Geriatric nutritional risk index predicts cancer prognosis in patients with local advanced rectal cancer undergoing chemoradiotherapy followed by curative surgery

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Abstract

**Aim:** The clinical significance of the geriatric nutritional risk index (GNRI) in locally advanced rectal cancer (LARC) patients undergoing preoperative chemoradiotherapy (CRT) followed by curative surgery has not been comprehensively evaluated.

**Methods:** This retrospective study enrolled 93 LARC patients diagnosed with clinical lymph node metastasis. The GNRI formula was as follows: 1.489×albumin (g/dl)+41.7×current weight/ideal weight. Patients were categorized as GNRI low (GNRI <104.25) or high (GNRI >104.25) according to the receiver operating characteristic (ROC) curve for survival analysis. The impact of GNRI status on the prognostic outcomes of curative surgery for LARC was examined.

**Results:** There were 55 (59.14%) and 3841 (40.86%) patients in the GNRI high and low groups, respectively. Of the investigated demographic factors, age, clinical tumor invasion, C-reactive protein (CRP)/albumin ratio (CAR), prognostic nutritional index (PNI) and modified Glasgow Prognostic Score (mGPS) were significantly associated with the GNRI value. In Kaplan–Meier analysis, overall survival (OS) and disease-free survival (DFS) were significantly shorter in the GNRI low group (OS: p=0.00020, DFS: p=0.0044, log-rank test). Multivariate analysis using a Cox proportional hazards model showed that a low GNRI was an independent risk factor for poor OS [hazard ratio (HR) =3.22; 95% confidence interval (CI), 1.37–8.23; p=0.0068] and DFS (HR=2.32; 95%CI=1.15-4.79; p=0.018). Additionally, for patients with pathological lymph node metastasis [ypN(+)], those with a low GNRI showed shorter OS and DFS (OS: p=0.033, DFS: p=0.032, log-rank test).

**Conclusions:** GNRI is a useful marker for LARC patients diagnosed with clinical lymph node metastasis and treated by preoperative CRT followed by curative surgery.

Introduction

Recent studies highlighted the significance of malnutrition as a risk factor for postoperative complications and worse prognoses in cancer patients [1]. Pretreatment malnutrition also predicts treatment tolerance and toxicity in patients administered chemotherapy and chemoradiotherapy (CRT), and early nutritional intervention provides beneficial outcomes to patients by maintaining their nutritional status and enhancing CRT treatment tolerance [2]. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends screening all cancer patients for nutritional risk early in the course of their care [3, 4]. The geriatric nutritional risk index (GNRI) is a new nutritional screening index of nutrition-related risk associated with the severity of malnutrition and mortality of hospitalized elderly patients [5]. The GNRI is calculated using serum albumin levels and the ratio of current body weight to ideal body weight. The GNRI is associated with prognosis in hemodialysis patients and those with heart failure and cholecystitis [6–10]. In addition, the relationship between the GNRI and prognostic outcomes in patients with malignancies was recently reported [11–16].
Preoperative CRT is widely used for local advanced rectal cancer (LARC) to decrease local recurrence and increase the sphincter preservation rate [17, 18]. However, this approach has not improved the rate of distant recurrence, which is now the major cause of death in LARC patients. In addition, the efficacy of adjuvant chemotherapy in patients with rectal cancer receiving preoperative CRT remains controversial [19, 20]. Therefore, the identification of predictive factors for poor prognosis (high risk of recurrence) and the introduction of new advanced treatments are important for LARC patients.

The present study aimed to investigate whether the GNRI is a reliable predictor of the prognostic outcome in LARC patients with suspected clinical lymph node metastasis undergoing CRT followed by rectal cancer resection.

Methods

Patients

Ninety-three LARC patients who underwent preoperative CRT followed by rectal cancer resection in Mie University Hospital (Tsu, Japan) between January 2001 and December 2019 were retrospectively analyzed. The criteria for preoperative CRT were as follows: Patients who had clinical stage III based on the International Union Against Cancer TNM classification with an Eastern Cooperative Oncology Group Performance Status of 0 or 1 [21]. All patients provided written informed consent. The investigations were performed in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Mie University School of Medicine, Mie, Japan.

CRT schedules and surgery

LARC patients underwent long-course (a dose of 45 Gy in 25 fractions for 4 weeks) or short-course (a dose of 20 Gy in four fractions for 1 week) radiotherapy using the 4-field approach. All patients received concurrent 5-fluorouracil (5-FU)-based chemotherapy, including 5-FU/leucovorin, tegafur/uracil, capecitabine and S-1. The time interval between preoperative CRT and surgery was 4–6 weeks for long-course and 2–3 weeks for short-course irradiation. After resection of the tumor, all specimens were analyzed for pathological TNM classification, and staging was determined according to the classification established by the American Joint Committee on Cancer [21]. The degree of histopathological tumor regression was defined based on the Guidelines for Clinical and Pathological Studies on Carcinoma of the Colon and Rectum and classified into 4 grades: grade 0, no necrosis or regressive change; grade 1a, 66% vital residual tumor cells (VRTCs); grade 1b, ~33–66% VRTCs; grade 2, <33% VRTCs; and grade 3, no VRTCs [22]. We defined responders as those with grades 2 and 3 and non-responders as patients with grades 0–1b. 5-FU-based adjuvant chemotherapy was administered following surgery for 6 months to 1 year according to the pathological staging.

Nutritional assessment

The GNRI formula was as follows: GNRI = (1.489 × albumin, g/l) + (41.7 × current/ideal body weight). As additional nutrition factors, we also measured the platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), albumin-globulin ratio (AGR), C-reactive protein
(CRP)/albumin ratio (CAR), prognostic nutrition index (PNI) and modified Glasgow Prognostic Score (mGPS). For the PLR, patients were categorized according to ratios of ≤ 150 or > 150 [23]. For the NLR, LMR, AGR, CAR and PNI, patients were divided into two groups using the best cut-off value for survival.

Statistical analyses

All statistical analyses were performed using JMP version 10 (SAS Institute, Cary, NC, USA). Associations between the GNRI and clinicopathological factors or blood sample tests were analyzed using the Mann–Whitney U test. Overall survival (OS) and disease-free survival (DFS) curves were analyzed using the Kaplan–Meier method, and differences were examined using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model to determine the factors affecting OS and DFS. Parameters with p < 0.05 in the univariate analysis were used for the multivariate analysis. Receiver operating characteristic (ROC) curves were established to determine the cutoff values for prognosis using the Youden index. Probability values less than 0.05 were considered statistically significant.

Results

Patient characteristics

Ninety-three patients were enrolled in this study. Their demographic and clinical characteristics are shown in Table 1. The median age of study subjects was 63 years (range 32–83 years), and the male to female ratio was 2.8:1. The pretreatment clinical T stages were cT3 (n = 68) and cT4 (n = 25). The pretreatment clinical N stages were cN1 (n = 51), cN2 (n = 26) and cN3 (n = 16). The pathological T stages were ypT0/1 (n = 11), ypT2 (n = 28), ypT3 (n = 49) and ypT5 (n = 5). Pathological lymph node metastasis (ypN1–3) was observed in 40 (43%) patients, and 81 patients (87%) had a well or moderately differentiated adenocarcinoma histological grade. Eleven patients (12%) experienced local recurrence, and 24 patients (26%) showed distant recurrence. The histopathological tumor regression grades were as follows: grade 0 (n = 1), grade 1a (n = 31), grade 1b (n = 27), grade 2 (n = 28) and grade 3 (n = 6). The median follow-up period was 60.03 months (range 12–172 months). The associations between the GNRI and clinicopathological factors were shown in Table 2. The GNRI was associated with age, clinical tumor invasion, CAR, PNI and mGPS. In constant, the GNRI exhibited no association with tumor regression grade or other nutritional markers.
Table 1
Characteristics of patients with locally advanced rectal cancer who underwent neoadjuvant chemoradiotherapy

| Category                        | n (%)    |
|---------------------------------|----------|
| Age (year)                      |          |
| ≤ 63                            | 48 (52%) |
| ≥ 63                            | 45 (48%) |
| Sex                             |          |
| male                            | 68 (73%) |
| female                          | 25 (27%) |
| Adjuvant therapy                |          |
| yes                             | 65 (70%) |
| no                              | 28 (30%) |
| Clinical T stage                |          |
| T3                              | 68 (73%) |
| T4                              | 25 (27%) |
| Clinical N stage                |          |
| N1                              | 51 (55%) |
| N2                              | 26 (28%) |
| N3                              | 16 (17%) |
| ypT stage                       |          |
| T0/T1                           | 11 (12%) |
| T2                              | 28 (30%) |
| T3                              | 49 (53%) |
| T4                              | 5 (5%)   |
| ypN stage                       |          |
| N0                              | 53 (57%) |
| N1–3                            | 40 (43%) |
| Pathological TNM stage          |          |
| 0/I                             | 29 (31%) |
| II                              | 23 (25%) |
| III                             | 41 (44%) |
| Radiotherapy                    |          |
| short-course (20 Gy/4 fractions)| 24 (26%) |
| long-course (45 Gy/25 fractions)| 69 (74%) |
| Pathological response           |          |
| non-responder (grade 0/1a/1b)   | 59 (63%) |
| responder (grade 2/3)           | 34 (37%) |
| Histology                       |          |
| well/moderate                   | 81 (87%) |
| poorly/mucinous/signet          | 12 (13%) |
| Category   | n (%) |
|------------|-------|
| Recurrence |       |
| absent     | 58 (62%) |
| local      | 11 (12%)  |
| distant    | 24 (26%)  |

yp, pathological status after neoadjuvant therapy; TNM, tumor node metastasis.
Table 2
Associations between the GNRI and clinicopathological factors in patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiotherapy

| Category                              | GNRI (mean ± SD) | p value |
|---------------------------------------|------------------|---------|
| Age (year)                            |                  |         |
| ≤ 63 (n = 48)                         | 108.73 ± 9.58    | 0.0012  |
| > 63 (n = 45)                         | 102.65 ± 8.32    |         |
| Sex                                   |                  |         |
| male (n = 68)                         | 105.78 ± 10.11   | 0.72    |
| female (n = 25)                       | 105.81 ± 7.54    |         |
| Pretreatment tumor invasion           |                  |         |
| T3 (n = 68)                           | 107.39 ± 9.12    | 0.017   |
| T4 (n = 25)                           | 101.44 ± 9.12    |         |
| Pretreatment lymph node metastasis   |                  |         |
| N1 (n = 51)                           | 107.11 ± 9.39    | 0.48    |
| N2 (n = 26)                           | 103.63 ± 10.71   |         |
| N3 (n = 16)                           | 105.08 ± 6.93    |         |
| Pathological tumor invasion           |                  |         |
| pT0–2 (n = 39)                        | 107.30 ± 7.95    | 0.20    |
| pT3–4 (n = 54)                        | 104.70 ± 10.34   |         |
| Pathological lymph node metastasis   |                  |         |
| pN0 (n = 53)                          | 105.16 ± 9.72    | 0.55    |
| pN1–2 (n = 40)                        | 106.62 ± 9.14    |         |
| Histology                             |                  |         |
| moderate/well (n = 81)                | 105.97 ± 9.74    | 0.47    |
| poorly/signet/mucinous (n = 12)       | 104.59 ± 7.50    |         |
| Lymphatic invasion                    |                  |         |
| absent (n = 53)                       | 105.62 ± 9.67    | 0.72    |
| present (n = 40)                      | 106.01 ± 9.27    |         |
| Venous invasion                       |                  |         |
| absent (n = 57)                       | 105.92 ± 8.96    | 0.98    |
| present (n = 36)                      | 105.58 ± 10.31   |         |
| Pathological response                 |                  |         |
| non-responder (grade0/1a/1b) (n = 59) | 105.02 ± 8.57    | 0.27    |
| responder (grade2/3) (n = 34)         | 107.12 ± 10.82   |         |
| CA19-9 (ng/ml)                        |                  |         |
| ≤ 37.0 (n = 75)                       | 106.40 ± 9.86    | 0.13    |
| > 37.0 (n = 18)                       | 103.25 ± 7.21    |         |
| CEA (ng/ml)                           |                  |         |
| ≤ 5 (n = 44)                          | 107.1 ± 8.95     | 0.37    |
| Category | GNRI (mean ± SD) | p value |
|----------|-----------------|---------|
| > 5 (n = 49) | 104.53 ± 9.80 | 104.53 ± 9.80 |
| CRP (ng/ml) | ≤ 0.2 (n = 62) | 107.16 ± 7.97 | 0.084 |
| > 0.2 (n = 31) | 103.04 ± 11.54 | |
| PLR | ≤ 150 (n = 55) | 106.21 ± 8.96 | 0.70 |
| > 150 (n = 38) | 105.18 ± 10.21 | |
| NLR | ≤ 1.67 (n = 24) | 108.62 ± 7.16 | 0.072 |
| > 1.67 (n = 69) | 104.80 ± 9.98 | |
| LMR | ≤ 5.10 (n = 55) | 104.37 ± 10.31 | 0.12 |
| > 5.10 (n = 38) | 107.84 ± 7.73 | |
| AGR | ≤ 1.61 (n = 71) | 105.06 ± 9.57 | 0.21 |
| > 1.61 (n = 22) | 108.15 ± 8.85 | |
| CAR | ≤ 0.03 (n = 45) | 108.28 ± 7.23 | 0.013 |
| > 0.03 (n = 48) | 103.45 ± 10.69 | |
| PNI | ≤ 51 (n = 49) | 101.23 ± 8.36 | < 0.0001 |
| > 51 (n = 44) | 110.87 ± 7.94 | |
| mGPS | 0 (n = 75) | 107.80 ± 8.21 | 0.0003 |
| 1 or 2 (n = 18) | 97.40 ± 9.9 | |

GNRI: geriatric nutritional risk index, SD: standard deviation, CA19-9: carbohydrate antigen 19–9, CEA: carcinoembryonic antigen, CRP: C-reactive protein, PLR: platelet-lymphocyte ratio, NLR: neutrophil-lymphocyte ratio, LMR: lymphocyte monocyte ratio, AGS: albumin-globulin ratio, CAR: CRP-albumin ratio, PNI: prognostic nutritional index, mGPS: modified Glasgow Prognostic Score

A low GNRI was significantly associated with poor prognosis

We determined the cutoff values (< 104.25) of the GNRI according to the ROC curve generated for multiple logistic regression analysis using the 5-year OS as the endpoint. Kaplan–Meier analysis showed significantly poorer OS in the GNRI low group than in the high group (p = 0.0002) (Fig. 1a). Univariate analysis for OS showed that carbohydrate antigen 19–9 (CA19-9) high (p = 0.0041), cancer embryonic antigen (CEA) high (p = 0.022), NLR high (p = 0.024), CAR high (p = 0.034) and GNRI low (p = 0.0003) were risk factors for poor OS. Furthermore, multivariate analysis using a Cox proportional hazards model
showed that GNRI low [hazard ratio (HR) = 3.22; 95% confidence interval (CI), 1.37–8.23; p = 0.0068] was an independent risk factor for poor OS (Table 3).
Table 3
Univariate and multivariate analyses of predictive factors associated with overall survival in patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiotherapy

| Variable                  | Univariate analysis |         |         | Multivariate analysis |         |         |
|---------------------------|---------------------|---------|---------|-----------------------|---------|---------|
|                           | HR                  | 95% CI  | p value | HR                    | 95% CI  | p value |
| Sex                       | Male vs. female     | 2.67    | 0.92–11.26 | 0.072                 |         |         |
| Age (years)               | > 63 vs. ≤63        | 1.06    | 0.49–2.31  | 0.88                  |         |         |
| Histological type         | Poor/mucinous vs. well/moderate | 1.36    | 0.40–3.57  | 0.58                  |         |         |
| CA19-9                    | >37.0 vs. ≤37.0 ng/ml | 2.56    | 1.04–5.75  | 0.0041                | 2.00    | 0.77–4.85 | 0.15 |
| CEA                       | >5 vs. ≤5 ng/ml     | 2.69    | 1.14–7.36  | 0.022                 | 1.93    | 0.77–5.48 | 0.16 |
| CRP                       | >0.2 vs. ≤0.2 mg/dl | 1.99    | 0.90–4.32  | 0.088                 |         |         |
| PLR                       | >150 vs. ≤150       | 1.07    | 0.47–2.32  | 0.87                  |         |         |
| NLR                       | >1.67 vs. ≤1.67     | 3.32    | 1.15–14.03 | 0.024                 | 2.85    | 0.95–12.33 | 0.063 |
| LMR                       | ≤5.10 vs. >5.10     | 2.25    | 0.99–5.78  | 0.054                 |         |         |
| AGR                       | >1.61 vs. ≤1.61     | 1.85    | 0.78–4.11  | 0.15                  |         |         |
| CAR                       | >0.034 vs. ≤0.034   | 2.39    | 1.07–5.83  | 0.034                 | 1.15    | 0.47–2.99 | 0.76 |
| PNI                       | ≤51 vs. >51         | 2.03    | 0.91–4.96  | 0.084                 |         |         |
| mGPS                      | 1,2 vs. 0           | 1.27    | 0.49–2.92  | 0.60                  |         |         |
| GNRI                      | ≤104.25 vs. >104.25 | 4.36    | 1.93–10.77 | 0.0003                | 3.22    | 1.37–8.23 | 0.0068 |

HR, hazard ratio; CI, confidence interval; CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; PLR, platelet-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; AGR, albumin-globulin ratio; CAR, CRP-albumin ratio; PNI, prognostic nutrition index; mGPS, modified Glasgow Prognostic Score;
A low GNRI was significantly associated with early recurrence

We also used the cutoff values (< 104.25) of the GNRI for recurrence analysis. Kaplan–Meier analysis showed significantly poorer DFS in the GNRI low group than in the high group (p = 0.0044) (Fig. 1b). Univariate analysis for DFS showed that CEA high (p = 0.044), LMR low (p = 0.023) and GNRI low (p = 0.0054) were risk factors for poor DFS. Furthermore, multivariate analysis using a Cox proportional hazards model showed that GNRI low (HR = 2.32; 95%CI = 1.15–4.79; p = 0.018) was an independent risk factor for poor DFS (Table 4).
Table 4
Univariate and multivariate analyses of predictive factors associated with disease-free survival in patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiotherapy

| Variable                  | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | HR                  | 95% CI                | p value | HR                  | 95% CI                | p value |
| Sex                       | Male vs. female     | 2.30                  | 0.97–6.76 | 0.060              |                      |         |
| Age (years)               | > 63 vs. ≤63        | 1.13                  | 0.57–2.22 | 0.74               |                      |         |
| Histological type         | Well/moderate vs.    | 1.53                  | 0.55–6.37 | 0.46               |                      |         |
|                           | poor/mucinous       |                      |         |                    |                      |         |
| CA19-9                    | > 37.0 vs. ≤37.0 ng/ml | 1.85                | 0.82–3.84 | 0.13               |                      |         |
| CEA                       | > 5 vs. ≤5 ng/ml    | 2.05                  | 1.02–4.37 | 0.044              | 1.77                  | 0.88–3.81 | 0.11 |
| CRP                       | > 0.2 vs. ≤0.2 mg/dl | 1.69                | 0.84–3.33 | 0.14               |                      |         |
| PLR                       | > 150 vs. ≤150      | 1.16                  | 0.57–2.28 | 0.67               |                      |         |
| NLR                       | > 1.67 vs. ≤1.67    | 2.03                  | 0.90–5.44 | 0.090              |                      |         |
| LMR                       | ≤ 5.10 vs. >5.10    | 2.31                  | 1.12–5.26 | 0.023              | 2.01                  | 0.96–4.60 | 0.066 |
| AGR                       | > 1.61 vs. ≤1.61    | 1.70                  | 0.79–3.41 | 0.16               |                      |         |
| CAR                       | > 0.034 vs. ≤0.034  | 1.85                  | 0.94–3.80 | 0.077              |                      |         |
| PNI                       | ≤ 51 vs. >51        | 1.56                  | 0.79–3.21 | 0.20               |                      |         |
| mGPS                      | 0 vs. 1,2           | 1.03                  | 0.41–2.25 | 0.94               |                      |         |
| GNRI                      | ≤ 104.25 vs. >104.25 | 2.65                | 1.33–5.42 | 0.0054             | 2.32                  | 1.15–4.79 | 0.018 |

HR, hazard ratio; CI, confidence interval; CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; PLR, platelet-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; AGR, albumin-globulin ratio; CAR, CRP-albumin ratio; PNI, prognostic nutrition index; mGPS, modified Glasgow Prognostic Score;
A low GNRI predicts poor prognosis and recurrence in patients with pathological lymph node metastasis

We demonstrated that pathological lymph node metastasis [ypN(+)] predicted poor prognosis and early recurrence in LARC patients (OS: $p = 0.00020$, DFS: $p = 0.00010$) (Fig. 2a and 2b). In contrast, adjuvant chemotherapy had no impact on prognosis in these patients (OS: $p = 0.50$, DFS: $p = 0.30$) (Figs. 2c and 3d). Next, we analyzed OS and DFS in patients with pathological lymph node metastasis [ypN(+)], and the results showed that adjuvant chemotherapy was not associated with a better prognosis in these patients (OS: $p = 0.26$, DFS: $p = 0.29$) (Fig. 3a and 3b). In contrast, the GNRI clearly divided the patients into better and poorer prognostic groups (OS: $p = 0.033$, DFS: $p = 0.032$) (Fig. 3c and 3d).

Discussion

To the best of our knowledge, this is the first study to investigate the GNRI and clinicopathological factors in LARC patients with suspected clinical lymph node metastasis undergoing CRT followed by curative resection. The current study revealed two significant findings: (1) A low GNRI is an independent predictor of both shorter OS and DFS in LARC patients with clinical lymph node metastasis. (2) A low GNRI is also associated with a significantly worse prognosis and earlier recurrence in patients with pathological lymph node metastasis [ypN(+)].

The GNRI is calculated using serum albumin and current/ideal body weight. Serum albumin and body mass index (BMI) are both definitive factors that can reflect the risk of poor survival and early recurrence in patients with malignancies [24–28]. Although the nutritional status was assessed using various markers, serum albumin is one of the most sensitive and accurate markers for nutritional status. The immune response is directly affected by the nutrition status; thus, a decline in serum albumin leads to immunodeficiency of cell-mediated immunity for the host defenses against cancer [29]. In addition, BMI is related to malnutrition. A low BMI is associated with poor cancer survival because body weight loss is often observed in cases of aggressive cancer or the presence of negative cell regulatory systems for cancer [30, 31]. Moreover, a previous study reported that overweight patients showed biochemical evidence for better nutrition than normal-weight patients because they have more adipose tissue, suggesting that they are less likely to suffer from energy deficits and may have a better tolerance for further postoperative treatment [32]. As a result, body weight loss or a low BMI is considered a negative prognostic factor for cancer patients. Thus, the combination of serum albumin and BMI increase the power of the GNRI as a prognostic indicator in LARC patients undergoing preoperative CRT followed by curative surgery. In fact, our present study demonstrated that the GNRI is a more effective prognostic marker compared with other nutritional markers by multivariate analysis using a Cox proportional hazards model for OS and DFS.
The selective use of pelvic CRT following the total mesorectal excision for LARC has dramatically reduced the local recurrence rate from ~25% to ~5–10% [18, 33, 34]. However, this treatment strategy has not significantly reduced the rate of distant recurrence [34, 35], which is now the major cause of rectal cancer-related death. Risk-adapted alternate strategies are being explored to reduce this recurrence and improve the survival of LARC patients. The use of postoperative adjuvant chemotherapy based on 5-FU or oxaliplatin has not supported the evidence of improved OS or DFS [36]. Recently, total neoadjuvant treatment (TNT), which is intensified neoadjuvant therapy and involves shifting adjuvant chemotherapy to the neoadjuvant setting, was suggested to be more effective for LARC patients with high-risk factors [37–40]. TNT consists of induction chemotherapy, concurrent CRT and consolidation chemotherapy. A conventional strategy is needed to achieve the appropriate interval between the completion of concurrent CRT and curative surgery. TNT has the advantages of starting systemic chemotherapy 3–4 months earlier than conventional concurrent CRT, which may potentially increase the long-term survival because of the sufficient control of systemic micro-metastasis and improved tolerance to chemo-related toxicities. The present study showed that pathological lymph node metastasis [pN(+)] determined prognosis, but postoperative adjuvant chemotherapy did not contribute to improved prognoses. In contrast, the GNRI was identified as a useful marker to predict survival and recurrence in LARC patients with lymph node metastasis [pN(+)] undergoing CRT followed by curative surgery, which allows for the selection of patients for TNT.

Several limitations of this study should be noted. First, our study consisted of a retrospective study design with a relatively small cohort, especially small recurrence number. Second, patient characteristics, such as neoadjuvant CRT regimens, were heterogeneous, and the time intervals between CRT and surgery were inconsistent. Therefore, further studies using large cohorts with a longer follow up and standard pretreatment characteristics are needed to validate these results.

In conclusion, we identified the GNRI as a significant independent biomarker of poor prognosis and early recurrence in LARC patients undergoing CRT followed by curative surgery. The GNRI is a convenient decision marker for treatment in LARC patients because it is easy to measure and does not require special techniques or expertise.

**Abbreviations**

CRT: chemoradiotherapy; ESPEN: European Society for Clinical Nutrition and Metabolism; GNRI: geriatric nutritional risk index; LARC: local advanced rectal cancer; 5-FU: 5-Fluorouracil; VRTCs: vital residual tumor cells; PLR: platelet-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; AGR: albumin-globulin ratio; CRP: C-reactive protein; CAR: CRP albumin ratio; PNI: prognostic nutrition index; mGPS: modified Glasgow Prognostic Score; OS: overall survival; DFS: disease-free survival; ROC: Receiver operating characteristic; CA19-9: carbohydrate antigen 19-9; CEA: carcinoma embryonic antigen; HR: hazard ratio; CI confidence interval; BMI: body mass index; TNT: total neoadjuvant treatment

**Declarations**
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Author's contributions

Study concept and design (Shozo Ide, Yoshinaga Okugawa, Yuji Toiyama); provision of samples (Yusuke Omura, Akira Yamamoto, Takashi Ichikawa); acquisition of data (Takahito Kitajima, Tadanobu Shimura, Hiroki Imaoka); analysis and interpretation of data (Hiroyuki Fujikawa, Hiromi Yasuda); statistical analysis (Takeshi Yokoe, Yoshiki Okita, Masaki Ohi); drafting of the manuscript (Shozo Ide, Yoshinaga Okugawa, Yuji Toiyama).

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Availability of data and materials

Primary research data are presented in a summative fashion. No publicly available datasets have been generated as part of this work.

Ethics approval and consent to participate

This study was approved by the institutional review board of Mie University Hospital (IRB number 3203). And this project was a retrospective observational study. We offered an opt-out for participants to provide the opportunity to reject participation in the study. This study was performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable

Competing interests

Shozo Ide and all co-authors have no conflict of interest to declare.

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Figures
Figure 1

Prognostic impact of the geriatric nutritional risk index (GNRI) prior to chemoradiotherapy (CRT) in patients with rectal cancer. (a) Kaplan–Meier curve for overall survival (OS) in patients with rectal cancer according to pre-CRT GNRI levels (n=93). OS was significantly higher in patients with a high GNRI (n=55) compared with those with a low GNRI (n=38) (p=0.00020, log-rank test). (b) Kaplan–Meier curve for disease-free survival (DFS) in patients with rectal cancer according to pre-CRT GNRI levels (n=93). DFS was significantly higher in patients with a high GNRI (n=55) compared with those with a low GNRI (n=38) (p=0.0044, log-rank test).
Figure 2

Prognostic impact of pathological lymph node metastasis and adjuvant chemotherapy in patients with rectal cancer. (a) Kaplan–Meier curve for overall survival (OS) in patients with rectal cancer according to the status of pathological lymph node metastasis (n=93). OS was significantly higher in patients with lymph node negative status [ypN(-)] (n=53) compared with those with lymph node positive status [ypN(+)] (n=40) (p=0.00020, log-rank test). (b) Kaplan–Meier curve for disease-free survival (DFS) in patients with rectal cancer according to the status of pathological lymph node metastasis (n=93). DFS was significantly higher in patients with lymph node negative status [ypN(-)] (n=53) compared with those with lymph node positive status [ypN(+)] (n=40) (p=0.00010, log-rank test). (c) Kaplan–Meier curve for OS in patients with rectal cancer according to adjuvant chemotherapy (n=93). OS was not significantly different
between adjuvant (+) (n=65) and adjuvant (-) (n=28) (p=0.50, log-rank test). (d) Kaplan–Meier curve for DFS in patients with rectal cancer according to adjuvant chemotherapy (n=93). DFS was not significantly different between adjuvant (+) (n=65) and adjuvant (-) (n=28) (p=0.30, log-rank test).

**Figure 3**

Prognostic impact of adjuvant chemotherapy and the geriatric nutritional risk index (GNRI) in local advanced rectal cancer (LARC) patients with pathological lymph node metastasis. (a) Kaplan–Meier curve for overall survival (OS) in patients with pathological lymph node metastasis according to adjuvant chemotherapy (n=40). OS was not significantly different between adjuvant (+) (n=34) and adjuvant (-) (n=6) (p=0.26, log-rank test). (b) Kaplan–Meier curve for disease-free survival (DFS) in rectal cancer patients with pathological lymph node metastasis according to adjuvant chemotherapy (n=40). DFS was...
not significantly different between adjuvant (+) (n=34) and adjuvant (-) (n=6) (p=0.29, log-rank test). (c) Kaplan–Meier curve for OS in patients with pathological lymph node metastasis according to GNRI levels (n=40). OS was significantly higher in patients with a high GNRI (n=24) compared with those with a low GNRI (n=16) (p=0.033, log-rank test). (d) Kaplan–Meier curve for DFS in patients with pathological lymph node metastasis according to GNRI levels (n=40). DFS was significantly higher in patients with a high GNRI (n=24) compared with those with a low GNRI (n=16) (p=0.032, log-rank test).