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Elevated Platelet Count as Predictor of Recurrence in Rectal Cancer Patients Undergoing Preoperative Chemoradiotherapy Followed by Surgery

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The impact of systemic inflammatory response (SIR) on prognostic and predictive outcome in rectal cancer after neoadjuvant chemoradiotherapy (CRT) has not been fully investigated. This retrospective study enrolled 89 patients with locally advanced rectal cancer who underwent neoadjuvant CRT and for whom platelet (PLT) counts and SIR status [neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR)] were available. Both clinical values of PLT and SIR status in rectal cancer patients were investigated. Elevated PLT, NLR, PLR, and pathologic TNM stage III [ypN(+)] were associated with significantly poor overall survival (OS). Elevated PLT, NLR, and ypN(+) were shown to independently predict OS. Elevated PLT and ypN(+) significantly predicted poor disease-free survival (DFS). Elevated PLT was identified as the only independent predictor of DFS. PLT counts are a promising pre-CRT biomarker for predicting recurrence and poor prognosis in rectal cancer.

Key words: Platelet – Neutrophil/lymphocyte ratio – Platelet/lymphocyte ratio – Rectal cancer – Prognosis – Chemoradiotherapy

Preoperative chemoradiotherapy (CRT) and total mesorectal excision for the management of locally advanced rectal cancer (LARC) have significantly decreased local recurrence rates and improved sphincter preservation and patient survival.[1,2] However, distant recurrence remains

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the major cause of mortality in patients who undergo preoperative CRT followed by Total Mesorectum Excision (TME). Further improvements in the survival rate cannot be achieved without the control of postsurgical distant recurrence.

Postoperative histopathologic features such as surgical margins (achievement of R0 resection) and lymph node metastases are recognized as predictors of local and distant recurrence in rectal cancer patients treated by preoperative CRT.[3–5] However, preoperative serum markers that could predict recurrence and/or poor prognosis[6] might present a convenient tool to permit intensification of either preoperative neoadjuvant or postoperative adjuvant chemotherapeutic strategies.

Aberrant activation of platelets (PLT) and the coagulation pathway are associated with malignancies. Increased PLT count may indicate poor prognosis in cancer patients,[7,8] nearly a third of whom have thrombocytosis at diagnosis and before treatment,[9] although the mechanisms by which thrombocytosis develops in malignancies remains unknown. Particularly in colorectal cancer, the prognostic significance of thrombocytosis was recently reported by Ishizuka *et al* and Craviotto-Villanueva *et al*.[10,11] Pretreatment thrombocytosis is also a predictor for CRT response and local recurrence in rectal cancer patients.[12]

However, the systemic inflammatory response (SIR), which is thought to be secondary to hypoxia or tumor necrosis, is associated with anti-apoptotic characteristics in cancer cells[13] and has been shown to act as a biomarker of outcome in a variety of malignancies.[14] Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are two representative indexes of systemic inflammation; their prognostic values have been studied in many cancer types.[15] High NLR or PLR reportedly predicts poor outcomes in colorectal cancer patients who undergo primary resection without lymph node metastases and who undergo hepatectomy for liver metastasis.[16–18] Recently, the clinical significance of NLR in rectal cancer patients undergoing CRT followed by surgery has been demonstrated, showing that it was predictor for recurrence and overall survival.[19]

In this study, we investigated the correlations between levels of PLT, NLR, and PLR in pretreatment blood tests, and clinicopathologic features in patients who undergo CRT followed by TME for locally advanced rectal cancer, and evaluated and compared their potentials as prognostic biomarkers.

Methods

Patients

A total of 89 patients with rectal cancer received preoperative CRT followed by TME at our institute between 2001 and 2012. The criteria for preoperative CRT was for patients with tumors in the lower two-thirds of the rectum and staged over T2 or T1 (tumor invading to submucosa) with clinical N1, which represent clinical stages I–III, based on the International Union Against Cancer's TNM classification, to improve resectability and improve chances of successfully performing sphincter-saving procedures, aged 80 years or younger, no invasion of the external sphincter muscle or elevator muscle of the anus, and no evidence of deep venous thrombosis. Pretreatment clinical stage was assessed based on digital examination, transrectal ultrasonography, computed tomography, and magnetic resonance imaging.

5-Fluorouracil-based chemoradiotherapy regimen

Patients with rectal cancer at our institution were randomly treated with short-course (n = 51: 20 Gy in 4 fractions) or long-course (n = 38: 45 Gy in 25 fractions) radiotherapy using a 4-field box technique, because the efficacy of short-course therapy has been shown to be almost the same as that of long-course therapy.[20] Patients underwent concurrent pharmacokinetic modulation chemotherapy [intravenous infusion of 5-fluorouracil (5-FU): 600 mg/m^2 for 24 h, and tegafur/uracil given as 400 mg/m^2 orally for 5 days] to take advantage of 5-FU-mediated radiosensitization.[21] The time interval between preoperative CRT and surgery was 2–3 weeks in short-course irradiation patients, and 4–6 weeks in long-course irradiation patients. All patients underwent standard surgery including TME, and received 5-FU-based adjuvant chemotherapy after surgery for 6 months to 1 year.

Laboratory measurement of PLT, neutrophils, and lymphocytes

PLT, neutrophils, and lymphocytes were analyzed in routine blood tests. Blood samples from each patient were obtained within 1 week prior to CRT. NLR was defined as the neutrophil-to-lymphocyte ratio, and patients were divided into two groups with a cut-off value of 3.[22] PLR was defined as the platelet count-to-lymphocyte ratio, and patients were categorized according to ratios of $\leq$150 or $>$150.[15] The cut-off

value for PLT was ≤300,000 μl and >300,000 μl, according to the previous report.[10] We obtained written informed consent from all patients according to guidelines approved by the Institutional Research Board.

Tumor regression after CRT and pathologic staging of surgical specimens

After resection, all specimens were analyzed histopathologically, and pathologic TNM classification and staging were determined according to the classification established by the American Joint Committee on Cancer. The degree of histopathologic tumor regression was based on the Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Colorectum, and was classified into 4 categories: grade 0, no necrosis or regressive changes; grade 1a, more than two-thirds vital residual tumor cells (VRTCs); grade 1b, approximately one-third to two-thirds VRTCs; grade 2, fewer than one-third VRTCs; and grade 3, no VRTCs.[23] We defined nonresponders as patients with histopathologic tumor regression grade 0–1b, and responders as those with grades 2–3.

Statistical analysis

Associations between PLT counts, SIR status and clinicopathologic findings were analyzed using χ^2 tests or Fisher's exact test. We estimated that 78 and 72 patients were needed to achieve 80% power to substantiate more that 20% differences in prognostic and recurrent outcomes, respectively, our cohort of 89 rectal cancer patients was therefore more than adequate. OS and DFS curves were analyzed using the Kaplan–Meier method; differences were examined using log-rank tests. Cox's proportional hazard regression test was used to estimate univariate and multivariate hazard ratios for recurrence and prognosis. All P values were two-sided. $P < 0.05$ was considered statistically significant. All statistical analyses were carried out using Medcalc 7.2 for Windows (Broekstraat 52, 9030, Mariakerke, Belgium).

Results

Patient characteristics

Patients' general characteristics are shown in Table 1. The median age was 65.0 years (range: 33–80 years), and the male-to-female ratio was 2.8:1. The pre-CRT clinical T stages were T1 (n = 2), T2 (n = 14), T3 (n = 57), and T4 (n = 16). Clinical N stages before CRT were N0 (n = 27) and N1–3 (n = 62). Post-CRT pathologic T stages were ypT0 (n = 4), ypT1 (n = 10), ypT2 (n = 27), ypT3 (n = 46), and ypT4 (n = 2). A total of 27 patients (39%) had lymph node metastases (ypN1–3). Seventy-eight tumors (87%) showed well- or moderately-differentiated adenocarcinoma histology. A total of 4 patients (4%) had local recurrence alone, and 17 patients (19%) had distant recurrence. The 5-point historical tumor regression grades were as follows: grade 0 (n = 0), grade 1a (n = 33), grade 1b (n = 21), grade 2 (n = 30), and grade 3 (n = 5). The median follow-up period was 56 months (range: 2–147 months).

Table 1 Patient characteristics

Category	Variable	N
Age (median:64.5)	≦64	44
	≧65	45
Gender	M	66
	F	23
Clinical T stage	T1/2	16
	T3/4	73
Clinical N stage	N0	27
	N1-3	62
Clinical TNM stage	I	13
	II	15
	III	61
ypT stage	T1/2	41
	T3/4	48
yp N stage	N0	62
	N1-3	27
Pathological TNM stage	0	2
	I	33
	II	24
	III	27
	IV	3
Radiotherapy	Short course (20 Gy/4 fractions)	51
	Long course (45 Gy/25 fractions)	38
Pathologic response	Non-responder (Grade 0/1a/1b)	54
	Responder (Grade 2/3)	35
Histology	Well/moderate	78
	Poorly/mucinous/signet	11
Recurrence	Absent	68
	Local	4
	Distant	17

Associations between pre-CRT PLT, NLR, and PLR, and clinicopathologic features

PLT and NLR were significantly correlated (ρ = 0.314, $P = 0.0027$; Fig. 1A), as were PLT and PLR (ρ =

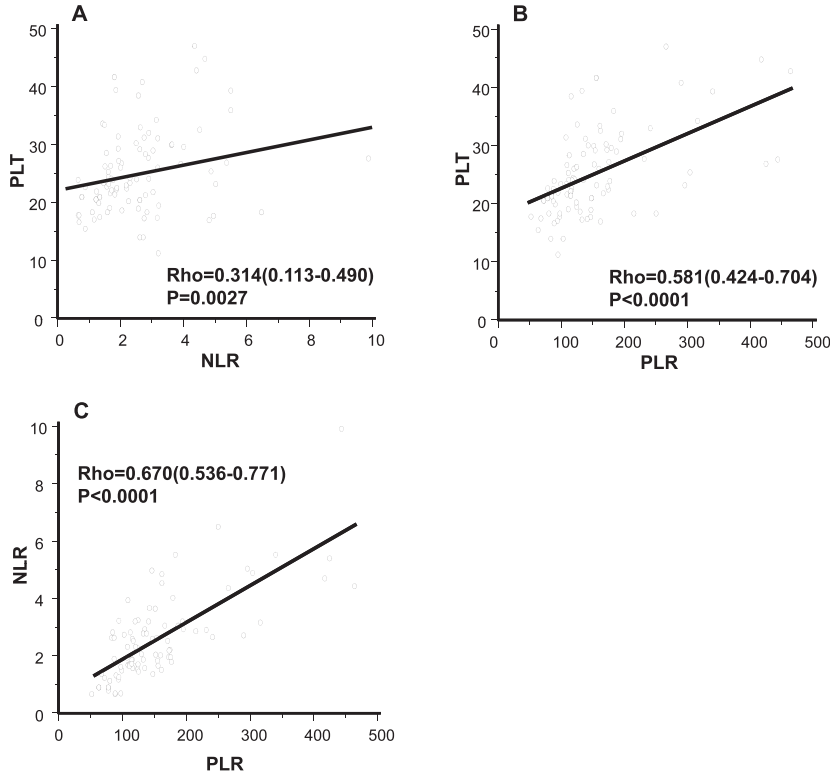

Fig. 1 Correlations between PLT counts and SIR status. (A) PLT counts and NLR values were significantly correlated [ρ (95% CI) = 0.314 (0.113–0.490); P = 0.0027]. (B) PLT counts and PLR values were significantly correlated [ρ (95% CI) = 0.581 (0.424–0.704); $P < 0.0001$]. (C) NLR and PLR values were significantly correlated [ρ (95% CI) = 0.670 (0.536–0.771); $P < 0.0001$].

0.581, $P < 0.0001$; Fig. 1B), and NLR and PLT (ρ = 0.670, $P < 0.0001$; Fig. 1C). No markers were statistically associated with pathologic findings including pathologic T, N stage, histologic findings and tumor regression grade by CRT (Table 2).

Pre-CRT PLT is an independent predictor of poor prognosis in rectal cancer patients who undergo CRT followed by TME

Patients with elevated PLT, NLR, and PLR had significantly poorer OS than patients with levels

Table 2 Association between platelet counts and SIR status (NLR and PLR) and clinicopathologic findings

	Platelet			NLR			PLR		
	≦30	>30	*P*	≦3	>3	*P*	≦0.015	>0.015	*P*
Age									
≦64	37	7	0.32	31	13	0.94	28	16	0.72
≧65	33	12		33	12		26	19	
Gender									
M	52	14	0.80	45	21	0.29	46	20	0.006
F	18	5		19	4		8	15	
Pathologic T									
0-II	34	7	0.51	30	11	0.99	23	18	0.54
III-IV	36	12		34	14		31	17	
Pathologic N									
Positive	20	7	0.67	19	8	0.96	38	24	0.95
Negative	50	12		45	17		16	11	
Histology									
Well/moderate	63	15	0.36	56	22	0.76	49	29	0.43
Poorly/signet/mucinous	7	4		8	3		5	6	
Pathologic response									
Nonresponder (Grade 0/1a/1b)	43	10	0.85	41	12	0.33	36	17	0.18
Responder (Grade 2/3)	27	8		23	12		18	17	

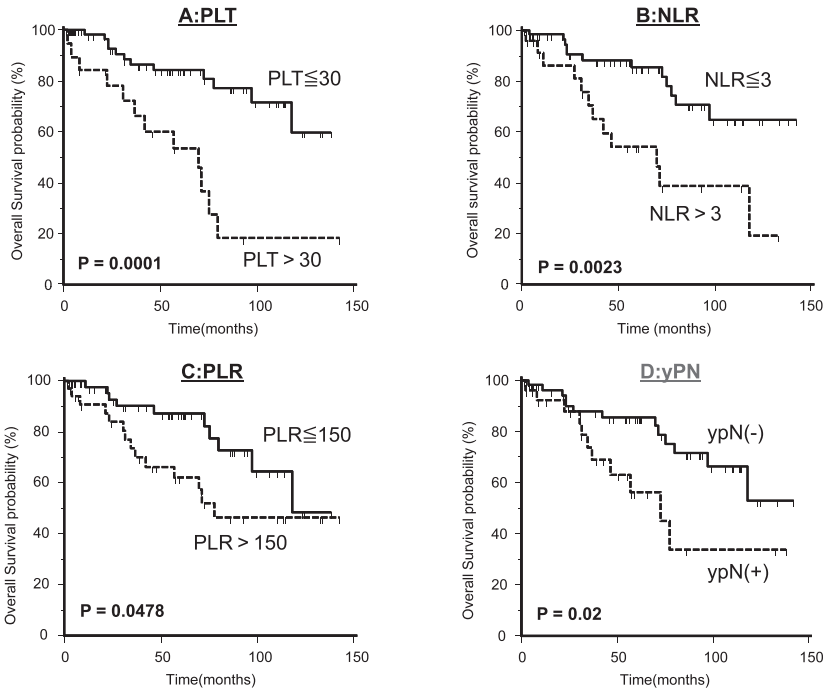

Fig. 2 Kaplan–Meier curves for OS, classified by PLT counts or SIR status prior to CRT or pathologic TNM stage of resected specimens in rectal cancer patients. (A) OS rates were significantly lower in rectal cancer patients with elevated PLT counts than in those with lower levels ($P = 0.0001$; log-rank test). (B) OS rates were significantly lower in rectal cancer patients with elevated NLR than in those with lower NLR ($P = 0.0023$; log-rank test). (C) OS rates were lower in rectal cancer patients with elevated PLR than in those with lower levels, but the difference was not significant ($P = 0.0478$; log-rank test). (D) OS rates were significantly lower in rectal cancer patients with pathologic TNM stage III [ypN(+)] than in those with TNM stage I–II [ypN(−)] ($P = 0.0204$; log-rank test).

below the cut-off values (log-rank test; PLT, $P = 0.0001$; NLR, $P = 0.0023$; PLR, $P = 0.0478$; Fig. 2A, B, C). Additionally, Kaplan–Meyer survival curves showed that pathologic TNM stage III [ypN(+)] was associated with significantly lower probabilities of OS than pathologic TNM stage I–II [ypN(–)] ($P = 0.02$; log-rank test; Fig. 2D). Univariate analysis identified pathologic TNM stage III [ypN(+)] ($P = 0.02$), elevated PLT ($P = 0.0004$), elevated NLR ($P = 0.004$) and elevated PLR ($P = 0.05$) as significant prognostic factors for poor OS (Table 3). Multivariate analysis using a Cox proportional hazards model showed that pathologic TNM stage III [ypN(+)] (hazard ratio, [HR] (95% confidence interval, [CI]) = 3.02(1.27–7.16), $P = 0.01$), elevated PLT [HR(95% CI) = 4.96(1.83–13.46), $P = 0.002$] and elevated NLR [HR(95% CI) = 2.85(1.13–7.14), $P = 0.02$] were independent predictors of poor prognosis in rectal cancer patients treated with CRT followed by TME (Table 3).

Pre-CRT PLT is an independent predictor of recurrence in rectal cancer patients who undergo CRT followed by TME

Patients with elevated PLT or pathologic TNM stage III [ypN(+)] had significantly poorer DFS than patients with levels below the cut-off values or pathologic TNM stages I–II [ypN(–)] (log-rank test; PLT, $P = 0.0145$; ypN, $P = 0.036$, respectively; Fig. 3A, B). In contrast, patients with elevated NLR or PLR also showed poorer OS than those with lower values, but the differences were not significant

Table 3 Uni- and multivariate analysis for prognosis of curative rectal cancer after chemoradiotherapy

	Univariate			Multivariate		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
Age (> 64 versus <64)	1.21	0.53–2.75	0.63	-	-	-
Gender (Female versus Male)	1.22	0.45–3.26	0.69	-	-	-
ypT (0–II versus III-IV)	1.98	0.82–4.75	0.12	-	-	-
ypN (+ versus −)	2.55	1.13–5.76	0.02	3.02	1.27–7.16	0.01
Pathology (poor versus mod/well differentiated)	1.97	0.67–5.82	0.21	-	-	-
Radiation effect (Grade 2–3 versus 0–1)	0.62	0.26–1.49	0.29	-	-	-
PLT (> 30 versus <30)	4.36	1.95–9.78	0.0004	4.96	1.83–13.46	0.002
NLR (> 3 versus <3)	3.27	1.46–7.29	0.004	2.85	1.13–7.14	0.02
PLR (> 150 versus <150)	2.22	1.0–4.98	0.05	0.7	0.23–2.07	0.52

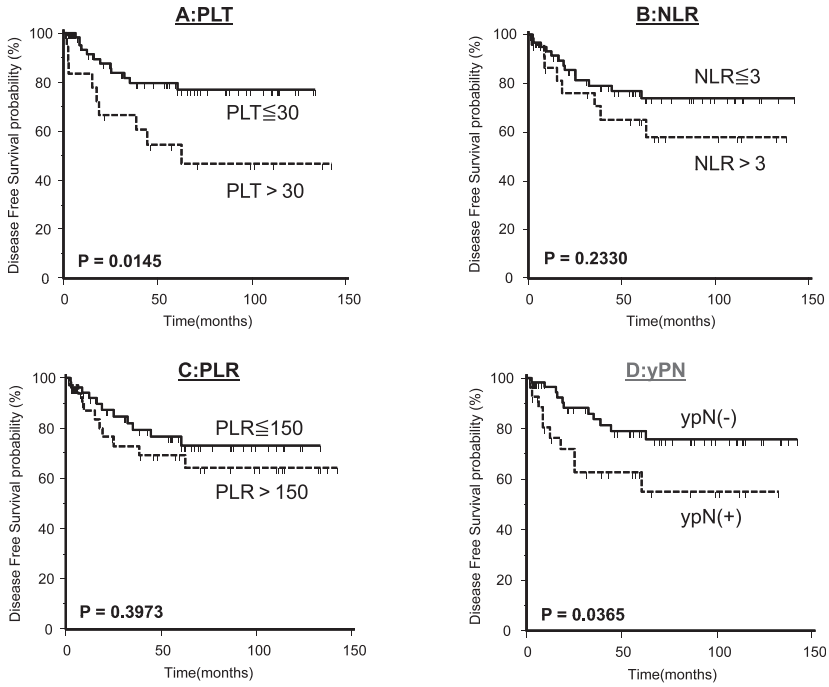

Fig. 3 Kaplan–Meier curves for DFS classified by PLT counts or SIR status prior to CRT or pathologic TNM stage of resected specimens in rectal cancer patients. (A) DFS rates were significantly lower in rectal cancer patients with elevated PLT counts than in those with lower levels ($P = 0.0145$; log-rank test). (B) DFS rates tended to be lower in rectal cancer patients with elevated NLR than in those with lower NLR, but the difference was not significant ($P = 0.233$; log-rank test). (C) DFS rates were lower in rectal cancer patients with elevated PLR than in those with lower levels ($P = 0.3973$; log-rank test). (D) DFS rates were significantly lower in rectal cancer patients with pathologic TNM stage III [ypN(+)] than in those with TNM stage I–II [ypN(−)] ($P = 0.0365$; log-rank test).

(log-rank tests; NLR, $P = 0.233$; PLR, $P = 0.3973$; Fig. 3C, D). In univariate analysis, both elevated PLT ($P = 0.019$) and ypN (+) ($P = 0.04$) were significant predictive factors for poor DFS (Table 4). Multivariate analysis based on a Cox proportional hazards model showed that only elevated PLT was an independent predictive marker for early recurrence in rectal cancer patients treated with CRT followed by TME (HR: 95%; CI = 2.55: 1.07–6.08, $P = 0.03$; Table 4).

High pre-CRT PLT predicts recurrence in rectal cancer patients with pathologic TNM stage I–II [ypN(–)]

Elevated PLT was associated with significantly poorer OS than normal PLT in pathologic TNM stage III [ypN(+)] ($P = 0.0008$; log-rank test; Fig. 4A). However, elevated PLT could not predict patients with poor DFS ($P = 0.7846$, Log-rank test; Fig. 4B). In contrast, elevated PLT was associated with significantly poorer OS and DFS than normal PLT in pathologic TNM stages I–II [ypN(–)] (OS, $P = 0.016$; DFS, $P = 0.0023$; log-rank test; Fig. 4C, D).

Discussion

The German Intergroup trial[24] showed that ypT, ypN, yp stage, and tumor regression grade were significantly associated with DFS in univariate analysis, and ypN stage was the strongest prognostic factor for DFS in multivariate analysis. Similarly, Bujko *et al*[25] and Kim *et al*[26] reported that ypN was an independent prognostic factor for DFS and OS. We also demonstrated that ypN(+) (pathologic stage III) patients had significantly poorer DFS and OS than ypN(–) (pathologic stage I–II) patients, and ypN status was an independent prognostic factor predicting OS. However, oncologic outcomes of patients who respond well to preoperative CRT for locally-advanced rectal cancer (ypT1–2N0) are significantly poorer in terms of DFS and OS than those of patients with early rectal cancer (pT1–2N0), even if the final TNM stages are the same.[27] Thus some rectal cancer patients treated with CRT will be wrongly assessed as having good outcomes, because their pathologic N stage is modified from ypN(+) to ypN(–), as a result of effective CRT.

Recent studies have shown that SIR[28] is associated with survival after surgery in patients with advanced cancer.[29–31] Because the chief mechanism of SIR is thought to be hypercytokinemic status based on tumor-versus-host interaction,[32] SIR-related clinical characteristics might indirectly reflect the magnitude and the continuance of inflammatory cytokines. Among cytokines associated with SIR induction, interleukin-6 (IL-6) is known to play a crucial role in protein synthesis in the liver and to stimulate cell proliferation in the bone marrow,[33]

Table 4 Uni- and multivariate analysis for predictors of recurrence in curative rectal cancer after chemoradiotherapy

	Univariate			Multivariate		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
Age (> 64 versus <64)	1.6	0.66−3.86	0.29	-	-	-
Gender (Female versus Male)	0.97	0.35−2.65	0.96	-	-	-
ypT(+ versus −)	1.63	0.66−4.03	0.28	-	-	-
ypN(+versus −)	2.42	1.03−5.70	0.04	2.18	0.92−5.15	0.07
Pathology (poor versus mod/well differentiated)	2.14	0.72−6.34	0.17	-	-	-
Radiation effect (Grade 2−3 versus 0−1)	0.85	0.35−2.06	0.73	-	-	-
PLT (> 30 versus <30)	2.8	1.18−6.63	0.019	2.55	1.07−6.08	0.03
NLR (> 3 versus <3)	1.69	0.70−4.08	0.23	-	-	-
PLR (> 150 versus <150)	1.44	0.61−3.38	0.39	-	-	-

promoting both neutrophil proliferation and differentiation of megakaryocytes to platelets.[33] Furthermore, NLR and PLR are both representative indexes of systemic inflammation, and their prognostic values have been studied in many types of cancer.[15] These results suggest that PLT, NLR, and PLR values in serum might change concertedly after IL-6 stimulation. In fact, our data showed significant correlation among PLT, NLR, and PLR in rectal cancer patients treated with CRT followed by surgery.

Previous investigators demonstrated the significance of tumor marker CEA,[34–37] absolute lymphocyte count,[38] NLR[19] and fibrinogen[39,40] as pre-CRT predictors of oncologic outcomes in rectal cancer patients treated with CRT followed by TME. However, to our knowledge, no studies have compared the prognostic values of pre-CRT PLT and SIR-status markers (NLR and PLR). The results of this study clearly demonstrated that elevated pre-CRT PLT, NLR, and PLR in rectal cancer patients treated with preoperative CRT were predictive of poorer OS. Additionally, multivariate analysis revealed that elevated PLT, NLR, and ypN-positivity (pathologic TNM stage III) were significant independent prognostic factors for OS, whereas elevated pre-CRT PLT levels and ypN-positivity (pathologic TNM stage III) also predicted early recurrence of rectal cancer. Furthermore, multivariate analysis

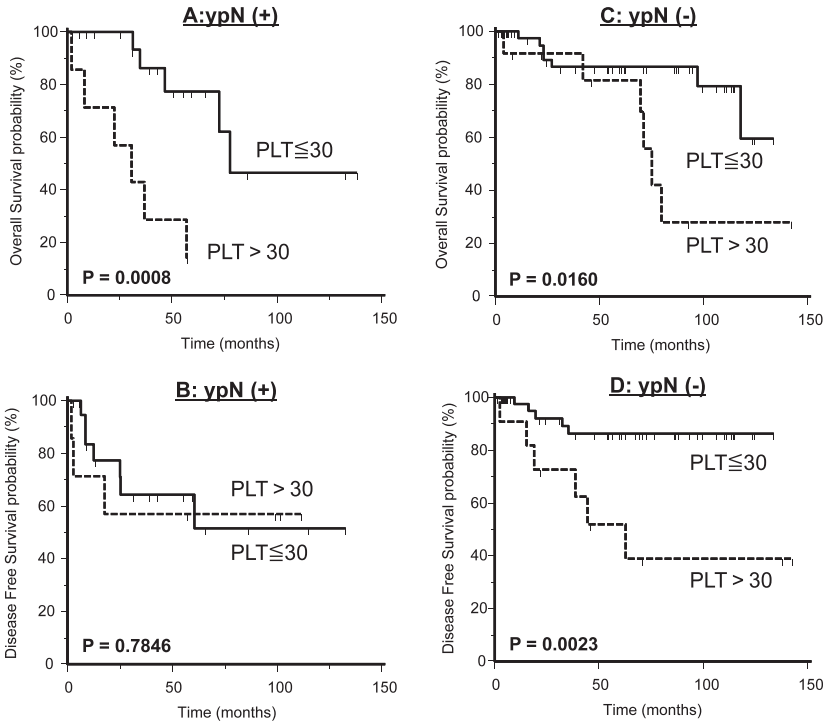

Fig. 4 Kaplan–Meier curves for OS and DFS in ypN(−) and ypN(+) rectal cancer patients classified according to pre-CRT PLT counts. (A) OS rates were significantly lower in ypN(+) rectal cancer patients with elevated PLT counts than in those with lower levels (P = 0.0008; log-rank test). (B) DFS rates were not significantly different in ypN(+) rectal cancer patients with elevated PLT counts than from those with lower levels (P = 0.7846; log-rank test). (C) OS rates were significantly lower in ypN(−) rectal cancer patients with elevated PLT counts than in those with lower levels (P = 0.016; log-rank test). (D) DFS rates were significantly lower in ypN(−) rectal cancer patients with elevated PLT counts than in those with lower levels (P = 0.0023; log-rank test).

showed that only elevated PLT was an independent predictor of DFS.

Although systemic postoperative adjuvant chemotherapy has a clear role to play in the management of pathologic stage III and high-risk stage II colon cancer, its value in locally advanced rectal cancer remains unclear, especially when pathologic staging is affected by preoperative CRT. Therefore, alternative intensified preoperative treatment strategies may be needed. In our study, among patients with pathologic TNM stage III [ypN(+)] disease, pre-CRT PLT could not differentiate those with recurrence, which indicates that postoperative chemotherapy might be needed in this subgroup. In contrast, we elegantly demonstrated that elevated pre-CRT PLT was associated with postoperative recurrence or cancer-specific death in rectal cancer patients with pathologic TNM stage I–II [ypN(–), and may thus help select patients who are likely to benefit from postoperative chemotherapy.

Some caveats apply to the data in this study. First, our conclusions are limited by the small number of patients (n = 89), especially those with recurrences (n = 21), and by the retrospective nature of the study. Second, this study included two neoadjuvant radiation regimens with different time intervals between pretreatment and surgery. Thus, a larger study population, longer follow-up, and standardization of pretreatments are needed to validate these results.

In conclusion, PLT can be determined from routine blood tests without the need for special techniques or expertise, and may represent an effective predictor of recurrence or poor prognosis in advanced rectal cancer patients who undergo CRT followed by TME.

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