Prognostic value of parameters derived from white blood cell and differential counts in patients receiving palliative radiotherapy

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Abstract. The aim of the present study was to identify white blood cell (WBC) parameters with high prognostic value for the survival of patients receiving palliative radiotherapy. The prognostic value of seven parameters derived from WBC and differential counts was retrospectively evaluated in patients who underwent palliative radiotherapy between October, 2010 and June, 2013. The analyzed parameters were the total WBC count, the absolute and relative lymphocyte count, the absolute and relative neutrophil count, and the neutrophil-to-lymphocyte and lymphocyte-to-monocyte ratios. Following univariate analysis, multivariate Cox regression analysis was performed to adjust for gender, age, disease type, previous chemotherapy, previous radiotherapy and the levels of albumin and lactate dehydrogenase. A total of 220 patients with a median survival of 4.7 months were identified. All seven parameters were found to be statistically significant predictors of survival on univariate Cox regression analysis ($P<0.05$). Of these parameters, the low relative lymphocyte and high relative neutrophil counts were consistent predictors of poor survival in patients who received chemotherapy within 1 month prior to blood sampling (n=68) and in patients who received steroid treatment at the time of sampling (n=49). Multivariate Cox regression analysis revealed that the relative lymphocyte and neutrophil counts were independent predictors of survival in all 220 patients ($P<0.05$). In conclusion, relative lymphocyte and neutrophil counts were of high prognostic value for the survival of patients receiving palliative radiotherapy, even in those receiving medications that affect WBC and differential counts.

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Introduction

The prediction of survival is crucial for determining the indications for radiotherapy (RT) and the dose fractionation schedule (1,2). Although various patient and tumor characteristics have been investigated for their prognostic value in patients receiving palliative RT (3-5), predicting prognosis remains a challenge (1,6).

Cancer-related inflammation affects the proliferation and survival of malignant cells, angiogenesis, tumor metastasis, the subversion of adaptive immunity and the tumor response to chemotherapeutic drugs and hormones (7,8). Parameters derived from white blood cell (WBC) and differential counts have been reported to be powerful prognostic predictors in patients with malignant and non-malignant diseases (9-11). The total WBC count (TWBC) (12), absolute lymphocyte count (ALC) (13-15), relative lymphocyte count (RLC) (12,13,16), absolute neutrophil count (ANC) (13,17,18), relative neutrophil count (RNC) (13,19), the neutrophil-to-lymphocyte ratio (N/L ratio) (13,20-22) and the lymphocyte-to-monocyte ratio (L/M ratio) (22-24) have been identified as significant prognostic factors in patients with malignant diseases. As the majority of these studies only evaluated one or a few of these parameters (12,14-24), their comparative assessment in patients undergoing palliative RT is required.

To identify WBC parameters with high prognostic value for the survival of patients receiving palliative RT, parameters derived from WBC and differential counts were retrospectively compared and subgroup analysis was performed to investigate the prognostic value of these parameters in patients on medication affecting their WBC count.

Patients and methods

Patients. This retrospective study was approved by the Kumamoto University Hospital Institutional Review Board (no. 986), and patient informed consent was waived due to the retrospective nature of the study. The inclusion criteria for this study were as follows: i) Patients treated with palliative RT between October, 2010 and June, 2013; ii) acquisition of laboratory data, including WBC and differential counts and albumin and lactate dehydrogenase (LDH) levels, within 2 weeks prior to the initiation of RT; and iii) availability of

chemotherapy data obtained within 1 month prior to blood sampling and of data on medications administered at the time of blood sampling. When more than one blood sample was obtained within 2 weeks prior to the initiation of RT, the latest sample was used for analysis. Patient, tumor and treatment data were collected from medical charts.

Prognostic factors of survival. Seven parameters, namely TWBC, ALC, RLC, ANC, RNC, N/L ratio and L/M ratio, were analyzed. The TWBC, RLC, and RNC were available from the patients' medical charts; the other 4 parameters were calculated based on these counts.

Statistical analysis. Data were summarized using descriptive statistics (frequency, percentage, median and range). Overall survival, calculated from the initiation of RT, was estimated using the Kaplan-Meier method; differences were assessed using the log-rank test. For this test, continuous variables were dichotomized based on our laboratory's reference values. Univariate Cox regression analysis was performed, first to assess the effect of the WBC parameters on the overall survival of all patients, and then on patients receiving medications that affect WBC and differential counts: The patients who had received chemotherapy within 1 month prior to blood sampling (subgroup A) and those who received steroids at the time of blood sampling (subgroup B). Finally, the parameters that were statistically significant predictors of survival in all patients and in the two subgroups, were subjected to multivariate analysis. Multivariate Cox regression analysis was performed to adjust for gender, age, disease type, previous chemotherapy, previous RT and albumin and LDH levels. For univariate and multivariate Cox regression analysis, the seven WBC parameters, age, and albumin and LDH levels, were used as continuous variables. Receiver operating characteristic (ROC) analysis was performed in patients who were followed up for >5 months or until death. The prognostic value of the WBC parameters for death within 5 months was evaluated using the area under the curve (AUC) of the ROC curves. Differences of $P<0.05$ were considered to indicate statistically significant differences. All statistical analyses were performed using SPSS software, version 22 (IBM SPSS, Armonk, NY, USA).

Results

Patients. A total of 220 patients with a median survival of 4.7 months (95% confidence interval: 3.7-5.7 months) were identified. The median follow-up period from the initiation of RT was 3.5 months (range, 0-53.5 months) for all patients. The patient characteristics and laboratory data are summarized in Table I. In 189 patients (86%) with solid tumors, the primary site was the lung (n=59), digestive tract (n=40), liver (n=10) and other sites (n=80). A total of 31 patients (14%) had hematological tumors; 16 presented with multiple myeloma, 9 with malignant lymphoma and 6 with other diseases. The median total radiation dose was 30 Gy (range, 3-60 Gy) and the median number of fractions was 10 (range, 1-30).

Prognostic factors for survival. In all 220 patients, univariate Cox regression analysis revealed that all seven WBC parameters were statistically significant predictors of survival (Table II). A low RLC and high RNC were consistent predictors of poor survival in the two subgroups (Table II). Multivariate Cox regression analysis revealed that RLC and RNC were independent predictors of survival in all 220 patients ($P<0.05$, Table III).

Survival curves were compared using the log-rank test (Fig. 1). The continuous variables were dichotomized

Table I. Patient characteristics and laboratory data (n=220).

Characteristics	No. of patients	%
Male gender	139	63
Age (years)		
Median	67	
Range	20-86	
Type of malignancy		
Solid	189	86
Hematological	31	14
Previous chemotherapy	150	68
Previous radiotherapy	82	37
Albumin (g/dl)		
Median	3.4	
Range	1.6-4.8	
LDH (U/l)		
Median	249.5	
Range	79-6,500	
TWBC ($x10^9$/l)		
Median	6.520	
Range	1.700-70.500	
ALC ($x10^9$/l)		
Median	1.066	
Range	0.110-3.969	
RLC (%)		
Median	16.0	
Range	1.3-55.9	
ANC ($x10^9$/l)		
Median	4.693	
Range	0.656-68.174	
RNC (%)		
Median	74.4	
Range	29.4-96.7	
N/L ratio		
Median	4.68	
Range	0.57-74.35	
L/M ratio		
Median	2.54	
Range	0.35-30.93	

LDH, lactate dehydrogenase; TWBC, total white blood cell count; ALC, absolute lymphocyte count; RLC, relative lymphocyte count; ANC, absolute neutrophil count; RNC, relative neutrophil count; N/L ratio, neutrophil-to-lymphocyte ratio; L/M ratio, lymphocyte-to-monocyte ratio.

Table II. Univariate Cox regression analyses for overall survival.

	All patients (n=220)			Subgroup A[a] (n=68)			Subgroup B[b] (n=49)		
Variables	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
TWBC (per increase of $1x10^9$/l)	1.05	1.03-1.07	<0.001	1.05	0.97-1.14	0.217	1.02	0.99-1.05	0.114
ALC (per increase of $1x10^9$/l)	0.55	0.40-0.74	<0.001	0.68	0.44-1.06	0.090	0.68	0.42-1.10	0.120
RLC (per 1% increase)	0.95	0.93-0.96	<0.001	0.97	0.95-0.99	0.005	0.95	0.91-0.99	0.007
ANC (per increase of $1x10^9$/l)	1.05	1.03-1.07	<0.001	1.06	0.99-1.15	0.116	1.02	0.99-1.05	0.085
RNC (per 1% increase)	1.04	1.03-1.05	<0.001	1.02	1.00-1.03	0.021	1.04	1.01-1.07	0.010
N/L ratio (per increase of 1)	1.02	1.01-1.03	0.002	0.99	0.98-1.02	0.944	1.00	0.99-1.02	0.707
L/M ratio (per increase of 1)	0.84	0.77-0.91	<0.001	0.96	0.89-1.04	0.350	0.99	0.92-1.06	0.715

[a]Patients who received chemotherapy within 1 month prior to blood sampling; [b]Patients who received steroids at the time of blood sampling. TWBC, total white blood cell count; ALC, absolute lymphocyte count; RLC, relative lymphocyte count; ANC, absolute neutrophil count; RNC, relative neutrophil count; N/L ratio, neutrophil-to-lymphocyte ratio; L/M ratio, lymphocyte-to-monocyte ratio; HR, hazard ratio; CI, confidence interval.

Table III. Multivariate Cox regression analyses for overall survival in all patients (n=220).

A, RLC

Variables	HR	95% CI	P-value
Male vs. female gender	0.86	0.62-1.21	0.387
Age (per 1 year increase)	1.02	1.00-1.03	0.028
Hematological vs. solid tumors	0.64	0.37-1.10	0.104
Previous chemotherapy (yes vs. no)	1.58	1.07-2.34	0.021
Previous radiotherapy (yes vs. no)	1.08	0.76-1.53	0.667
Albumin (per 1 g/dl increase)	0.70	0.55-0.90	0.006
LDH (per 1 U/l increase)	1.00	1.00-1.00	0.001
RLC (per 1% increase)	0.96	0.94-0.98	<0.001

B, RNC

Variables	HR	95% CI	P-value
Male vs. female gender	0.87	0.63-1.22	0.427
Age (per 1 year increase)	1.01	1.00-1.03	0.053
Hematological vs. solid tumors	0.62	0.36-1.07	0.086
Previous chemotherapy (yes vs. no)	1.60	1.08-2.36	0.019
Previous radiotherapy (yes vs. no)	1.14	0.80-1.61	0.473
Albumin (per 1 g/dl increase)	0.67	0.52-0.86	0.001
LDH (per 1 U/l increase)	1.00	1.00-1.00	0.001
RNC (per 1% increase)	1.02	1.01-1.04	0.001

LDH, lactate dehydrogenase; RLC, relative lymphocyte count; RNC, relative neutrophil count; HR, hazard ratio; CI, confidence interval.

according to the reference values in our laboratory. The lower limit of RLC and the upper limit of RNC were 19 and 75%, respectively. Among all patients, those with an RLC of ≥19% had significantly better overall survival compared with those with an RLC of <19% (P<0.001); this was also true for subgroups A (P=0.040) and B (P=0.016). Overall survival for all patients and subgroup B was significantly better for RNC<75% compared with RNC≥75% (P<0.001 and P=0.020, respectively); the difference was not statistically significant in subgroup A (P=0.138).

ROC analysis was performed in184 patients (84%) who were followed up for >5 months or until death. Table IV shows the

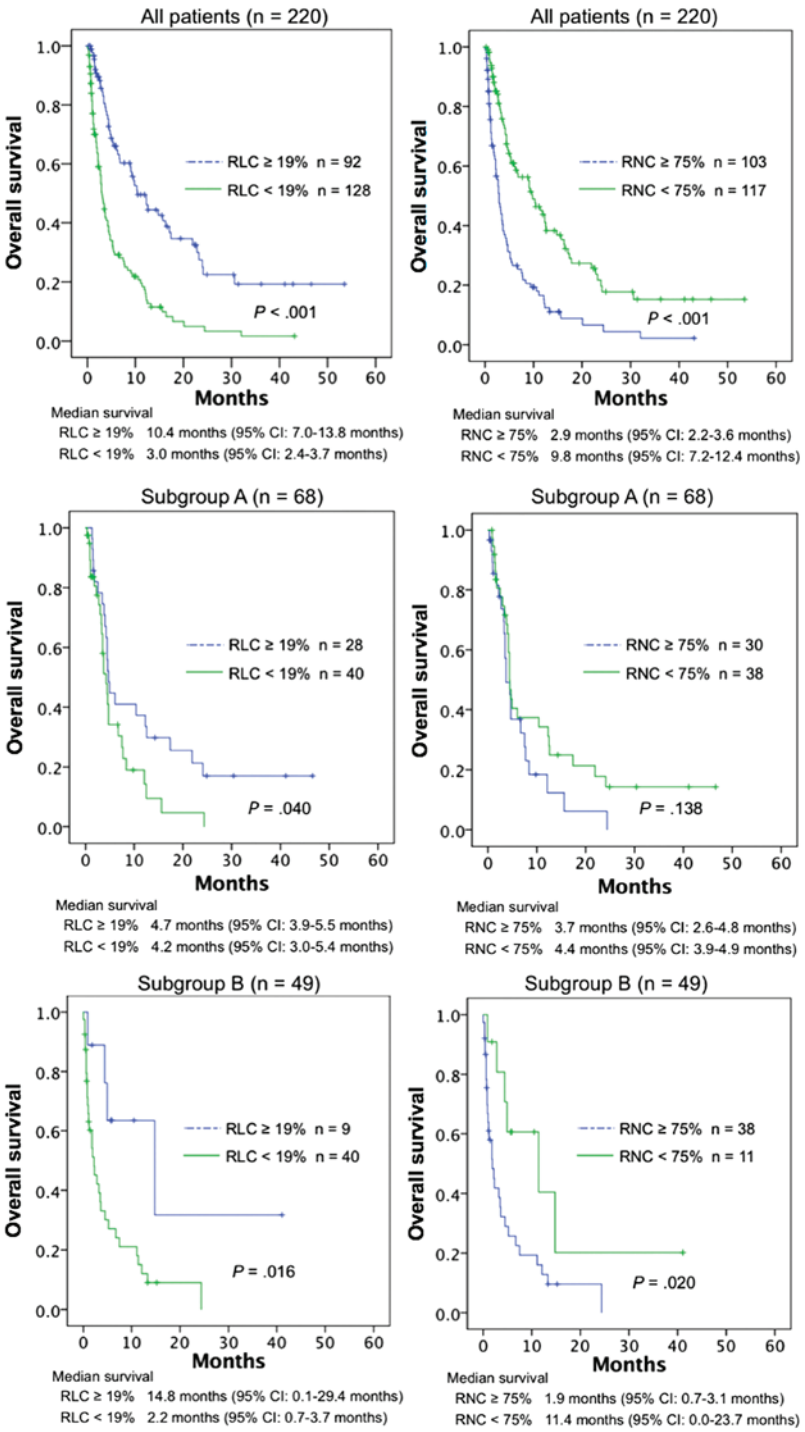

Figure 1. Overall survival based on relative lymphocyte and neutrophil counts. The continuous variables were dichotomized according to the reference values in our laboratory. The lower limit of RLC and the upper limit of RNC were 19 and 75%, respectively. RLC, relative lymphocyte count; RNC, relative neutrophil count; CI, confidence interval; Subgroup A, patients who received chemotherapy within 1 month prior to blood sampling; subgroup B, patients who received steroids at the time of blood sampling.

AUC for the ROC curves for each WBC parameter. RLC and the N/L and L/M ratios were slightly better at predicting death within 5 months compared with the remaining 4 parameters.

Discussion

Of the seven WBC parameters investigated, RLC and RNC were of high prognostic value for the survival of patients receiving palliative RT. Overall, patients with low RLC and those with high RNC had poor overall survival; this was also true for patients receiving steroids or chemotherapy. The RLC value was a slightly better predictor, as its prognostic value was consistently significant in our subgroup analyses using the log-rank test, and its AUC value in the ROC curve analysis was higher.

Data on the prognostic value of parameters derived from WBC and differential counts in patients receiving palliative RT are limited. Gripp *et al* (25) found that an elevated TWBC

Table IV. Receiver operating characteristic curve analysis to predict death within 5 months (n=184).

Variables	AUC	95% CI	P-value
TWBC	0.625	0.532-0.717	0.027
ALC	0.697	0.594-0.800	<0.001
RLC	0.777	0.694-0.861	<0.001
ANC	0.671	0.581-0.761	0.002
RNC	0.727	0.635-0.819	<0.001
N/L ratio	0.766	0.680-0.851	<0.001
L/M ratio	0.774	0.691-0.858	<0.001

TWBC, total white blood cell count; ALC, absolute lymphocyte count; RLC, relative lymphocyte count; ANC, absolute neutrophil count; RNC, relative neutrophil count; N/L ratio, neutrophil-to-lymphocyte ratio; L/M ratio, lymphocyte-to-monocyte ratio; AUC, area under the curve; CI, confidence interval.

was associated with a poor prognosis in 216 patients recently referred for palliative RT. Others reported that decreased ALC values were a prognostic factor for poor survival in 104 patients with brain metastases who received whole-brain RT (26) and in 130 patients with brain metastases from breast cancer who received whole-brain RT (27). Survival prediction is critical for determining the dose fractionation schedule in patients receiving palliative RT (1,2). Our findings may contribute to the identification of appropriate parameters for survival prediction in these patients.

Our subgroup analyses demonstrated that RLC and RNC were useful predictors of survival, even in patients receiving medications that affect WBC and differential counts. Certain patients receiving palliative RT are also treated with chemotherapy or steroids. Earlier studies on the prognostic value of WBC parameters excluded patients receiving steroids or chemotherapy (14,24,28); our subgroup analysis renders our findings applicable to such patients.

WBC parameters have been shown to be of prognostic value in patients with various malignancies (9,12-24). Palliative RT is delivered to heterogeneous patient populations, i.e., patients with solid tumors from different primary sites and patients with hematological tumors. In such patients, disease-specific factors, such as tumor stage (20,29-31), tumor size (31,32), or tumor-specific markers (33-35) do not appear to be useful for the prediction of prognosis. However, RLC and RNC may represent useful prognostic factors in heterogeneous patients receiving palliative RT.

Our study had certain limitations. First, as it was retrospective, potential confounders, such as performance status, could not be included in the multivariate analysis. Furthermore, the size of the subgroups was limited and parameters other than RLC or RNC may be found to be of prognostic value in larger patient populations.

In summary, the prognostic value of seven WBC parameters was compared and low RLC and high RNC levels were found to predict poor survival in patients receiving palliative RT. Our subgroup analyses demonstrated that these were significant prognostic factors, even in patients treated with medications affecting WBC and differential counts. As the investigated parameters are derived from complete blood counts, they may be used in daily clinical practice. Our findings may contribute to the selection of appropriate treatment schedules for patients receiving palliative RT.

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