calculated for patients with stage II disease was 84.3% with 5FU alone, rising to 87% when oxaliplatin was added[51].

Data about the duration of treatment for patients in the IDEA collaboration with high-risk stage II CRC were recently published. When comparing 3 months with 6 months of therapy, 1254 of 3273 patients received FOLFOX, and a lower incidence of grade 3 toxicity was observed in the 3-month group. The other 2019 patients, who received CAPOX, experienced less toxicity (HR: 1.02; 80% CI: 0.88 to 1.17; p for noninferiority: 0.087). In high-risk stage II disease, the HR for the 5-year DFS was 1.18 (80% CI: 1.05 to 1.31; p for noninferiority: 0.404)[59]. Paralleling the results for stage III disease, a lower HR was also observed in the CAPOX group, implying that 3 months and 6 months of treatment offer similar levels of efficacy in terms of OS.

The TOSCA trial, which compared 6 months with 3 months of treatment using either CAPOX or FOLFOX in patients with high-risk stage II CRC, demonstrated the superiority of 6 months of treatment for recurrence-free survival (HR: 1.41; 95% CI: 1.05 to 1.89) at both 3 and 5 years after treatment[54]. Therefore, when considering oxaliplatin-based chemotherapy, a 6-month duration is clearly superior to a 3-month duration, particularly in cases of high-risk stage II CRC. The lack of a statistically significant survival benefit with the use of oxaliplatin compared with 5FU in stage II CRC suggests that 5FU is potentially the chemotherapy agent of choice in that group.

FUTURE DIRECTIONS

To date, there are number of areas of interest and crucial questions that require answering.

Prognosis

Circulating Tumour DNA

Circulating tumour DNA (ctDNA) is found in the blood of patients with CRC as a result of neoplastic cell necrosis and DNA release. Recently, interest in ctDNA as a potential diagnostic and prognostic marker, a marker for disease recurrence, and a target for patient-specific tailored therapy has grown[60]. Numerous studies have been evaluating the clinical efficacy of ctDNA as a promising diagnostic marker. In April 2019, Osumi *et al.*[61] reviewed the use of ctDNA in CRC and found that patients with detectable ctDNA in plasma, compared with those without it, experienced worse OS and progression-free survival. They also found that the absence of ctDNA after resection was associated with improved prognosis and a lower risk of relapse and that the increased presence of mutations in ctDNA is indicative of resistance to therapy or impending treatment failure[61]. Tie *et al.*[62] further demonstrated inferior recurrence-free survival when ctDNA was detected in a prospective cohort of 230 patients with resected stage II CRC after adjuvant chemotherapy. Future studies involving ctDNA, such as the Australian DYNAMIC study (ACTRN1261500381583) and the Canada–U.S. COBRA study will be eagerly awaited.

PI3K

The PI3K (phosphatidylinositol-3-kinase) family of lipid kinases are important cell membrane elements and second messengers in cell signalling. Mutations in the *PI3KCA* gene are present in a variety of cancers and in 10%–20% of patients with CRC[63]. In *KRAS* wild-type cancers, *PI3KCA* mutations have predicted a poor response to anti-EGFR therapy and worse clinical outcomes in some studies. Malinowsky *et al.*[64] found that activation of the PI3K pathway was correlated with lower DFS in stage II CRC after resection. Furthermore, *PI3KCA* mutations have been shown to be associated with increased resistance to traditional metastatic chemotherapy with 5FU–oxaliplatin or 5FU–irinotecan[65]. In another 24-patient cohort study, *PI3KCA* mutations, in combination with *TP53* mutations, were associated with shorter OS in patients with stage II or III CRC treated with 5FU[66]. A deeper understanding of the prognostic value of *PI3KCA* mutations is required before their presence can be used in clinical risk stratification; however, interestingly, such mutations have demonstrated benefit as an indicator for successful treatment with aspirin in stages I–III disease: for patients with *PI3KCA*-mutated CRC, the regular use of aspirin after diagnosis was associated with superior cancer-specific survival and OS[67].

Treatment

The *DPYD* gene codes for dihydropyrimidine dehydrogenase, the rate-limiting enzyme of pyrimidine breakdown that also breaks down 5FU and other pyrimidine analog drugs[68]. Polymorphisms in *DYPD* are associated with increased severity of adverse events after the administration of fluoropyrimidine-based chemotherapy. Specifically, the *DPYD* IVS14+1G>A and c.2846A>T polymorphisms were found to be predictors of severe capecitabine toxicity in an analysis of germline DNA collected in the CAIRO2 trial[69]. That finding suggests that patients with those haplotypes should receive reduced doses of capecitabine to avoid severe grades 3–4 toxicities. Moreover, in the largest study to date, the *DYPD* variants DPYD*2A and D949V were associated with an increased incidence of grade 3 or greater adverse events in patients treated with adjuvant 5FU-based combination chemotherapy. Genotyping individuals for polymorphisms in this enzyme could be useful for predicting which patients would be more susceptible to adverse events secondary to administration of a 5FU-based chemotherapy.

An analysis from the IDEA collaboration suggested that 3 months of CAPOX was not inferior to 6 months for patients at low risk of recurrence; however, studies comparing FOLFOX with CAPOX in 3-month adjuvant therapy are needed.

Surprisingly, irinotecan-based chemotherapy has shown a lack of any benefit in the adjuvant setting. A phase III study (Fédération Nationale des Centres de Lutte Contre le Cancer Accord02/FFCD9802) compared leucovorin–5FU with leucovorin–5FU–irinotecan, finding no a difference in the 3-year DFS (HR: 1.19; 95% CI: 0.90 to 1.59; adjusted HR: 0.98; 95% CI: 0.74 to 1.31; $p = 0.92$)[70]. Another phase III study, PETACC-3, also compared leucovorin–5FU with leucovorin–5FU–irinotecan for high-risk stage II or III cancers and saw no difference in the 5-year DFS (54.3% vs. 56.7%, $p = 0.106$), with the irinotecan group having an increased incidence of grade 3 or 5 gastrointestinal and neutropenic adverse events. For those reasons, irinotecan use has not been translated into practice in that setting. However, in the metastatic setting at least, adding irinotecan to FOLFOX—that is, FOLFIRINOX—has resulted in a significant survival advantage[71]. The results of the IROCAS study (ongoing UNICANCER IROCAS/CCTG CO.27 phase III trial) are eagerly awaited[72].

Immunotherapy showed a benefit in MSI-H or dMMR metastatic colon cancer; however, the benefit of introducing immunotherapy into the adjuvant setting for CRC is unknown. Currently, PD-1, CTLA-4, and CIK inhibitors are under study in multiple registered clinical trials (NCT02466906, NCT02280278, NCT02415699, NCT01929499, and NCT03026140 at https://ClinicalTrials.gov/). In the future, their results could provide better treatment options for patients with resected early-stage colon cancer. Currently, an ongoing randomized phase III interventional clinical trial (NCT02912559) is comparing adjuvant chemotherapy alone with adjuvant chemotherapy plus atezolizumab for effectiveness in patients with dMMR stage III colon cancer. The study's estimated completion date is December 2020, and its results will be crucial for potentially providing a more effective combination therapy in the adjuvant setting for stage III colon cancer with dMMR[73].

SUMMARY

Considering the range and heterogeneity of colon cancer, drawing conclusions about the use and duration of adjuvant chemotherapy for stages II and III disease has proved to be challenging.

As demonstrated in numerous clinical trials, the "gold standard" adjuvant treatment for stage III colon cancer in the postsurgical setting is an oxaliplatin-containing regimen such as FOLFOX or CAPOX. Those combinations have repeatedly demonstrated survival benefits. In contrast, adjuvant treatment for stage II disease remains controversial because of conflicting trial results. At a U.S. National Institutes of Health conference in 1990, a consensus was reached to recommend adjuvant 5FU therapy for all patients with stage III disease; however, "the panel [could not] recommend any specific adjuvant therapy at [the] time for Stage II patients outside of clinical trials"[74]. After nearly 30 years, that statement remains relatively unchanged. Two innate problems render any assessment of the benefits of adjuvant therapy in stage II disease challenging. The first problem is that stage II colon cancer, despite being a "local disease," demonstrates considerable heterogeneity. A stage IIA (pT3N0) tumour invades through the muscularis propria into the pericolorectal tissue; a stage IIB (pT4aN0) tumour penetrates into the surface of the visceral peritoneum; and a stage IIIC (pT4bN0) tumour can directly invade or adhere to adjacent organs or structures[4]. The overall 5-year survival rate varies significantly for stages IIA (66.7%), IIB (60.6%), and IIC (45.7%)[75]. Because the last cancer staging manual from the American Joint Committee on Cancer (8th edition) was developed in 2016 (effective 2018), it relies on pathology findings and does not account for other advanced prognostic factors that have come to be understood as important in CRC. The second challenge is that patients with stage II CRC innately do well and that, from a statistical perspective, not enough of the relevant population has been studied to demonstrate a true benefit[76]. Current clinical guidelines therefore recommend early and open patient-centred discussions that consider the benefits and risks associated with adjuvant chemotherapy in this setting, given the inherent toxicity of oxaliplatin.

The duration of adjuvant therapy remains a subject of debate. Results from clinical trials have demonstrated inconsistent trends in OS and DFS for 3-month and 6-month regimens, depending both on the staging of the cancer and the patient's risk status and on the type of chemotherapy used. Acceptable modalities of chemotherapy include oxaliplatin-based regimens (CAPOX, FOLFOX), capecitabine, and 5FU–leucovorin. The duration of treatment varies from 3 months to 6 months, largely depending on risk stratification and patient preference.

Numerous disease-specific tools such as laterality, genomic profiling, and various molecular markers have been conceived with the goal of improving the accuracy of risk stratification for CRC and guiding decision-making. Analysis of the latest studies about the duration of adjuvant oxaliplatin-based chemotherapy (3 months vs. 6 months) has demonstrated that the duration of FOLFOX should remain at 6 months, but CAPOX could be administered for 3 months in the presence of low-risk characteristics in stage II and III CRCs. In high-risk stage II disease, the most recent data favour a 6-month duration of oxaliplatin-based therapy as opposed to 3 months. Future technologies might involve the detection and analysis of CTDNA or PI3K (or both) to establish more descriptive and useful prognoses for patients with CRC.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Gerald Bronfman Department of Oncology, McGill University Faculty of Medicine, Montreal, QC; †University of Hawaii Internal Medicine Program and ‡University of Hawaii Cancer Center, Honolulu, HI, U.S.A.

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