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Monocyte-to-lymphocyte ratio is a prognostic predictor for patients with non-small cell lung cancer treated with stereotactic body radiation therapy

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ABSTRACT

Background: The monocyte-to-lymphocyte ratio (MLR), a systemic inflammation biomarker, has been shown to predict patient outcomes in several types of cancer. This study aimed to determine the association between MLR and local control (LC) and cause-specific survival (CSS) rates in patients with non-small cell lung cancer (NSCLC) treated with stereotactic body radiation therapy (SBRT).

Materials and methods: The median age of the 194 included participants (144 men, 50 women) was 80 (range, 50–96) years. The median follow-up period was 19 (range, 1–108) months. The LC and CSS rates were calculated using the Kaplan–Meier method. Univariate and multivariate Cox proportional hazard regression models were used to estimate the LC and CSS rates.

Results: Local recurrence was observed in 25 patients during the follow-up. Univariate Cox proportional hazards regression analysis revealed that MLR, performance status, and tumor diameter were significant factors for LC. Multivariate analysis showed MLR and tumor diameter as significant factors ($p = 0.041$ and 0.031, respectively). The 1- and 2-year LC rates for the lower and higher MLR groups were 97.5% and 97.5%, and 89.7% and 81.2%, respectively. During the follow-up period, 14 patients died due to NSCLC. Although MLR tended to predict CSS in univariate analysis ($p = 0.086$), none of the parameters was significant in predicting CSS. However, MLR as a continuous variable was a significant factor for CSS in the univariate analysis ($p = 0.004$).

Conclusions: Our data suggest that MLR is correlated with LC and CSS rates in NSCLC patients treated with SBRT.

Key words: non-small cell lung cancer; stereotactic body radiation therapy; systemic inflammation biomarker

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Introduction

The estimated age-standardized incidence rates of lung cancer are the highest among all cancer types in men, and the third highest in women, after breast cancer and colon cancer. The estimated age-standardized mortality rate of lung cancer is the highest among both sexes [1].

Stereotactic body radiation therapy (SBRT) is an appropriate option for patients with primary and metastatic lung cancer and has achieved good primary tumor control rates [2–4].

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The monocyte-to-lymphocyte ratio (MLR), a systemic inflammation biomarker (SIB), has been shown to predict responses to therapy and patient outcomes in several types of cancer [5, 6]. Many reports have proposed SIBs as prognostic factors in cancer. Most of these included advanced cancers treated with surgery or chemotherapy [7-9]. However, to our knowledge, few studies have assessed the correlation between MLR and outcomes of patients with NSCLC treated with SBRT [10, 11]. Determining the MLR is inexpensive and can be easily derived from complete blood counts. Various prognostic factors have been reported for SBRT in NSCLC [12–14]. However, it would be useful if the inexpensive and convenient MLR could be used as a prognostic factor.

Thus, this study evaluated the potential association between MLR and local control (LC), progression-free survival (PFS) and cause-specific survival (CSS) rates in patients with NSCLC treated with SBRT.

Materials and methods

Patients

This retrospective study enrolled patients treated in two hospitals after receiving approval from the Institutional Review Board of Yamaguchi University Hospital and Gifu University Hospital, and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before radiation therapy. The inclusion criteria were: patients with localized NSCLC, with N0M0 disease, who were medically inoperable or who refused to undergo surgery, treated with SBRT, and for whom blood count data were available within 2 weeks before SBRT.

Cases in which the pathological diagnosis could not be confirmed were treated as NSCLC if a joint conference of respiratory surgeons, pulmonologists, radiologists, and radiation oncologists came to that consensus. The exclusion criteria were other malignancies, and a history of thoracic radiotherapy. In total, 194 patients met these criteria.

Planning and treatment

Before radiation treatment planning, the patients were evaluated using X-ray fluoroscopy or four-dimensional computed tomography (4DCT) to measure the amount of tumor movement caused by respiration. For 4DCT, a real-time positioning management (RPM) system (Varian Medical Systems, USA) was used.

In Yamaguchi University Hospital, patients with a respiratory tumor motion ≥ 1.0 cm underwent planning for the implantation of three fiducial markers by bronchoscopy near the tumor to be treated with respiratory-gated radiation therapy. All patients underwent a computed tomography (CT) scan under light exhalation breath-holding and 4DCT was performed using RPM. The clinical target volume (CTV) was defined as the gross tumor volume (GTV) and was equal to the internal target volume (ITV). The planning target volume (PTV) was determined by adding 5 mm around the ITV.

In Gifu University Hospital, patients with a respiratory motion of ≥ 1.0 cm were treated with breath-holding using an Abches (APEX Medical, Tokyo, Japan) respiratory monitoring system. The patients were scanned three times to obtain CT datasets under a light exhalation breath-hold. The three datasets were fused, and the GTV was contoured to each dataset. The GTV was used to calculate ITV. The PTV was determined by adding a 5-mm margin to the ITV.

In both hospitals, patients with respiratory motion of the tumor < 1.0 cm underwent a CT scan under light exhalation breath-hold, and 4DCT was performed. The ITV was calculated by summation of the GTVs defined at every respiratory phase of the 4DCT. PTV was determined by adding 5 mm around the ITV.

The linear accelerators used were MHCL-15DP (Mitsubishi Electronics, Japan) and TrueBeam (Varina Medical Systems, USA) in Yamaguchi University Hospital, and Novalis Tx (Varian Medical Systems) in Gifu University Hospital. Treatment planning used 6-8 beams with 6 MV photons, including non-coplanar beams.

Treatment for patients with implanted fiducial markers was performed under motion tracking using a real-time tumor tracking system. Briefly, the system consists of two sets of X-ray tubes under the floor and image intensifiers on the ceiling. The fiducial marker implanted near the tumor is easily visible on radiography and can be tracked in real time. The marker position was treated as a surrogate of the tumor position. The treatment beam

was activated only when the marker was located within a designated area [15].

Analysis

Medical charts were reviewed, and data including age, sex, performance status (PS), presence of pathological or cytological confirmation, tumor diameter, treating hospital, and MLR value were obtained.

MLR was determined from blood samples obtained within 2 weeks before SBRT. In cases where multiple samples were obtained, the data closest to the SBRT start date were utilized. MLR was calculated using the formula: monocyte count / lymphocyte count.

Additionally, biological effective dose (BED) was calculated to compare various dose fractionation regimens.

The survival periods were calculated from SBRT completion. LC, PFS and CSS rates were calculated using the Kaplan–Meier method, and group comparisons were made using log-rank tests. Univariate and multivariate Cox proportional hazard regression models were used to estimate the LC, PFS and CSS rates. Variables with $p < 0.10$ in the univariate analysis were included in the multivariate analysis. Receiver-operating characteristic (ROC) analysis was performed to determine the optimal cut-off MLR value. A $p < 0.05$ was considered to indicate a statistically significant difference.

Results

The median age of the 194 participants (144 men, 50 women) was 80 (range, 50–96) years. The patient characteristics are shown in Table 1. The median follow-up period was 19 (range, 1–108) months. A total of 92, 86, 14, and 2 patients presented with a PS of 0, 1, 2, and 3, respectively. The median tumor diameter was 20 (range, 7–52) mm. Among the patients, 89 (45.9%) had pathologically confirmed lung cancer. Cases in which the pathological diagnosis could not be confirmed were treated as NSCLC if a joint conference of respiratory surgeons, pulmonologists, radiologists, and radiation oncologists came to that consensus.

In principle, the prescribed dose to the peripheral tumors was 48 Gy in four fractions (BED: 105.6 Gy) (n = 130, 67.0%) or 50 Gy in five fractions (BED: 100.0 Gy) (n = 51, 26.3%). Tumors with central lesions located near organs at risk were treated with 60 Gy in eight fractions (BED: 105.0 Gy) (n = 11, 5.7%). A central tumor was defined as a tumor with a distance from the proximal bronchial tree of ≤ 2 cm. The median monocyte and lymphocyte counts and calculated MLR were 990 (range, 171–1123) /L, 1359 (range, 324–3941) /L, and 0.2605 (0.095–1.113), respectively. The optimal cut-off values for MLR for the LC, PFS and CSS rates were 0.198 (sensitivity, 0.960; specificity, 0.303), 0.278 (sensitivity, 0.625;

Table 1. Patient characteristics (n = 194)

Age [years]	Median (range)	80 (50–96)
Sex	Male/female	144 (74.2%) / 50 (25.8%)
Performance status	0/1/2/3/4	92 (47.4%)/86 (44.3%)/14 (7.2%)/2 (1.0%)
Tumor diameter [mm]	Median (range)	20 (7–52)
Pathology	Confirmed/unknown	89 (45.9%)/105 (54.1%)
Monocyte	Median (range)	990 (171–1123)
Lymphocyte	Median (range)	1359 (324–3941)
MLR	Median (range)	0.2605 (0.095–1.1126)
OTT [days]	Median (range)	10 (4–22)
Follow-up period [months]	Median (range)	19 (1–108)
Institution	Yamaguchi Univ/Gifu Univ	76 (39.2%)/118 (60.8%)
Dose fractionation	48 Gy in 4 fractions	130 (67.0%)
	50 Gy in 5 fractions	51 (26.3%)
	60 Gy in 8 fractions	11 (5.7%)
	48 Gy in 6 fractions	2 (1.0%)

MLR — monocyte-to-lymphocyte ratio; OTT — overall treatment time; Univ — University

Table 2. Univariate and multivariate analysis for the estimation of local control

Variables		Univariate (p-value)	Multivariate (p-value)
Age [years]	< 80 *vs.* ≥ 80	0.483	
Sex	Male *vs.* female	0.580	
Performance status	0 *vs.* 1–3	0.043	0.083
Tumor diameter [mm]	< 20 *vs.* ≥ 20	0.043	0.031
Pathology	Confirmed *vs.* unknown	0.416	
Institution	Yamaguchi Univ *vs.* Gifu Univ	0.104	
OTT [days]	≤ 7 *vs.* > 7	0.106	
BED [Gy]	> 100 *vs.* ≤ 100	0.249	
MLR	< 0.198 *vs.* ≥ 0.198	0.031	0.041

Univ — University; OTT — overall treatment time; BED — biological effective dose; MLR — monocyte-to-lymphocyte ratio

specificity, 0.415) and 0.340 (sensitivity, 0.428; specificity, 0.783), respectively.

Local recurrence was observed in 25 patients during the follow-up period. Univariate Cox proportional hazards regression analysis revealed the MLR, PS, and tumor diameter as significant factors for LC. Multivariate analysis identified MLR and tumor diameter as significant factors (p = 0.041 and 0.031, respectively) (Tab. 2). Using the Kaplan-Meier method, LC rates with high MLR were significantly poorer than those with lower MLR (p = 0.009). The 1- and 2-year LC rates for the lower and higher MLR groups were 97.5% and 97.5%, and 89.7% and 81.2%, respectively (Fig. 1).

During the follow-up, recurrence occurred in 48 patients. Of these, 23 experienced local recurrence first, while the remaining 25 patients had non-localized recurrence, including cases of intrapulmonary metastases (10), mediastinal, hilar, or supraclavicular lymph node metastases (8), pleural dissemination (2), brain metastases (2), liver metastases (2), and bone metastasis (1). Univariate Cox proportional hazard regression models did not reveal significant factors for PFS (Tab. 3).

During the follow-up period, 34 patients died. Among these, 14 were due to NSCLC. The remaining 20 patients died from other causes [five due to pneumoniae (including aspiration pneumoniae); four due to cerebral stroke; three due to other can-

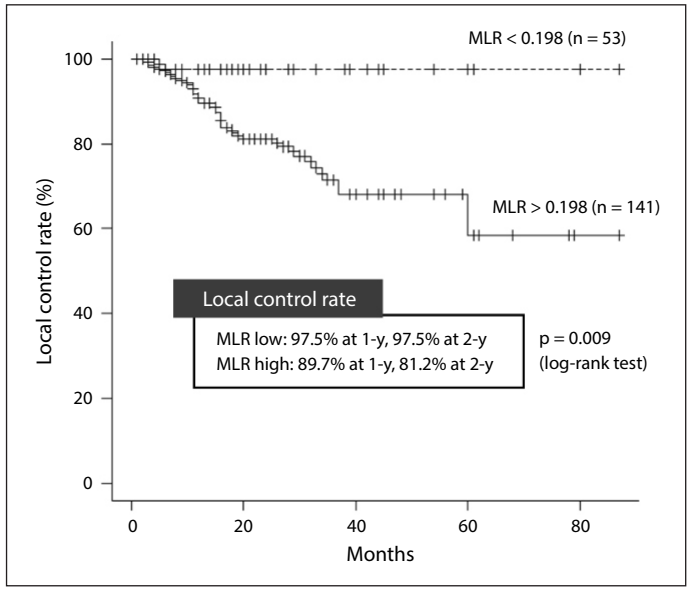

Figure 1. Local control rates in the high and low monocyte-to-lymphocyte ratio (MLR) groups

Table 3. Univariate analysis for the estimation of progression-free survival

Variables		Univariate (p-value)
Age [years]	< 80 *vs.* ≥ 80	0.944
Sex	Male *vs.* female	0.224
Performance status	0 *vs.* 1–3	0.087
Tumor diameter [mm]	< 20 *vs.* ≥ 20	0.231
Pathology	Confirmed *vs.* unknown	0.131
Institution	Yamaguchi Univ *vs.* Gifu Univ	0.421
OTT [days]	≤ 7 *vs.* > 7	0.442
BED [Gy]	> 100 *vs.* ≤ 100	0.558
MLR	< 0.278 *vs.* ≥ 0.278	0.799

Univ — University; OTT — overall treatment time; BED — biological effective dose; MLR — monocyte-to-lymphocyte ratio

Table 4. Univariate and multivariate analysis for the estimation of cause-specific survival

Variables		Univariate (p-value)	Multivariate (p-value)
Age [years]	< 80 *vs.* ≥ 80	0.980	
Sex	Male *vs.* female	0.301	
Performance status	0 *vs.* 1–3	0.376	
Tumor diameter [mm]	< 20 *vs.* ≥ 20	0.879	
Pathology	Confirmed *vs.* unknown	0.815	
Institution	Yamaguchi Univ *vs.* Gifu Univ	0.585	
OTT [days]	≤ 7 *vs.* > 7	0.581	
BED [Gy]	> 100 *vs.* ≤ 100	0.012	0.006
MLR	< 0.340 *vs.* ≥ 0.340	0.086	0.036

Univ — University; OTT — overall treatment time; BED — biological effective dose; MLR — monocyte-to-lymphocyte ratio

cers (bladder, hepatic, pancreatic); two due to senile decay, one due to hepatic failure; one each due to renal failure and phlegmon; and three due to unknown causes]. The results of the Cox proportional hazards regression models for CSS are shown in Table 4. In the univariate analysis, BED was a significant factor (p = 0.012), and MLR showed a significant trend (p = 0.086). Multivariate analysis revealed significant differences in both BED and MLR (p = 0.006 and 0.036, respectively).

Discussion

The usefulness of MLR, a type of SIB, as a prognostic predictor has been reported in various carcinomas [5, 6, 16] as well as non-neoplastic diseases [17–19]. In NSCLC, its usefulness has been reported in cases administered various types of treatment, such as surgery, chemoradiotherapy, and chemotherapy [20–26]. Jin et al. reported that the lymphocyte-monocyte ratio (LMR), the reciprocal of MLR, is a prognostic factor for PFS and OS in lung cancer cases involving various treatment modalities [27]. However, there are few reports on cases in which SBRT was performed for NSCLC. Giuliani et al. reported that the MLR was a predictor of disease-related failure in 122 patients with NSCLC treated with SBRT [10]. Luo et al. reported that the LMR was a predictor of OS in 63 patients with NSCLC who underwent SBRT [11]. A few reports also indicated that other SIBs; namely, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio, were also predictors of PFS and OS [28–30]. Our study focused on determining the usefulness of the MLR as a prognostic predictor of LC, PFS and CSS.

In this study, MLR did not emerge as a significant predictor of PFS in the univariate Cox proportional hazards regressions model (p = 0.799). However, when MLR was treated as a continuous variable, a significant trend was observed (p = 0.092). It is plausible that the selected cut-off value may not have

Table 5. Univariate and multivariate analysis for the estimation of local control for patients with histological diagnosis

Variables		Univariate (p-value)	Multivariate (p-value)
Age [years]	< 80 *vs.* ≥ 80	0.861	
Sex	Male *vs.* female	0.456	
Performance status	0 *vs.* 1–3	0.589	
Pathology	Adenocarcinoma *vs.* others	0.044	0.057
Tumor diameter [mm]	< 20 *vs.* ≥ 20	0.308	
Institution	Yamaguchi Univ *vs.* Gifu Univ	0.633	
OTT [days]	≤ 7 *vs.* > 7	0.648	
BED [Gy]	> 100 *vs.* ≤ 100	0.684	
MLR	< 0.210 *vs.* ≥ 0.210	0.068	0.077

Univ —University; OTT — overall treatment time; BED — biological effective dose; MLR — monocyte-to-lymphocyte ratio

been optimal. Regarding CSS, BED emerged as a significant factor. To explore why BED held significance in CSS, a comparison was made between the patient backgrounds of the high and low BED groups. However, no discernible differences were observed in the backgrounds of these two groups.

This study included several patients with an unconfirmed pathological diagnosis. Additional analyses were performed in 89 patients, excluding those without a histologic diagnosis, to evaluate the prognostic differences based on histologic type. The histological diagnoses included adenocarcinoma in 48 cases, squamous cell carcinoma in 37 cases, and NSCLC, not otherwise specified in four cases. The cut-off value of the MLR for LC was set to 0.210 (sensitivity, 1.000; specificity, 0.297) using ROC analysis. Table 5 illustrates the analysis using Cox proportional hazard regression models. In the univariate analysis, histological diagnosis (adenocarcinoma *vs.* non-adenocarcinoma) was a significant factor ($p = 0.044$), and MLR showed a significant trend (p = 0.068). In multivariate analysis, both histological diagnosis and MLR were marginally significant (p = 0.057 and 0.077, respectively). LC is preferable for lesions without solid components for lung adenocarcinoma treated by SBRT [31]. In this study, the LC of adenocarcinoma patients was significant owing to the inclusion of adenocarcinoma patients with poor solid components. Histological diagnosis was not a significant factor for PFS or CSS.

The MLR is calculated as the ratio of monocytes to lymphocytes. Monocytes become macrophages in tissue, promote tumors angiogenesis, induce tumor infiltration and metastasis, and promote immune avoidance, resulting in treatment resistance [32, 33]. Lymphocytes play a central role in immunity, suppress tumors, and limit dissemination by providing a local protective immune response [34, 35]. That is, an increase in monocytes works favorably for the tumor and is disadvantageous for the host. In contrast, a decrease in lymphocytes works favorably for the tumor and is disadvantageous for the host. Thus, MLR with monocytes as the numerator and lymphocytes as the denominator, a large number is advantageous for tumors. Although the number of monocytes and lymphocytes themselves may be correlated with prognosis, it is inferred that the prognosis can be better predicted by using value. As the name implies, the SIB is an index that reflects the immune status from peripheral blood to systemic inflammation. The more that inflammation spreads throughout the body, the more accurately the condition is reflected in the numerical value. In the case of neoplastic diseases, more advanced disease is better indicated by the SIB value. Therefore, most previous reports have targeted advanced cancers. As lung cancer treated with SBRT, the focus of the present study, is not advanced cancer, whether SIB could be a predictor of prognosis was uncertain. However, the use of MLR, which divides monocytes and lymphocytes as an index, sensitively reflected the status of antitumor immunity showed promise as a prognostic predictor for even localized small lung cancer.

This study had some limitations. It did not consider the nature of the tumor (solid or ground glass) or the diameter of the solid component. However, many patients are not histologically diagnosed. Patients with complications of other malignancies and those with a history of thoracic radiotherapy were excluded; however, other complications were

not considered. Moreover, the treatment after recurrence was undefined and variable.

Conclusion

In conclusion, our data suggested that the MLR was correlated with LC and CSS rates in patients with NSCLC treated with SBRT.

Conflicts of interest

Authors declare no conflict of interest.

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