Preoperative Neutrophil–Lymphocyte Ratio Is a Predictor of Bowel Obstruction Due to Colorectal Cancer Growth

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Abstract. *Background: Bowel obstruction is commonly encountered in patients with advanced colorectal cancer; however, the cause of obstruction remains unknown. This study aimed to clarify a predictor of bowel obstruction due to colorectal cancer growth. Materials and Methods: Between January 2005 and December 2013, the medical records of 140 patients with T3 or T4 colorectal cancer who underwent curative resection (R0) at our Hospital were investigated retrospectively. This study consisted of 26 patients with obstructive colorectal cancer (OCC) and 114 patients with non-obstructive colon cancer (non-OCC). Results: Significant differences in clinicopathological factors including age, gender, T category, stage, primary tumor site, tumor diameter, macroscopic type, pathological type, lymphatic invasion, venous invasion, and lymph node metastasis were not observed between the two groups. Preoperative hematological/biochemical parameters including leukocyte count (p=0.004), neutrophil count (p=0.003), C-reactive protein (CRP) level (0.001), and neutrophil-to-lymphocyte ratio (NLR) (p=0.001) were significantly higher in the OCC group than in the non-OCC group. However, a significant difference in lymphocyte count was not observed between the two groups (p=0.634). Significant differences in the levels of the serum tumor markers CEA and CA19-9 were not observed between the two groups. Conclusion: Preoperative NLR seems to be a useful predictor of bowel obstruction due to colorectal cancer growth.*

Bowel obstruction is encountered in 25-40% of patients with advanced colorectal cancer (1, 2). These patients often require chemotherapy or radiotherapy before tumor resection or palliative treatment. Some studies have reported that elective surgery for obstructive colorectal cancer (OCC) offered better results (3, 4). However, other studies indicated that OCC had a poor prognosis even with interventions (1, 5, 6). Surgical outcomes remain controversial, and the cause of obstruction due to tumor growth remains unknown. This study aimed to clarify a predictor of bowel obstruction due to colorectal cancer growth.

Patients and Methods

Patients. The Ethics Committee for Biomedical Research of the Nishisaitama Chuo National Hospital Institutional Review Board approved the protocol (12-30). Between January 2005 and December 2013, the medical records of 140 patients with T3 or T4 colorectal cancer who underwent curative resection (R0) at our hospital were investigated retrospectively. This study consisted of 26 patients with OCC and 114 patients with nonobstructive colon cancer (non-OCC). The medical records of all patients were reviewed, and the stages of their tumors were classified according to the Japanese Classification of Colorectal Carcinoma (7). According to this classification, T3 corresponds to the invasion of the subserosa, and T4a corresponds to serosal invasion, excluding direct extension into adjacent structures or organs, which is classified as T4b.

Hematological/biochemical parameters including the total leucocyte count, serum total protein, albumin level, C-reactive protein (CRP) level, carcinoembryonic antigen (CEA) level, and carbohydrate antigen 19-9 (CA19-9) level were measured before surgery. The preoperative neutrophil to lymphocyte ratio (NLR) was calculated by the number of neutrophils and lymphocytes.

Follow-up after surgery and postoperative chemotherapy. All patients were followed for 5 years, with their serum CEA and CA19-9 levels measured every 3 months, computed tomography (CT) performed every 6 months and colonoscopy performed every 12 months. When we suspected recurrence, CT and positron emission tomography were performed at that time. Patients with stage II or III disease received oral S-1 (Taiho Pharmaceuticals Co., Ltd., Tokyo, Japan) or capecitabine (Xeloda; Hoffmann-La Roche, Basel, Switzerland) for 6 months after surgery. The other patients with stage IV disease received intensive chemotherapy, including oxaliplatin-based regimens [infusional 5-fluorouracil and folinic

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acid plus oxaliplatin (FOLFOX), S-1 (Taiho Pharmaceuticals Co., Ltd., Tokyo, Japan) plus oxaliplatin (SOX), or capecitabine plus oxaliplatin (XELOX)] for six months after surgery, depending on their physical status.

Statistical analysis. Continuous variables are expressed as means and ranges. The Wilcoxon rank sum test was used to compare differences in the continuous variables, and the Chi-square test was used to compare differences in the categorical data. Disease-free survival (DFS) after surgery was examined by the Kaplan-Meier method and by log-rank analysis. A *p*-value less than 0.05 was used to indicate significance. All data were analyzed using the Statistical Package for Social Sciences (SPSS) v. 24.0 (IBM SPSS, Tokyo, Japan).

Results

Comparison of clinical features between the OCC and the non-OCC groups. The mean age of the OCC group was 72.2 (47-87) years, while that of the non-OCC group was 70.0 (35-89) years. There was no significant difference between the two groups. Significant differences in the other clinicopathological factors including age, gender, T category, stage, primary tumor site, tumor diameter, macroscopic type, pathological type, lymphatic invasion, venous invasion, and lymph node metastasis were not identified between the two groups (Table I).

Comparison of hematological/biochemical parameters between the OCC and the non-OCC groups. Preoperative hematological/biochemical parameters including leukocyte count, neutrophil count, CRP level, and the NLR of the OCC group, were significantly higher than those of the non-OCC group. However, a significant difference in lymphocyte count was not observed between the two groups. Serum total protein and albumin levels in the OCC group were significantly lower than those in the non-OCC group. Significant differences in the levels of the serum tumor markers CEA and CA19-9, were not observed between the two groups (Table II).

Comparison of DFS between the OCC and non-OCC groups with stage II colorectal cancer. The 3-year DFS of 14 patients with OCC at stage II was 91.7%, whereas that of 49 patients with non-OCC at stage II was 87.2%, which was not a significant difference (Figure 1).

Comparison of DFS between the OCC and non-OCC groups with stage III colorectal cancer. The 3-year DFS of 9 patients with OCC at stage III was 58.3%, whereas that of 54 patients with non-OCC at stage III was 68.0%, which was not a significant difference (Figure 2).

Discussion

Many researchers have accepted that inflammation is related to not only carcinogenesis, but also to cancer progression (8,

Table I. *Comparison of clinicopathological features between the two groups.*

Characteristic	OCC (n=26)	non-OCC (n=114)	*p*-Value
Mean age (range), years	72.2 (57-87)	70.0 (35-89)	0.475
Gender, n (%)			0.048
Male	19 (73)	57 (50)	
Female	7 (27)	57 (50)	
T category			0.206
T3, n (%)	17 (65)	89 (78)	
T4, n (%)	9 (35)	25 (22)	
Stage			0.498
II, n (%)	14 (54)	49 (43)	
III, n (%)	9 (35)	54 (47)	
IV, n (%)	3 (11)	11 (10)	
Primary tumor site			0.064
Colon, n (%)	22 (85)	75 (66)	
Rectum, n (%)	4 (15)	39 (34)	
Tumor diameter (range), mm	54.7 (20-120)	55.4 (15-200)	0.877
Macroscopic type of tumor			0.372
I, n (%)	2 (8)	3 (2)	
II, n (%)	19 (73)	98 (86)	
III, n (%)	3 (11)	9 (8)	
IV, n (%)	2 (8)	4 (4)	
Pathological type of tumor			0.592
Well dif. adenoca., n (%)	5 (19)	24 (21)	
Moderately dif. Adenoca., n (%)	19 (73)	79 (70)	
Poorly dif. adenoca., n (%)	0 (0)	6 (5)	
Others, n (%)	2 (8)	5 (4)	
Lymphatic invasion			0.516
Present, n (%)	15 (58)	56 (49)	
Abscent, n (%)	11 (42)	58 (51)	
Venous invasion			0.798
Present, n (%)	5 (19)	26 (23)	
Abscent, n (%)	21 (81)	88 (77)	
Lymph node metastasis			0.389
Present, n (%)	12 (46)	64 (56)	
Abscent, n (%)	14 (54)	50 (44)	

OCC: Obstructive colorectal cancer, dif. adenoca.: differentiated adenocarcinoma.

9). Tumor growth is promoted by preinflammatory cytokines and chemokines that are released from tumor-infiltrating leukocytes, which are themselves stimulated by the tumor. Therefore, inflammatory markers, such as CRP and interleukin-6 (IL-6), are elevated in various types of malignant diseases and closely related to the prognosis of patients with those malignant diseases (10-12). Total leukocyte and neutrophil counts have historically been used as infection markers. The NLR, which is defined by the neutrophil count divided by the lymphocyte count, is also an inflammatory biomarker. Several studies have reported that an elevated NLR, a simple index of systemic inflammation, is associated with poor prognosis in patients with various types of malignant diseases (13-21).
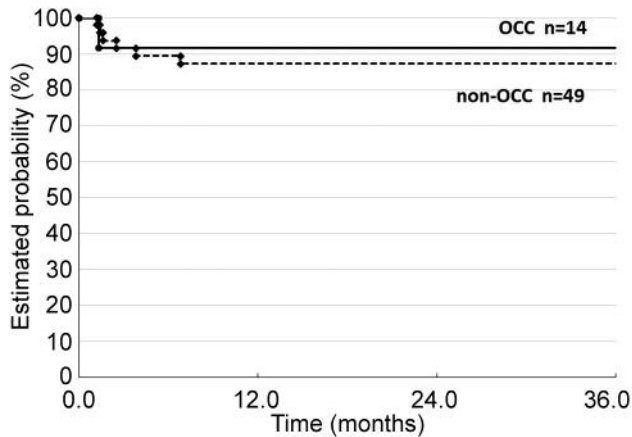
Figure 1. *Comparison of DFS between the OCC and non-OCC groups in stage II. No significant difference was identified between the two groups.*
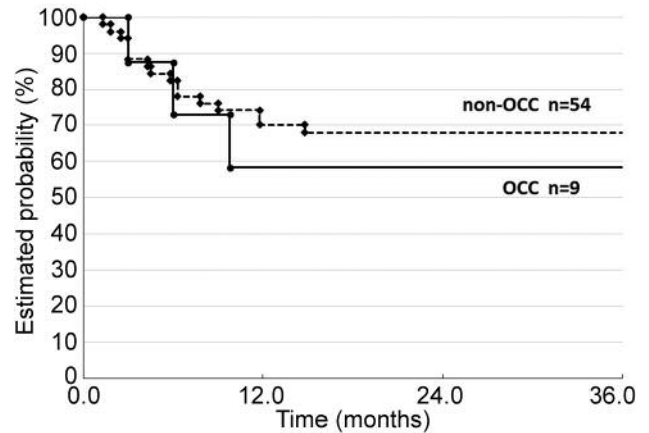

Figure 2. *Comparison of DFS between the OCC and non-OCC groups in stage III. No significant difference was identified between the two groups.*

Table II. *Comparison of hematological/biochemical parameters between the two groups.*

Characteristic	OCC (n=26)	non-OCC (n=114)	*p*-Value
Leucocyte count, mean (range)/mm^3	7790.9 (4000-12100)	6613.5 (2800-14500)	0.004
Neutropil count, mean (range)/mm^3	5642.3 (2320-8712)	4458.2 (644-12180)	0.003
Lymphocyte counts, mean (range)/mm^3	1629.3 (677-2800)	1797.6 (558-5080)	0.634
Neutrophil to lymphocyte ratio, (range)	3.9 (1.7-6.8)	2.7 (0.4-7.6)	0.001
Total protein, mean (range) g/dl	6.3 (4.1-8.6)	6.9 (5.7-8.6)	0.024
Albumin, mean (range) g/dl	3.5 (1.9-5.4)	3.9 (2.8-5.0)	0.009
C-reactive protein, mean (range) U/l	3.0 (0.0-33.0)	0.94 (0.0-7.9)	0.001
Serum CEA			0.665
Normal, n (%)	14 (54)	54 (47)	
>5.0 ng/ml, n (%)	12 (46)	60 (53)	
Serum CA19-9			0.609
Normal, n (%)	19 (73)	89 (78)	
>37.0 U/ml, n (%)	7 (27)	25 (22)	

OCC: Obstructive colorectal cancer; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

In this study, the inflammatory marker levels, leucocyte count, neutrophil count, CRP level, and NLR of the OCC group were significantly higher than those of the non-OCC group; however, significant differences in lymphocyte counts were not observed between the two groups. This is a specific phenomenon of malignant diseases that distinguishes it from inflammatory diseases caused by infection. Therefore, the NLR seems to be a more useful predictor than CRP level in malignant diseases. We found that the NLR was associated with bowel obstruction due to colorectal cancer growth. However, a large-scale prospective or retrospective study is needed to clarify this issue.

Serum albumin levels have been studied as part of the Glasgow Prognostic Score (GPS), which is based on a combination of albumin and CRP levels. Several reports have revealed that the GPS has a prognostic value in patients with advanced colorectal cancer (22, 23). In the present study, the serum total protein and albumin levels of the OCC group were significantly lower than those of the non-OCC group; however, these factors did not contribute to their outcomes. Previous studies have reported that patients with OCC have a significantly worse oncological outcome than patients with non-OCC (1, 5, 6). A significant difference in the 3-year DFS was not observed between the OCC and non-OCC groups with either stage II or III disease in our study. One reason for a good outcome might be the performance of complete tumor resection (R0) and extended D2/D3 lymph node dissection, the so-called Japanese standard lymph node

dissection. Complete tumor resection is required for good outcomes even if patients have OCC (24).

In conclusion, preoperative NLR seems to be a useful predictor of bowel obstruction due to colorectal cancer growth.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding this study.

Authors' Contributions

All Authors performed operations, analyzed the data of patients regarding their clinical features, and have been involved in drafting the manuscript. KY had given final approval of the version to be published. All Authors read and approved the final manuscript.

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