KJCO Korean Journal of Clinical Oncology
Korean Journal of Clinical Oncology 2023;19:3-10
https://doi.org/10.14216/kjco.23002
pISSN 1738-8082 · eISSN 2288-4084
Original Article

Clinical influence of neoadjuvant chemoradiotherapy on immunonutritional status in locally advanced rectal cancer

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Purpose: Cancer patients receiving various anti-cancer treatments commonly experience malnutrition, and many studies have reported that nutritional status is associated with survival and prognosis. Although standard neoadjuvant chemoradiotherapy (CRT) is commonly used in patients with locally advanced rectal cancer owing to its tumor-downsizing and downstaging effects, there is a lack of research on the impact of patients' nutritional status on the efficacy of neoadjuvant CRT.
Methods: We investigated the immunonutritional markers before and after long-course neoadjuvant CRT in 131 patients diagnosed with locally advanced rectal cancer from March 2013 to March 2022.
Results: We divided the patients into two groups: a low prognostic nutritional index (PNI) with a cutoff value of 50.92, and a high PNI. In both groups, significant decreases in lymphocyte count and PNI and an increase in neutrophil-to-lymphocyte ratio (NLR) were observed before and after CRT ($P<0.001$). Furthermore, a higher proportion of patients experienced adverse effects in the low PNI group than in the high PNI group (76.6% in low PNI vs. 54.8% in high PNI, $P=0.013$). The most commonly reported CRT-induced adverse effect was lower gastrointestinal tract toxicity.
Conclusion: By measuring the PNI and NLR without additional tests prior to starting neoadjuvant CRT in patients with locally advanced rectal cancer, it is possible to predict the risk of acute adverse effects caused by CRT. Additionally, providing external nutritional support to reduce the immunonutritional changes that occur during CRT can decrease side effects and potentially increase treatment compliance.

Keywords: Rectal neoplasms, Chemoradiotherapy, Nutritional status

INTRODUCTION

Rectal cancer is the third most common cause of cancer-related deaths worldwide [1]. Surgical methods for rectal cancer vary depending on the size and location of the tumor and the degree of infiltration into the surrounding tissues, including transanal local excision and transabdominal resection. In the case of locally advanced rectal cancer (LARC), preoperative chemoradiotherapy (CRT) is also an important treatment modality. Standard neoadjuvant CRT has shown the expected effects in patients, including tumor downsizing, downstaging, and sphincter preservation. Pathological complete response rates range from 15% to 38%; however, the associated adverse effects cannot be ignored [2]. The common adverse effects of maintenance CRT include loss of appetite, nausea, fecal incontinence, and anal pain. Severe adverse effects include fistula formation and an increased risk of postoperative anastomotic leakage. In particular, fecal incontinence caused by radiotherapy (RT) has been shown to have a significant negative impact on the patients' quality of life [3].

Nutritional status is a significant prognostic factor in cancer patients, and even patients who were initially well-nourished can easily experience malnutrition due to cancer-induced metabolic dyshomeostasis. Malnutrition can affect immune function, physical performance, and overall quality of life, as well as negatively impact the efficacy of anti-cancer treatments including chemotherapy and radiation therapy. It has been reported that up to 10%–20% of deaths

Received: Jun 22, 2023 **Revised:** Jun 28, 2023 **Accepted:** Jun 29, 2023
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in cancer patients are attributed to malnutrition rather than for the tumor itself [4,5]. In colorectal cancer, nutritional status is particularly crucial as malnutrition may increase the risk of anastomotic leakage and delay the recovery of intestinal functions. Consequently, prolonged hospitalization, increased postoperative complications, and reduced treatment response and survival rates are observed in these patients [6].

As mentioned above, while CRT is a useful treatment, its associated adverse effects cannot be ignored. In cancer patients commonly affected by malnutrition, the impact of nutritional status on various anti-cancer treatments, as well as its relationship with survival rates, is being studied in lung, cervical, breast, and rectal cancers. However, research on this topic is lacking. Therefore, this study aimed to investigate the differences in adverse effects of neoadjuvant CRT based on the nutritional status of patients with LARC who received neoadjuvant CRT and to examine the changes in nutritional status before and after CRT.

METHODS

Study population

This retrospective study was conducted at Soonchunhyang University Cheonan Hospital between March 2013 and March 2022. We included patients who were histologically diagnosed with LARC and received long-course CRT. The following exclusion criteria were applied: (1) patients who did not undergo surgery after CRT; (2) patients with incomplete medical records; and (3) patients with psychiatric conditions requiring medication that could affect treatment compliance. In total, 131 patients were enrolled in this study. Preoperative RT was delivered at a dose of 5,000 to 5,040 cGy in 25 to 28 fractions. Concurrent chemotherapy was administered with either oral capecitabine or 5-fluorouracil/leucovorin according to the National Comprehensive Cancer Network guidelines. This study complied with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board of the Soonchunhyang University Cheonan Hospital (IRB No. 2022-06-022). The informed consent was waived because this design is a retrospective study.

Data collection

We extracted information from the medical records, including age at diagnosis, sex, body weight, body mass index (BMI), medical history, CRT regimen, CRT duration, American Society of Anesthesiologists (ASA) physical status classification, and Charlson Comorbidity Index (CCI). The clinical cancer stage was determined based on imaging tests performed before CRT initiation, and radiation therapy records, surgical procedures, and postoperative histopathological results were reviewed. Blood tests conducted within 1 month before CRT initiation and within 2 months after completion were used to assess serum albumin, hemoglobin, neutrophil count, lymphocyte count, carcinoembryonic antigen levels, and carbohydrate antigen 19-9 levels. The neutrophil-to-lymphocyte ratio (NLR) was calculated as the neutrophil count divided by the lymphocyte count. The pathological tumor regression grade (TRG) was determined based on the histopathological results after surgery using the Dworak grading system, which categorizes TRG into five grades: complete regression (TRG4), near-complete regression (TRG3), moderate regression (TRG2), minimal regression (TRG1), and no regression (TRG0). The adverse effects of CRT reported by the patients during the CRT period until 2 months after completion were classified according to the Acute Radiation Scoring criteria of the toxicity criteria of the Radiation Therapy Oncology Group (RTOG).

Statistical analyses

The chi-square test, Fisher exact test, and Mann-Whitney U test were used to compare groups using the Statistical Package for the Social Sciences 26.0 (IBM Corp.). The cutoff value for the pre-CRT PNI was calculated using adverse effect-dependent receiver operating characteristic curves. All patients were divided into two groups according to the PNI cutoff value. Univariate analysis was used to analyze the relationship between each variable and acute adverse effects of neoadjuvant CRT. Multivariate analysis adjusted for age, sex, ASA grade, CCI, pre-CRT BMI (kg/m^2), clinical cancer stage, pre-CRT PNI, pre-CRT NLR, PNI change value, and NLR change value was performed using multivariate logistic regression. Statistical significance was set at $P < 0.05$.

RESULTS

In total, 131 patients were included. Based on the presence or absence of adverse effects, the pre-CRT PNI cutoff value was 50.92 (sensitivity 86.0%, specificity 49.4%, area under the curve = 0.676). Table 1 summarizes the characteristics of the low PNI and high PNI groups based on the cutoff value of the pre-CRT PNI. High PNI patients had a significantly lower mean age than those with low PNI ($P < 0.001$). Furthermore, when comparing the ASA grades before surgery, the percentage of patients with ASA grade 3 differed between the low (19.1%) and high (6.0%) PNI groups. Differences were considered statistically significant. The severity of comorbidities, as indicated by a CCI score of 5 or higher, was considered severe. In the low PNI group, 89.4% of the patients had a CCI score of 5 or higher, which was significantly higher than that in the high PNI group ($P < 0.001$). There were no differences between the

Table 1. Demographic and clinical characteristics of patients

Characteristic	Type	Total (n = 131)	Low PNI (n = 47)	High PNI (n = 84)	P-value
Age (yr), mean ± SD (range)		70.1 ± 10.7 (44–89)	75.4 ± 8.3 (58–89)	67.1 ± 10.8 (44–88)	< 0.001
Age group (yr)	< 65	40 (30.5)	7 (14.9)	33 (39.3)	< 0.004
	≥ 65	91 (69.5)	40 (85.1)	51 (60.7)	
Sex	Male	93 (71.0)	34 (72.3)	59 (70.2)	0.799
	Female	38 (29.0)	13 (27.7)	25 (29.8)	
ASA grade	1	25 (19.1)	6 (12.8)	19 (22.6)	0.039
	2	92 (70.2)	32 (68.1)	60 (71.4)	
	3	14 (10.7)	9 (19.1)	5 (6.0)	
Hypertension	Yes	63 (48.1)	25 (53.2)	38 (45.2)	0.382
	No	68 (51.9)	22 (46.8)	46 (54.8)	
Diabetes mellitus	Yes	35 (26.7)	16 (34.0)	19 (22.6)	0.156
	No	96 (73.3)	31 (66.0)	65 (77.4)	
Other medical history	Yes	40 (30.5)	19 (40.4)	21 (25.0)	0.066
	No	91 (69.5)	28 (59.6)	63 (75.0)	
CCI	Mild (1-2)	4 (3.1)	0	4 (4.8)	< 0.001
	Moderate (3-4)	39 (29.8)	5 (10.6)	34 (40.5)	
	Severe (≥ 5)	88 (67.2)	42 (89.4)	46 (54.7)	
Clinical T stage	T1	1 (0.8)	1 (2.1)	0	0.221
	T2	5 (3.8)	0	5 (6.0)	
	T3	50 (38.2)	18 (38.3)	32 (38.1)	
	T4	75 (57.3)	28 (59.6)	47 (56.0)	
Clinical N stage	N0	35 (26.7)	13 (27.6)	22 (26.2)	0.912
	N1	77 (58.8)	28 (59.6)	49 (58.3)	
	N2	19 (14.5)	6 (12.8)	13 (15.5)	
CEA (ng/mL)		7.79 ± 9.45	8.77 ± 12.64	7.25 ± 7.11	0.630
CA19-9 (U/mL)		14.38 ± 19.58	15.27 ± 14.41	13.64 ± 21.62	0.128
Chemoradiotherapy regimen	LV+5FU	89 (67.9)	35 (74.5)	54 (62.3)	0.231
	Capecitabine	42 (32.1)	12 (25.5)	30 (35.7)	
Radiotherapy	Duration (day)	36.0 ± 6.0	36.0 ± 4.7	36.0 ± 6.6	0.220
Radiotherapy dose	180 cGy × 28 fractions	51 (38.9)	23 (48.9)	28 (33.3)	0.079
	200 cGy × 25 fractions	80 (61.1)	24 (51.1)	56 (66.7)	
Radiotherapy discontinued	Yes	3 (2.3)	0	3 (3.6)	0.553
	No	128 (97.7)	47 (100.0)	81 (96.4)	
Change of BMI	≤ −5	17 (13.0)	6 (12.7)	11 (13.1)	0.103
	> −5 to < 5	97 (74.0)	31 (66.0)	66 (78.6)	
	≥ 5	17 (13.0)	10 (21.3)	7 (8.3)	

PNI, prognostic nutritional index; SD, standard deviation; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; LV+5-FU, leucovorin/5-fluorouracil; BMI, body mass index.

two groups in terms of the clinical cancer stage before CRT or tumor markers. The total amount of radiation varied slightly depending on the timing of treatment; however, the dose ranged from 5,000 to 5,040 cGy. The total duration of radiation therapy was 36 days, and there was no difference between the two groups. The chemotherapy regimens used were leucovorin/5-fluorouracil and capecitabine, and there were no statistically significant differences. Three patients (2.3% of the total patients) discontinued CRT, and all three had a high PNI. The reasons for discontinuation were deterioration of the general condition, loss of appetite, uncontrolled anal pain, and fecal incontinence.

There was no statistically significant difference in body weight and BMI before and after neoadjuvant CRT (Table 2). However, both the low and high PNI groups showed statistically significant differences in lymphocyte count, PNI, and NLR ($P < 0.001$) (Fig. 1). The neutrophil count also showed a significant difference between

Table 2. Changes in laboratory tests and immunonutritional markers according to neoadjuvant chemoradiotherapy

Index	Total patient			Low PNI			High PNI		
	Pre-CRT	Post-CRT	P-value	Pre-CRT	Post-CRT	P-value	Pre-CRT	Post-CRT	P-value
Body weight (kg)	61.44 ± 10.97	61.47 ± 10.87	0.619	57.63 ± 10.34	58.24 ± 10.56	0.174	63.57 ± 10.79	63.28 ± 10.68	0.377
Body mass index (kg/m^2)			0.810			0.155			0.402
Underweight (< 18.5)	11 (8.4)	8 (6.1)		10 (21.3)	7 (14.9)		1 (1.2)	1 (1.2)	
Normal (18.5 to < 23)	59 (45.0)	62 (47.3)		20 (42.6)	21 (44.7)		39 (46.4)	41 (48.8)	
Overweight (23 to < 25)	23 (17.6)	23 (17.6)		5 (10.6)	6 (12.8)		18 (21.4)	17 (20.2)	
Obesity (≥ 25)	38 (29.0)	38 (29.0)		12 (25.5)	13 (27.7)		26 (31.0)	25 (29.8)	
Serum albumin (g/dL)	4.17 ± 0.46	4.16 ± 0.44	0.851	3.74 ± 0.39	3.84 ± 0.45	0.117	4.41 ± 0.29	4.35 ± 0.32	0.103
Hemoglobin (g/dL)	13.67 ± 11.85	12.36 ± 1.78	0.203	11.61 ± 1.92	11.74 ± 1.54	0.476	14.83 ± 14.63	12.70 ± 1.82	0.186
Neutrophil count (cells/mm^3)	4,638 ± 1,739	3,897 ± 1605	< 0.001	4,547 ± 1892	4,179 ± 1,859	0.248	4,688 ± 1,656	3,740 ± 1,432	< 0.001
Lymphocyte count (cells/mm^3)	2,156 ± 700	1,151 ± 441	< 0.001	1,707 ± 538	1,070 ± 388	< 0.001	2,407 ± 655	1,197 ± 464	< 0.001
PNI	52.47 ± 6.23	47.38 ± 5.04	< 0.001	45.96 ± 3.95	43.71 ± 5.15	0.001	56.11 ± 3.84	49.44 ± 3.62	< 0.001
NLR	2.35 ± 1.14	3.91 ± 2.65	< 0.001	2.86 ± 1.38	4.58 ± 3.35	0.001	2.07 ± 0.85	3.54 ± 2.10	< 0.001

Values are presented as mean ± standard deviation or number (%).
CRT, chemoradiotherapy; PNI, prognostic nutritional index; NLR, neutrophil-lymphocyte ratio.

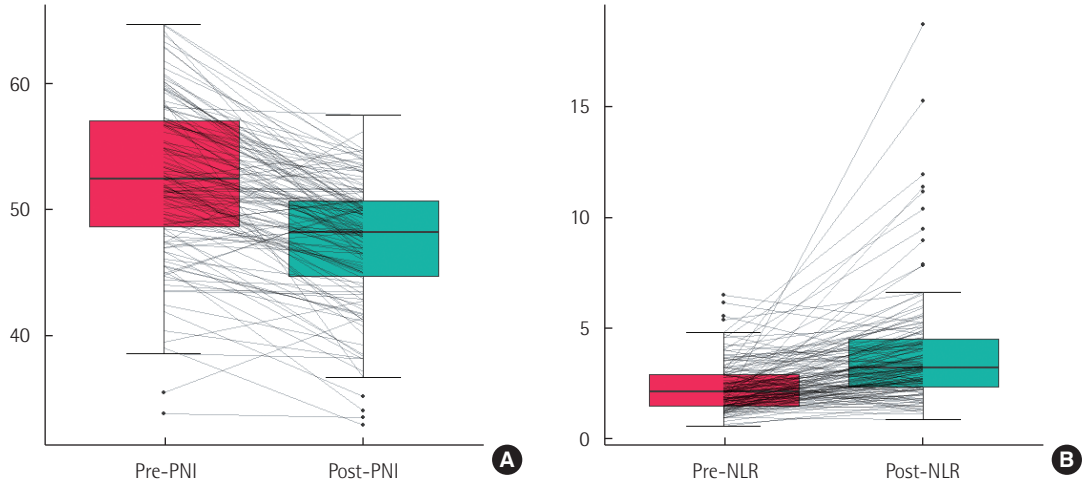

Fig. 1. Spaghetti plot and box plot of PNI (A) and NLR (B) before and after neoadjuvant CRT. When analyzed with total 131 patients, left image demonstrates the difference in PNI before and after neoadjuvant CRT, while the right image shows the difference in NLR using Spaghetti plot and box plot. There were statistically significant difference (P<0.001). PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; CRT, chemoradiotherapy.

the total patient group and the high PNI patients (P < 0.001). Hemoglobin tended to decrease post-CRT compared with pre-CRT, but the difference was not statistically significant. Serum albumin showed no statistical significance, but it decreased from 4.41 ± 0.29 to 4.35 ± 0.32 in the high PNI group (P = 0.103), while it increased from 3.74 ± 0.39 to 3.84 ± 0.45 in the low PNI group (P = 0.117). Despite these changes in serum albumin levels, the significant decrease in the PNI in all groups was attributed to a significant decrease in the lymphocyte count. Similarly, the NLR increased in both groups for the same reason (P < 0.001).

According to the medical records, adverse effects reported by patients during CRT were classified according to the RTOG toxicity criteria (Table 3). Symptoms such as anorexia, nausea, and vomiting were classified under the upper gastrointestinal category, whereas fecal incontinence, rectal discomfort, and proctitis were classified under the lower gastrointestinal category. Other categories included the genitourinary, hematologic, and central nervous system categories, resulting in a total of five categories. The proportion of patients who experienced adverse effects was higher in the low PNI group than in the high PNI group, and the difference between the two groups was statistically significant (76.6% vs. 54.8%, P = 0.013). In other words, the risk of CRT-induced adverse effects in the high PNI group was 0.370 times lower than that in the low PNI group (odds ratio, 0.370; 95% confidence interval, 0.166–0.824). The most

Table 3. Neoadjuvant chemoradiotherapy-induced adverse effects

Adverse effects	Score	Total	Low PNI	High PNI	P-value
Radiotherapy induced adverse effects					0.013
No		49 (37.4)	11 (23.4)	38 (45.2)	
Yes		82 (62.6)	36 (76.6)	46 (54.8)	
Upper gastrointestinal (n = 23)	1	18 (22.0)	11 (30.6)	7 (15.3)	
	2	5 (6.1)	3 (8.3)	2 (4.3)	
Lower gastrointestinal (n = 50)	1	19 (23.2)	9 (25.0)	10 (21.7)	
	2	31 (37.8)	8 (22.2)	23 (50.0)	
Genitourinary (n = 7)	1	2 (2.4)	1 (2.8)	1 (2.2)	
	2	5 (6.1)	2 (5.5)	3 (6.5)	
Hematologic (n = 1)	1	-	-	-	
	2	-	-	-	
	3	1 (1.2)	1 (2.8)	-	
Central nervous system (n = 1)	1	-	-	-	
	2	1 (1.2)	1 (2.8)	-	

Values are presented as number (%).
The RTOG (Radiation Therapy Oncology Group) grading system assigns a numerical score to each adverse effect based on its severity. The scores range from 0 to 5, with higher scores indicating more severe side effects.

Table 4. Differences in postoperative pathologic stage and tumor regression grade between two groups classified by PNI

Index	Type	Total	Low PNI	High PNI	P-value
Surgery name	Low anterior resection	102 (77.9)	31 (66.0)	71 (84.5)	0.014
	Hartmann's operation	3 (2.3)	1 (2.1)	2 (2.4)	
	Miles' operation	6 (4.6)	6 (12.8)	0	
	Transanal excision	17 (12.9)	8 (17.0)	9 (10.7)	
	Palliative loop ileostomy	3 (2.3)	1 (2.1)	2 (2.4)	
Pathologic stage	No residual tumor	13 (9.9)	5(10.6)	8 (9.5)	0.941
	1	31 (23.7)	12 (25.5)	19 (22.6)	
	2	43 (32.8)	16 (34.1)	27 (32.2)	
	3	25 (19.1)	6 (12.8)	19 (22.6)	
	4	2 (1.5)	1 (2.1)	1 (1.2)	
	No data	17 (13.0)	7 (14.9)	10 (11.9)	
Tumor regression grade	0	6 (4.6)	1 (2.1)	5 (5.9)	0.228
	1	31 (23.7)	15 (31.9)	16 (19.0)	
	2	64 (48.8)	19 (40.4)	45 (53.6)	
	3	16 (12.2)	8 (17.0)	8 (9.5)	
	4	14 (10.7)	4 (8.5)	10 (11.9)	

PNI, prognostic nutritional index.

common adverse effects were related to the lower gastrointestinal tract, which was consistent in both groups. However, in the low PNI group, more cases were classified as RTOG grade 1 than RTOG grade 2, which required medication or intervention, whereas the high PNI group had more cases classified as RTOG grade 2.

The most commonly performed surgical method in both groups was low anterior resection, and all six cases of the Miles operation were in the low PNI group. The number of patients who underwent transanal excision was second highest in each group, with 17.0% in the low PNI group and 10.7% in the high PNI group (Table 4). The difference in surgical methods between the two groups was statistically significant (P = 0.014). The pathological stage and TRG were compared based on the pathology report. Evaluation was conducted using Dworak TRG, and both groups had the highest proportion of moderate regression (TRG2), with slightly more patients with complete regression (TRG4) in the high PNI group (11.9%) than in the low PNI group (8.5%), but it was not statistically significant.

Table 5. Univariate and multivariate analysis according to acute adverse effects of CRT

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.172 (0.546–2.514)	0.684	0.887 (0.361–2.178)	0.794
Sex	2.022 (0.881–4.643)	0.097	1.658 (0.680–4.045)	0.267
ASA grade		0.222		
ASA grade (1)	1.908 (0.777–4.681)	0.158		
ASA grade (2)	0.923 (0.249–3.417)	0.905		
CCI		0.508		
Pre-CRT BMI		0.289		
Pre-CRT BMI (1)	0.402 (0.079–2.036)	0.271		
Pre-CRT BMI (2)	0.204 (0.036–1.157)	0.073		
Pre-CRT BMI (3)	0.381 (0.072–2.020)	0.257		
Clinical cancer stage		0.694		
Clinical cancer stage (1)	0.643 (0.053–7.832)	0.729		
Clinical cancer stage (2)	0.912 (0.080–10.425)	0.941		
Pre-CRT PNI	0.978 (0.924–1.037)	0.461	0.900 (0.827–0.978)	0.014
Pre-CRT NLR	0.930 (0.682–1.269)	0.648	0.889 (0.598–1.321)	0.561
PNI change value[a]	0.926 (0.858–1.000)	0.050	0.848 (0.761–0.945)	0.003
NLR change value[b]	1.232 (1.010–1.504)	0.040	1.155 (0.926–1.440)	0.202

We compare stratification variable based on a reference variable (ASA grade 1, underweight and clinical cancer stage I). e.g., (1) is compared to grade 2, and (2) is compared to grade 3 based on ASA grade 1.

CRT, chemoradiotherapy; OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists physical status classification; CCI, Charlson Comorbidity Index; BMI, body mass index; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio.

[a]PNI change value = (post-CRT PNI value–pre-CRT PNI value). [b]NLR change value = (post-CRT NLR value–pre-CRT NLR value).

Table 5 presents the results of univariate and multivariate analyses conducted on variables that may influence acute adverse effects. In the univariate analysis, the PNI change value (P = 0.050) and NLR change value (P = 0.040), representing the difference in values before and after CRT, were found to be significant. However, ASA grade and CCI, despite showing a statistically significant difference when comparing low PNI and high PNI, were not found to have an impact on acute adverse effects. In the multivariate analysis, the pre-CRT PNI (P = 0.014) and PNI change (P = 0.003) were found to be statistically significant. However, NLR showed no meaningful P-value in both the pre-CRT measurement and the change value.

DISCUSSION

We observed two main findings in this study. First, in patients with LARC, there was a noticeable decrease in lymphocyte count, leading to a decrease in the PNI and an increase in NLR before and after the initiation of long-course CRT. Second, we found that a lower PNI before the initiation of CRT was associated with an increased incidence of acute adverse effects.

The prevalence of malnutrition among patients with colorectal cancer is 39.3%, and in patients receiving RT and CRT, the proportion of malnourished patients increases from 44% to 88% [7]. During CRT, fat-free mass is lost, and CRT-induced toxicity occurs, resulting in a decrease in quality of life and decreased survival rates [8,9]. CRT-induced toxicities can be classified into acute and late toxicities; severe late toxicity is associated with weight loss during CRT, whereas the presence of acute toxicity does not increase the risk of late toxicity [10]. We distinguished CRT-induced toxicities in patients with rectal cancer based on symptoms reported by the patients and the use of medications, as recorded in the medical records following the RTOG criteria. Diarrhea was the most common toxicity, followed by upper gastrointestinal toxicities such as anorexia and nausea. These symptoms directly lead to a decrease in dietary intake and worsen malnutrition.

The PNI was initially designed to assess the immunonutritional status of patients with gastrointestinal cancer and has since been used for various cancer types. The PNI has been validated as a predictor of postoperative complications and overall survival in patients with colorectal cancer who undergo surgery [11,12]. Serum albumin, which is used to calculate PNI, is a marker of nutritional status. Due to the systemic inflammatory response to tumors, albumin synthesis is suppressed, leading to a rapid decrease in serum

albumin levels in response to malnutrition [13]. Lymphocytes play an important role in the host cytotoxic immune response and reflect the systemic inflammatory response to tumors [14]. NLR has also been identified as an independent prognostic factor for progression-free survival and overall survival in colorectal cancer patients receiving neoadjuvant CRT [12]. Similar to our study, other studies have shown a decrease in PNI levels post-CRT compared with pre-CRT in patients with rectal cancer. They also mentioned that the pre-CRT PNI had an impact on overall survival and disease-free survival [15]. Okugawa et al. [16] did not find a significant correlation between the pre-CRT PNI and adverse CRT effects, but a low pre-CRT PNI was an independent risk factor for the ineffectiveness of CRT. However, as the data are not shown, it is difficult to provide a detailed interpretation. In our study, we did not examine the survival rate; however, the acute adverse effects of CRT were more common in the low-PNI group than in the high-PNI group. This finding is consistent with a study conducted in patients with cervical cancer, which showed that as nutritional status worsens, the adverse effects of CRT worsen, leading to a decrease in treatment completion [17]. This is thought to be related to skeletal muscle loss caused by anti-cancer treatments [18]. Studies targeting cervical, head, and neck cancers have shown that clinical nutritional support reduces or prevents the adverse effects of CRT, positively affecting quality of life and prognosis [19,20]. In our study, a significant decrease in lymphocytes was observed before and after CRT; however, the difference in serum albumin levels was not significant. Serum albumin level can predict neutropenia during CRT, but it reflects systemic influences rather than nutritional status [21]. Therefore, serum albumin level alone may be limited as an indicator of malnutrition and the occurrence of adverse effects during CRT.

According to the classification based on the pre-CRT PNI, patients with a high PNI were younger, indicating a difference in immunonutritional status according to age. The age difference between the groups also led to statistically significant differences in the CCI and ASA grades. Previous studies have shown that age affects acute RT toxicity [22]. Contrary to our expectations, there were no statistically significant changes in body weight or BMI before and after CRT. Without examining specific changes in body composition, such as changes in weight and BMI, it is not possible to definitively conclude that there were no changes in the patients' nutritional status. After surgery, the local excision rate and pathological TRG changes were examined to determine whether there were differences in the response to radiation therapy based on the pre-CRT PNI. A P-value of 0.228 indicated no significant difference in the pathological TRG between the two groups. However, in terms of the surgical method, only the low PNI group had patients who underwent Miles' operation (n = 6, 12.8%), whereas the high PNI group had the highest proportion of low anterior resections.

Patients with high PNI showed a more significant decrease in PNI and an increase in NLR than those with low PNI, with a greater decrease in neutrophil and lymphocyte counts. This suggests a more pronounced systemic immune response, which may be associated with a higher rate of lower gastrointestinal toxicities (RTOG grade 2) including diarrhea. However, the exact mechanism is unknown, and a detailed explanation is needed regarding the significant differences in PNI and NLR before and after CRT, with higher PNI values before treatment associated with larger differences. This study aimed to minimize bias from external factors through a prospective design and to provide an explanation for these findings.

The limitations of our study are as follows: First, it was a retrospective study based on a small number of patients and medical records, and there was a lack of information on patients' nutritional intake during the CRT period, making it difficult to exclude these variables. Second, the two chemotherapy drug regimens used in CRT varied among patients, leading to uncontrolled bias. In this study, it is observed that the cutoff value of PNI has high sensitivity, resulting in few false negative results. However, there is a limitation of low specificity. Therefore, in subsequent studies, it is necessary to select a cutoff value that not only has high sensitivity but also high specificity.

Nevertheless, through this study, we confirmed statistically significant changes in PNI and NLR in patients with LARC receiving neoadjuvant CRT, and we found that measuring pre-CRT PNI and the PNI change that occur during CRT can predict the occurrence of acute adverse effects. A prospective study is needed to investigate the relationship between changes in PNI due to external nutritional support and acute adverse effects. However, it can be expected that reducing PNI decline through external nutritional supplementation would decrease acute adverse effects and potentially improve treatment compliance.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

This study was supported by the Soonchunhyang University Research Fund and a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (grant nos. 2021 R1G1A1094891).

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