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Integrative Treatment for Colorectal Cancer: A Comprehensive Approach

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Abstract

A comprehensive approach to integrative treatment of colorectal cancer (CRC) patients involves three spheres of intervention: lifestyle, biology, and conventional treatment. Individualization of treatment is emphasized. The lifestyle sphere includes nutritional therapies, biobehavioral strategies with circadian interventions, and physical care modalities. The biology sphere comprises six host factors in the patient's internal biochemical environment or ''terrain'': inflammation, glycemia, oxidative stress, immune dysregulation, coagulopathy, and stress chemistries. Laboratory testing of these factors guides integrative lifestyle and supplement recommendations. The conventional treatment sphere includes individualized lifestyle recommendations, and supplements or drugs used to enhance tolerability or effectiveness of conventional treatments. Innovative strategies are implemented, including chronomodulated chemotherapy, chemosensitivity testing, and using results of molecular genomic testing to guide nutritional infusions and supplement recommendations. In the lifestyle sphere, substantial evidence from cohort studies supports recommendations for a diet that emphasizes plant and fish proteins, healthful fats in amounts that are tailored to the clinical circumstance of the patient, and carbohydrates based on unrefined whole grains, vegetables and whole fruits. High glycemic diets and refined carbohydrates, especially sugar-sweetened beverages, should be avoided. Biobehavioral strategies include practice of the relaxation response and related approaches. In addition, specific strategies to promote robust circadian organization (CO) are used to combat quality of life concerns and worsened survival that accompany disrupted CO. Physical activity, including aerobic activity and muscle strengthening, is recommended at all disease stages. In the biology sphere, supplements and lifestyle recommendations for inflammation and glycemia are discussed. In the conventional treatment sphere, supplements and innovative and complementary therapies that may remedy treatment toxicities are reviewed. Approaching CRC treatment with a comprehensive, individualized intervention enables safe and beneficial outcomes in this patient population, which can vary widely in individual biology, treatment toxicities, and disease complications. Further research in integrative therapies for CRC patients is needed.

Keywords: integrative cancer treatment, colorectal cancer, plant-based diet, circadian rhythms, inflammation, glycemia

Introduction

Colorectal cancer (CRC) has declined in incidence and mortality in the United States for the last several decades due to decreases in smoking and red meat consumption, increased aspirin use, wide practice of screening tests, and improved treatment.[1] In 2017, 135,430 U.S. cases are estimated to have occurred, with 50,260 deaths. CRC rates globally are expected to increase to 1,678,127 by 2020, associated with the spread of Western lifestyles.[2,3]

CRC patients use complementary and alternative treatments during conventional therapy at rates similar to those of other cancer patients—82.8% in a recent survey.[4] Also, with known diet and lifestyle risks for CRC incidence, this cancer seems a natural focus for integrative treatment. This article presents an integrative strategy for CRC based on the Life Over Cancer (LOC) system, a comprehensive integrative approach in clinical use at the Block Center for Integrative Cancer Treatment, described in detail elsewhere.[5,6] The current state of supportive evidence is discussed, in hopes

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of stimulating further research and practice innovations for integrative CRC treatment.

The LOC system approaches cancer in three spheres of intervention: improving lifestyle, regulating biology, and enhancing treatment. Clinical testing guides individualized tailoring of therapies in each sphere. Sphere 1, improving lifestyle, entails nutritional interventions, physical care (exercise and body-based therapies), and biobehavioral strategies, including optimizing circadian rhythms. Sphere 2, regulating biology, takes into account the potential broad-spectrum impacts of lifestyle or personal health behaviors, natural products, and medication on the growth hallmarks of cancers.[7] Assessing patients' biological landscapes or ''terrains'' of factors, including inflammation, glycemia, oxidative stress, coagulopathy, immune dysregulation, and stress chemistries, guides decisions about individual lifestyle recommendations, dietary supplements, and off-label drugs to facilitate development of a host environment less supportive of cancer growth. Reregulating the terrain aids patients in responding to the challenges of cancer: reducing tumor growth and spread; reducing tumor bulk and improving treatment response; tolerating conventional treatment; optimizing daily functioning; and diminishing the risk of life-threatening complications. Finally, Sphere 3, enhancing treatment, uses integrative therapies such as supplements, repurposed medications, and complementary treatments to support patients' tolerance of conventional treatment and enhance their ability to respond to it. By adopting this comprehensive and individualized system, our patients are able to better tolerate treatment with good quality of life (QOL) and physical function as well as beneficial treatment outcomes.[6]

The evidence supporting integrative treatment of CRC has grown rapidly over recent years, signaling further improvements for patients facing this widespread disease. However, evidence is somewhat limited. Cohort studies in CRC patients suggest relationships of lifestyle and disease outcomes; randomized trials are not generally available. Cohort data (Table 1) may rely on lifestyle assessments performed before diagnosis (prediagnostic) or after diagnosis (postdiagnostic). Improved performance status and lifestyle effects on outcomes may reflect the development of less aggressive disease with better overall health status, rather than impacts of postdiagnostic lifestyle change. Human studies or studies with CRC patients are not available for some interventions discussed. However, in view of the QOL and survival deficits experienced by advanced CRC patients, many clinicians feel comfortable with lower levels of evidence for efficacy as long as interventions are safe[8] and proposed mechanisms of action are supported with data.

Nutrition

Nutrition is a basic Sphere 1 intervention. Table 1 summarizes epidemiological studies of dietary patterns and foods that predict good outcomes in CRC, offering a platform for credible nutritional guidelines. Diets that conform to the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) cancer prevention guidelines, or that emphasize vegetables, fruit, whole grains, legumes, and nut consumption predict better overall and CRC-specific survival after diagnosis.[9,10] ''Western'' diets focused on dairy, refined grains, red and processed meats, and desserts are associated with higher CRC recurrence rates than ''prudent'' diets.[11,12] Although most work on the Mediterranean diet concerns CRC prevention, a Mediterranean dietary pattern was associated with lower all-cause and CRC-specific mortality in African American women, although not in other ethnic groups.[13] Table 2 summarizes nutritional and other recommendations as they are applied clinically in the LOC system.

Protein

Red meat has long been linked to CRC risk. Although study results are mixed, processed meat consumption was associated with elevated recurrence and cancer-specific mortality.[14,15] Postdiagnostic red meat did not predict survival, but those who ate more than the median intake of four servings per week had elevated cancer-specific mortality (Table 1).[14,16,17] Red meat is associated with higher inflammatory and glycemic markers in women, both relevant for CRC.[18] Poultry, while not optimal, has lower risks compared to red meat. On the other hand, dark marine fish consumption predicts longer disease-free and overall survival,[14] and given that a pesco-vegetarian diet pattern was linked to the lowest risk of CRC in a recent meta-analysis, fish appears to be a significantly better choice than poultry or red meat.[19] Although dairy products may reduce CRC risk, they have not been linked to cancer-specific mortality in patient cohorts, only to overall mortality.[20,21] Calcium has an unclear link to CRC mortality.[14,15] The ability of milk, even if hormone and chemical free, to raise insulin-like growth factor 1 (IGF-1) levels in a cross-section of various populations is concerning.[22] Conflicting results have also been found for vitamin D levels. Meta-analyses of observational studies find an inverse relationship with CRC-specific and all-cause mortality, but a randomized trial of vitamin D supplements in metastatic CRC found no survival advantage.[14,23] Legumes are a protein source with healthful amounts of fiber, some of which contain genistein.[24] A diet emphasizing plant and cold-water fish proteins appears optimal for CRC patients.

Macronutrients: fat

The WCRF/AICR guideline supports limitation of energy-dense foods, suggesting that healthful foods lower in fat and sugar such as vegetables, whole grains, and legumes should be emphasized over fatty meats and rich pastries. Cancer cells use fatty acids (FAs) for energy,[25] and high-fat diets adversely alter gut microbiota.[26] Of major importance is the type of dietary fat. Plasma oleic and linoleic acid were correlated with lower CRC risk, while arachidonic and stearic acid raised risk, suggesting that saturated fats and proinflammatory FAs are unfavorable, while omega-3 FAs improve survival.[27,28] Coconut oil, a currently popular saturated fat source, increases total and low-density lipoprotein cholesterol, which is concerning for CRC patients, who are at elevated risk for cardiovascular disease.[29] However, the medium-chain triglyceride fraction of coconut oil appears safe,[30] and can be helpful for weight-losing patients. In cohort studies, eating at least two servings of tree nuts per week predicted better disease-free and overall survival than avoiding nuts (Table 1).[10,31] Ketogenic and low-carbohydrate diets that emphasize meats and high-fat foods are receiving research attention, but little has been done in CRC. The lack of whole grain fiber needed by gut bacteria,[32] the ability of cancer cells to adapt to ketones as fuel,[25] and low palatability are concerns with these approaches, and they are not recommended until data demonstrate safety and efficacy. Fat content of the

Table 1. Cohort Studies of Dietary Patterns and Foods Related to Colorectal Cancer Outcomes

Dietary pattern/food	*Population*	*CRC stage*	*Outcome*	*HR (95% CI)*	*Reference*
Dietary patterns					
WCRF/AICR prevention guidelines	Prediagnostic CRC	I–III	CRC-specific mortality	0.70 (0.56–0.89)	Romaguera et al.[9]
Western diet	Postdiagnostic CRC	III	CRC recurrence	2.85 (1.75–4.63)	Meyerhardt et al.[11]
Prudent diet			All-cause mortality	2.32 (1.36–3.96)	
			Recurrence and mortality	NS	
Processed meat diet	Prediagnostic colon	I–IV	CRC recurrence	2.29 (1.19–4.40)	Zhu et al.[12]
Prudent vegetable diet			Overall mortality	2.13 (1.03–4.43)	
High-sugar diet			Recurrence and mortality	NS	
			Recurrence and mortality	NS	
Healthy diet (Alternate Healthy Eating Index)	Postdiagnostic CRC	I–III	Overall mortality	0.70 (0.52–0.98)	Fung et al.[10]
Mediterranean (Alternate Mediterranean Diet score)	Prediagnostic CRC, African-American women	I–IV	All-cause mortality	0.88 (0.81–0.96)	Jacobs et al.[13]
			CRC-specific mortality	0.86 (0.77–0.96)	
Proteins					
Red meat	Prediagnostic and postdiagnostic CRC	I–III	CRC-specific and all-cause mortality	NS	McCullough et al.[16]
Red meat, >4 servings/week			CRC-specific mortality	1.79 (1.11–2.89)	
Total meat, red meat	Prediagnostic CRC	I–III	CRC-specific mortality	NS	Zell et al.[17]
Red meat	Postdiagnostic CRC	I–III	CRC-specific and all-cause mortality	NS	Fung et al.[10]
Red meat	Diabetes-free healthy females		Elevated CRP	2.42 (2.24–2.61)	Ley et al.[18]
			Elevated insulin	5.36 (5.03–5.71)	
Dark marine fish ≥1 serving/week	Postdiagnostic CRC	III	CRC recurrence	0.65 (0.48–0.87)	Van Blarigan et al.[14]
Dairy milk	Postdiagnostic CRC	I–III	CRC-specific mortality	NS	Yang et al.[20]
			All-cause mortality	NS	
Dairy products	Prediagnostic CRC	I–IV	CRC-specific and all-cause mortality	NS	Dik et al.[21]
Fats					
Marine PUFA	Postdiagnostic CRC	III	CRC recurrence	0.72 (0.54–0.97)	Van Blarigan et al.[14]
Nuts	Postdiagnostic CRC	I–III	CRC-specific mortality	0.69 (0.49–0.97)	Fung et al.[10]
			Overall mortality	NS	
Nuts ≥2 servings/week	Postdiagnostic CRC	III	CRC recurrence	0.43 (0.25–0.74)	Fadelu et al.[31]
			Overall mortality	NS	
Carbohydrates					
High dietary glycemic load	Postdiagnostic CRC	III	CRC recurrence	1.97 (1.39–2.79)	Meyerhardt et al.[11]
Total carbohydrates			All-cause mortality	1.74 (1.20–2.51)	
			CRC recurrence	2.06 (1.45–2.91)	
			All-cause mortality	1.80 (1.25–2.60)	
Sugar-sweetened drinks, ≥2/day	Postdiagnostic CRC	III	CRC recurrence	1.75 (1.04–2.94)	Fuchs et al.[34]
Sugar-sweetened drinks and fruit juices	Postdiagnostic CRC	I–III	CRC-specific mortality	1.16 (0.99–1.35)	Fung et al.[10]
			Overall mortality	1.11 (1.01–1.23)	
Dietary fiber, per 5 g daily increment	Postdiagnostic CRC	I–III	CRC-specific mortality	0.78 (0.65–0.93)	Song et al.[32]
			All-cause mortality	0.86 (0.79–0.93)	
Cereal fiber, per 5 g daily increment			CRC-specific mortality	0.67 (0.50–0.90)	
			All-cause mortality	0.78 (0.68–0.90)	
Vegetable fiber, per 5 g daily increment			CRC-specific mortality	NS	
			All-cause mortality	0.83 (0.72–0.96)	
Fruit fiber			CRC-specific mortality	NS	
Whole grains, per 20 g/day, adjusted for fiber			All-cause mortality	NS	
			CRC-specific mortality	0.77 (0.62–0.96)	

Table shows effects of high consumption of dietary pattern or food type compared to low consumption.
CRC, colorectal cancer; CRP, C-reactive protein; HR, hazard ratio; NS, not significant; PUFA, polyunsaturated fatty acids; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research cancer prevention guidelines.

diet should be tailored to individual caloric requirements, with an emphasis on lower density of fat and calories during survivorship.

Macronutrients: carbohydrates

High glycemic load and total carbohydrate intake after CRC diagnosis increased risk of recurrence and mortality (Table 1).[11] However, high fiber intake reduced CRC-specific and all-cause mortality. Specifically, cereal fiber from whole grains reduced both CRC and all-cause mortality, while vegetable fiber reduced only all-cause mortality and fruit fiber reduced neither.[32] Lower leafy green vegetable intake after diagnosis predicted increased all-cause mortality.[15] Vegetables and fruits, however, have important laboratory-validated antiangiogenic and other anticancer

Table 2. Integrative Oncology Summary for Colorectal Cancer, Based on the Life Over Cancer System

Sphere 1: Lifestyle

Diet: implement a plant-based diet
- Emphasize vegetables, including cruciferous and allium vegetables. Eat whole fruits.
- Carbohydrates: high-fiber whole grains, minimally processed with portion sizes appropriate to body weight and clinical circumstances.
- Proteins: emphasize fiber-rich legumes and omega-3-rich fish; also, soy foods, egg whites, and whey or vegetarian protein supplements. Avoid or reduce red and processed meat, poultry.
- Fats: limit intake to healthful fats, and amount tailored to clinical circumstances. Emphasize omega-3 fatty acids, tree nuts, flax seeds, avocado, and medium-chain triglycerides.
- Reduce dairy products; alternatives include unsweetened soy, grain, and nut-based milks.
- Avoid refined sugars, refined grain products, sugar-sweetened beverages, and fruit drinks or juices. Substitute whole fruits, stevia, and natural sweeteners.

Biobehavioral: impact patient's biology through reducing effects of stress hormones and optimizing circadian health
- Emphasize health and stress management fundamentals such as practice of the relaxation response, relaxed abdominal breathing, progressive muscle relaxation, supportive groups, cognitive-behavioral therapy, and meditative approaches.
- Engage dependable support and connection with social network.
- Enhance circadian health and increase sleep efficiency.

Physical care: optimize physical activity
- Engage in moderate aerobic and resistance exercise throughout disease course. Avoid inactivity. Interval training and flexibility exercises may be helpful.
- Physical therapy consultation is recommended. Consult with physician about exercise contraindications during treatment.

Sphere 2: Biology

The cancer terrain: individualize a regimen for a patient's disrupted terrain factors

Assess terrain factors and intervene with diet, lifestyle recommendations, supplements, and off-label medications depending on results of assessments. Selected examples of laboratory tests and interventions are shown.

Inflammation
- Laboratory tests: C-reactive protein, interleukin-6.
- Avoid smoking, excess alcohol; emphasize regular sleep, relaxation practices, and healthful fats.
- Consider fish oil, ginger, turmeric, low-dose aspirin, and statins.

Glycemia
- Laboratory tests: insulin, IGF-1, and blood glucose.
- Avoid inactivity, sugar, and other refined carbohydrates; use daily relaxation practices.
- Consider resveratrol, green tea, cinnamon, chromium, and metformin.

Oxidation
- Laboratory tests: vitamins C and E, and coenzyme Q10.
- Avoid smoking, excessive alcohol, and iron-rich foods; emphasize moderate regular exercise.
- Consider balanced moderate-dose formula of multiple antioxidants.

Immunity
- Laboratory tests: red and white blood cells, natural killer cells, and activated T cells.
- Avoid inactivity, unhealthful fats; emphasize moderate exercise and daily relaxation practices.
- Consider zinc or selenium, prebiotic/probiotics, and cimetidine.

Coagulopathy
- Laboratory tests: fibrinogen antigen, cholesterol panel, and triglycerides.
- Avoid smoking, inactivity, and saturated fats; emphasize omega-3 fatty acids and vegetables.
- Consider grapeseed extract, omega-3 fatty acids, and garlic.

Stress hormones/melatonin
- Laboratory tests: salivary cortisol and melatonin; assess daily rhythm and levels.
- Avoid caffeine and inactivity. Regularize schedules of sleep, activity, and relaxation practices.
- Consider L-theanine, magnesium, and melatonin.

Sphere 3: Treatment: adapt lifestyle and supplements to treatment regimens and disease characteristics

Surgery
- Consider perioperative prebiotics/probiotics

Chemotherapy
- Consider chronomodulated chemotherapy and short-term fasting.
- CIPN prevention/treatment: Exercise, glutamine, intravenous glutathione, B-vitamins, and *N*-acetylcysteine.
- Nausea/vomiting: ginger, aerobic exercise, and cannabis.
- Diarrhea/mucositis: glutamine, probiotics, and zinc.

Radiation
- Diarrhea/mucositis: glutamine, probiotics, and zinc

Molecular target testing
- Consider matching supplements/repurposed drugs to mutations found in genetic testing of patient's tumors, for example, statin drugs for KRAS mutation

CIPN, chemotherapy-induced peripheral neuropathy; IGF-1, insulin-like growth factor 1.

properties, and should constitute a major part of the diet.[33] Fruit consumption is not always beneficial, however. Sugar-sweetened beverages and fruit juices increased recurrence and all-cause mortality.[10,34] Complex carbohydrates from whole grains, vegetables, or whole fruits should play a role in CRC diets, but it is important to consume unrefined grains with as little processing as possible, and to eat carbohydrates accompanied by protein foods to reduce glycemic load.[35]

Body weight

Obesity increases the risk of CRC.[36] However, below-normal body mass index (BMI) at diagnosis increases CRC-specific and all-cause mortality (hazard ratio [HR] 1.5–2.0), while overweight (BMI 25–29.9) predicts better survival than normal BMI. Obesity (BMI >30) in nonmetastatic patients is modestly associated with worse all-cause and CRC-specific mortality, but survival of obese metastatic patients is similar to those with normal BMI.[15] Lean body mass (LBM) is of interest, since low LBM predisposes patients to neuropathy from 5-fluorouracil-leucovorin-oxaliplatin (FOLFOX) regimens.[37] Interventions that increase or reduce body weight should be carefully individualized for the CRC patient population.

Fasting

Fasting 24–36 h before undergoing platinum-based chemotherapy (not including oxaliplatin or CRC patients) was found to be safe and feasible, resulting in a lowering of IGF-1 levels and a trend toward less neutropenia with longer fasts.[38] Fasting, properly supervised by medical/dietetic staff, may thus be a feasible means of reducing chemotherapy side effects. Patients who have low BMI, who have lost more than 10% of body weight, or who do not regain at least 25% of weight loss between treatment cycles should not fast.

Nutritional Supplements

Used with clinical acumen, supporting evidence, and matching to the biology of individual patients, nutritional supplements can play a significant role in CRC treatment. Such matching is addressed in the LOC system by Sphere 2, the biology sphere, using the model of the cancer terrain. The proposed cancer terrain consists of six cancer-promoting conditions commonly called host factors or ''terrain factors,'' measured with standard laboratory tests: inflammation,[39,40] oxidative stress,[41,42] glycemia,[43,44] immune dysregulation,[45,46] coagulopathy,[47,48] and stress hormone chemistries.[49,50] In our clinical workups, patients are tested for each of these. If results are abnormal, we suggest lifestyle changes, biobehavioral approaches, dietary supplements, and medications as needed with the goal of rendering the host environment less supportive of cancer growth. Selected laboratory tests, and lifestyle and supplement recommendations are shown in Table 2. Of note, supplements are formulated by the Center specifically for cancer to avoid concerning nutrients such as iron, copper, or excessive folate.[51,52] Further matching occurs in Sphere 3, the treatment sphere, comprising dietary supplements and lifestyle changes that can alleviate treatment side effects or improve treatment efficacy. Because of space limitations, we will review nutritional supplements for only two terrain factors and selected treatment-enhancing supplements.

Terrain factors

Inflammation. Inflammation is a pervasive factor in cancer outcomes and QOL. Elevated inflammatory markers predict poor prognosis in CRC patients after resection, and in Stage III and metastatic patients during chemotherapy.[53,54] Elevated C-reactive protein (CRP) or interleukin (IL)-6 also predicts severe side effects, low QOL, and premature discontinuation of chemotherapy.[55,56]

Patients with elevated inflammation are counseled on anti-inflammatory diets and appropriate supplements such as omega-3 FAs. For CRC patients, omega-3 FAs reduced IL-6 and increased albumin perioperatively, and reduced CRP during chemotherapy,[57] while fish oil increased time to tumor progression.[58] Stage II patients who used fish oil had better physical function than nonusers.[59] Fish oil supplements need testing for heavy metals and other contaminants.

Turmeric and its constituent curcumin have well-known anti-inflammatory and anticancer properties.[24] Bioavailabilty of oral curcumin is a known problem, and several methods are used to improve this. Curcuminoids given to solid tumor patients during chemotherapy reduced inflammatory markers and improved QOL relative to controls.[60] When curcumin was given with FOLFOX chemotherapy, explants derived from patients' liver metastases showed antiproliferative and proapoptotic effects and reduced stem cell markers.[61] Turmerone, another turmeric constituent, enhances curcumin's antitumor activity in mice.[24]

Glycemia. Glycemia and the insulin-IGF axis are critical factors in CRC. Relevant laboratory tests include insulin, IGF-1, C-peptide, blood glucose, and insulin resistance.[62,63] High levels of IGF-1, for instance, predict the severity of tumors.[64,65] Diet and lifestyle modification reduce abnormal glycemic parameters. For example, eating frequent small meals may reduce IGF-1.[66] Exercise is also linked to IGF-1 levels[65]; and correct food choices can lower glycemic index or postprandial insulin response.[67]

Resveratrol, one relevant supplement for glycemia, is absorbed into colorectal tissues, and *in vitro* study shows its potential relevance to CRC.[24,68] In controlled trials in diabetics, resveratrol reduced elevated blood glucose and insulin, both important for improving CRC outcomes.[69,70]

Among other supplements for glycemia, green tea was shown to affect glycemic markers in a meta-analysis of trials in various populations.[24,71,72] Other glycemic-control herbal supplements include chromium, alpha-lipoic acid, and cinnamon; however, trials in CRC patients are lacking.[73,74]

Supplements to support conventional treatment in CRC. Clinical trials have explored supplements that support and enhance conventional CRC treatment, the focus of the third sphere of the LOC system. We will detail only two supplements, probiotics and glutamine. Table 3 shows supplements that are less well-studied in CRC treatment regimens, including B vitamins,[75] zinc,[76,77] *N*-acetylcysteine,[78] and herbal formulas.[79]

The intestinal and total microbiome are receiving increasing attention in CRC. CRC patients show reduced gut bacterial diversity, especially lactic acid bacteria (e.g., *Lactobacillus*).[26] Bacteria produce butyrate and ferment dietary fiber to form short-chain FAs, providing critical energy for

Table 3. Dietary Supplements with Potential Effects on Toxicity of Colorectal Cancer Treatment Regimens

Supplement	*Symptoms*	*Publication type and reference*
Probiotics/prebiotics	Diarrhea—chemotherapy and radiotherapy	Systematic review; Wang et al.[82]
	Perioperative—infection	Systematic review; Anderson et al.[80]
	Perioperative—mucosal barrier	Meta-analysis; Liu et al.[81]
Glutamine	Oral, intestinal mucositis	Reviews; Sayles et al.[83]; Leung and Chan[84]
	CIPN	Clinical study; Wang et al.[85]
B vitamins	CIPN	Review; Schloss and Colosimo[75]
Kampo/TCM herbal formulas	CIPN	Review; Derksen et al.[79]
N-acetylcysteine	CIPN	Clinical study; Lin et al.[78]
Zinc	Oral mucositis	Meta-analysis; Lee[76]
	Quality of life/fatigue	Clinical study; Ribeiro et al.[77]

CIPN, chemotherapy-induced peripheral neuropathy; TCM, Traditional Chinese Medicine.

colon cells and promoting protective immunity.[26] High-fat diets, on the other hand, produce secondary bile acids, changing the microbiome and resulting in increased reactive oxygen species, nuclear factor-κB, and DNA damage.[26] Perioperative prebiotic or probiotic use may reduce postoperative infections and help maintain the intestinal mucosal barrier.[80,81] During chemotherapy and radiation, probiotics may reduce treatment-related diarrhea.[82] Appearance of probiotic bacteria in the bloodstream has been a concern, but is quite rare. The gut microbiome appears to support the anticancer action of oxaliplatin, and bacteria in the genus *Bifidobacterium* are crucial to optimizing the anticancer action of anti-programmed death ligand 1 drugs.[26]

Glutamine may reduce treatment-induced mucositis and peripheral neuropathy. Meta-analyses suggest that it is useful for radiation-induced oral mucositis and intestinal mucositis from chemotherapy and radiation.[83,84] It may reduce chemotherapy-induced peripheral neuropathy (CIPN).[85] Use of glutamine is controversial, because it can be used as a fuel by cancers.[25] However, this may not apply to CRC, since colon cancers do not excessively reduce glutamine content of the intestinal blood supply[86]; furthermore, dietary glutamic acid intake is not correlated with CRC incidence.[87] As a precaution, glutamine supplements should be stopped after conventional treatment.

Biobehavioral Strategies

Biobehavioral strategies are an integral part of Sphere 1 in the LOC system, and are interconnected with Sphere 2 factors. The term biobehavioral refers to the complex interactions of social, psychological, and behavioral factors with biological processes and their consequent impact on the progression or effective treatment of disease. While research on biobehavioral strategies for CRC patients is limited, findings reveal that among recently diagnosed CRC patients, loneliness independently predicted higher levels of proangiogenic vascular endothelial growth factor (VEGF).[88] Depression and anxiety also predict higher VEGF in CRC patients after surgery, while positive affect and functional well-being negatively correlated with VEGF.[89] Elevated plasma VEGF predicts disease recurrence and shortens overall survival in CRC and other cancers.[90] A number of nonpharmacological interventions relieve stress triggers and block their unwanted consequences.[91] Mindfulness training reduced cortisol blunting (abnormally low cortisol reactivity) in CRC patients during chemotherapy,[92] and alleviated fatigue and cognitive impairment in a pilot study.[93,94] Progressive muscle relaxation improved anxiety and QOL in CRC patients.[95] Psychosocial interventions, including education, cognitive-behavioral therapy, relaxation training, and support groups, were found in a recent literature review to improve CRC patients' abilities to cope with stomas, anxiety and depression, length of hospital stay, and QOL.[96] Further research on biobehavioral interventions for CRC patients is needed.

Lifestyle: Physical Activity, Alcohol, and Smoking

Prospective cohort studies of CRC survivors have found that higher levels of physical activity (PA) after diagnosis predicted a 42% reduction in all-cause mortality and a 39% reduction in CRC-specific mortality. Women who increased their PA after diagnosis had a 52% reduction in CRC mortality.[14] Sitting more than 6 h a day predicted increased CRC-specific mortality.[15]

PA may affect CRC outcomes through anti-inflammatory effects,[14] effects on the insulin-IGF axis,[65,97] effects on visceral adipose tissue,[98] or effects on mitochondrial function.[99] Most controlled clinical studies of exercise in CRC concern Stages I–III patients, such as a study of home-based aerobic and resistance exercise that reduced tumor necrosis factor-α and insulin.[65] Aerobic exercise reduced visceral adipose tissue, with longer exercise periods resulting in greater reductions versus controls,[98] as well as improved physical function, sleep, fatigue, and QOL.[100] A meta-analysis showed no effect of exercise on fatigue, but noted that none of the trials was performed in fatigued CRC survivors.[101]

Studies of exercise for CIPN and cachexia are limited for CRC patients. For cancer patients in general, exercise improves QOL and independence in CIPN.[102] In addition, patients who adhered to general PA guidelines had less CIPN.[79] Endurance, resistance, and balance therapy stabilized CIPN symptoms in stage IV CRC patients during chemotherapy, while CIPN worsened in controls.[103] Resistance exercise may improve cancer cachexia,[99] but clinical trials are lacking.[104]

In the absence of more specific evidence, and because of the potential for CIPN, cachexia, fatigue, and QOL issues, CRC patients should follow general exercise guidelines to avoid inactivity and participate in aerobic and strengthening

exercise, although more research is needed due to common CRC complications and comorbidities.[105] Referral to a physical therapist or other professional should be considered. Flexibility exercises such as yoga may improve QOL,[106] and interval training offers debilitated patients a feasible means of rehabilitation.[107]

Alcohol and smoking

Alcohol increases CRC risk, especially in men. However, moderate alcohol consumption is linked to better post-diagnosis survival than abstinence.[15] This observation may be confounded by patients stopping alcohol for comorbid conditions that affect survival. Smoking after diagnosis is associated with higher cancer-specific and all-cause mortality.[15]

Innovative and Complementary Therapies

Some innovative and complementary therapies are attracting attention in CRC, including therapies based on circadian rhythms. Varying levels of evidence support these.

Circadian health and chronomodulated chemotherapy

The circadian timing system has recently been proposed as a target for oncology interventions. The body's daily circadian (24-h) rhythm is regulated by several genes, and governs cell proliferation, apoptosis, drug metabolizing enzymes, and other cancer targets. Fifteen percent of all metabolites display circadian oscillations.[108] Half of metastatic cancer patients display disrupted circadian organization (CO), showing irregular patterns of rest and activity, fatigue, appetite loss, and sleep problems.[108] For lung, renal, breast, and CRC patients, disrupted CO predicts poor survival; for metastatic CRC patients, those with robust CO had an overall survival of 22 months, while those with disrupted CO survived only 14.7 months.[109] Chemotherapy disrupts circadian rhythms in CRC patients.[110,111]

Interventions to improve CO for cancer patients include developing routine sleep habits, exposure to early morning bright light, dispelling incorrect notions about sleep, and keeping bedrooms cool and dark, as well as melatonin supplementation.[112] Cognitive-behavioral therapy for insomnia is effective for sleep problems in most cancers.[113]

Circadian oscillations of drug-metabolizing enzymes and tolerability form the basis of chronomodulated chemotherapy (chronotherapy) regimens, which have been studied extensively in CRC and can reduce the circadian disruption of cancer treatment. For both oxaliplatin and 5-FU, time-sensitive administration during the night is indicated,[114] using specialized chemotherapy pumps that gradually release multiple drugs in sine-wave administration curves that can peak at a programmed time for each drug. This system has been in use in our clinic for 28 years. Studies of cancer chronotherapy, including a meta-analysis of chronotherapy for advanced CRC patients, suggest marked increases in tolerance and survival outcomes,[115,116] but effectiveness decreases for patients with disrupted CO,[108,117] which may be more common in women with CRC than men.[118] Integrative support for side effects and CO should be provided for all patients receiving chronotherapy to improve its effectiveness for those with disrupted CO.

Repurposed and off-label drugs

The repurposing of non-oncology drugs for cancer treatment is gaining research and regulatory acceptance.[119] Off-label drugs relevant to CRC include low-dose aspirin with anti-inflammatory effects, associated with improved overall and CRC-specific mortality,[120] and statin drugs, known for targeting of KRAS.[121] In both cases, observational data with variable results suggest that further research is needed. Metformin, used for blood glucose control, was associated with better recurrence-free (HR 0.63), overall (HR 0.69), and cancer-specific (HR 0.58) survival in early-stage CRC.[122] Metformin, statin, and aspirin use during neoadjuvant radiotherapy of rectal cancer were associated with downstaging and increased survival for diabetics.[123] The KRAS activity of statins and other agents is used at the Center in matching off-label drugs and supplements to the results of molecular genetic testing of patients' cancers. Other off-labels are cimetidine, chloroquine, low-dose naltrexone, and beta-blockers.[124–127] However, more research is needed in this area.

Integrative therapies needing further research

Several intravenous (IV) therapies are now being used in integrative oncology. In a systematic review, IV glutathione reduced oxaliplatin neurotoxicity in three randomized studies.[128] Negative impacts of antioxidants on chemotherapeutic efficacy were not evident in systematic reviews, but drug interaction concerns persist.[129,130] As yet, there is limited evidence to support the use of high-dose IV vitamin C or phytochemicals in cancer.[131–134] IV therapies should only be given at centers fully equipped to deal with hypersensitivity and anaphylactic reactions.

For management of painful symptoms and side effects, limited studies suggest possible efficacy of acupuncture and similar treatments for CIPN.[135,136] A pilot study in CRC patients receiving oxaliplatin found that low-level laser treatment of acupuncture points improved CIPN symptoms.[137] The Kampo formula goshajinkigan was found not to reduce CIPN in a recent meta-analysis.[138] Classical foot massage and reflexology relieved pain in a small clinical trial with CRC patients during chemotherapy.[139] There is conclusive or substantial evidence for cannabis use in pain, nausea and vomiting of chemotherapy, and sleep disturbances.[140] Specific clinical trials in CRC are lacking for cannabis.

There is limited evidence for the use of Traditional Chinese Medicine in CRC integrative therapy. A lifestyle intervention based on Chinese herbal therapy improved CRC survival in a propensity-matched observational study.[141] Numerous randomized trials of Traditional Chinese herbal Medicine suggest efficacy in CRC, but the low quality of the trials warrants a cautious approach.[142]

Gentle yoga is safe for cancer patients and improves sleep, fatigue, musculoskeletal conditions, distress, and cognitive issues during cancer treatment.[143] Little study of yoga has been done in CRC; one study demonstrated feasibility of a yoga intervention, but another study found no QOL differences between yoga and control groups, with high attrition and low adherence.[144,145] Barriers to yoga participation in CRC should be explored.

Conclusion

Substantial evidence from epidemiological, preclinical, and some clinical studies supports an integrative approach to CRC. Table 2 summarizes the interventions used at the Block Center.[5] Marked differences in the needs of CRC patients with varying comorbidities and biological terrains, as well as different disease stages and treatment regimens suggest the need for a comprehensive, individually adjusted integrative program based on clinical assessments for safety reasons.

Future research needs for integrative approaches to CRC include clinical trials to validate the data from prospective observational studies shown in Table 1, as well as exercise and nutritional supplementation approaches. More could be done to elucidate which biobehavioral strategies are best for CRC patients, as well as complementary therapies. Circadian biology as a cancer target appears quite relevant for CRC, but much more study is needed to fully understand this area. The studies cited in this article, however, do offer a credible base of support for making comprehensive integrative care a beneficial option for patients facing and combating a diagnosis of CRC.

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Author Disclosure Statement

K.I.B. is the owner and Medical and Scientific Director of the Block Center for Integrative Cancer Treatment; P.B.B. is Executive Director and Director of Integrative Systems of the Block Center for Integrative Cancer Treatment; and C.G. is the Research Manager of the Block Center for Integrative Cancer Treatment.

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