Predictive Value of the Prognostic Nutritional Index in Neoadjuvant Chemoradiotherapy for Rectal Cancer

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Abstract. Background/Aim: Prognostic nutritional index (PNI) and neutrophil-to-lymphocyte ratio (NLR) indicate nutritional status and host immunity. We used immunohistochemistry and apparent diffusion coefficient (ADC) values calculated using diffusion-weighted imaging (DWI) to investigate relationships of these factors with pathological and radiological characteristics in rectal cancer treated with neoadjuvant chemoradiotherapy (nCRT). Patients and Methods: We evaluated expression levels of VEGFA, CD8, CD33, and ADC values in tumors pre/post nCRT; and analyzed the relationships between those factors and PNI, NLR in 32 patients. Results: Pretreatment PNI negatively correlated with change in tumor stromal CD8+ T cells and positively correlated with ADC values. Pretreatment NLR and PNI change correlated with recurrence-free survival (RFS). Conclusion: Patients with higher pretreatment PNI had greater changes in ADC values and stromal CD8+ T-cell counts, and those with greater PNI reduction from nCRT had a worse prognosis. Proper nutritional management during nCRT benefits patients and may lead to better prognosis in rectal cancer.

Colorectal cancer (CRC), one of the most common cancers worldwide in terms of morbidity and mortality, whilst being the second most commonly diagnosed cancer in women and the third most in men (1, 2). In locally advanced rectal cancer (LARC), neoadjuvant chemoradiotherapy (nCRT) and radical surgery are currently standard treatments in the North America and Europe (3). In Japan, preoperative chemoradiotherapy (CRT) is applied in some cases to improve R0 resectability to preserve anal sphincter function (3, 4). However, tumor response to nCRT varies individually. Approximately 20% of these patients may not respond to nCRT and even suffer severe side-effects and lose their surgical chance (5). It is thus important to explore ways to predict treatment response and prognosis of patients who undergo nCRT, which will allow the selection of the patients most likely to benefit from nCRT. Survival outcomes of CRC are predicted with tumor-associated factors and host-related factors (6). Tumor-associated factors include tumor-node-metastasis (TNM) stage, tumor location, histological type, and tumor markers (7-9), whereas host-related factors include age, sex, life style, nutritional status,
and systemic inflammatory response (6, 10-12).

Prognostic nutritional index (PNI) is a parameter used to decide the nutritional and immune status of patients with malignant cancers of the gastrointestinal tract and is calculated from the values of serum albumin concentration and peripheral blood lymphocyte count (13). Although some studies have reported PNI to be a good predictor in CRC (12, 14), few reports have addressed how tumors are both pathologically and radiologically affected by PNI in vivo.

The tumor microenvironment has been broadly studied and reported to interfere tumor response to CRT (15). Tumor-infiltrating lymphocytes (TILs), such as CD4, CD8, and CD33 and angiogenic factors such as vascular endothelial growth factor (VEGF) have been identified as markers that predict the pathological reaction to nCRT in rectal cancer (16, 17).

Diffusion-weighted imaging (DWI), one of functional sequences of magnetic resonance imaging (MRI), visualizes the random movement of water molecules within the tissue. DWI shows differences in contrast that reflect the microstructure within the tissue (18, 19). DWI is expected to aid in predicting both pathological T and N stages and also the response of LARC to nCRT (18).

Herein, we investigated the tumor response by performing pathological evaluation and imaging of the patients who underwent nCRT and subsequent surgery for rectal cancer. Pathological evaluation included CD8+, CD33+ TILs expression and expression level of VEGF A (VEGFA) in tumor tissue.

Further, to quantify the tumor status with imaging, we applied DWI, which quantifies the restriction of the random Brownian motion of water molecules in tissues as the apparent diffusion coefficient (ADC) (18). We used PNI and neutrophil-to-lymphocyte ratio (NLR) as the respective indicators of nutritional status and immune status. NLR is a systemic inflammatory response factor of CRC that is associated with poor prognosis (20). Finally, we investigated how PNI and NLRs are related to ADC values and pathological changes.

Patients and Methods

Patients and study design. This retrospective study was approved by the Institutional Review Board of Gifu University Hospital (IRB number 2021-076). Informed consent was obtained from all patients prior to treatment for clinical research.

Between September 2013 and June 2020, 32 patients with primary CRC were included in this retrospective study. Inclusion criteria were 1) histologically diagnosed rectal cancer, 2) treatment by surgical resection combined with nCRT, 3) availability of surgical specimens, and 4) availability of MRI including DWI.

Preoperative radiotherapy was delivered at a dose of 45 Gy in 15 fractions to the pelvis. Concurrent chemotherapy was administered using one of two regimens, oral capecitabine (twice/day at a dose of 825 mg/m2) on days 1–5, 8–12, 15–19, 22–26, and 29–33 or infusion of oxaliplatin (50 mg/m2) on days 1, 8, 22, and 29 plus oral S-1 (80 mg/m2/day) on days 1-5, 8-12, 22-26, and 29-33. Clinical characteristics of the patients were obtained from their medical records and comprised sex, age, clinical regimen, histological type, pathological stage, distant metastasis, CEA levels, CA19-9 levels, PNI, and NLRs. The PNI was calculated as $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)} (13)$. The NLR was calculated as the number of neutrophils divided by the number of lymphocytes (20).

Immunohistochemistry (IHC). Paraffin-embedded samples were sliced into 4-μm-thick sections and IHC were performed using antibodies for VEGFA (rabbit monoclonal IgG; prediluted; cat no. ab27620), CD8 (rabbit monoclonal IgG; 1:500; cat no. ab93278), and CD33 (rabbit monoclonal IgG; 1:100; cat no. ab199432) (all from Abcam, Cambridge, UK). Following baking in a 65°C oven for 30 min, the samples were deparaffinized in xylene with dehydration in graded alcohol, and then transferred to a container of tap water. For antigen retrieval, the sections were placed in a pressure cooker for 10 min at 110°C in citrate buffer at pH 6.0 for the VEGFA antigen and Tris-EDTA buffer at pH 9.0 for the CD8 and CD33 antigens. Then, the samples were put to room temperature and rinsed with phosphate-buffered saline (PBS) twice for 5 min. The activity of endogenous peroxidase was blocked by 3% hydrogen peroxide-methanol for 10 min at room temperature. The slides were incubated with primary antibodies at 4°C overnight. The peroxidase-conjugated secondary antibodies were added onto the slides at room temperature and rinsed with phosphate-buffered saline (PBS) three times for 5 min. All slides were washed three times again and had 3, 3′-diaminobenzidine applied. Finally, the slides were counterstained with hematoxylin for 2 sec and dehydrated, and a cover slip was mounted.

Evaluation of immunohistochemistry. Two authors (C. M. and H. T., an experienced pathologist) conducted histological assessments without knowledge of the clinical information of each patient. The expression of VEGFA was assessed by staining intensity and percentage of positive tumor cells on each slide (21). The staining intensity was scored classifying as 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). The percentage of positive tumor cells was divided into 0-10, 11-25, 26-50, 51-75, and >75% and scored as 0, 1, 2, 3, and 4, respectively. The scores of staining intensity were multiplied by the scores of the percentage of stained cells (0-100%), and the final scores of 0-1, 2-3, 4-6, and 7-12 were classified as −, +, ++, and ++++, respectively (Figure 1). For CD8 and CD33 immunohistochemistry, all slides were firstly scanned at lower-power magnification (10×), and the 5 regions with the densest accumulation of intratumoral and stromal CD8+ and CD33+ T cells were identified (22). Within these regions, CD8+ or CD33+ T cells were then counted in 5 high-power fields (HPF) each (40×; area=0.1886 mm2) (Figure 2). The average number of infiltrating T cells per HPF was determined for each area and applied for statistical analysis.

MRI imaging and ADC evaluation. All MRI scans with DWI sequence had been performed before the neoadjuvant and surgical therapies. Patients were imaged in a 1.5-T MR magnet (Intera Achieva 1.5-T Pulsar, Philips Medical Systems, Best, The Netherlands), using a phased-array body coil. All MR images were obtained at a section thickness of 5 mm with 2-mm intersection gap. Axial T2-weighted fast spin-echo [repetition time/echo time (TR/TE)=2,999-6,832/90-100 ms; FOV 28×28 cm] and DW single-
shot spin-echo echo planar (TR/TE=3,999-6,008/60-100 ms; FOV 28x28 cm; b-value=0 and 1,000 s/mm²) images were obtained. The MR images were analyzed by a radiologist with 5 years of post-training experience in reading rectal MRI examinations, and the clinicopathological patient data was blinded. Mean ADC was calculated from a sample of three round/oval-shaped regions of interest (ROIs) that were manually placed in the solid tumor parts of three independent tumor-containing slices. The size and position of the ROIs were chosen to include as much of the solid tumor portion as possible. Patients with mucinous-appearing tumors on the primary staging MRI were excluded because these tumors are known to have low cellular density and show high ADC values and, as such, could potentially introduce bias in the study results (23). The amount of change in the ADC values between pretreatment status and post nCRT status was used to define the change in ADC values. Examples of T2-MRI images and DWI-MRI images of a good response case and a poor response case are shown in Figure 3.

**Statistical analysis.** Characteristics of patients are presented as the median and interquartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables. The relationship of pretreatment PNI, pretreatment NLR, and changes in PNI and NLR to histopathological findings was evaluated by multivariable linear regression models. Pretreatment PNI, pretreatment NLR, and changes in PNI and NLR were also assessed using multivariable linear regression models to determine whether they were associated with changes in ADC. Each model incorporated either the change in NLR or in PNI and an adjustment variable as an explanatory variable. Each model was adjusted for age and histological type because these variables were considered to bias the conclusions. A Cox proportional hazards regression model adjusted for age was used to explore factors affecting recurrence-free survival (RFS) times. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Clinicopathological characteristics.** The clinicopathological features of the patients are shown in Table I. In total, 32 patients with LARC who underwent nCRT followed by surgical resection were included in the present study. Imaging data were available for 30 patients, and biopsy specimens were available for 20 patients. The median age was 68 years (IQR=59-74 years; range=45-82 years) and 23 patients (71.9%) were male. Nineteen patients (59.4%) received capecitabine and 13 patients (40.6%) received S-1 plus oxaliplatin during the CRT period. The mean ADC value was 0.9×10⁻³ mm²/s (range=0.651-1.25×10⁻³ mm²/s). After nCRT, 21 (72.4%) patients had T3-4 tumors. In total,
Figure 2. Representative immunohistochemical staining for CD8 (A, B, E, F) and CD33 (C, D, G, H) in rectal cancer tumor tissues. Well- and poor-infiltrated cases of positive cells are shown in CD8 and CD33. IHC was performed for biopsy samples before treatment (A-D) and surgical resected samples (E-H). Intratumoral (arrow heads) and stromal (arrows) positive cells of CD8+ and CD33+ T-cells were identified in each slide. Original magnification, ×400.
Figure 3. Example of a good response case and a poor response case. Small arrows on each slide indicate the tumor location. (A-D) Images of a good response case. (E-H) Images of a poor response case. (A) Axial T2-MRI image (TR/TE, 3,886/90 ms) before chemoradiation. (B) Corresponding DWI-MRI. (C) Axial T2-MRI image (TR/TE, 4,860/100 ms) after chemoradiation showing significant tumor shrinkage. (D) Corresponding DWI-MRI showing resolution of diffusion restriction. (E) Axial T2-MRI image (TR/TE, 6,793/100 ms) before chemoradiation. (F) Corresponding DWI-MRI. (G) Axial T2-MRI image (TR/TE, 5,767/100 ms) after chemoradiation with slight change of tumor size. (H) Corresponding DWI-MRI showing poor change of diffusion restriction.
26 patients (81.2%) showed tubular adenocarcinoma histology, and 10 (31.2%) and 4 (12.5%) patients had lymph node and distant metastases, respectively.

**Histopathological findings.** Surgical specimens were available for all 32 patients, and biopsy specimens were available for 20 patients. Among the 20 patients, 2 were diagnosed as having pathological complete response to CRT, so they were excluded from evaluation of CD8 and CD33 staining. In the surgical specimens, stromal CD8+ T cells were more frequent (median cell count/HPF 44.6 cells) than intratumoral CD8+ T cells (median cell count/HPF 2.2 cells). A similar pattern was observed for CD33+ T cells: median cell count of stromal CD33+ T cells=5.2 cells and intratumoral CD33+ T cells=0 cells). Similar patterns were observed in the biopsy specimen as were seen in the surgical specimens. Stromal CD8+ T cells were more frequent (median cell count/HPF 50.2 cells) than intratumoral CD8+ T cells (median cell count/HPF 2.2 cells). Stromal CD33+ T cells were more frequent (median cell count/HPF 16.2 cells) than intratumoral CD33+ T cells (median cell count/HPF 0 cells). VEGFA staining was localized in the cytoplasm of the tumor cell and in the vasculature of tumor stroma (Figure 1).

**Correlation between histopathological findings and PNI and NLR.** There was a statistically significant inverse correlation between the change in stromal CD8+ T-cell numbers in tumor tissue and pretreatment PNI [coefficient (β)=−3.78, 95% confidence interval (CI)=−7.07 to −0.5; p=0.028] (Figure 4A). There was also a significant inverse correlation between the change in VEGFA score and change in NLR (β=−0.7; 95% CI=−1.41 to −0.0; p=0.049). However, there was no association between pretreatment NLR and histopathological changes or between CD33+ T cells in tumor tissue and PNI and NLR.

**Radiological findings and correlation between ADC/PNI and NLR.** The mean ADC value was 0.9×10−3 mm²/s (range=0.651-1.25×10−3 mm²/s) for the whole patient population. There was a positive correlation between pretreatment PNI and the change in ADC values (β=0.03, 95% CI=−0.01 to 0.0; p=0.013) (Figure 4B) and an inverse correlation between the change in NLR and that in ADC values (β=−0.03, 95% CI=−0.07 to 0; p=0.038). There was no association between pretreatment NLR and ADC values.

**Association between preoperative factors and RFS.** Five cases with distant metastasis were excluded from the prognostic analysis. The increased positive changes in PNI [hazard ratio (HR)=0.89; 95% CI=0.80-0.97; p=0.013] and in lower pretreatment NLR [HR=1.86; 95% CI=1.17-2.93; p=0.008] were associated with favorable RFS times (Table II). The increased change in ADC values also tended to show a strong association with favorable RFS times (HR=0.17; 95% CI=0.02-1.33; p<0.09). Higher pretreatment ADC values were strongly associated with unfavorable RFS times (HR=6.86; 95% CI=1.19-39.57; p=0.031).

**Discussion**

nCRT for LARC has been reported to result in a reduced incidence of local recurrence while improving both disease-free survival and overall survival (OS) (24) and increasing the rates of resectability and sphincter-saving surgery (25). However, patients who do not respond well to nCRT may
suffer tumor growth and distant metastases during nCRT and the following surgery. Therefore, the prediction of tumor response before nCRT is a proper issue. The assessment of preoperative nutritional status is generally considered to be useful in predicting perioperative risk, reducing the incidence of postoperative involvements, and improving prognosis. The PNI was originally proposed by Buzby et al. and includes serum albumin, triceps skinfold thickness, serum transferrin, and lagged hypersensitivity reaction in the calculation (26). The formula is intricate and hard to use constantly in the clinical setting. Thus, Onodera et al. made the formula simpler to be based on serum albumin levels and the peripheral blood lymphocyte count (13). These formulas were exploited to expect the risk of perioperative complications by preoperative assessment with the PNI and to decide the timing of surgical treatment. Kanda et al. described that low preoperative PNI was an independent risk factor for perioperative complications and a significant poor prognostic factor for RFS and OS in patients with pancreatic and gastric cancer (27, 28). Jian-hui et al. reported that the low PNI cohort had a worse OS than the high PNI cohort (five-year survival rate 56.1 vs. 64.8%, respectively; p<0.05) in CRC (14). In addition, Okugawa et al. reported a low pre-nCRT PNI to be a more powerful indicator of poor prognosis and early recurrence in patients with lymph node metastasis in rectal cancer (29). Similarly, Kosuga et al. reported that low PNI combined with preoperative CT findings in advanced gastric cancer may predict pathological lymph node metastasis (30). These suggest that PNI, when combined with other clinical information, may contribute to pathological diagnosis and prognosis in addition to predicting the risk of perioperative complications.

Table II. Preoperative factors associated with RFS.

<table>
<thead>
<tr>
<th>Preoperative factors</th>
<th>HR</th>
<th>95%LCL</th>
<th>95%UCL</th>
<th>p-Value</th>
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<tr>
<td>ADC values change</td>
<td>0.17</td>
<td>0.02</td>
<td>1.33</td>
<td>0.092</td>
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<tr>
<td>PNI change</td>
<td>0.89</td>
<td>0.80</td>
<td>0.97</td>
<td>0.013</td>
</tr>
<tr>
<td>NLR change</td>
<td>1.06</td>
<td>0.96</td>
<td>1.16</td>
<td>0.239</td>
</tr>
<tr>
<td>Pretreatment ADC values</td>
<td>6.86</td>
<td>1.19</td>
<td>39.57</td>
<td>0.031</td>
</tr>
<tr>
<td>Pretreatment PNI</td>
<td>1.02</td>
<td>0.93</td>
<td>1.12</td>
<td>0.651</td>
</tr>
<tr>
<td>Pretreatment NLR</td>
<td>1.86</td>
<td>1.17</td>
<td>2.93</td>
<td>0.008</td>
</tr>
<tr>
<td>Pretreatment CEA</td>
<td>1.00</td>
<td>0.99</td>
<td>1.02</td>
<td>0.471</td>
</tr>
<tr>
<td>Pretreatment CA19-9</td>
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<td>1.00</td>
<td>1.01</td>
<td>0.336</td>
</tr>
<tr>
<td>Intratumoral CD8+ T-cells a</td>
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<td>0.83</td>
<td>1.20</td>
<td>0.992</td>
</tr>
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<td>0.99</td>
<td>1.03</td>
<td>0.403</td>
</tr>
<tr>
<td>Intratumoral CD33+ T-cells a</td>
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<td>0.61</td>
<td>5.00</td>
<td>0.298</td>
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<td>Stromal CD33+ T-cells a</td>
<td>1.02</td>
<td>0.95</td>
<td>1.10</td>
<td>0.540</td>
</tr>
<tr>
<td>VEGFA scores</td>
<td>0.84</td>
<td>0.67</td>
<td>1.05</td>
<td>0.122</td>
</tr>
</tbody>
</table>

*aAnalyzed on biopsy specimen. Each HR was obtained from a Cox proportional hazards model with one preoperative factor and age as explanatory variables. HR, Hazard ratio; LCL, lower confidence limit; UCL, upper confidence limit.

First, we investigated pathological and imaging changes in patients with a high versus low pretreatment PNI during nCRT and confirmed that the prognosis of the patients with low PNI was poor in this study. Therefore, PNI could be a potential prognostic factor as indicated in previous reports (12, 29). Thus, although PNI is well known to be associated with prognosis, how nutrition as reflected by the PNI affects not only prognosis but also the nCRT process in rectal cancer is not well known.

Second, we evaluated the ADC values and histopathological changes in the high PNI group to examine whether we could
predict the effect of nCRT from preoperative images. DWI has been applied to the detection and depicition of malignant tumors in the abdominal region and to pathological differentiation of lesions because it can quantify the restriction of random movement of water molecules in tissues as the ADC (31). Malignant tumors generally have high cellularity, tissue disorganization, and increased tortuosity of the extracellular space, which limit the diffusion of water molecules, thus resulting in a low ADC value (32). Recently several studies reported ADC values to be a reliable biomarker in the assessment of tumor response to nCRT in rectal cancer. According to Schurink et al., all studies they reviewed reported an increase in mean tumor ADC during nCRT, which is thought to be a result of radiation-induced cellular damage and necrosis (33). Furthermore, several studies reviewed Schurink et al. found higher pre-nCRT values in the unfavorable response groups (34, 35). A high ADC is thought to be associated with tissue necrosis, which in turn leads to decreased tissue perfusion and hypoxia, making the tumor less susceptible to the effects of CRT (36).

We also investigated the relationship between ADC values and PNI before and after nCRT. The amount of change in ADC values was significantly higher in the patients with higher pretreatment PNI. In addition, RFS tended to be longer in the group with a higher change in ADC values. These results indicate that the change in ADC values after nCRT may reflect a positive change in tumor response. Thus, we examined how the changes in ADC values reflect the tumor microenvironment. Some studies reported a relationship between ADC values and pathological findings including gene mutation. Xu et al. retrospectively analyzed the differences in radiological characteristics of rectal cancers with different KRAS gene status and found that the KRAS mutant cohort tended to have higher T-stage and lower ADC values than the K-RAS wild-type cohort (t=7.086, p=0.029; t=–2.708, p=0.008, respectively) (37). In the future, MRI imaging may be able to predict biomarkers in addition to gene expression, including BRAF and microsatellite instability.

There are some reports of ADC values negatively correlating with CD3+ T cell counts and CD3+ levels, which both are a similar indicator of T lymphocyte influx into tumor tissue to CD8+ T-cell (38, 39). Swartz et al. surmised that lymphocytes are very small and have a high nucleus-to-cytoplasm ratio; thus, high numbers of TILs should theoretically lead to lower ADC values (38). Another report noted that the high density of CD8+ T cells in cancer biopsy samples was intensively correlated with tumor downstaging and was an independent factor for nCRT in CRC (16); inversely, McCoy et al. described that CD8+ T cells had no significant association with the regression grade of tumors (40). In the present study, pretreatment PNI was negatively correlated with stromal CD8+ T-cell expression. There are two possible reasons for this. First, this may be due to different methods to count cells such as objective lens magnification, selection for observation field of tumor nodules. In some of the cases we observed, much fibrotic tissue was present near the tumor nodules, and even though abundant lymphocytes were present, they did not extend to the tumor nodules. Lieubeau et al. suggested that due to their contractive characteristics and presumably also their accompanied extracellular matrix, myofibroblasts may prevent the penetration of immune cells within tumors, thus creating a physical barrier against immune reaction while promoting tumor growth and progression (41). Second, this might be a result of tumor resistance. Radiotherapy is thought to activate anti-tumor immunity throughout the body, as represented by the abscopal effect (42), whereas the tumor itself is thought to strengthen the immune escape mechanism. Sato et al. speculated that DNA damage signaling may, in part, lead to the increase in PD-L1 expression in tumors when DNA repair and signaling are downregulated, especially in patients who are treated with radiochemotherapy (43). In recent years, there have been increasing reports that expect the combination of CRT and PD-1/PD-L1 inhibitors to overcome the immune escape mechanism used by tumors (44, 45).

We also focused on NLR, a marker of inflammation, and found that lower changes in PNI and lower pretreatment NLR were associated with poorer prognosis suggesting that both PNI and NLR could be used as markers to predict clinical outcome. Yang et al. evaluated the prognostic value of pretreatment inflammatory indexes including NLR, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and systemic immune-inflammation index in CRC patients taking nCRT. Their study revealed that distant metastasis and NLR were the independent prognostic factors of progression-free survival and OS (46). Although our study showed no notable correlations between pretreatment NLR and changes in ADC values or in histopathology, Chen et al. described that high NLR correlated with increased expression of VEGF in metastatic CRC (47).

The present study has several limitations. First, the sample size was small and conducted at a single institution. Second, heterogeneity of TILs in the tumor remains a complicated topic. Lastly, the relationships between the characteristics and long-term outcomes, i.e., OS could not be determined because of the limited observation period. However, to the best of our knowledge, this is the first study to assess the impact of PNI on nCRT for rectal cancer using the relationship between changes in ADC values as well as pathological changes. The combination of PNI, ADC changes, and pathological changes may allow to know more accurate prognosis after treatment. Therefore, these relationships need to be validated in further studies with large sample size and long period for observation.

In conclusion, the study patients with higher pretreatment PNI had greater changes in ADC values and stromal CD8+ ...
T-cell counts, and those with a large decrease in PNI during nCRT had a worse prognosis. This study suggests that PNI may be useful as a prognostic factor for nCRT in rectal cancer, and that patients with better pretreatment and presurgical PNI may benefit from the treatment. Patient management that maintains or improves their nutritional status during treatment may lead to better a prognosis in rectal cancer.

Conflicts of Interest

None to be declared.

Authors’ Contributions

CM and NM, HT conceived the study and its design. CM, NM, HT, TT, TS, JT, SK, IY, YT, NO, KM, MF, MK, TI, MM, TM, AH, and KY acquired the data. CM, NM, HT, TI analyzed and interpreted the data and drafted the article. CM, NM, KT, and KY performed critical revision of the article. HT and KY supervised the study. CM, NM, and HT confirm the authenticity of all the raw data. All Authors read and approved the final manuscript.

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