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REVIEW ARTICLE

Sustainable Clinical Development of Adjuvant Chemotherapy for Colon Cancer

Eiji Oki[1] | Koji Ando[1] | Hiroya Taniguchi[2] | Takayuki Yoshino[3] | Masaki Mori[4]

[1]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[2]Aichi Cancer Center Research Institute, Nagoya, Japan

[3]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

[4]Tokai University School of Medicine, Isehara, Japan

Correspondence
Eiji Oki, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
Email: okieiji@surg2.med.kyushu-u.ac.jp

Abstract

Numerous clinical studies in an adjuvant setting have been conducted and the combination therapy of 5-fluorouracil and oxaliplatin has been established as the standard treatment for Stage III and as an option for high-risk Stage II patients. Biologics such as bevacizumab and antiepidermal growth factor receptor antibodies have failed to show additional survival benefits. The indication of adjuvant chemotherapy has been determined according to the pathological stage. Nevertheless, a pathological diagnosis does not necessarily result in selection of the optimal treatment. To improve treatment decisions, many trials have aimed to stratify patients into treatment groups using genomic testing. Recently, gene signature, Immunoscore, and circulating tumor DNA (ctDNA) assays have been reported and among them, ctDNA was shown to be a promising accurate predictive marker for recurrence. Treatment of ctDNA-positive patients with aggressive chemotherapy may reduce recurrence rates. The ultimate goal is to accurately predict the risk of recurrence and to prevent recurrence in colon cancer patients. In this review we focus on the clinical development of adjuvant chemotherapy and stratification of patients according to risk of recurrence and the future direction of adjuvant chemotherapy.

KEYWORDS

adjuvant chemotherapy, BRAF, colon cancer, ctDNA, MSI, RAS

1 | INTRODUCTION

Colon cancer is the most common gastrointestinal malignancy worldwide, with ~1.15 million new cases diagnosed and 576,858 people dying of colon cancer each year.[1] Currently, surgery, radiotherapy, and systematic chemotherapy are the standard of care for colon cancer patients. Approximately 72% of newly diagnosed colon cancer patients present with local or regional disease,[2] which provides an opportunity for curative-intent treatment. Despite curative surgery and adjuvant chemotherapy, ~30% of patients experience recurrence.[3]

The role of adjuvant chemotherapy is to reduce recurrence after curative surgery. The strategy of administering adjuvant chemotherapy has changed dramatically in two decades. The treatment regimen has been established as a combination therapy of 5-fluorouracil/leucovorin (5-FU/LV) and oxaliplatin (FOLFOX),[3,4] or capecitabine and oxaliplatin (CAPOX). In addition, treatment duration has been investigated in the IDEA collaboration to reduce cumulative peripheral

sensory neurotoxicity (PSN).[5,6] However, further studies are needed because some patients have recurrence even if their pathological diagnosis is Stage I, and a certain number of Stage II or Stage III patients have recurrence even though receiving standard adjuvant chemotherapy.

To reduce recurrence, developing new chemotherapeutic agents for adjuvant therapy and stratification of patients are important. There have been many studies that have tried to determine the utility of gene signatures in predicting adjuvant chemotherapy efficacy.[7] However, none of them were able to change the current clinical standards used in selecting an adjuvant treatment for colon cancer. Currently, circulating tumor DNA (ctDNA) is attracting attention as a promising marker of recurrence.[8,9]

This review presents an overview of published studies on adjuvant chemotherapy and the clinical utility of genetic analysis for the management of patients with localized colon cancer.

2 | HISTORY OF ADJUVANT CHEMOTHERAPY FOR COLON CANCER

2.1 | Standard adjuvant chemotherapy for colon cancer

The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-01 started an adjuvant trial in 1977 (Table 1).[10] This was the first large-scale clinical trial that showed an effect of postoperative adjuvant chemotherapy on survival in colon cancer patients. In the study, 1166 Stage II/III colon cancer patients after curative resection were randomly assigned to three groups: a surgery-alone group, a chemotherapy group (MOF: methyl-CCNU + vincristine + 5-FU), and a BCG (bacillus Calmette–Guérin vaccine) group. Compared with the surgery-alone group, the chemotherapy group showed a significant prolongation in both disease-free survival (DFS) ($P = .02$) and overall survival (OS) ($P = .05$). Subsequently, the NSABP C-03 study was conducted to investigate the utility of 5-FU/LV chemotherapy compared with MOF chemotherapy as the control group.[11] As a result, a significant increased effect of 5-FU/LV compared with MOF was shown for both DFS and OS (5-FU/LV vs MOF, 3-year DFS = 73% vs 64%, $P = .004$, respectively; 3-year OS = 84% vs 77%, $P = .003$, respectively). Furthermore, a randomized controlled trial of the de Gramont regimen (infusional 5-FU) vs the Mayo regimen (bolus 5-FU) for Stage II/III (Dukes' B/C) colon cancer patients was conducted by GERCOR, an oncology multidisciplinary research group.[12] Although there were no survival differences, it was shown that the toxicity profile was clearly better in the infusional 5-FU group. Therefore, it was considered that the de Gramont regimen was the most favorable administration method for 5-FU/LV. Since then, it has been shown that oral regimes such as uracil-tegafur (UFT) with LV[13] or capecitabine are equivalent to 5-FU/LV.[14]

After the effects of oxaliplatin, irinotecan, bevacizumab, and antiepidermal growth factor receptor antibodies were examined in patients with recurrent or unresectable colorectal cancer (CRC) a randomized trial comparing combination therapy with these drugs and 5-FU/LV monotherapy was carried out in the adjuvant setting. In a European and American randomized controlled trial, FOLFOX or CAPOX as postoperative adjuvant chemotherapy for Stage III colon cancer patients resulted in improved recurrence-free survival (RFS) and/or OS.[3,4,15] However, the combination of irinotecan with bolus 5-FU/LV (IFL) or irinotecan with folinic acid plus infusional 5-FU (FOLFIRI) was not shown to improve RFS or OS in randomized control trials.[16,17] Furthermore, in subsequent clinical trials, the addition of molecular targeted drugs such as bevacizumab and cetuximab to FOLFOX or CAPOX did not improve survival outcomes (NSABP C-08 study [FOLFOX ± bevacizumab]; AVANT study [FOLFOX ± bevacizumab, CAPOX + bevacizumab][18,19]; QUASAR-2 study [Capecitabine ± bevacizumab][20]; N0147 study [FOLFOX ± cetuximab]; and PETACC-8 study [FOLFOX ± cetuximab]).[21,22] Therefore, the current standard adjuvant chemotherapy for Stage III colon cancer patients is postoperative 6-mo FOLFOX or CAPOX.

For Stage II patients, improvement by adjuvant chemotherapy has not been established compared with Stage III patients. Thus, the recurrence risk of Stage II patients was divided into low, intermediate, and high risk according to the major clinicopathological features, and the patients were treated according to the risk assessment. In the ESMO guideline, <12 lymph nodes examined and T4 tumors are considered important high-risk features, and genetic analysis, which is mentioned later, will be added to the risk assessment in the future. In Japan, the SACURA trial failed to show the superiority of adjuvant tegafur and uracil (UFT) over surgery alone in Stage II colon cancer.[23] However, ad-hoc analysis showed that poorly differentiated patients in the chemotherapy group achieved greater improvement (9.1%) than the surgery-alone group.[24] Additionally, treatment decisions according to risk assessment are deemed necessary and should be established in Asian counties as well as in Western countries.

2.2 | Duration of chemotherapy

Despite the efficacy of FOLFOX or CAPOX chemotherapy for patients with Stage III colon cancer, this treatment leads to significant toxicity. In particular, oxaliplatin-induced cumulative dose-dependent PSN is clinically relevant; therefore, efforts to reduce neurotoxicity have been conducted. Calcium/magnesium and the Japanese herbal medicine Gosha-jinki-gan were found to decrease a neurotoxic symptom in a randomized phase II study.[25,26] However, in the phase III study, neurotoxicity was shown to increase.[27,28] It was difficult to lessen oxaliplatin-mediated neurotoxicity even with a combination of a supportive care drug. Therefore, international cooperative clinical trials were conducted to decrease adverse events by shortening the duration of adjuvant chemotherapy treatment. The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration performed a pooled prospective meta-analysis of individual patient data (IPD) from six concurrently conducted phase III trials carried out at sites in 12 countries to determine whether 3 or 6 mo

TABLE 1 Pivotal phase III trial for adjuvant chemotherapy in colon cancer

Study name	Publication Years	Control vs test arm	Sample size	DFS			OS		
				3 or 5 year (%)	HR	*P*	3 or 5 year (%)	HR	*P*
NSABP-C-03[11]	1993	5-FU/LV	521	73 (3 y)	ND	.0004	71 (3 y)	ND	.003
		MOF	524	64 (3 y)			55 (3 y)		
Andre T et al[12]	2003	LV5FU2 (noninferiority)	452	73 (3 y)	1.04	.74	86 (3 y)	1.265	.18
		Mayo regimen	453	72 (3 y)			87 (3 y)		
NSABP C-06[13]	2005	UFT/LV (noninferiority)	551	77.8 (5 y)	1.004	.0236	87.5 (5 y)	1.014	ND
		5-FU/LV(RPMI)	550	79.3 (5 y)			88.4 (5 y)		
X-ACT[14]	2005	Capecitabine (noninferiority)	1004	65.5 (3 y)	1.06	$P < .001^*$	81.3 (3 y)	0.84	.05
		5-FU/LV(RPMI)	983	61.9 (3 y)			77.6 (3 y)		
MOSAIC[3]	2009	FOLFOX4	1123	73.3 (5 y)	0.80	.003	78.5 (6 y)	0.84	.046
		LV5FU2	1123	67.4 (5 y)			76.0 (6 y)		
NSABP C-07[4,79]	2011	FLOX	1209	69.4 (5 y)	0.82	.002	80.2 (5 y)	0.88	.08
		5-FU/LV (RPMI)	1200	64.2 (5 y)			78.4 (5 y)		
NO16968/ XELOXA[80]	2015	CAPOX	944	63 (7 y)	0.80	.004	73 (7 y)	0.83	.04
		5-FU/LV (Mayo or RPMI)	942	56 (7 y)			67 (7 y)		
CALGB 89803[16]	2007	IFL	635	61 (5 y)	ND	.85	68 (5 y)	ND	.74
		RPMI	629	59 (5 y)			71 (5 y)		
PETACC-3[17]	2009	FOLFIRI	1050	56.7 (3 y)	0.86 (adjusted)	.106	73.6 (3 y)	0.83 (adjusted)	.094
		LV5FU2	1044	54.3 (3 y)			71.3 (3 y)		
NSABP C08[18]	2011	mFOLFOX6 + Bevacizumab	1334	77.4 (3 y)	0.89	.15	-	-	-
		mFOLFOX6	1338	75.6 (3 y)			-		
AVANT[19]	2012	A: mFOLFOX6 + Bevacizumab	955	76 (3 y)	1.17 (A vs C)	.443 (A vs C)	-	1.27 (A vs C)	.02
		B:CAPOX + Bevacizumab	960	73 (3 y)			-		
		C:mFOLFOX6	952	75 (3 y)			-		
QUASAR 2[20]	2016	Capecitabine + Bevacizumab	973	75.4 (3 y)	1.06	.54	87.5 (3 y)	1.11	.33
		Capecitabine	968	78.4 (3 y)			89.4 (3 y)		
PETACC-8[21]	2014	FOLFOX4 + Cetuximab	791	75.1 (3 y)	1.05	.6562	88.3 (3 y)	1.09	.5583
		FOLFOX4	811	78.0 (3 y)			90.5 (3 y)		

Abbreviations: CAPOX, capecitabin/oxaliplatin; DFS, disease-free survival; FOLFIRI, irinotecan/leucovorin/5FU; FOLFOX, oxaliplatin/leucovorin/5FU; HR, hazard ratio; LV5FU2, leucovorin/infusional 5-FU; MOF, methyl-CCNU/Vincristine/5-FU; ND, not determined; OS, overall survival; *P*, probability.

*Noninferiority test.

of therapy altered DFS 3 years after therapy with either FOLFOX or CAPOX.[5] This study included 12,834 patients who fulfilled the criteria and who were randomly divided into 3- or 6-mo adjuvant chemotherapy duration groups.[29] A shorter duration of adjuvant therapy was associated with significantly lower rates of adverse events than a longer duration, which was not related to the chemotherapy regimen. Neurotoxicity of grade 2 or higher was significantly lower in the 3-mo (16.6% in FOLFOX and 14.2% in CAPOX) than in the 6-mo therapy group (47.7% in FOLFOX and 44.9% in CAPOX). However, the noninferiority of 3 mo in comparison with 6 mo of treatment was not elucidated in the modified intention-to-treat (mITT) population (hazard ratio [HR]: 1.07; 95% confidence interval [CI]: 1.00–1.15 [the upper limit CI cutoff being 1.12]); it was confirmed only with CAPOX (HR: 0.95; 95% CI: 0.85–1.06) but not with FOLFOX (HR: 1.16; 95% CI: 1.06–1.26). Three months of therapy was noninferior to 6 mo in patients with T1, T2, or T3 and N1 cancers (HR, 1.01; 95% CI, 0.90–1.12) in an exploratory analysis. In patients with cancers classified as T4 and/or N2, the DFS rate in the 6-mo adjuvant chemotherapy duration was superior to the 3-mo adjuvant chemotherapy duration group (64.4% vs 62.7%) (HR, 1.12; 95% CI, 1.03–1.23; $P = .01$ for superiority). In the final analysis with a median follow-up of 72.3 mo, noninferiority was not statistically proved in the mITT population.[30] However, the absolute difference in median OS was 0.4% between the 3- and 6-mo groups. It was important that the neurotoxicity was clearly decreased.[29,31] Therefore, the study group concluded that 3 mo of CAPOX treatment was clinically acceptable. In the American Society of Clinical Oncology, the European Society for Medical Oncology, and the Japanese Society of Medical Oncology guidelines, 3 mo of CAPOX therapy is recommended for low-risk Stage III (T1-3 and N1) colon cancer patients, while it is considered an option for those with high-risk Stage III (T4 and/or N2) disease.

3 | RISK STRATIFICATION OF COLON CANCER PATIENTS

3.1 | Microsatellite instability (MSI)

Microsatellite instability is found in approximately 10%–20% of Stage II/III and 3% of Stage IV colon cancer patients.[32] MSI characterizes tumors with deficient DNA mismatch repair (dMMR) associated with loss of function (because of mutation or silencing) of one of the four DNA mismatch repair genes: MLH1, MSH2, MSH6, or PMS2. MSI is used clinically as a molecular marker for screening of Lynch syndrome and has a role as a prognostic marker in Stage II and III colon cancer. MSI status is also considered an important biomarker when selecting patients for adjuvant therapy. Ribic et al first showed the relationship between patients with Stage II and III colon cancer and microsatellite status using data from clinical trials.[33] All patients received 5-FU-based adjuvant chemotherapy; however, those who were low MSI/microsatellite stable had a better OS than those who were MSI-H. Many studies have demonstrated a predictive role for dMMR/MSI-H in patients treated with 5-FU-based adjuvant chemotherapy regimens, and Stage II colon cancer patients who are dMMR/MSI-H do not benefit from 5-FU-based adjuvant chemotherapy.[34-36] Therefore, treating Stage II patients who are MSI-H with adjuvant chemotherapy should be avoided.[37] However, the MOSAIC (Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) study, after a 10-year follow-up, found that FOLFOX-4 was associated with better OS (HR, 0.41) compared with LV5FU2 in MSI-H, Stage III colon cancer patients. The ACCENT clinical trial database also showed that adding oxaliplatin to fluoropyrimidine improves OS and DFS in patients with MSI low-risk Stage III colon cancer.[38]

3.2 | BRAF V600E mutation

BRAF mutations are present in 5% of CRC patients. More than 80% of mutations are found at the V600E position, with valine (V) changed to glutamic acid (E) and transversion of the 1799th T to an A at codon 600.[37] During classification of intrinsic subtypes in CRC, the BRAF mutation and MSI-H are sometimes categorized into the same group.[39] The reason is that MSI-H tumors often contain a BRAF mutation, except in patients with Lynch syndrome, because the BRAF mutation, MSI-H, and genome-wide DNA methylation (CpG islands methylated phenotype: CIMP) are strongly related.[40-42] The role of BRAF V600E mutations as a predictive biomarker in the adjuvant setting is unclear. Many retrospective studies showed that colon cancer patients with a BRAF mutation have a poor prognosis even after curative resection.[43] The presence of BRAF mutations was found to reduce patient survival in Stage III and IV but not Stage II CRC.[44] Although larger studies are needed, many previous studies did not include Stage I/II colon cancer patients.[39,45,46] In addition, 30% of colon cancer patients with a BRAF mutation are MSI-H, and MSI-H have good outcomes even in cases with a BRAF mutation.[43,47]

3.3 | RAS mutations

In CRC patients, RAS mutations are present in 45% of Stage IV and approximately 20%–40% of Stage II/III tumors, and they are more often found in MSS compared with MSI colorectal tumors.[48,49] There have been many reports demonstrating the prognostic value of RAS mutation status.[37,45,49-51]. Large post-hoc analysis of data collected from adjuvant clinical studies including N0147 and PETACC-8 has found that RAS was a prognostic marker in MSS but not in MSI patients.[45] However, the results were conflicting, with some studies reporting a poor prognostic impact of RAS mutations and others suggesting no prognostic value.[39,45,50] MSI-H tumors are located in the proximal colon in the majority of cases. Therefore, the KRAS gene might only be associated with a worse prognosis in patients with a distal tumor.[48] For Stage II patients, the presence of clinical high-risk features (poorly differentiated histology, vascular invasion, perineural invasion, examination of <12 lymph nodes, bowel obstruction, or localized perforation) have been used in the selection

of adjuvant chemotherapy. Currently, the MSI, RAS, and BRAF mutation status may help stratify patients with these clinical features. MSI status is the first selection criterion, and patients may be stratified using their BRAF/RAS mutation status if the patient is MSS with clinical high-risk features.

3.4 | Gene signatures

To date, some multigene assay systems have been developed to evaluate recurrence risk in patients with CRC, which are independent of currently used prognostic parameters (Table 2). The Oncotype DX Recurrence Score (RS) developed by Genomic Health is a quantitative reverse transcription polymerase chain reaction (RT-qPCR) assay using RNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor tissue to assess recurrence risk in Stage II/III colon cancer patients.[52] This assay has been validated in Stage II and III colon cancer without chemotherapy in Western countries, Korea, and Japan.[53-57] In a Japanese study, a cohort sampling design was employed, and 630 Stage II/III patients treated with surgery alone were sampled with a 1:2 ratio of recurrence to nonrecurrence. Association of RS with the recurrence-free interval was assessed using weighted Cox regression. The patients in the Oncotype DX high-risk Stage II group had a 5-year risk of recurrence similar to patients with Stage IIIA/IIIB disease in the low-risk group (19% vs 20%), and Stage IIIA/IIIB patients in the high-risk group showed similar RSs to that of Stage IIIC patients in the low-risk group.

ColDx (Almac, Craigavon, UK) is a microarray-based 634-transcript gene signature that identifies high-risk and low-risk Stage II colon cancer patients after surgery using FFPE samples.[58] Similar to the Oncotype DX Colon Cancer assay, the ColDx assay uses FFPE tissue, which has the benefit that the test can be performed on archived samples rather than on fresh tissue. In the validation study, the signature predicted 5-year RFS of ~70% in the low-risk group and 40% in the high-risk group (HR: 2.53; 95% CI: 1.54–4.15; $P < .001$).[58,59] The disadvantage of ColDx is that there have been few validation studies performed to date.

ColoPrint developed by Agendia (Irvine, CA) is an 18-gene prognostic classifier that involves performing RT-PCR on fresh frozen tumor tissue obtained during surgery to determine survival risk.[60] This signature was validated in patients with Stage I, II, and III disease.[61,62] This signature classified 60% patients as low risk for recurrence and 40% as high risk for recurrence with a 5-year RFS rate of 87.6% and 67.2%, respectively.[62] A prospective clinical validation study in Stage II and III patients is underway at the MD Anderson Cancer Institute, and an international Prospective Assessment of Risk Stratification of ColoPrint (PARSC) study of 575 patients is also underway in Stage II and III patients in the United States, Asia, and Europe.[63]

Consensus molecular subtypes (CMSs) for CRC that include over 600 genes were first reported by Guinney et al.[64] The classifier allowed characterization of the originally unlabeled samples from a network analysis. The CMS was generated by an international consortium with large-scale data sharing from several gene signature analyses, and consists of four CMSs with distinguishing features: CMS1 (MSI immune, 14%), hypermutated, microsatellite unstable, and strong immune activation; CMS2 (canonical, 37%), epithelial, and marked WNT and MYC signaling activation; CMS3 (metabolic, 13%), epithelial and evident metabolic dysregulation; and CMS4 (mesenchymal, 23%), prominent transforming growth factor β activation, stromal invasion, and angiogenesis.[64] The CMS1 tumors were frequently diagnosed in females with right-sided lesions, and the CMS1 patients showed good RFS but had a very poor survival rate after relapse in comparison with other subtypes. CMS may be a prognostic or predictive biomarker for adjuvant chemotherapy in Stage II/III CRC.[65-67] However, a microarray-based system is not practical for daily use because of the difficulty in preparing samples for RNA extraction. The use of an analytical system that reduced the number of the genes required has been reported recently. A 55-gene classifier (55GC) and RAS mutations in colon cancer are being validated in resected Stage II/III patients treated with adjuvant chemotherapy in Japan.[68]

3.5 | Immunoscore

The tumor microenvironment and immune cell infiltration have been shown to have predictive and prognostic value rather than the classic pathological criteria, including T and N stage or metastatic status.[69,70] The Immunoscore relies on the quantification of lymphocyte populations, especially CD3- and CD8-positive T cells in the tumor

TABLE 2 Overview of four gene signatures and the Immunoscore

Assay	Gene characteristics	Method	Requirement
Oncotype DX	12 gene (7 prognostic genes and 5 reference genes)	RT-PCR	Formalin-fixed paraffin embedded tissue
ColoPrint	18 genes	RT-PCR	Fresh-frozen tissue
ColDX	634 genes	Microarray	Formalin-fixed paraffin embedded tissue
Curebest 55GC Colon	55 genes selected from Microarray	Microarray	Fresh-frozen tissue or formalin-fixed paraffin embedded tissue
Immunoscore	Proportion of CD3- and CD8-positive T cells	Immunohistochemistry	Formalin-fixed paraffin embedded tissue

Abbreviations: RT-PCR, reverse transcription real-time polymerase chain reaction.

center and the invasive margin. This system was developed using an automated digital imaging system controlled via dedicated software (Immunoscore Analyzer, HalioDx, Richmond, VA). A worldwide Immunoscore consortium identified a strategy to demonstrate the feasibility and reproducibility of the Immunoscore, and it validated its major prognostic power in colon cancer Stage I/II/III patients.[71] The Immunoscore was shown to contribute the most to determining risk among all clinical parameters; therefore, the Immunoscore may be integrated into TNM staging as TNM-I in the clinical setting[71] in Western countries. Immunoscore has demonstrated benefits in determining the risk of recurrence for Stage II patients in addition to the pathological features. However, its role in predicting chemotherapy benefit remains uncertain.

3.6 | ctDNA

ctDNA is derived from cancer cells and released into the bloodstream as a result of tumor cell necrosis. ctDNA represents only a small fraction of circulating DNA, but this fraction is highly variable, ranging from less than 0.1% to greater than 10% depending on tumor stage, disease burden, biologic shedding, or proliferation, and on anatomic factors such as disease site.[8,72]

Once in the circulation, ctDNA is cleared rapidly from the bloodstream with a half-life of approximately 2 h. ctDNA can be found in both the early stage and metastatic disease across different solid tumor types, but the detection rate varies between tumor types and different stages of the same tumor type.[72] Recently, a novel technology for detecting minimal residual disease using ctDNA has been discovered.[73-75] Tie et al reported that ctDNA was detected postoperatively in 14 of 178 (7.9%) patients, 11 (79%) of whom developed recurrence at a median follow-up of 27 mo. Recurrence occurred in only 16 (9.8%) of 164 patients with negative ctDNA (HR: 18, 95% CI: 7.9–40) in patients not treated with adjuvant chemotherapy. Another report also showed that ctDNA-positive patients at postoperative day 30 were 7.2 times more likely to relapse than ctDNA-negative patients, in Stage II/III patients.[73,76,77] Currently, new prospective studies are in progress all over the world. In Japan, nationwide large-scale clinical trials have already been initiated. CIRCULATE-Japan consists of a prospective observational study and two accompanying interventional studies.[78] Clinical Stage II–III as well as R0-intent Stage IV patients are being enrolled. The sample size of the observational study named GALAXY is 5000, and ctDNA will be analyzed at regular timepoints pre- and possurgery over a 2-year period using the Signatera (Natera, San Carlos, CA) system. High-risk Stage II / low-risk Stage III patients who are ctDNA-negative at 4-week postsurgery will be included in the interventional study named the VEGA trial, which is a phase III study comparing surgery alone with adjuvant 4-cycle CAPOX. Studies for ctDNA-negative patients will be included in a prospective meta-analysis as the global CIRCULATE IDEA project, which will be conducted in more than 10 countries. As part of the CIRCULATE-Japan platform, a randomized phase III trial named ALTAIR will be performed to compare an investigational new drug with a placebo in patients who are ctDNA-positive at any timepoint even though they have been treated with standard adjuvant chemotherapy. Approximately 150 institutions across Japan and Taiwan are joining in the CIRCULATE-Japan project.[78] Currently, postoperative (4 weeks) ctDNA-positive status was detected in 18% (140/797) of the patients, with 5% (3/66), 5% (15/278), 25% (74/301), and 32% (48/152) in pStage I, II, III, and IV, respectively, in the GALAXY study by Shiras H et al, which was reported in the ESMO World Congress on Gastrointestinal Cancer 2021.

4 | SUMMARY

The purpose of adjuvant postoperative treatment is to prevent recurrence in colon cancer patients. Until now, efforts to maximize drug intensity for adjuvant chemotherapy have been pursued. In future research, it is important to stratify patients using genomic analysis. ctDNA may be the most promising method among the various genomic tests to optimally risk-stratify patients. Sustainable research and development of more efficacious adjuvant treatments and prognostic/predictive stratification assays are necessary to generate the ultimate colon cancer therapy.

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ORCID

Eiji Oki https://orcid.org/0000-0002-9763-9366

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