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Value of Prognostic Nutritional Index as a Predictor of Lymph Node Metastasis in Gastric Cancer

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Abstract. *Background/Aim: This study examined whether the prognostic nutritional index (PNI) is a useful predictor of pathological lymph node metastasis (pN+) in gastric cancer (GC). Patients and Methods: This study retrospectively examined 167 patients with advanced GC (cT2-T4) undergoing curative gastrectomy. The predictive ability of PNI for pN+ was evaluated in comparison with that of clinical lymph node metastasis (cN+) determined by computed tomography (CT). Results: The optimal cut-off value of PNI for predicting pN+ was 46 according to the receiver operating characteristic curve analysis. Multivariate analysis revealed a PNI<46 [odds ratio (OR)=2.905; 95% confidence interval (CI)=1.347-6.638, p=0.006], cN+ (OR=2.323; 95%CI=1.204-4.579, p=0.012), and undifferentiated-type adenocarcinoma (OR=2.032; 95%CI=1.060-3.947, p=0.033) to be independent predictors of pN+. PNI detected pN+ with a higher specificity (84.9%) and positive predictive value (PPV) (75.6%) than cN+ (68.5% and 68.1%, respectively). When the subjects were limited to patients with cN+, the specificity and PPV of a PNI<46 for pN+ became markedly high (91.3% and 90.5%, respectively). Conclusion: PNI predicts pN+ with a high specificity in patients with a clinical diagnosis of advanced GC; therefore, PNI may aid in the definitive diagnosis of pN+, especially in combination with CT findings.*

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer death worldwide (1). Recent advances in surgical techniques have improved the short- and long-term outcomes of patients with GC; however, the incidence of pathological lymph node metastasis (pN+) in advanced GC is high, and patients with pN+ frequently develop cancer recurrence even after curative resection (2, 3). Therefore, perioperative adjuvant chemotherapy should be performed in such patients (4). In east Asia, although standard adjuvant care is postoperative chemotherapy alone (5, 6), it is being investigated whether addition of neoadjuvant chemotherapy (NAC) further improves survival of patients with a clinical diagnosis of advanced GC with lymph node metastasis (cN+).

Precise prediction of pN+ is essential to plan the optimal treatment strategy for GC. The assessment of cN+ is generally performed by computed tomography (CT), but the diagnostic accuracy can be improved through the development of additional diagnostic tools (3, 7, 8). The immuno-nutritional status of patients is closely associated with the extent of GC progression (9-11); therefore, the prognostic nutritional index (PNI) may be a novel predictor of pN+ in GC. Onodera's PNI, calculated from serum albumin (Alb) and peripheral total lymphocyte counts (TLC), was found to be associated with postoperative short- and long-term outcomes in several malignancies (12-14); however, its clinical value for the prediction of pN+ in GC patients remains unclear.

The present study investigated whether Onodera's PNI can predict pN+ in patients with a clinical diagnosis of advanced GC. The diagnostic power of PNI for pN+ was compared with that of cN+ determined by CT findings. Thus, the aim of this study was to examine whether PNI alone or in combination with CT findings can aid in the precise screening of GC patients with pN+ before surgery.

Patients and Methods

Patients. Between January 2008 and May 2013, 578 patients received surgical treatment for GC at the Division of Digestive Surgery of Kyoto Prefectural University of Medicine (KPUM) in Japan. Of these, the present study targeted only patients with a clinical diagnosis of advanced GC (cT2-T4) who underwent

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preoperative CT followed by curative gastrectomy (R0). To remove the potential influences of treatment factors on the stage of disease and diagnostic accuracy for pN+, patients who underwent NAC and those undergoing non-curative gastrectomy (R1/R2) were excluded. Patients having distant metastasis of GC and those with simultaneous malignancies other than GC were also excluded. In total, 167 patients were included in this retrospective study. The present study conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. Patients granted written informed consent for surgery and the use of clinical data, which was approved by the institutional review board of our institute (ERB-C-1373).

Patient and tumor characteristics. The following patient and tumor characteristics were obtained from the medical records: sex, age, smoking history, comorbid diseases (hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic liver disease, and chronic renal failure), Borrmann type, tumor differentiation (differentiated- or undifferentiated-type adenocarcinoma), tumor location, clinical T stage (cT), clinical N stage (cN), Onodera's PNI, pathological T stage (pT), and pathological N stage (pN).

Assessment of Onodera's PNI. Alb and TLC were measured within one week before surgery, and Onodera's PNI was calculated as 10×Alb (g/dl)+0.005×TLC (per mm^3) (15).

Evaluation of the cT and cN. All patients underwent upper endoscopy, upper gastrointestinal X-ray (fluoroscopy) using contrast media such as barium, and chest and abdominal CT before surgery. The cT was diagnosed using the gastroscopy and CT findings by gastroenterologists and radiologists, respectively. On the other hand, the cN was diagnosed using the CT findings by at least two radiologists. CT was performed at KPUM or Oike clinic (Kyoto, Japan), a consociated medical center, employing a multidetector CT with 64 or 320 layers. Contrast-enhanced CT (CECT) with iopamidol or iohexol was the recommended standard; however, patients who had iodine allergy, active asthma, or severe thyroid, heart, liver or renal disease did not undergo CECT. Lymph nodes having a minor axis of 8 mm or greater or a major axis of 10 mm or greater on CT were regarded as "cN+" according to previous studies (3, 7, 8). In this study, none of the patients underwent endoscopic ultrasound (EUS) for the assessment of cN.

Evaluation of the pT and pN. Gastrectomy with lymphadenectomy was performed according to the Japanese GC treatment guidelines (JGCTG) (16). Resected specimens were microscopically examined by at least two pathologists, and pT and pN were evaluated based on the current Japanese classification of gastric carcinoma (JCGC) (17).

Statistical analysis. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value of Onodera's PNI to predict pN+. Goodness of fit was assessed by the area under the curve (AUC), and the optimal cut-off value was determined using the Youden index. Differences between the two groups were analyzed by the χ^2-test for categorical variables and the Student's *t*-test for continuous variables. In the analyses of associated factors for pN+, clinical variables with $p<0.05$ in univariate analyses were entered into the multiple logistic regression model to identify independent factors. All statistical analyses were performed with JMP 12 (SAS Institute, Cary, NC, USA), and $p<0.05$ was considered to indicate statistically significant differences.

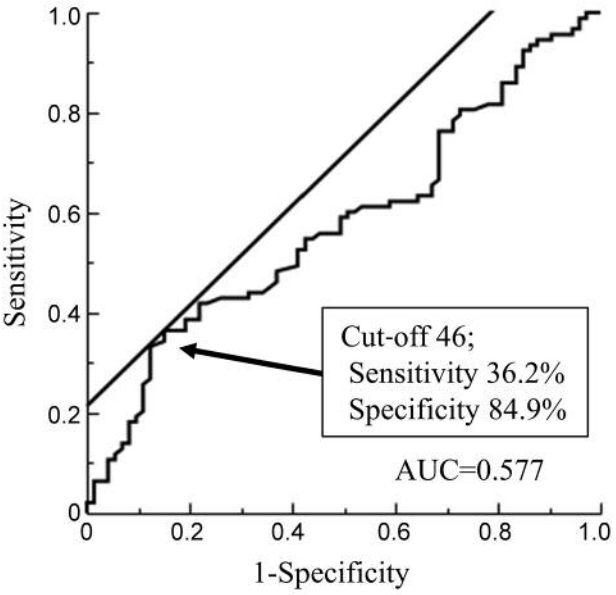

Figure 1. *ROC curve for PNI as a predictive factor for pN+ in patients with clinical diagnosis with advanced gastric cancer. ROC: Receiver operating characteristic; PNI: prognostic nutritional index; AUC: area under the curve.*

Results

Patient characteristics. The clinicopathological characteristics of the 167 patients with a clinical diagnosis of advanced GC are summarized in Table I. Patients were pathologically diagnosed with pT1 (n=33) or pT2-T4 (n=134). Although 73 patients (43.7%) were diagnosed with cN+, the number of patients actually diagnosed with pN+ was 94 (56.3%). The preoperative value of Onodera's PNI ranged from 26.1 to 66.2 (median, 49.5).

ROC curve analysis. The AUC value indicating the predictive power of Onodera's PNI for pN+ was 0.577, and the optimal cut-off value of preoperative PNI for predicting pN+ was 46 (sensitivity, 36.2%; specificity, 84.9%) (Figure 1). Then, all patients were divided into the two groups according to the preoperative PNI value: the low PNI (PNI<46) or high PNI (PNI≥46) group.

Clinicopathological factors associated with preoperative PNI. The differences in the clinicopathological factors

Table I. *Clinicopathological characteristics of patients*.

	All patients (n=167)	PNI<46 (n=45)	PNI≥46 (n=122)	*p*-Value
Clinical characteristics				
Gender, n (%)				0.974
Male	111 (66.5)	30 (66.7)	81 (66.5)	
Female	56 (33.5)	15 (33.3)	41 (33.5)	
Age (years)				0.002
Median (range)	69 (29-89)	73 (56-85)	68 (29-89)	
Mean±SD	67.7±11.6	72.2±8.0	66.1±12.3	
Smoking history				0.557
Present	73 (43.7)	18 (40.0)	55 (45.1)	
Absent	94 (56.3)	27 (60.0)	67 (54.9)	
Hypertension				0.681
Present	48 (28.7)	14 (31.1)	34 (27.9)	
Absent	119 (71.3)	31 (68.9)	88 (72.1)	
Diabetes mellitus				0.143
Present	29 (17.4)	11 (24.4)	18 (14.8)	
Absent	138 (82.6)	34 (75.6)	104 (85.2)	
Cardiovascular disease				0.006
Present	25 (15.0)	13 (28.9)	12 (9.8)	
Absent	142 (85.0)	32 (71.1)	110 (90.2)	
Cerebrovascular disease				0.309
Present	12 (7.2)	5 (11.1)	7 (5.7)	
Absent	155 (92.8)	40 (88.9)	115 (94.3)	
Chronic liver disease				1.000
Present	5 (3.0)	1 (2.2)	4 (3.3)	
Absent	162 (97.0)	44 (97.8)	118 (96.7)	
Chronic renal failure				0.345
Present	6 (3.6)	3 (6.7)	3 (2.5)	
Absent	161 (96.4)	42 (93.3)	119 (97.5)	
Borrmann type				0.053
0	28 (16.8)	2 (4.4)	26 (21.3)	
1	17 (10.2)	7 (16.6)	10 (8.2)	
2	44 (26.4)	11 (24.4)	33 (27.0)	
3	61 (36.5)	18 (40.0)	43 (35.3)	
4	17 (10.1)	7 (15.6)	10 (8.2)	
Tumor differentiation				0.065
Differentiated type	79 (47.3)	16 (35.6)	63 (51.6)	
Undifferentiated type	88 (52.7)	29 (64.4)	59 (48.4)	
Tumor location, n (%)				0.084
Upper	46 (27.6)	10 (22.2)	36 (29.5)	
Middle	55 (32.9)	11 (24.4)	44 (36.1)	
Lower	66 (39.5)	24 (53.4)	42 (34.4)	
cT, n (%)				0.011
T2	117 (70.0)	26 (57.8)	91 (74.6)	
T3	41 (24.6)	13 (28.9)	28 (22.9)	
T4	9 (5.4)	6 (13.3)	3 (2.5)	
cN, n (%)				0.671
N0 (negative)	94 (56.3)	23 (51.1)	71 (58.2)	
N+ (positive)	73 (43.7)	22 (48.9)	51 (41.8)	
PNI				<0.001
Median (range)	49.5 (26.1-66.2)	43.5 (26.1-45.9)	51.5 (46.1-66.2)	
Mean±SD	49.5±6.2	42.1±4.4	52.3±4.1	
Pathological characteristics				
pT, n (%)				0.284
T1	33 (19.8)	6 (13.3)	27 (22.1)	
T2	36 (21.6)	9 (20.0)	27 (22.1)	
T3	52 (31.1)	13 (28.9)	39 (32.0)	
T4	46 (27.5)	17 (37.8)	29 (23.8)	
pN, n (%)				0.002
N0 (negative)	73 (43.7)	11 (24.4)	62 (50.8)	
N+ (positive)	94 (56.3)	34 (75.6)	60 (49.2)	

SD: Standard deviation; cT: clinical T stage; cN: clinical lymph node metastasis; PNI: prognostic nutritional index; pT: pathological T stage; pN: pathological lymph node metastasis.

between the low and high PNI groups are summarized in Table I. Low PNI (PNI<46) was significantly associated with older age, presence of cardiovascular disease, advanced cT category, and pN+. Although the differences were not statistically significant, low PNI tended to correlate with Borrmann Type, tumor differentiation, and tumor location. However, preoperative PNI did not show significant correlation with cN and pT.

Clinical factors associated with pN+. The univariate and multivariate analyses of clinical factors associated with pN+ in patients with a clinical diagnosis of advanced GC are shown in Table II. pN+ was significantly associated with undifferentiated-type adenocarcinoma, cN+ and low PNI in the univariate analysis. The multivariate analysis identified tumor differentiation [odds ratio (OR)=2.032; 95% confidence interval (CI)=1.060-3.947, p=0.033], cN (OR=2.323; 95%CI=1.204-4.579, p=0.012) and PNI (OR=2.905; 95%CI=1.347-6.638, p=0.006) as independent associated factors.

Clinical value of Onodera's PNI for the prediction of pN+. The diagnostic accuracy of preoperative PNI and cN+ for pN+ in patients with a clinical diagnosis of advanced GC is presented in Table III. The sensitivity and specificity of PNI for pN+ were 36.2% and 84.9%, respectively. Thus, the sensitivity was lower and the specificity was higher than those (sensitivity; 52.1%, and specificity; 68.5%) of cN+ determined by the CT findings. To further explore the clinical value of PNI as a complementary diagnostic tool to CT, the diagnostic accuracies of PNI for pN+ were separately examined according to the cN status (Table IV). When the subjects were limited to patients with cN+, the specificity and positive predictive value (PPV) for pN+ became markedly high (91.3% and 90.5%, respectively). Even in patients with cN0, the specificity and PPV for pN+ were 82.0% and 62.5%, respectively.

Table II. *Associated clinical factors for pN+.*

Variables	Pathological lymph node metastasis							
	Univariate analysis					Multivariate analysis		
	pN+		pN0		*p*-Value	OR	95%CI	*p*-Value
	n (94)	%	n (73)	%				
Gender					0.139			
Male	58	61.7	53	72.6				
Female	36	38.3	20	27.4				
Age					0.405			
<65	29	30.9	27	37.0				
≥65	65	69.1	46	63.0				
Smoking history					0.978			
Present	41	43.6	32	43.8				
Absent	53	56.4	41	56.2				
Hypertension					0.995			
Present	27	28.7	21	28.8				
Absent	67	71.3	52	71.2				
Diabetes mellitus					0.586			
Present	15	16.0	14	19.2				
Absent	79	84.0	59	80.8				
Cardiovascular disease					0.685			
Present	15	16.0	10	13.7				
Absent	79	84.0	63	86.3				
Cerebrovascular disease					1.000			
Present	7	7.4	5	6.9				
Absent	87	92.6	68	93.1				
Chronic liver disease					-			
Present	0	0.0	5	6.9				
Absent	94	100.0	68	93.1				
Chronic renal failure					1.000			
Present	3	3.2	3	4.1				
Absent	91	96.8	70	95.9				
Borrmann type					0.512			
0/1/2	48	51.1	41	56.2				
3/4	46	48.9	32	43.8				
Tumor differentiation					0.020			0.033
Differentiated type	37	39.4	42	57.5		1		
Undifferentiated type	57	60.6	31	42.5		2.032	1.060-3.947	
Tumor location					0.914			
Upper	34	36.2	27	37.0				
Middle/Lower	60	63.8	46	63.0				
cT					0.771			
T2	65	69.2	52	71.2				
T3/T4	29	30.8	21	28.8				
cN					0.013			0.012
N0	45	47.9	49	67.1		1		
N+	49	52.1	24	32.9		2.323	1.204-4.579	
PNI					0.002			0.006
Low (<46)	34	36.2	11	15.1		2.905	1.347-6.638	
High (>46)	60	63.8	62	84.9		1		

PNI: Prognostic nutritional index; cT: clinical T stage; cN: clinical lymph node metastasis; pN: pathological lymph node metastasis.

Discussion

Onodera's PNI, originally developed as a predictor of complications after colorectal cancer surgery in Japan, is increasingly used for hospitalized patients to evaluate the immuno-nutritional status (15). The PNI is readily available by blood tests only, and a PNI value of at least 50 is categorized as normal nutritional status, with values between

Table III. *Diagnostic accuracy of cN+ and PNI for pN+.*

A: cN+ determined by the CT findings

	pN+	pN0	n
cN+	49	23	72
cN0	45	50	95
n	94	73	167

B: PNI

	pN+	pN0	n
Low PNI (<46)	34	11	45
High PNI (>46)	60	62	122
n	94	73	167

C: Diagnostic accuracy for pN+

	Pathological lymph node metastasis	
	cN+ (CT findings)	PNI
Sensitivity	52.1%	36.2%
Specificity	68.5%	84.9%
Positive predictive value	68.1%	75.6%
Negative predictive value	52.6%	50.8%

PNI: Prognostic nutritional index; CT: computed tomography.

Table IV. *Diagnostic accuracy of PNI for pN+ separately examined according to cN in patients with advanced gastric cancer.*

A: cN+

	pN+	pN0	n
Low PNI (<46)	19	2	21
High PNI (>46)	30	21	51
n	49	23	72

	Pathological lymph node metastasis PNI
Sensitivity	38.8%
Specificity	91.3%
Positive predictive value	90.5%
Negative predictive value	41.2%

B: cN0

	pN+	pN0	n
Low PNI (<46)	15	9	24
High PNI (>46)	30	41	71
n	45	50	95

	Pathological lymph node metastasis PNI
Sensitivity	33.3%
Specificity	82.0%
Positive predictive value	62.5%
Negative predictive value	57.7%

PNI: Prognostic nutritional index.

45 and 50 indicating mild malnutrition, values between 40 and 45 indicating moderate to severe malnutrition, and values lower than 40 indicating serious malnutrition. The present study set the optimal cut-off value of PNI for predicting pN+ at 46 according to the ROC curve analysis, which reflects mild to moderate malnutrition.

When the cut-off value was set at 46, preoperative PNI was identified to be an independent predictor for pN+ in patients with a clinical diagnosis of advanced GC (cT2-T4). Meanwhile, when targeting 280 patients with a clinical diagnosis of early GC (cT1) who underwent curative gastrectomy at KPUM in the same study period, a PNI<46 was not useful in the prediction of pN+ (data not shown). In patients with cT2-T4, a PNI<46 detected pN+ with a lower sensitivity and higher specificity than cN+ determined by the CT findings. Accordingly, a low PNI can be useful for the definitive diagnosis of pN+ in advanced GC, whereas care should be taken for the high occurrence of false-negatives when using PNI alone for the prediction of pN+. Because cN+ was also identified to be an independent predictor for pN+, it may be more beneficial if preoperative PNI is used in combination with the CT findings. Notably, when the subjects were limited to those with cT2-T4 with cN+, the sensitivity and PPV for pN+ increased further (91.3% and 90.5%, respectively).

Preoperative PNI may aid in clarifying the extent of lymph node dissection. Based on the high specificity and PPV for pN+, patients with a PNI<46 and/or cN+ should be treated with D2 lymphadenectomy as determined by the JGCTG (16). On the other hand, low PNI may also be associated with the occurrence of postoperative complications due to tissue vulnerability, impaired wound healing and high susceptibility to infection (9-11). Kanda *et al*. have previously identified PNI<47 as an independent predictor of postoperative morbidity in GC patients undergoing R0 (9). However, Sakurai *et al*. have reported that PNI<45 was not significantly associated with the occurrence of postoperative intra-abdominal complications in GC patients undergoing R0 (10). Although the influence of PNI on the occurrence of postoperative morbidity must be discussed further, surgeons should carefully proceed with R0 under the assumption of pN+, and provide detailed perioperative management, including nutritional support, especially for advanced GC patients with low PNI and cN+ (18-20).

When the ideal target of NAC is advanced GC with pN+, PNI may aid in the definitive selection of reliable candidates among advanced GC patients with cN+. In particular, when considering the use of highly toxic chemotherapeutic agents, the clinical PNI value can be considerable because of the minimal occurrence of false-positives. Many researchers have previously demonstrated that PNI can be a predictor of overall and cancer-specific survival in patients with GC, independent of the pathological stage of GC (9-11). Therefore, a low PNI itself may be a better indication for NAC. However, Kanda *et al*. have found that advanced GC patients with PNI<47 received no survival benefit from postoperative adjuvant chemotherapy because of further deterioration of immunocompetence induced by the adverse effects of chemotherapy that accelerated tumor progression (9). Although the regimen, intensity, and effects of adjuvant chemotherapy may differ between preoperative and postoperative treatments, it should be performed with effective nutritional support in order to prevent further deterioration of the immuno-nutritional status of patients with a low PNI.

The present study has some limitations. This was a retrospective study with a small sample size, which may limit the statistical power and generate statistical bias. Although the optimal cut-off value of PNI for predicting pN+ was set at 46 in this study, the lower sensitivity is a problem to be solved. Furthermore, the present study did not reveal specific measures to improve the short- and long-term outcomes of GC patients with low PNI. However, to the best of our knowledge, this study is the first to present the novel potential of PNI for the prediction of pN+ in patients with clinical diagnosis of advanced GC. Notably, in combination with the CT findings, PNI may aid in the definitive diagnosis of pN+ with a markedly high specificity and PPV. The results of the present study, as well as the optimal cut-off value of PNI, need to be validated in further studies with large sample sizes for the precise screening of GC patients with pN+ before surgery.

Conclusion

Onodera's PNI was able to predict pN+ with a high specificity in patients with clinical diagnosis of advanced GC; therefore, PNI may aid in the definitive diagnosis of pN+, especially in combination with CT findings.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

Study conception and design: T Kosuga; Acquisition of data: T Kosuga, T Konishi; Analysis and interpretation of data: T Kosuga, T Konishi, T Kubota, KS, HK, AS, KO, HF, MK, TA, RM, YM, YK, HI, MN; Drafting of manuscript: T Kosuga, and T Konishi; Critical revision of manuscript: EO.

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