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ORIGINAL ARTICLE

A decrease in the prognostic nutritional index is associated with a worse long-term outcome in gastric cancer patients undergoing neoadjuvant chemotherapy

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Abstract
Purpose The aim of this study was to evaluate the prognostic impact of the prognostic nutritional index (PNI) in gastric cancer patients undergoing neoadjuvant chemotherapy (NAC).
Methods This study reviewed 54 patients with gastric cancer who underwent NAC and a subsequent R0 gastrectomy. The PNI before starting NAC and before gastrectomy were calculated using the following formula: $10 \times$ serum albumin (g/dl) $+ 0.005 \times$ total lymphocyte count (per mm^3). A multivariate analysis was performed to identify the predictors of overall survival (OS).
Results The mean pre-NAC and preoperative PNI were 48.3 ± 5.1 and 48.2 ± 4.7, respectively ($p = 0.934$). The PNI decreased after NAC in 31 patients (57.4%). The pre-NAC PNI and preoperative PNI were not significantly associated with the OS rate. The 3-year OS rate in patients with the decreased PNI values was significantly lower than that in the patients whose PNI values were either maintained or increased (41 vs. 76.4%, $p = 0.003$). A multivariate analysis revealed that a decreased PNI value was an independent predictor of a poor OS ($p = 0.006$).
Conclusions Decreased PNI values were associated with worse long-term outcomes in gastric cancer patients undergoing NAC.

Keywords Prognostic nutritional index · Gastric cancer · Neoadjuvant chemotherapy

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Introduction

There is increasing evidence to suggest that the nutritional and immunological status has a strong impact on the outcome of cancer treatment. Previous studies have shown that a poor nutritional and immunological status is associated with a higher risk of postoperative complications, a decreased response and tolerance to anti-cancer treatment, a lower survival rate, and a poor quality of life [1–6]. Various parameters have been used to assess the patient nutritional and immunological status. The prognostic nutritional index (PNI), which is calculated based on the serum albumin level and the total lymphocyte count in the peripheral blood, is initially used to evaluate the risk of postoperative complications and mortality in patients undergoing gastrointestinal surgery [7]. In gastric cancer, the PNI has been demonstrated to predict both postoperative complications and the postoperative survival time [4, 8, 9].

In Japan, postoperative adjuvant chemotherapy using S-1 has been established as the standard treatment after D2 gastrectomy in patients with stage II and III disease based on a large phase III study [10]. However, the long-term survival rate of patients with stage III tumors remains insufficient [11]. Recently, neoadjuvant chemotherapy (NAC) has been gaining increased attention because it offers some theoretical benefits over adjuvant chemotherapy [12], and various chemotherapeutic regimes have been used in a neoadjuvant setting to treat patients with locally advanced gastric cancer [13–15]. Chemotherapy is frequently associated with a variety of gastrointestinal adverse effects, including anorexia, nausea, vomiting, stomatitis and diarrhea, which can lead to the deterioration of a patient's nutritional status [16, 17]. In contrast, chemotherapy has the potential to reduce both the tumor bulk and micrometastasis. Therefore, an improved nutritional status may be achieved in responders to chemotherapy [5, 18]. Thus far, there is no information about the influence of NAC on the nutritional and immunological status or its impact on the postoperative prognosis in gastric cancer patients. In the present study, we investigated the changes in various nutritional and immunological parameters, including the PNI, and further evaluated the prognostic impact of the PNI in gastric cancer patients who underwent NAC.

Methods

A total of 71 patients with gastric cancer underwent neoadjuvant chemotherapy and subsequent gastrectomy between January 2003 and December 2014 in Nara Medical University hospital. We excluded nine patients who underwent R1 or R2 resection and eight patients whose PNI values before the start of NAC or before gastrectomy were unavailable. As a result, a total of 54 patients were analyzed in the present study. This study was approved by the Local Ethics Committee on Clinical Investigation of Nara Medical University (no. 1334). Written informed consent was obtained from all of the patients.

The eligibility criteria were as follows: histologically proven gastric adenocarcinoma, a tumor with a depth of invasion of T3 or deeper and lymph node metastasis or a type 4 tumor with a depth of invasion of T3 or deeper according to the third edition of the Japanese Classification of Gastric Carcinoma [19], 20–79 years of age, an Eastern Cooperative Oncology Group performance status of 0–1, the absence of uncontrolled infection or cardiopulmonary disease, adequate bone marrow, renal and hepatic functions. The operation was principally performed at 2–4 weeks after the completion of NAC.

The clinicopathological characteristics were obtained retrospectively from the patients' medical records; these included the age, sex, preoperative chemotherapeutic regimen, tumor depth, lymph node metastasis, distant metastasis, tumor stage, clinical and pathological responses to chemotherapy, surgical procedure, extent of lymph node metastasis, use of combined organ resection and postoperative complications. The clinical response of the primary tumor to chemotherapy was evaluated according to the criteria of the Japanese Gastric Cancer Association (JGCA) [19]. The pathological response to chemotherapy was evaluated according to the histological evaluation criteria of the JGCA [19]. Adverse events due to chemotherapy were evaluated by the National Cancer Institute Common Toxicity Criteria version 4.0. The extent of lymph node dissection was classified according to the Japanese Gastric Cancer Treatment Guidelines 2010 (version 3) [20]. The severity of postoperative complications was defined according to the Clavien–Dindo classification [21].

We also collected data about the blood test results before the initiation of NAC and just prior to gastrectomy, including the serum levels of total protein, albumin, cholinesterase, total cholesterol and hemoglobin, and the total lymphocyte count in the peripheral blood. The PNI was then calculated using the following formula: $10 \times$ serum albumin value (g/dl) $+ 0.005 \times$ total lymphocyte count in the peripheral blood (per mm^3) [7]. In addition, the body weight and height were obtained, and body mass index (BMI) was calculated as the patient's weight (in kilograms) divided by the square of the height (in meters).

The NAC regimens included S-1 ($n = 8$), combination chemotherapy with S-1 and cisplatin ($n = 14$), a combination of S-1 and docetaxel ($n = 12$), a combination of 5-fluorouracil (5-FU) and cisplatin ($n = 1$), and a combination of S-1, docetaxel and cisplatin ($n = 19$).

Statistical analysis

Continuous variables were expressed as the mean and standard deviation, and the means were compared using the *t* test. The mean values of nutritional and immunological parameters before NAC and before surgery were compared using the paired *t* test. The categorical variables were presented as numbers and percentages, and the groups were compared using the Chi-squared test or Fisher's exact test. In the present study, the cutoff PNI value was set at 48, as reported previously [4]. The PNI change after NAC was calculated by subtracting the pre-NAC PNI from the preoperative PNI. If the value was ≥ 0, the change in the PNI was defined as maintained or increased; otherwise, the change in the PNI value was defined as a decrease.

At the time of the final follow-up (May 2016), the mean follow-up period was 41.5 months. Overall survival (OS) was defined as the duration from the operation to death. Disease-specific survival (DSS) was defined as the duration from the operation to death from gastric cancer. The relapse-free survival (RFS) was defined as the duration from the operation to the relapse of gastric cancer or death. The survival curves were estimated by the Kaplan–Meier method, and differences between the curves were analyzed using the log-rank test. Univariate and multivariate hazard ratios (HRs) were calculated using the Cox proportional hazards model. All variables with a p value of <0.1 were entered into the multivariate analysis. P values <0.05 were considered to indicate statistical significance, and 95% confidence intervals (CI) were calculated. The statistical analyses were performed using the SPSS software program (version 22.0, SPSS, Chicago, Illinois, USA).

Table 1 The clinicopathological and surgical findings

Variables	*N* (%)
Age (years)[a]	63.3 ± 9.3
Sex	
Male	41 (75.9)
Female	13 (24.1)
Clinical tumor stage[b]	
IIA, IIB	12 (22.2)
IIIA, IIIB, IIIC	35 (64.8)
IV	7 (13)
NAC regimen	
S-1 monotherapy	8 (14.8)
Doublet	27 (50)
Triplet	19 (35.2)
Clinical response of the primary tumor to NAC[c]	
CR	1 (1.9)
PR	12 (22.2)
SD	31 (57.4)
PD	2 (3.7)
NE	8 (14.8)
Surgical procedure	
Distal gastrectomy	16 (29.6)
Total gastrectomy	38 (70.4)
Lymph node dissection[d]	
D1+	1 (1.9)
D2 without station 10	5 (9.3)
D2	33 (61.1)
D2+	15 (27.8)
Combined organ resection	
Spleen	31 (57.4)
Gallbladder	5 (9.3)
Left adrenal gland	4 (7.4)
Liver	3 (5.6)
Pancreas	2 (3.7)
Postoperative complication	
Any	16 (29.6)
Grade ≥ 3[e]	7 (13)
Pathological tumor stage[b]	
CR	5 (9.3)
IA, IB	1 (1.9)
IIA, IIB	12 (22.2)
IIIA, IIIB, IIIC	28 (51.9)
IV	8 (14.8)
Pathological response to NAC[f]	
Grade 0	8 (14.8)
Grade 1a	23 (42.6)
Grade 1b	11 (20.4)
Grade 2	7 (13)
Grade 3	5 (9.3)

NAC neoadjuvant chemotherapy, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluated

[a]The value is expressed as the mean and standard deviation

[b]According to the third edition of the Japanese Classification of Gastric Carcinoma

[c]According to the criteria of Japanese Gastric Cancer Association

[d]According to the Japanese Gastric Cancer Treatment Guidelines 2010 (version 3)

[e]According to the Clavien–Dindo classification

[f]According to the histological evaluation criteria of the Japanese Gastric Cancer Association

Results

The clinicopathological and surgical findings of the patients are shown in Table 1. Thirty-eight (70.4%) patients underwent total gastrectomy, while 16 (29.6%) patients underwent distal gastrectomy. Postoperative complications occurred in 29.6% of the patients, and the rate of grade 3 or greater complications was 13%. The clinical response of the primary tumor to NAC was a complete response (CR) in 1 (1.9%) patient, partial response (PR) in 12 (22.2%), stable disease (SD) in 31 (57.4%) and progressive disease (PD) in 2 (3.7%). A pathological response to NAC of grade ≥ 1b was observed in 23 (42.6%) patients. Four patients with sufficient oral intake underwent planned preoperative supplementation of nutrients, and three patients with insufficient oral intake received parenteral nutrition.

We compared the nutritional and immunological parameters before NAC with those before the operation. The serum levels of cholinesterase and BMI were significantly decreased after NAC (Table 2). The mean pre-NAC and preoperative PNI values were 48.3 ± 5.1 and 48.2 ± 4.7, respectively ($p = 0.934$). The distributions of the pre-NAC PNI and the preoperative PNI are shown in Fig. 1. The PNI was decreased after NAC in 31 (57.4%) patients, maintained in 1 (1.9%) and increased in 22 (40.7%).

We next investigated the impact of the PNI on postoperative survival. Before NAC, 22 (40.7%) patients had a PNI of <48, and 26 (48.1%) patients had a PNI of <48 before the operation. Neither the pre-NAC nor the preoperative PNI was significantly associated with the OS (Fig. 2a, b). We further investigated the impact of the changes in the nutritional and immunological parameters and the clinical response to chemotherapy on the rate of postoperative

Table 2 The comparison of the nutritional and immunological parameters before neoadjuvant chemotherapy and before gastrectomy

Variables	Before NAC	Before gastrectomy	*p* value
Total protein (g/dl)[a]	6.9 ± 0.5	6.7 ± 0.6	0.059
Albumin (g/dl)	4.1 ± 0.4	4.0 ± 0.4	0.811
Cholinesterase (U/l)[b]	263.5 ± 72.2	229.3 ± 68	<0.001
Total cholesterol (mg/dl)[c]	189.6 ± 37.2	183.9 ± 42.2	0.429
Hemoglobin (g/dl)	12.0 ± 2.3	11.6 ± 1.5	0.092
Total lymphocyte count (/mm^3)	1550.2 ± 502	1568.3 ± 508.8	0.746
BMI[d]	21.6 ± 2.7	21.2 ± 2.8	0.008
PNI	48.3 ± 5.1	48.2 ± 4.7	0.934

NAC neoadjuvant chemotherapy, *BMI* body mass index, *PNI* prognostic nutritional index

The values are expressed as the mean and standard deviation

[a]Data not available for one patient

[b]Data not available for four patients

[c]Data not available for 13 patients

[d]Data not available for two patients

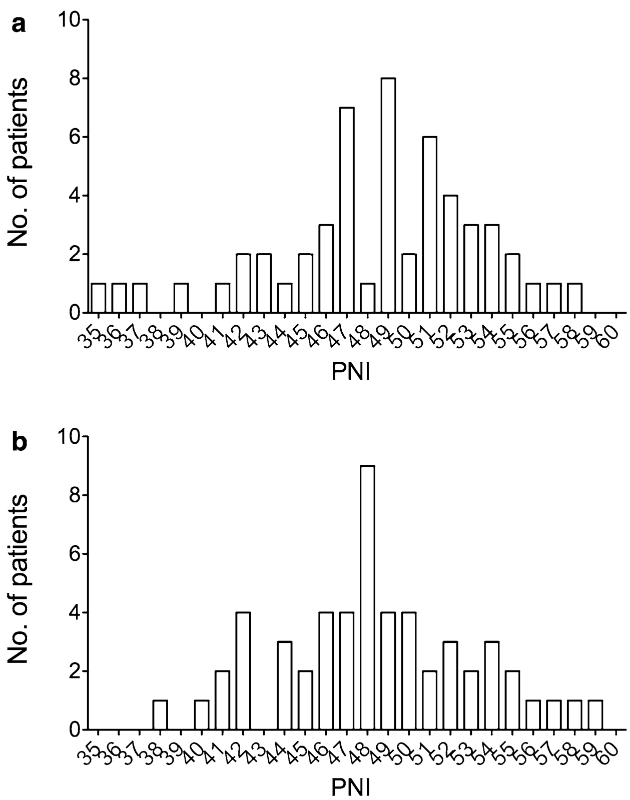

Fig. 1 The distributions of the pre-NAC PNI (**a**) and the preoperative PNI (**b**)

survival (Table 3). A decrease in the serum albumin levels and the PNI after NAC was associated with a reduced OS rate. The 3-year OS rate was 76.4% in the patients with a maintained or increased PNI and 41% in the patients with a decreased PNI ($p = 0.003$; Fig. 3a). The clinical response to chemotherapy was not associated with the OS rate (Table 3). The 3-year DSS and RFS rates were also

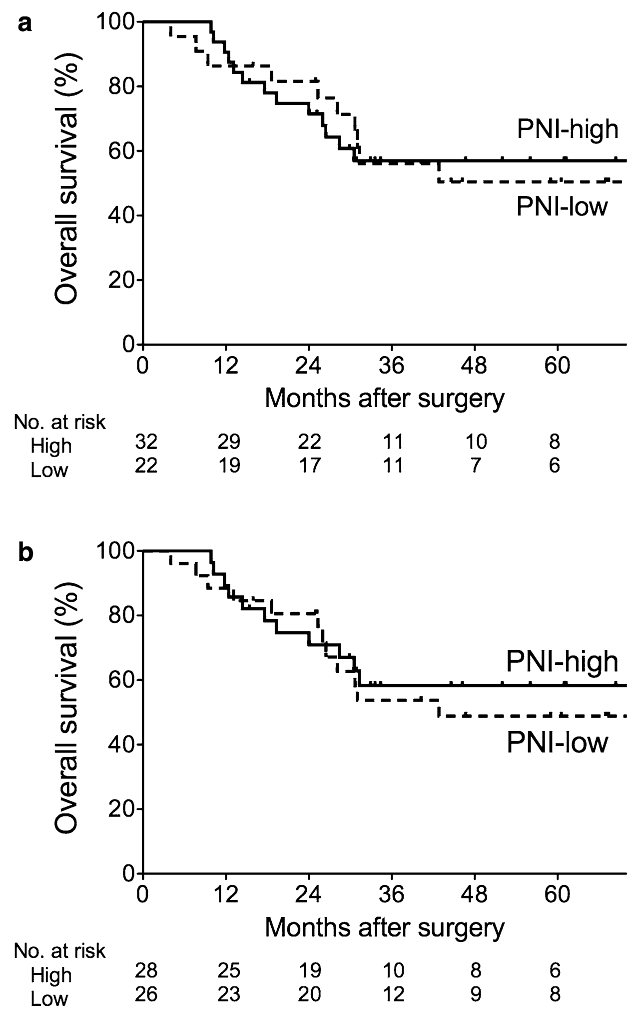

Fig. 2 The Kaplan–Meier estimates of the overall survival according to the pre-NAC PNI (**a**, $p = 0.9$) and the preoperative PNI (**b**, $p = 0.535$)

Table 3 The changes in the nutritional and immunological parameters, clinical response to NAC and the postoperative survival

Variables	*N*	3-year OS rate	*p* value
Total protein			
Maintained or increased	21	58.7	0.403
Decreased	32	55.9	
Albumin			
Maintained or increased	29	64.3	0.046
Decreased	25	46.8	
Cholinesterase			
Maintained or increased	11	71.6	0.490
Decreased	39	53.7	
Total cholesterol			
Maintained or increased	13	59.3	0.564
Decreased	28	47.4	
Hemoglobin			
Maintained or increased	18	67.5	0.409
Decreased	36	51	
Total lymphocyte count			
Maintained or increased	29	56.4	0.779
Decreased	25	56.2	
BMI			
Maintained or increased	21	59.2	0.392
Decreased	31	54.8	
PNI			
Maintained or increased	23	76.4	0.003
Decreased	31	41	
Clinical response of the primary tumor to NAC[a]			
CR, PR	13	75.5	0.116
SD, PD	33	50.3	

NAC neoadjuvant chemotherapy, *OS* overall survival, *BMI* body mass index, *PNI* prognostic nutritional index, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

[a]According to the criteria of the Japanese Gastric Cancer Association

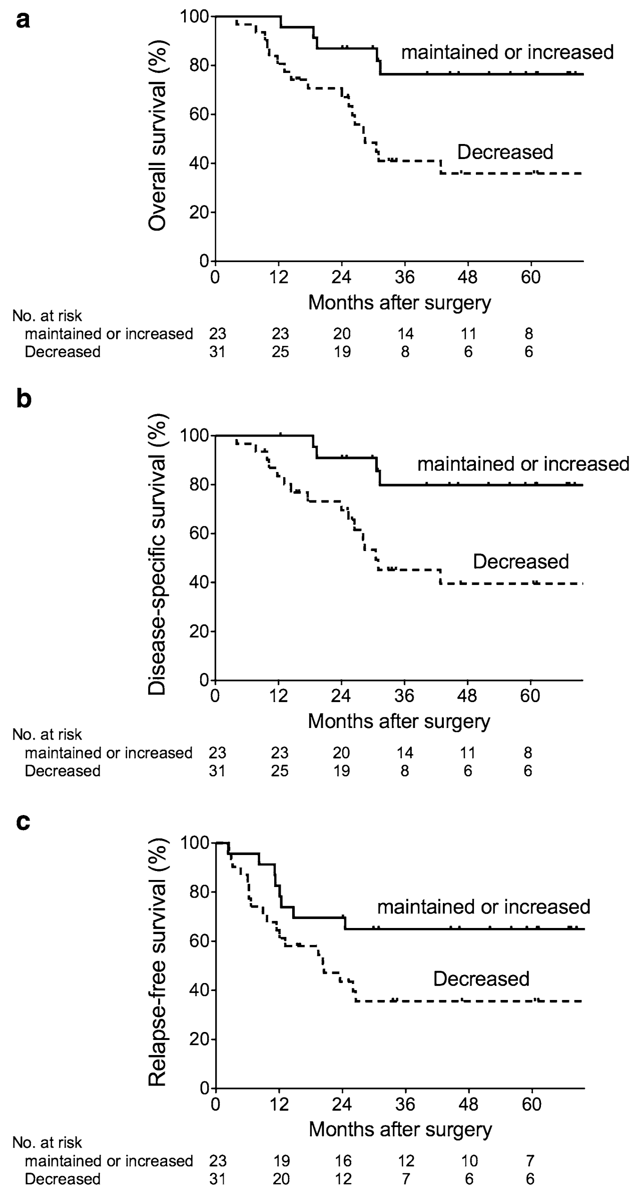

Fig. 3 The Kaplan–Meier estimates of the overall survival (**a**, $p=0.003$), disease-specific survival (**b**, $p=0.005$) and relapse-free survival (**c**, $p=0.047$) according to the changes in the PNI

significantly lower in the patients with a decreased PNI than in the patients with an increased PNI (DSS; 45.1 vs. 79.9%, $p=0.005$, RFS; 35.6 vs. 64.9%, $p=0.047$). At the time of the final follow-up, 24 (44.4%) patients had died; these included 5 (21.7%) of the 23 patients with a maintained or increased PNI and 19 (61.3%) of the 31 patients with a decreased PNI ($p=0.004$).

According to a univariate analysis of the factors associated with the OS, the HR for a decreased PNI was 3.99 (95% CI 1.48–10.71, $p=0.006$). The other factors correlated with the OS were the pathological tumor depth ($p=0.093$), pathological lymph node metastasis ($p=0.078$) and pathological distant metastasis ($p=0.011$). A multivariate analysis revealed that the change in the PNI was an independent predictor of the OS ($p=0.006$; Table 4). The change in the PNI was also an independent predictor of the DSS but not the RFS. In the univariate analysis of the OS, DSS and RFS, the HR for the clinical response to chemotherapy of SD and PD was 2.61 (95% CI 0.75–9.01, $p=0.13$), 3.44 (95% CI 0.77–15.15, $p=0.105$), 3.36 (95% CI 0.99–11.36, $p=0.052$), respectively. The clinical response to chemotherapy was not found to be an independent predictor of the RFS.

We then evaluated the relationship between the change in the PNI and the clinicopathological characteristics of the patients (Table 5). The patients with a decreased PNI were more likely to have distant metastasis ($p=0.008$)

Table 4 The results of the multivariate survival analysis

Variables	Overall survival		Disease-specific survival		Relapse-free survival	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Clinical response of primary tumor to NAC[a]						
CR, PR	–	–	–	–	1	
SD, PD					1.26 (0.31–5.08)	0.746
Pathological tumor depth						
T0, T1, T2	1		1		1	
T3, T4	2.52 (0.74–8.59)	0.139	3.26 (0.75–14.19)	0.116	3.44 (0.98–12.1)	0.055
Pathological lymph node metastasis						
Negative	1		1		1	
Positive	3.58 (0.99–12.93)	0.051	8.19 (1.08–62.09)	0.042	2.91 (0.73–11.56)	0.129
Pathological distant metastasis						
No	1		1		1	
Yes	1.74 (0.66–4.62)	0.267	1.63 (0.56–4.72)	0.368	3.54 (1.1–11.44)	0.034
Change of PNI						
Increased or maintained	1		1		1	
Decreased	4.4 (1.53–12.62)	0.006	4.75 (1.5–15.08)	0.008	1.58 (0.6–4.19)	0.355

CI confidence interval, *NAC* neoadjuvant chemotherapy, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *PNI* prognostic nutritional index

[a]According to the criteria of the Japanese Gastric Cancer Association

than the patients with an increased PNI. In addition, a decreased PNI was more commonly observed in patients whose duration from the last day of NAC to the operation was <20 days than in patients whose duration was ≥20 days ($p = 0.026$).

Discussion

Much attention has recently been paid to the prognostic impact of the nutritional and immunological indices in cancer patients. In the present study, we evaluated the prognostic value of the PNI in the patients with gastric cancer who underwent NAC and subsequent R0 gastrectomy. Several studies have shown that the PNI is a reliable predictor of the long-term postoperative outcomes in patients with gastric cancer [8, 9]. We also reported that the preoperative PNI was an independent predictor of long-term survival in gastric cancer patients, and suggested that patients with a low preoperative PNI are at higher risk for both gastric cancer death and non-cancer death [4]. Although these studies included patients who underwent preoperative chemotherapy, the prognostic value of the PNI in the patients who underwent NAC remains unclear. In the present study, the PNI was decreased after NAC in more than half of the patients, although there was no significant difference between the mean pre-NAC value and the preoperative value. The OS rate was significantly lower in the patients with a decreased PNI than in the patients in whom the PNI was maintained or increased. Furthermore, the multivariate analysis revealed that a decreased PNI was an independent predictor of poor OS. Thus, the change in the PNI can be a reliable predictor of the long-term outcome in gastric cancer patients undergoing NAC.

In the present study, the cutoff value of the PNI was set at 48, as reported previously [4], and we found no association of the pre-NAC PNI value and the preoperative value with the OS. Regardless of the cutoff values of the PNI, neither the pre-NAC PNI nor the preoperative PNI was significantly associated with the OS (data not shown). Therefore, the change in the PNI value may be more important to consider in patients undergoing NAC than the PNI value itself.

The present study clearly demonstrated that a decreased PNI after NAC predicts a poorer oncological outcome in patients with gastric cancer. A recent deterioration in nutritional status has been associated with shorter survival times in several types of cancer. Previous studies have shown that preoperative body weight loss is an independent predictor of the postoperative prognosis in gastric cancer [1, 6]. In addition, body weight loss at presentation was identified as an independent prognostic factor in gastrointestinal cancer patients who had undergone chemotherapy [2]. Thus far, there is little data about the prognostic impact of a change in the PNI. One study investigated the impact of the change from the preoperative PNI to the postoperative

Table 5 The relationship between the change in the PNI and the clinicopathological characteristics of the patients

Variables	Change of the PNI		*p* value
	Increased (*n* = 23, %)	Decreased (*n* = 31, %)	
Age (years)[a]	60.7 ± 9.1	65.3 ± 9	0.071[e]
Sex			
Male	18 (78.3)	23 (74.2)	0.730[f]
Female	5 (21.7)	8 (25.8)	
Clinical tumor stage[b]			
II	7 (30.4)	5 (16.1)	0.211[f]
III, IV	16 (69.6)	26 (83.9)	
Clinical response of the primary tumor to NAC[c]			
CR, PR	7 (33.3)	6 (24)	0.484[f]
SD, PD	14 (66.7)	19 (76)	
Pathological tumor depth			
T0, T1, T2	5 (21.7)	9 (29)	0.545[f]
T3, T4	18 (78.3)	22 (71)	
Pathological lymph node metastasis			
Negative	5 (21.7)	7 (22.6)	0.941[f]
Positive	18 (78.3)	24 (77.4)	
Pathological distant metastasis			
Negative	23 (100)	23 (74.2)	0.008[g]
Positive	0 (0)	8 (25.8)	
Pathological stage[b]			
CR, I, II	11 (47.8)	7 (22.6)	0.052[f]
III, IV	12 (52.2)	24 (77.4)	
Pathological response to NAC[d]			
Grade 0, 1a	14 (60.9)	17 (54.8)	0.658[f]
Grade 1b, 2, 3	9 (39.1)	14 (45.2)	
Grade ≥ 3 adverse events following NAC			
No	15 (65.2)	26 (83.9)	0.113[f]
Yes	8 (34.8)	5 (16.1)	
Duration from the end of NAC to gastrectomy (days)			
<20	5 (21.7)	16 (51.6)	0.026[f]
≥20	18 (78.3)	15 (48.4)	
Postoperative complications			
Any	5 (21.7)	11 (35.5)	0.274[f]
Pancreatic fistula	2 (8.7)	5 (16.1)	
Anastomotic leakage	0 (0)	2 (6.5)	
Ileus	2 (8.7)	0 (0)	
Delayed gastric emptying	1 (4.3)	1 (3.2)	
Lymphorrhea	0 (0)	1 (3.2)	
Wound infection	0 (0)	1 (3.2)	
Pneumonia	1 (4.3)	1 (3.2)	
Enterocolitis	0 (0)	1 (3.2)	

PNI prognostic nutritional index, *NAC* neoadjuvant chemotherapy, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

[a]The value is expressed as the mean and standard deviation

[b]According to the third edition of the Japanese Classification of Gastric Carcinoma

[c]According to the criteria of the Japanese Gastric Cancer Association

[d]According to the histological evaluation criteria of the Japanese Gastric Cancer Association

[e]Indicates a value obtained from the *t*- est

[f]Indicates a value obtained from a Chi-squared test

[g]Indicates a value obtained from Fisher's exact test

PNI in patients with hepatocellular carcinoma, and found that a decreased PNI was independently associated with poor overall and relapse-free survival [22]. The present study also demonstrated that a decreased PNI value after NAC was independently associated with poor OS. Furthermore, the DSS rate was also significantly lower in the patients with a decreased PNI in comparison to those in whom the PNI was maintained or increased, and the change in the PNI was also identified as an independent predictor of the DSS. These results indicate that the ongoing deterioration of the nutritional and immunological status after NAC increases the risk of gastric cancer death. However, the change in the PNI was not an independent predictor of the RFS. Further investigations will be required to determine the reason underlying the relatively poor prognosis in the patients with a decreased PNI.

Chemotherapy has the potential to worsen a patient's nutritional status due to chemotherapy-related toxicities [16, 17], but chemotherapy can improve the nutritional status by reducing the tumor bulk [5, 18]. To date, the influence of NAC on the nutritional and immunological status of gastric cancer patients has remained uncertain. In esophageal cancer, some studies have demonstrated significant decreases in various nutritional parameters, such as albumin, prealbumin, transferrin and hemoglobin, after preoperative chemotherapy [16, 17]. In the present study, we observed significant declines in the cholinesterase levels and BMI values after NAC. These results suggest that NAC may have a negative impact on the nutritional status of patients with gastric cancer.

Many factors seem to affect the nutritional and immunological status of the patients receiving NAC. In the present study, we investigated the relationship between the change in the PNI and various clinicopathological characteristics in patients with gastric cancer. The patients with a decreased PNI were more likely to have distant metastasis than those in whom the PNI was maintained or increased. These results suggest that it may be difficult to maintain the nutritional and immunological status of patients with more advanced disease. On the other hand, previous studies have suggested that the effect of chemotherapy on the nutritional status in responders to chemotherapy differs to that in non-responders. Qiu et al. showed that among patients with stage IV gastric cancer, in comparison to non-responders, responders to chemotherapy more frequently showed an improved nutritional status [5]. Steyn et al. reported that there was a weight increase in the majority of patients who responded to NAC for esophageal cancer, whereas non-responders tended to lose weight [18]. In contrast to these studies, the present study found no significant correlation between the change in the PNI and the clinical and pathological responses to NAC. Further studies are needed to clarify the mechanism(s) involved in the change in the PNI after NAC in gastric cancer patients.

Based on our findings, the maintenance of the PNI during NAC may be of great importance in avoiding worse long-term outcomes in patients with gastric cancer, even if their oral food intake is sufficient. Recently, several investigators have demonstrated that supplemental immunonutrition containing n-3 polyunsaturated fatty acids was able to maintain and/or improve the nutritional status of the patients receiving chemotherapy [23, 24]. Furthermore, immunonutrition has been shown to improve the response rate to chemotherapy, and is suggested to have the potential to prolong the survival time [25]. In addition, individual nutritional counseling and advice are essential to maintaining the nutritional status [26, 27]. More recently, it has been suggested that the administration of synthetic ghrelin is effective for treating appetite loss and body weight loss [28]. In the present study, the PNI was increased in 3 (75%) of the 4 patients who received planned preoperative nutrient supplementations. However, the effects of nutritional intervention during NAC on the change in the PNI and the long-term outcomes of cancer patients remain unclear. Thus, further trials are required to clarify whether nutritional intervention during NAC maintains and/or improves the nutritional and immunological parameters and thereby contributes to prolonging the survival time of gastric cancer patients. In addition, the present study showed that patients in whom the duration between the end of NAC and gastrectomy was <20 days more frequently showed a decreased PNI than the patients with a duration of ≥20 days. These results suggest that an adequate interval between the completion of NAC and gastrectomy may also be important to recover the nutritional and immunological status at gastrectomy.

The present study is associated with some limitations. Firstly, it was a retrospective analysis with a small study population. Second, the patients received various chemotherapeutic regimens. Furthermore, the timing of the operation was determined by each surgeon without any clear criteria, based instead on the patient's general condition, the extent of adverse events from chemotherapy, patient requests, and other related factors. These limitations make it difficult to draw any definite conclusions. Further investigations are therefore needed to validate our results.

In conclusion, the present study demonstrated that a decreased PNI was associated with a worse long-term outcome in gastric cancer patients who received NAC. Our results confirmed that the nutritional and immunological status should be considered, and suggested that nutritional intervention is necessary for gastric cancer patients undergoing NAC, even if their oral intake is sufficient.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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