ORIGINAL RESEARCH ARTICLE

Nutritional status predicts adjuvant chemotherapy outcomes for stage III colorectal cancer

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Abstract:

Objectives: Previously, adjuvant chemotherapy using oxaliplatin was a standard treatment for patients with node-positive colorectal cancer (CRC) who underwent curative surgery. The factor predicting adverse events and therapeutic effect have not yet been established. Methods: A retrospective cohort of 42 patients diagnosed with stage III CRC between April 2009 and March 2013 in our institution were included in this study. The indicators of host nutritional status were body weight (BW), body mass index (BMI), serum albumin, Onodera's prognostic nutritional index (OPNI), and Glasgow Prognostic Score (GPS). The indicators of host immunocompetence was total lymphocyte counts, total neutrophil counts, granulocytes/lymphocytes ratio (G/L ratio). Results: The overall recurrence rate was 26.1%. Patients who had a recurrence were more likely to be older. The recurrence was not associated with type of regimen or adverse events. The cases with a few cumulative doses and relative dose intensity of oxaliplatin experienced significantly more recurrence. Nutritional status indicators, such as the serum albumin level, OPNI, and the modified Glasgow prognostic score (mGPS) were associated with the adjuvant chemotherapy outcome. Our study results indicated worse nutritional status induced worse disease-free survival (DFS) and more recurrence. Conclusion: The host's nutritional status associated with outcomes in stage III CRC patients.

Keywords:
colorectal cancer, nutrition, relative dose intensity

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Introduction

The prognosis of Stage III colorectal cancer (CRC) is relatively good. These patients can receive curative resection[1]. But, when it recurs once, radical cure is difficult even with progressive chemotherapy. The aim of adjuvant chemotherapy is to prevent a recurrence and cure the disease. Recent developments in chemotherapy have dramatically improved the survival of metastatic or recurrent CRC patients[2]. However, not all patients benefit from adjuvant chemotherapy and experience a recurrence. On the other hand, some patients are cured even if they do not receive chemotherapy. Therefore, these patients receive unnecessary treatment. In other words, it is important to consider individual profit and loss when adjuvant chemotherapy is planned.

In patients with stage III colon cancer, oxaliplatin with 5-fluorouracil and leucovorin (5-FU/LV), or oxaliplatin with capecitabine, are the preferred adjuvant chemotherapy regimens[3-5]. However, the oxaliplatin-containing regimen has been shown to decline with performance status and QOL[6]. Therefore, it is important to predict adverse events and therapeutic effects to select patients who will benefit from cancer chemotherapy.

There is little information on the relationship between prognosis, nutritional status, and immunocompetence in metastatic or recurrent CRC. Onodera's prognostic nutritional

index (OPNI) is thought to be a simple parameter for determining patients' nutritional and immunological status[7]. The Glasgow prognostic score (GPS), defined the presence of an elevated systemic inflammatory response, as evidenced by elevated circulating concentrations of C-reactive protein and hypoalbumin, was associated with poor survival in patients undergoing curative resection for CRC. Moreover, the GPS has been found to be a useful prognostic factor in several types of cancer[8].

This study aimed to clarify the relationship between the host's nutritional status, prior to adjuvant chemotherapy and therapeutic effect, and whether these nourishment indexes could predict long-term convalescence in CRC.

Methods

Patient characteristics

Patients with stage III CRC who received curative resection at our institution between 2009 and 2013 were enrolled in this retrospective study. Curative resection was defined as surgery that removes all malignant tissue with a surgical resection margin that was pathologically negative for tumor invasion. All patients underwent combination chemotherapy followed by primary surgery.

Detection of nutritional status and immunocompetence

Host nutritional status indicators were body weight (BW), body mass index (BMI), serum albumin, OPNI, and GPS. The OPNI was calculated using the following formula: $10 \times$ serum albumin concentration (g/dL) + $0.005 \times$ lymphocyte count (number/mm^2) in peripheral blood. The OPNI cutoff value was determined to be 40 based on an original investigation[7]. The GPS was scored 0, 1, or 2 based on CRP level (>1.0 mg/dL) and albumin (<3.5 g/dL) from blood samples taken before chemotherapy. For patients with neither of the above, the CRP level and hypoalbumin were allocated a score of 0. If patients had only one of the above, the CRP level or hypoalbumin were allocated a score of 1. Patients with both of the above the level of CRP and hypoalbunin were allocated a score of 2. The indicators of host immunocompetence was total lymphocyte counts, total neutrophil counts, granulocytes/lymphocytes ratio (G/L ratio). All blood samples were collected one or two days prior to administration of chemotherapy.

Assessments

The endpoints of the long-term outcome study were disease-free survival (DFS). DFS was the length of time, after primary resection, that a patient survives without any signs or symptoms of that cancer.

Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Categorical analysis of variables was performed using either the chi-squared test or Fisher's test, as significance was evaluated by performing Student's t-test, analysis of variance, Mann-Whitney U test, and Chi-squared test. Survival curves were plotted according to the Kaplan-Meier method and any differences were analyzed using the log-rank test. Differences were considered significant if the P value was less than 0.05.

A multivariate analysis with Cox proportional hazards model was adopted to clarify the independent prognostic factors. Inclusion of the relevnt diagnosis items in the multivariable model were based on clinical knowledge and P value (P value <0.05).

Results

Study population and characteristics

Between 2009 and 2013, 143 patients with pathologically confirmed as stage III CRC were treated in our hospital. Of these patients, 42 (29.4%) received adjuvant chemotherapy using multidrug regimens containing oxaliplatin. These patients' clinical characteristics are detailed in Table 1. The median age was 64.4 years, and the cohort consisted of 27 males and 15 females. By the univariate analysis of factors associated with recurrence, patients who had a recurrence were more likely to be older. However, according to the other factors, including gender, location, tumor size, and histology, there was no difference between the recurrence and non-recurrence groups.

Short term outcome of adjuvant chemotherapy

Table 2 demonstrates the outcome of adjuvant chemotherapy. The recurrence rate was 26.1%. The most commonly initiated regimen was oxaliplatin plus capecitabine (54.8%). The median relative dose intensity (RDI) of oxaliplatin was 75.4%. The univariate analysis of factors associated with recurrence, hematotoxicity, and non-hematotoxity were no significant difference between two groups. The total oxaliplatin dosage and RDI were associated with recurrence. The cases with few cumulative doses and RDI of oxaliplatin experienced significantly more recurrence. The relationship between a patient's nutritional status and prognosis are shown in Table 3. The recurrence group had a significantly lower serum albumin level, poor OPNI, and poor GPS. These results demonstrated the relationship between nutritional status before chemotherapy administration and therapeutic effect.

Table 1. Clinico-pathological Characteristics.

Factors		Non-recurrent (n=31)	Recurrent (n=11)	Total (n=42)	p-value
Age		62.5 (34-81)	69.7 (64-79)	64.4 (34-81)	0.03
Gender	Male	21	6	27	0.43
	Female	10	5	15	
Location	Right	7	4	11	0.37
	Left	24	7	31	
Size		42 (11-82)	41 (28-70)	42 (11-82)	0.5
Histological type	Differentiated	27	10		0.74
	Undifferentiated	4	1	5	
Depth of tumor invasion	<SS	5	1	6	0.9
	≥SS	26	10	36	
Harvested lymph node	<12	6	5	11	0.2
	≥12	25	6	31	
Serum CEA		4.2 (1-74.1)	5.9 (1-21.2)		0.44
Harvest lymph node		25.1 (5-130)	18.4 (4-39)	23.6 (4-130)	0.17
Metastatic lymph node		3.3 (1-11)	4 (1-9)	3.5 (1-11)	0.34
Operative method	Open	21	9	30	0.37
	Laparoscopic	10	2	12	

Table 2. Outcome of Adjuvant Chemotherapy.

Factors		Non-recurrent (n=31)	Recurrent (n=11)	Total (n=42)	p-value
Adjuvant chemotherapy	XELOX	17	6	23	0.4
	FOLFOX	10	5	15	
	SOX	4	0	4	
Hematotoxicity	Non	13	5	18	0.83
	≥G1	18	6	24	
Nonhematotoxicity	Non	17	4	21	0.29
	≥G1	14	7	21	
Total oxaliplatin dose (mg)		1090.3 (450-2160)	813.6 (150-1330)	1017.1 (150-2160)	0.07
Relative dose intensity (RDI)		81.2 (25-100)	59.1 (1.5-100)	75.4 (1.5-100)	0.02

Table 3. Association between Nutritional Status and Prognosis.

Factors		Non-recurrent (n=31)	Recurrent (n=11)	Total (n=42)	p-value
Body mass index (BMI)		21.7 (16-36.3)	22.1 (18.1-22.3)	21.8 (16-36.3)	0.25
Serum albumin		4.02 (2.9-4.9)	3.05 (2.3-3.3)	3.77 (2.3-4.9)	<0.01
Lymphocyte		1613 (856-3234)	1753 (881-3372)	1649 (856-3372)	0.27
Granulocyte/lymphocyte (GLR)		2.42 (0.93-8.61)	2.88 (0.92-5.99)	2.54 (0.92-8.61)	0.16
Onodera's prognostic nutritional index (OPNI)		48.35 (39-60.1)	39.3 (29.6-44.7)	46 (29.6-60.1)	<0.01
mGPS	0	28	0	28	<0.01
	1	3	3	6	
	2	0	8	8	

Disease-free survival

There was no case that recurred during adjuvant chemotherapy enforcement. The univariate analysis of factors associated with DFS are shown in Table 4. Receipt of >80% RDI was associated with better DFS (P=0.02) than was receipt of ≤80% RDI.

The serum albumin level, OPNI, and GPS were significantly associated with DFS (Figure 1). Receipt of <3.5 serum albumin level (P<0.01), <40 OPNI (P<0.01), and GPS 1, 2 (P<0.01) were associated with increased mortality and recurrence.

In multivariate analysis, serum albumin level was an independent prognostic factor (Table 5; p=0.03). But OPNI and GPS was not an independent factor (p=0.27, p=0.85).

Table 4. Univariate Analysis for Disease Free Survival (DFS).

Factors (n=42)		p-value
Age	<65	0.02
	≥65	
Gender	Male	0.4
	Female	
Location	Right	0.26
	Left	
Histological type	Differentiated	0.69
	Undifferentiated	
Depth of tumor invasion	<SS	0.6
	≥SS	
Harvested lymph node	<12	0.15
	≥12	
Operative method	Open	0.43
	Laparoscopic	
Relative dose intensity	<80	0.69
	≥80	
Body mass index	<18.5	0.25
	≥18.5	
Serum albumin	<3.5	<0.01
	≥3.5	
Lymphocyte	<1500	0.51
	≥1500	
Granulocyte/lymphocyte (GLR)	<3	0.07
	≥3	
Onodera's prognostic nutritional index (OPNI)	<40	<0.01
	≥40	
mGPS	0	<0.01
	1	
	2	

Discussion

The RDI of oxalipain is the problem of adjuvant chemotherapy for CRC because of the peripheral sensory neuropathy that is a characteristic adverse event. The MOSAIC trial reported that continuation of treatment is often interrupted by the development of severe peripheral sensory neuropathy and allergic reactions or allergic anaphylaxis[3]. In our study, the nonhematotoxity, including peripheral sensory neuropathy, occurred in 50% of patients. It is similar to the ASCOT trial[9] and the XELOXA trial[10]. Our study fills an important void in the literature regarding an association between RDI of oxaliplatin and DFS among patients receiving adjuvant chemotherapy. There have been several reports for correlation between RDI and prognosis. Aspinall et al reported that patients with Stage III colon cancer had improved 5-year overall survival rates with >70% RDI[11]. It shows the possibility that prognosis is improved by keeping RDI regularly. Other studies have reported an association between age, marital status and comorbidities, and completion of chemotherapy[12,13]. In our study, elderly patients have been associated with poorer survival because they could not keep appropriate RDI.

Nutritional status is an important prognostic marker in patients with various cancers, such as esophageal cancer, stomach cancer, pancreatic cancer, and malignant pleural meso-

Table 5. Multivariate Analysis for Disease Free Survival (DFS).

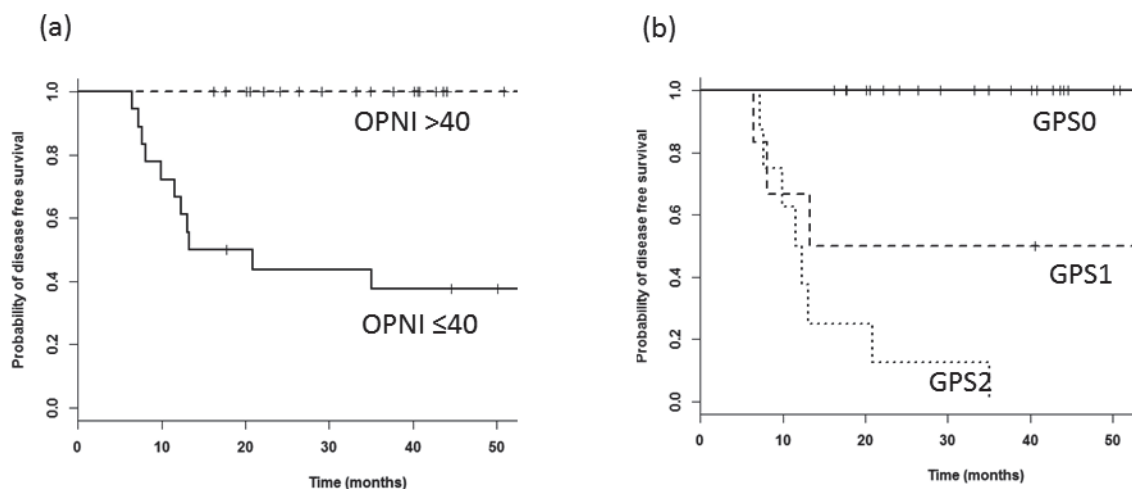| Factors	HR (95% CI)	p-value
Serum albumin	0.044 (0.002-0.784)	0.03
Onodera's prognostic nutritional index (OPNI)	2.102 (0.558-7.923)	0.27
mGPS	1.211 (0.155-9.469)	0.85

Figure 1. Kaplan-Meier disease free survival curves of colorectal cancer patients stratified by (a) OPNI (p<0.01), (b) mGPS (p<0.01).
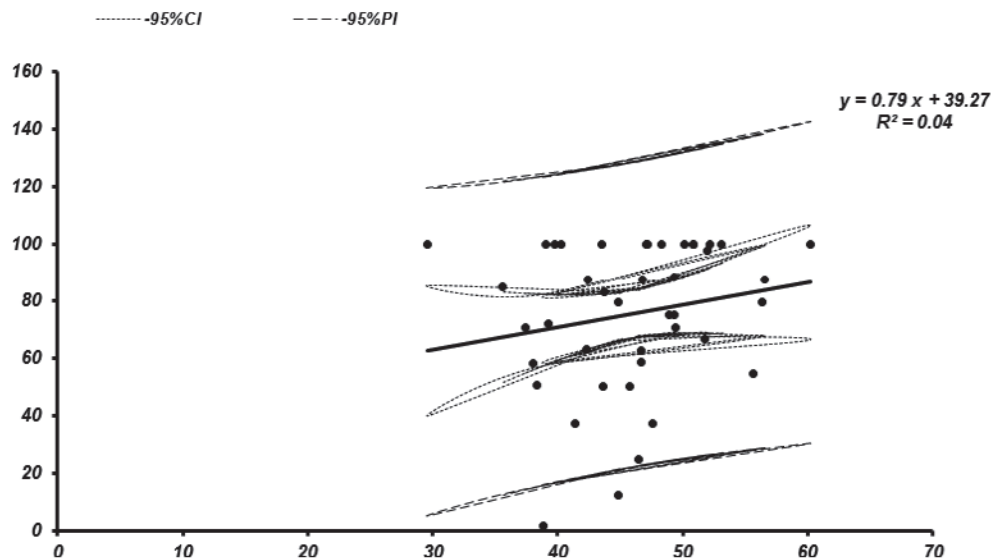
Figure 2. The correlation between OPNI and oxaliplatin RDI (p=0.04).

thelioma by several studies[14-18]. Preoperative malnutrition is associated with postoperative complications, tumor progression, and poor clinical outcome[19]. Along with the relationship between nutritional status and prediction of long-term outcome in CRC, Boonpipattanapong et al. showed that preoperative CEA and albumin were predictors of patient survival[20]. The role of pretreatment albumin as a prognostic marker was demonstrated by many studies. Albumin is a most famous marker of nutritional status. However, it is not only a surrogate of nutritional status but also a marker of inflammation and stress as induced by surgery. To minimize the systemic inflammatory response's impact on the changes in the albumin level, all blood samples were collected one or two days before administration of chemotherapy in our study. And we also used other nutritional indicators for analysis.

The OPNI, which is calculated using the serum albumin level and blood lymphocyte counts, was initially used to assess the immune-nutritional status of stomach cancer patients[7]. Nozoe et al. showed that the OPNI can be a prognostic indicator in CRC[16]. McMillan et al. showed that the GPS was associated with poor survival in patients undergoing colorectal surgery[8].

In our study, patients with worse pre-chemotherapeutic nutritional status had worse therapeutic effects and prognoses. The results were similar to another study for nonresectable CRC. However, the OPNI and the GPS were not independent prognostic factors in our study.

The reason may be due to the small number of patients.

Patients with poor nutritional status were forced to reduce or interrupt their chemotherapy doses. Therefore, they could not keep appropriate RDI and had poor prognoses (Figure 2).

There were several limitations of our study. This was a retrospective, single-institution study with a limited number of patients. The outcomes may have been influenced by unmeasured clinical characteristics because our study was retrospective observational and had a small sample size.

In conclusion, it is important to maintain nutritional status during adjuvant chemotherapy so the patient can tolerate an effective dose.

Conflicts of Interest
There are no conflicts of interest.

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