International Journal of Colorectal Disease (2019) 34:105–112
https://doi.org/10.1007/s00384-018-3174-8

ORIGINAL ARTICLE

Nadir/pre-chemoradiotherapy ratio of white blood-cell count can predict tumor response and recurrence-free survival in locally advanced rectal cancer: a multi-institutional analysis

Joo Hwan Lee[1] · Jae Uk Jeong[2] · Sung Hwan Kim[1] · Taek Keun Nam[2] · Jong Hoon Lee[1] · Songmi Jeong[3] · Mina Yu[4] · Hong Seok Jang[5]

Accepted: 1 October 2018 / Published online: 22 October 2018

Abstract

Purpose The objective of this study was to evaluate whether change of white blood-cell (WBC) count before and during chemoradiotherapy (CRT) might be associated with susceptibility to radiation and tumor response.

Methods Medical records of 641 patients with rectal cancer who received preoperative CRT followed by curative surgery were retrospectively reviewed in five tertiary centers. Complete blood cell with differential count was measured weekly during the period of CRT. We assessed nadir/pre-CRT ratio of WBC count as a predictor for tumor response to CRT and a prognostic factor for recurrence-free survival.

Results Enrolled patients were divided into low WBC ratio (LWR) and high WBC ratio (HWR) arms with cut-off value of 0.49 calculated by receiver operating characteristic curve. Of 641 patients, 490 (76.4%) and 151 (23.6%) were categorized into HWR (> 0.49) arm and LWR (≤ 0.49) arms, respectively. Complete pathologic response rate after CRT was significantly higher in LWR arm than that in HWR arm (23.8% vs. 12.2%, $p = 0.001$). In logistic regression analysis, carcinoembryonic antigen (CEA) level over 5 ng/ml [adjusted odds ratio (OR) 0.566, 95% confidence interval (CI) 0.351–0.912; $p = 0.019$) and HWR (adjusted OR 0.412, 95% CI 0.256–0.663; $p = 0.001$) were significantly negative factors of pathologic complete response. The 5-year recurrence-free survival rate was significantly higher in the LWR group than that in the HWR group (83.3% vs. 67.6%, $p = 0.001$).

Conclusion Low nadir/pre-chemoradiotherapy ratio during preoperative CRT can predict good tumor response. It is significantly associated with improved recurrence-free survival in rectal cancer.

Keywords Chemoradiation · Rectal cancer · Response · White blood cell

Joo Hwan Lee and Jae Uk Jeong equally contributed to this work.

✉ Jong Hoon Lee
koppul@catholic.ac.kr

[1] Center for Colorectal Cancer, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

[2] Department of Radiation Oncology, Chonnam National University School of Medicine, Gwangju, Republic of Korea

[3] Department of Radiation Oncology, Ewha Women's University School of Medicine, Seoul, Republic of Korea

[4] Department of Radiation Oncology, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

[5] Department of Radiation Oncology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Introduction

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) has been the optimal treatment for patients with locally advanced rectal cancer [1–3]. Preoperative CRT increases progression-free survival and the chance to avoid abdominoperineal resection which sacrifices an anal sphincter [4]. Response to CRT varies from patient to patient with rectal cancer. Approximately 10 to 15% of patients achieve pathologic complete response after preoperative CRT [5, 6]. Response to radiation is an independent prognostic factor of rectal cancer. Good responders to CRT have significantly improved survival than non-responders [7]. Thus, many researchers have tried to find a predictor of radiation response before surgical resection in rectal cancer.

Inflammatory response has been reported as a prognostic factor that influenced recurrence and survival in several solid

tumors [8]. Parameters that reflect inflammatory response such as C-reactive protein, serum albumin, and interleukin have been reported as poor prognostic factors [9–11]. Some predictive markers need additional examination or labor-intensive complex assay to measure them accurately. Thus, researchers have tried to find simpler and more useful method that can reflect an inflammatory response in cancer treatment. Blood-cell differential count in routine blood sampling is a somewhat convenient indicator of inflammation. Many recent studies have reported that the absolute number or proportion of blood components is a prognostic factor for some solid tumors [12, 13]. However, there is no definite consensus for them in rectal cancer. Thus, the objective of this study was to determine whether change of WBC count during preoperative CRT in patients with locally advanced rectal cancer could predict their tumor response and recurrence-free survival.

Materials and methods

Patients

We analyzed medical records of 641 patients with locally advanced rectal cancer who underwent preoperative CRT and curative surgery at five tertiary institutions from 1998 to 2015. Inclusion criteria were (1) histologically confirmed adenocarcinoma of the rectum; (2) distal margin of the tumor located ≤ 10 cm from the anal verge; (3) clinical T3–4 and N0–2 classification determined by magnetic resonance imaging (MRI); (4) pre-treatment WBC count between 4,000/mm^3 and 10,000/mm^3; (5) completion of planned radiotherapy and concurrent chemotherapy; (6) no evidence of distant metastasis at diagnosis; and (7) Karnofsky performance status above 70. Patients with any history of other cancer or coexistence of hematologic or metabolic disorder were excluded from this study. Each center obtained approval from respective Institutional Review Board before enrolling patients.

Treatment

All patients received preoperative CRT to the pelvis followed by TME. Radiation dose was 45 Gy in 25 fractions to the pelvis and additional 5.4 Gy in three fractions to the primary tumor over 5.5 weeks. 5-Fluorouracil (5-FU)-based concurrent chemotherapy was administrated, including 2 cycles of bolus 5-FU (400 mg/m^2/day) and leucovorin (20 mg/m^2/day) with continuous infusion of 5-FU (225 mg/m^2/day) during CRT or capecitabine (825 mg/m^2) twice daily. TME was performed within 4 to 8 weeks after completion of CRT. Adjuvant chemotherapy with 5-FU or capecitabine was administrated according to institutional treatment policy. Basically, patients with clinical T3–4 or node-positive disease were recommended for adjuvant chemotherapy. However, patients with old age, poor general condition, or treatment morbidity after chemoradiation and surgery were considered to omit adjuvant chemotherapy.

Evaluation

All patients underwent staging evaluations prior to preoperative CRT consisting of pathologic confirmation by endoscopy, digital rectal examination, chest and abdominal pelvic computed tomography, pelvic MRI, and blood tests including carcinoembryonic antigen (CEA), complete blood-cell counts (CBC), and blood chemistry.

CBC with differential count was measured weekly during the period of CRT. Nadir WBC count was defined as the lowest count during CRT. WBC ratio was defined as the ratio of Nadir WBC count during CRT to WBC count before CRT. Response to CRT was evaluated by pathologic examinations after surgical resection. Downstaging was defined as ypT0-2N0M0 with no lymph node involvement in pathologic examination. Pathologic complete response (pCR) was defined as ypT0N0M0 with complete absence of a viable tumor with only fibrotic mass in the pathologic specimen. Other pathologic evaluations included histologic grade, presence of lymph node metastasis, lymphovascular invasion (LVI), perineural tumor invasion (PNI), circumferential radial margin (CRM), and distal resection margin (DRM). CRM and DRM involvement was defined when surgical clearance was within 1 mm and 1 cm, respectively.

Statistical analysis

Recurrence-free survival (RFS) was defined as the time from surgery to the first event of either recurrence of rectal cancer, the last day of follow-up, or death. Overall survival (OS) was defined as the time from surgery to death from any cause or

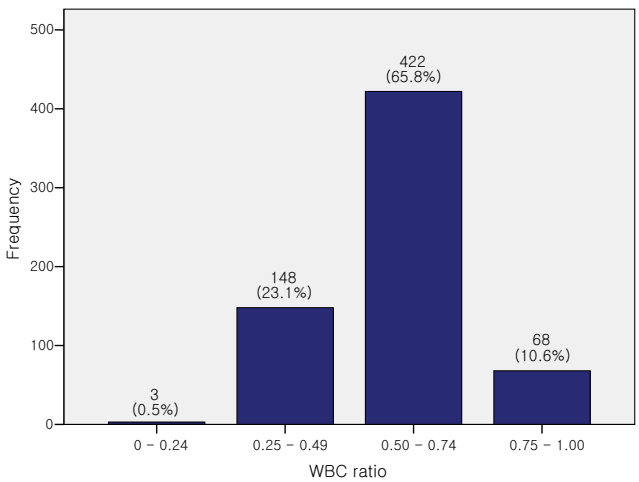

Fig. 1 Distribution of the ratio of Nadir to WBC count before chemoradiotherapy

the day of the last follow-up. Recurrence was defined as radiologic and/or pathologic evidence of locoregional recurrence or distant metastasis. Receiver operating characteristic (ROC) analysis and relative area under the curve (AUC) statistics were used to assess the optimal cut-off value for WBC ratio to tumor response. The ratio closest to the point with the Youden index [maximum (sensitivity + specificity − 1)] was selected as the optimal cut-off value. Correlation of factors to pCR and downstaging was compared using chi-square test in the univariate analysis. Logistic regression analysis was performed to evaluate factors for the multivariate analysis. Survival curve was plotted using Kaplan-Meier method. Log-rank test was used to compare survivals between the two groups. Cox proportional hazards model was used to estimate the hazard ratio of prognostic factors in multivariate analysis. Statistical significance was considered at $p < 0.05$. All data were analyzed using SPSS statistical software package, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Distribution of patients according to WBC ratio is shown in Fig. 1. The median of WBC ratio was 0.58 (range 0.13–1.0). Of 641 patients, 422 (65.8%) belonged to third quartile (0.5–0.74) in WBC ratio. ROC curve and AUC analysis revealed that the optimal cut-off value of WBC ratio for pCR after CRT was 0.49 (Fig. 2). WBC ratio showed an average value for predicting pCR (AUC = 0.587, 95% CI 0.524–0.649, $p = 0.007$). Its sensitivity and specificity were 0.38 and 0.78, respectively. According to the estimated cut-off value, patients were divided into two groups: high WBC ratio (HWR > 0.49; $n = 490$) and low WBC ratio (LWR ≤ 0.49; $n = 151$).

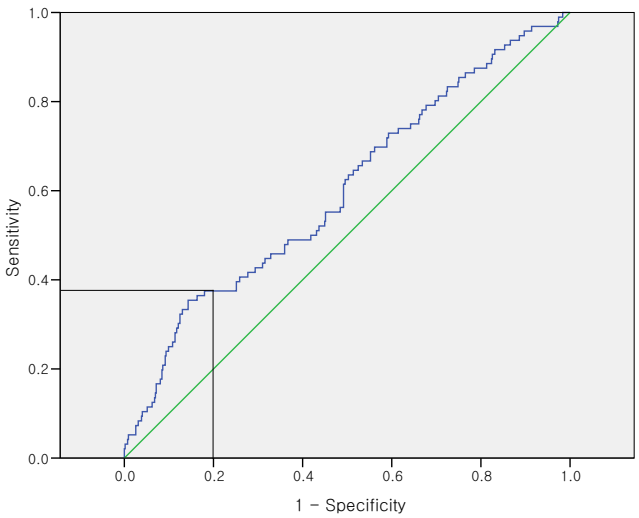

Fig. 2 Receiver operating characteristic curve to identify the optimal cut-off value of WBC ratio for tumor response after chemoradiotherapy

Patient characteristics are summarized in Table 1. A total of 117 (77.5%) of 151 patients with LWR had significantly higher positive lymph node involvement than 327 (66.7%) of 490 patients with HWR ($p = 0.016$). LWR arm showed higher clinical T classification than HWR arm with marginal significance (15.9% vs. 9.8%, $p = 0.054$). Other factors such as age, gender, pre-CRT CEA, distance of tumor from the anal

Table 1 Patient and tumor characteristics ($n = 641$)

Characteristics	Low WBC ratio arm ($n = 151$)	High WBC ratio arm ($n = 490$)	p value
Age (year)			0.958
≤ 60	64 (42.4%)	211 (43.1%)	
> 60	87 (57.6%)	279 (56.9%)	
Gender			0.411
Male	94 (62.3%)	325 (66.3%)	
Female	57 (37.7%)	165 (33.7%)	
CEA (ng/mL)			0.365
≤ 5	84 (55.6%)	295 (60.2%)	
> 5	67 (44.4%)	195 (39.8%)	
Clinical T stage			0.054
cT3	127 (84.1%)	442 (90.2%)	
cT4	24 (15.9%)	48 (9.8%)	
Clinical N stage			0.016
cN−	34 (22.5%)	163 (33.3%)	
cN+	117 (77.5%)	327 (66.7%)	
Tumor differentiation			0.765
Well	29 (19.2%)	104 (21.2%)	
Moderate	113 (74.8%)	352 (71.8%)	
Poor	9 (6.0%)	34 (6.9%)	
Distance of tumor from anal verge (cm)			0.173
≤ 5	61 (40.4%)	231 (47.1%)	
> 5	90 (59.6%)	259 (52.9%)	
Circumferential resection margin			0.789
Negative	143 (94.7%)	459 (93.7%)	
Positive	8 (5.3%)	31 (6.3%)	
Distal resection margin			0.879
Negative	139 (92.1%)	447 (91.2%)	
Positive	12 (7.9%)	43 (8.8%)	
Lymphovascular invasion			0.082
Negative	132 (87.4%)	396 (80.8%)	
Positive	19 (12.6%)	94 (19.2%)	
Perineural invasion			0.739
Negative	132 (87.4%)	421 (85.9%)	
Positive	19 (12.6%)	69 (14.1%)	
Adjuvant chemotherapy			0.385
No	32 (21.2%)	123 (25.1%)	
Yes	119 (78.8%)	367 (74.9%)	

CEA carcinoembryonic antigen, *WBC* white blood-cell count

verge, histologic grade, LVI, PNI, or CRM did not show any significant difference between the two groups.

Tumor response analysis

Tumor response to CRT was evaluated by pathologic examination after surgery. Results of tumor response according to WBC ratio are summarized in Table 2. Patients with lower WBC ratio achieved significantly higher pCR rate than patients with higher WBC ratio (23.8% vs 12.2%; $p = 0001$). Downstaging rate was also significantly higher in LWR arm than that in HWR arm. Among 151 patients with LWR, 73 (48.3%) were downstaged after CRT, while 185 patients (37.8%) of 490 patients with HWR were downstaged. The difference in downstaging rate was statistically different between the two arms ($p = 0.026$).

Predictive factors affecting tumor response are summarized in Table 3. In the univariate analysis, pCR rate was significantly associated with CEA ($p = 0.004$) and WBC ratio ($p < 0.001$). Multivariate analysis with a logistic regression model confirmed that CEA [adjusted odds ratio (OR) 0.566, 95% confidence interval (CI) 0.351–0.912; $p = 0.019$] and WBC ratio (adjusted OR 0.412, 95% CI 0.256–0.663; $p = 0.001$) were independent prognostic factors for pCR after CRT.

Survival analysis

After median follow-up time of 50.1 months, 5-year RFS rate was 83.3% in LWR arm and 67.6% in HWR arm, showing significant difference between the two groups ($p = 0.001$; Fig. 3A). A total of 486 (75.8%) of 641 patients received postoperative chemotherapy. 5-FU/leucovorin was delivered to 367 (57.3%) patients. Capecitabine was administered to 79 (12.3%) patients, while 5-FU/oxaliplatin/leucovorin was given to 40 (6.2%) patients. Five-year locoregional recurrence rate in LWR arm was lower than that in HWR arm with a marginal significance (5.2% vs. 9.1%, $p = 0.064$; Fig. 3B). Patients with LWR showed significantly lower 5-year distant metastasis rate than patients with HWR (11.0% vs. 23.2%, $p = 0.003$; Fig. 3C). Patients with LWR showed a tendency of higher OS at 5 years than patients with HWR (85.7% vs. 76.8%, $p = 0.069$; Fig. 3D). Prognostic factors affecting RFS are shown in Table 4. In multivariate analysis, CEA ($p = 0.003$), pathologic T ($p = 0.025$) and N ($p < 0.001$) classification, CRM ($p = 0.009$), perineural invasion ($p = 0.040$), and WBC ratio (hazards ratio 1.633, 95% CI 1.089–2.540; $p = 0.019$) were independent prognostic factors for RFS.

Table 2 Tumor response according to the WBC ratio

Tumor response (No. (%))	Low WBC ratio arm ($n = 151$)	High WBC ratio arm ($n = 490$)	p value
Pathologic complete response (ypT0N0)			0.001
Yes	36 (23.8%)	60 (12.2%)	
No	115 (76.2%)	430 (87.8%)	
Downstaging (ypT0-2N0)			0.026
Yes	73 (48.3%)	185 (37.8%)	
No	78 (51.7%)	305 (62.2%)	

WBC white blood-cell count

Discussion

Inflammation around the tumor can change biological circumstances by increasing vascular permeability, angiogenesis, cell proliferation, cell growth, and cell mobilization [13]. Thus,

Table 3 Analyses of factors associated with pathologic complete response after chemoradiotherapy

Factor	Univariate (p)	Adjusted odds ratio and 95% confidence interval	Multivariate (p)
Age (year)	0.373		0.454
≤ 60		Referent	
> 60		1.190 (0.756–1.873)	
Gender	0.201		0.279
Male		Referent	
Female		1.286 (0.815–0.028)	
CEA (ng/mL)	0.004		0.015
≤ 5		Referent	
> 5		0.554 (0.345–0.890)	
Clinical T classification	0.385		0.241
cT3		Referent	
cT4		0.622 (0.282–1.375)	
Clinical N classification	0.720		0.809
cN−		Referent	
cN+		0.942 (0.579–1.531)	
Distance of tumor from anal verge (cm)	0.267		0.205
≤ 5		Referent	
> 5		0.746 (0.475–1.173)	
WBC ratio	< 0.001		< 0.001
Low		Referent	
High		0.430 (0.270–0.686)	
Interval between radiation and operation (week)	0.661		0.428
≤ 7		Referent	
> 7		1.203 (0.761–1.902)	

CEA carcinoembryonic antigen, *WBC* white blood-cell count

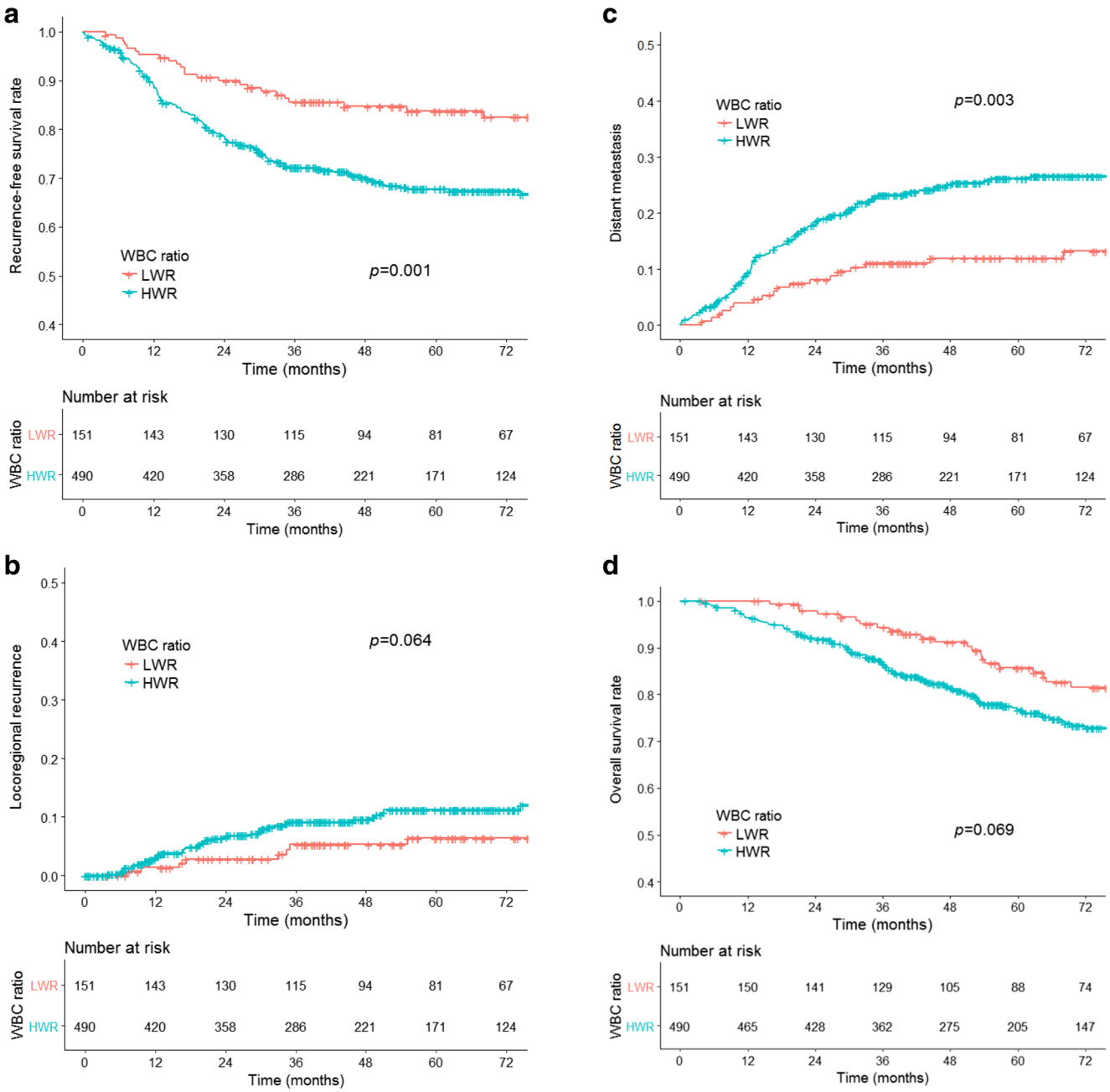

Fig. 3 **A** Recurrence-free survival between low and high WBC ratio groups. **B** Locoregional recurrence between low and high WBC ratio groups. **C** Distant metastasis between low and high WBC ratio groups. **D** Overall survival between low and high WBC ratio groups

proliferation or metastasis of tumor cells could be stimulated by inflammatory process [10]. Several studies have suggested that serum inflammatory cytokines including interleukin 1, 6, and 8, and TNF alpha are prognostic factors of patients with solid tumor [14]. These substances are directly associated to the degree of inflammation. However, enzyme-linked immunosorbent assays (ELISAs) should be performed to quantify these cytokines which need additional expense and time.

Clinical researchers have suggested more convenient markers suitable for clinical circumstances. Erlinger et al. have suggested CRP as a negative prognostic factor [11]. McMillan et al. have proposed inflammation-based prognostic system with CRP and serum albumin [15, 16]. With this system, they reported that they could predict survival rate of patients with several solid tumors. Others have suggested prognostic markers based on blood cell count. Cho et al. have reported that leukocytosis over 9000/m^3 is correlated with poor radiation response and prognosis in cervical cancer patients [17]. Unlike CEA, there is no absolute cut-off value in cell counting. Thus, the ratio of cell component is also a point of interest. Neutrophil-lymphocyte ratio (NLR) is the most interesting ratio indicator. Biologically, neutrophilia represents increased

Table 4 Analyses of factors associated with recurrence-free survival

Factor	5-year rate (%)	Univariate (*p*)	Adjusted hazards ratio and 95% confidence interval	Multivariate (*p*)
Age (year)		0.034		0.124
≤ 60	67.3		Referent	
> 60	75.0		0.705 (0.521–1.254)	
Gender		0.621		0.683
Male	71.9		Referent	
Female	71.1		1.068 (0.779–1.463)	
Distance of tumor from anal verge (cm)		0.074		0.119
≤ 5	69.1		Referent	
> 5	73.8		0.693 (0.510–1.141)	
CEA (ng/mL)		< 0.001		0.003
≤ 5	76.4		Referent	
> 5	64.7		1.595 (1.175–2.165)	
WBC ratio		0.001		0.019
Low	83.7		Referent	
High	67.8		1.663 (1.089–2.540)	
Interval between radiation and operation (week)		0.249		0.356
≤ 7	74.1		Referent	
> 7	69.8		1.353 (0.993–1.845)	
Pathologic T classification		< 0.001		0.025
pT0–2	88.3		Referent	
pT3–4	67.5		1.882 (1.083–3.271)	
Pathologic N classification		< 0.001		< 0.001
pN−	79.4		Referent	
pN+	51.6		2.003 (1.431–2.804)	
Circumferential resection margin		< 0.001		0.009
Negative	73.5		Referent	
Positive	43.2		1.887 (1.168–3.048)	
Lymphovascular invasion		< 0.001		0.057
Negative	76.4		Referent	
Positive	48.5		1.448 (0.990–2.117)	
Perineural invasion		< 0.001		0.040
Negative	75.7		Referent	
Positive	46.2		1.477 (1.101–2.181)	

CEA carcinoembryonic antigen, *WBC* white blood-cell count

inflammation response, while lymphopenia indicates decreased immune response to tumor cells. Therefore, high NLR might be a poor prognostic factor for cancer patients. Many reports support this theory [18–20], although cut-off value of each study is different without consensus. Moreover, there are even negative reports on that [21, 22].

Pre-treatment prediction of survival in cancer patients is a valuable idea. However, biological environment around the tumor can change significantly by intensive treatment including chemotherapy and radiation therapy [23, 24]. Thus, changes by the treatment should be considered when evaluating prognosis. In patients with locally advanced rectal cancer, it is easy to evaluate the effect of treatment because preoperative CRT is performed before surgery and pathologic specimen can be obtained thereafter. Several studies have evaluated post-CRT inflammation markers. Sung et al. have analyzed NLR before and after CRT and concluded that persistent elevation of NLR after CRT increases the risk of distant metastasis [20]. To the best of our knowledge, this is the first study showing that further decrease in WBC count during CRT (equivalent to LWR group) is significantly associated with better oncologic results in terms of tumor response to radiation and RFS. Our study focused on change of Nadir/pre-CRT WBC ratio during CRT. In this study, patients in the LWR

group showed 10% higher pathologic complete response rate than patients in the HWR group. Biologically, higher WBC count is associated with systemic inflammation [17]. Thus, decrease of WBC ratio after CRT means reduction of inflammation which is a good prognostic factor for local treatment response and distant metastasis as well as RFS in this study. Although LRR and OS did not reach statistical significance, they also showed a tendency to favor patients with LWR.

The limitations of this study were as follows: First, tit was performed retrospectively in five institutions, and it had a long recruitment period of nearly 20 years [25, 26]. Thus, treatment modalities and regimens were more or less heterogeneous institution by institution and year by year. Second, although we analyzed the WBC ratio as a prognostic factor of treatment response for CRT in the multivariate analysis, WBC count itself can be altered due to complications during the treatment. Another concern was comorbidity disease that could influence systemic inflammation or WBC count. Thus, we included patients within normal WBC range. However, it was impossible to exclude all irrelevant patients in a retrospective study. Thus, our results should be interpreted with caution. Efforts to analyze and quantify the extent of systemic inflammation and its influence on prognosis of cancer need to be continued. No firm consensus in either marker or cut-off value has yet been reached. Prospective studies are needed in the future.

In conclusion, reduction in nadir/pre-chemoradiotherapy ratio of WBC count during CRT predicts good tumor response. It is significantly associated with increased RFS in rectal cancer.

Acknowledgements Statistical analyses performed in this article were advised by Catholic Medical Center Clinical Research Coordinating Center.

Compliance with ethical standards

Each center obtained approval from respective Institutional Review Board before enrolling patients.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. MacFarlane JK, Ryall RD, Heald RJ (1993) Mesorectal excision for rectal cancer. Lancet 341:457–460
2. Song JH, Jeong JU, Lee JH, Kim SH, Cho HM, Um JW, Jang HS, Korean Clinical Practice Guideline for Colon and Rectal Cancer Committee (2017) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy for stage II-III resectable rectal cancer: a meta-analysis of randomized controlled trials. Radiat Oncol J 35: 198–207
3. Gérard J-P, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, Untereiner M, Leduc B, Francois É, Maurel J, Seitz JF, Buecher B, Mackiewicz R, Ducreux M, Bedenne L (2006) Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 24:4620–4625
4. Bosset J-F, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Ollier JC, EORTC Radiotherapy Group Trial 22921 (2006) Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355:1114–1123
5. Collette L, Bosset JF, den Dulk M, Nguyen F, Mineur L, Maingon P, Radosevic-Jelic L, Piérart M, Calais G, European Organisation for Research and Treatment of Cancer Radiation Oncology Group (2007) Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer radiation oncology group. J Clin Oncol 25:4379–4386
6. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R, German Rectal Cancer Study Group (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731–1740
7. Govindarajan A, Reidy D, Weiser MR, Paty PB, Temple LK, Guillem JG, Saltz LB, Wong WD, Nash GM (2011) Recurrence rates and prognostic factors in ypN0 rectal cancer after neoadjuvant chemoradiation and total mesorectal excision. Ann Surg Oncol 18: 3666–3672
8. Maas M, Nelemans PJ, Valentini V, Crane CH, Capirci C, Rödel C, Nash GM, Kuo LJ, Glynne-Jones R, García-Aguilar J, Suárez J, Calvo FA, Pucciarelli S, Biondo S, Theodoropoulos G, Lambregts DMJ, Beets-Tan RGH, Beets GL (2015) Adjuvant chemotherapy in rectal cancer: defining subgroups who may benefit after neoadjuvant chemoradiation and resection: a pooled analysis of 3,313 patients. Int J Cancer 137:212–220
9. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, Calvo FA, García-Aguilar J, Glynne-Jones R, Haustermans K, Mohiuddin M, Pucciarelli S, Small W Jr, Suárez J, Theodoropoulos G, Biondo S, Beets-Tan RGH, Beets GL (2010) Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 11:835–844
10. Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420:860–867
11. Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ (2004) C-reactive protein and the risk of incident colorectal cancer. JAMA 291:585–590
12. Forrest LM, McMillan DC, McArdle CS et al (2003) Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer 89:1028–1030
13. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674
14. Fankhauser CD, Sander S, Roth L, Gross O, Eberli D, Sulser T, Seifert B, Beyer J, Hermanns T (2018) Systemic inflammatory markers have independent prognostic value in patients with metastatic testicular germ cell tumours undergoing first-line chemotherapy. Br J Cancer 118:825–830
15. McMillan DC (2013) The systemic inflammation-based Glasgow prognostic score: a decade of experience in patients with cancer. Cancer Treat Rev 39:534–540
16. McMillan DC, Crozier JEM, Canna K et al (2007) Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Color Dis 22:881–886
17. Cho Y, Kim KH, Yoon HI, Kim GE, Kim YB (2016) Tumor-related leukocytosis is associated with poor radiation response and clinical outcome in uterine cervical cancer patients. Ann Oncol 27:2067–2074

18. Khan AA, Akritidis G, Pring T, Alagarathnam S, Roberts G, Raymond R, Varcada M, Novell R (2016) The neutrophil-to-lymphocyte ratio as a marker of lymph node status in patients with rectal cancer. Oncology 91:69–77
19. Kim IY, You SH, Kim YW (2014) Neutrophil-lymphocyte ratio predicts pathologic tumor response and survival after preoperative chemoradiation for rectal cancer. BMC Surg 14:94
20. Sung S, Son SH, Park EY, Kay CS (2017) Prognosis of locally advanced rectal cancer can be predicted more accurately using pre- and post-chemoradiotherapy neutrophil-lymphocyte ratios in patients who received preoperative chemoradiotherapy. PLoS One 12:e0173955
21. Shen L, Zhang H, Liang L, Li G, Fan M, Wu Y, Zhu J, Zhang Z (2014) Baseline neutrophil-lymphocyte ratio (>/=2.8) as a prognostic factor for patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation. Radiat Oncol 9:295
22. Caputo D, Caricato M, Coppola A, la Vaccara V, Fiore M, Coppola R (2016) Neutrophil to lymphocyte ratio (NLR) and derived neutrophil to lymphocyte ratio (d-NLR) predict non-responders and postoperative complications in patients undergoing radical surgery after neo-adjuvant radio-chemotherapy for rectal adenocarcinoma. Cancer Investig 34:1–12. https://doi.org/10.1080/07357907.2016.1229332
23. Garcia-Barros M, Paris F, Cordon-Cardo C, Lyden D, Rafii S, Haimovitz-Friedman A, Fuks Z, Kolesnick R (2003) Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science 300:1155–1159
24. Vatner RE, Formenti SC (2015) Myeloid-derived cells in tumors: effects of radiation. Semin Radiat Oncol 25:18–27
25. Kim YJ, Kim JH, Yu CS, Kim TW, Jang SJ, Choi EK, Kim JC, Choi W (2017) Effect of time interval between capecitabine intake and radiotherapy on local recurrence-free survival in preoperative chemoradiation for locally advanced rectal cancer. Radiat Oncol J 35:129–136
26. Kim JH (2017) Controversial issues in radiotherapy for rectal cancer: a systematic review. Radiat Oncol J 35:295–305