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Monocyte-to-lymphocyte ratio as a prognostic indicator in head and neck squamous cell carcinoma treated with radiotherapy

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► ***Original article***

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ABSTRACT

***Background*:** The monocyte-to-lymphocyte ratio (MLR) has been reported as a useful prognosticator in various types of cancers. We studied the usefulness of MLR as a prognosticator for head and neck squamous cell carcinoma (HNSCC) in patients with oropharyngeal, hypopharyngeal, and laryngeal cancer who received radical concurrent chemoradiotherapy (CRT) or bioradiotherapy (BRT). ***Materials and Methods*:** This study included 76 HNSCC patients diagnosed between January 2015 and April 2020. We obtained their haematological records within one month before radiotherapy and calculated the MLR. Kaplan-Meier method and Cox proportional hazard model were performed to evaluate the association of MLR with locoregional recurrence-free survival (LRFS), progression-free survival (PFS), and overall survival (OS). ***Results*:** The Kaplan–Meier survival analysis for MLR showed a significant difference (p = 0.0326) in OS. Univariate and multivariate analysis revealed that the lower MLR group was associated with better OS (hazard ratio [HR] = 0.345, 95 % confidence interval [CI] = 0.124–0.960, p = 0.042 and HR = 0.305, 95% CI = 0.102-0.916, p = 0.034, respectively). Multivariate analysis also revealed that N 2-3 was significant independent predictor of LFRS and PFS (HR = 4.47, 95% CI = 1.43–14.0, p = 0.0286 and HR = 4.94, 95% CI = 1.84-13.2, p < 0.01, respectively). ***Conclusion*:** MLR was useful as a prognostic predictor for OS in patients with HNSCC who received radical concurrent CRT or BRT. MLR may be more reflective of OS than of LRFS or PFS.

INTRODUCTION

Head and neck cancer (HNC) is the 8th most common cancer worldwide and the 6th leading cause of cancer-related deaths [1], with squamous cell carcinoma being the most common HNC. Approximately one-third of all patients with head and neck squamous cell carcinoma (HNSCC) are diagnosed at an early stage, and 70%–90% of patients are successfully treated. However, a substantial number of patients with locally advanced HNSCC have a poor prognosis because of the high propensity for locoregional recurrence or metastases after treatment [2]. Smoking, alcohol consumption, and tumour stage are known prognostic factors for HNC [3-6]. Radiotherapy (RT) and chemoradiotherapy (CRT) play an important role in preserving vocal function during HNC treatment [7, 8].

Recently, studies have reported that macrophages are a major constituent of the tumour microenvironment and play an important role in promoting tumorigenesis and suppressing the anti-tumour immune response [9]. The monocyte-to-lymphocyte ratio (MLR) is a systemic inflammation biomarker that is used as a prognostic marker for lung cancer, pancreatic cancer, colorectal cancer, ovarian cancer, and HNC [10-13]. The MLR test is inexpensive and easy to perform by routine examination of peripheral blood.

Bonner *et al.* reported that bioradiotherapy (BRT) had better outcomes than RT alone for HNC [14]. Furthermore, Tang *et al.* reported that CRT had better outcomes than BRT for HNC [15], although in clinical practice, BRT is often preferred over CRT for older patients and those with renal dysfunction. The usefulness of MLR as a prognosticator of HNC has been reported for patients undergoing surgery and receiving, chemotherapy, RT, and CRT [16–20]; however, but few studies reports include patients receiving BRT. Therefore, in this study, we examined the usefulness of MLR as a prognosticator of HNSCC (oropharyngeal, hypopharyngeal, and laryngeal cancers) in patients treated with both CRT and BRT.

MATERIALS AND METHODS

This study was approved by Institutional Review Board of Yamaguchi University Hospital (25/08/2020-094). Written informed consent was obtained from all the patients before treatment initiation.

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Patients

In this study, the medical records of patients with HNSCC treated with radical CRT or BRT at Yamaguchi University Hospital between January 2015 and April 2020 were reviewed. The 8th edition of the Union International Cancer Control TNM Classification of Malignant Tumours was used for cancer staging. Those evaluated in the 7th edition were evaluated and revised in the 8th edition. The exclusion criteria for this study were as follows: (1) recurrent cancer, (2) postoperative CRT or BRT, (3) no haematological records within one month before the start of treatment, (4) discontinuation of RT, and (5) presence of autoimmune disorders or active inflammatory diseases. （6） early stage of laryngeal cancer. Of the 101 patients with HNSCC who underwent radical CRT or BRT, 25 were excluded. Finally, data from 76 patients were used for the analysis.

Peripheral blood was collected within 1 month before the start of radiotherapy.

Treatment

Patients underwent intensity-modulated radiotherapy (IMRT), although patients with laryngeal cancer usually undergo three-dimensional conformal radiotherapy (3DCRT). Computed tomography (CT) images, including plain and contrast-enhanced (obtained 90 s after bolus tracking), of patients with fixture shells from parietal to the tracheal bifurcation, with a slice thickness of 2 mm for IMRT and 3 mm for 3DCRT, were acquired using SOMATOM Definition AS Open (Siemens, Munich, Germany) and sent to the Eclipse (Varian Medical Systems, Alto Palo, CA, USA), a treatment planning system. Primary and lymph node gross tumour volume (GTV) were defined using contrast-enhanced CT, magnetic resonance imaging (MRI), ^{18}F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT), and fiberscope. The GTV node was defined as lymph nodes with FDG-PET/CT positivity or short axis diameters of ≥ 10 mm. The primary clinical target volume (CTV) included an isotropic margin of 1 cm from the primary GTV. The CTV node was obtained by adding to the GTV node a 5 mm isotropic margin and with an extracapsular extension including an isotropic margin of 1 cm. The CTV margin was anatomically adapted. Planning target volume (PTV) 1 was contoured by adding an isotropic expansion of 5 mm to the combination of primary CTV and CTV nodes with prophylactic lymph node areas. PTV2 was defined as PTV1, excluding the prophylactic lymph node areas. The irradiation dose was 70 Gray (Gy) with IMRT and 66 Gy with 3DCRT. PTV1 was irradiated with 40-46 Gy, and PTV2 was irradiated with 20–30 Gy with 4 or 6 Megavoltage (4 MV or 6 MV) photon beams. Irradiation was administered at 2 Gy/ fraction per day, five days per week. The radiotherapy units used in this study were TrueBeam (Varian Medical Systems, Alto Palo, CA, USA), and MHCL-15DP (Mitsubishi Electric, Tokyo, Japan). Concurrent chemotherapy was performed largely with cisplatin or a combination of carboplatin and fluorouracil. Cetuximab was used for BRT.

Statistical analysis

EZR v. 1.50, was used for statistical analysis [21]. Locoregional recurrence-free survival (LRFS), progression-free survival (PFS), and overall survival (OS) were assessed using Kaplan–Meier survival analysis, and variables were compared using the log-rank test. The survival rate was calculated after completion of RT. Locoregional recurrence was defined as local recurrence or regional lymph node recurrence. The Cox proportional hazard model was used to assess the significance of the variables associated with survival outcomes. Multivariate analysis was performed with the inclusion of variables with a p-value < 0.2 in the univariate analysis. A two-tailed p-value of <0.05 was considered significant. The variables included age, sex, smoking, alcohol consumption, and MLR. MLR was calculated by dividing the number of monocyte by the number of lymphocyte. Receiver operating characteristic (ROC) curves for LRFS, PFS, and OS were plotted to verify the optimal cut-off values of MLR.

RESULTS

Clinical characteristics

Patient characteristics are listed in table 1. This study included 68 men (89.4%) and 10 women (10.6%) with a median age of 66 years (range, 38–87 years). There were 25 patients (32.9%) with oropharyngeal cancer, 40 patients (52.6%) with hypopharyngeal cancer, and 11 patients (14.5%) with laryngeal cancer. 18 patients (23.7%) were diagnosed at an early stage (I or II), and 58 patients (76.3%) were diagnosed at a late stage (III or IV). The median follow-up period was 21 months (range, 1–58 months).

The optimal cut-off values of MLR were 0.252 for LRFS, 0.253 for PFS, and 0.257 for OS. The areas under the curve for LRFS, PFS, and OS were 0.526, 0.579, and 0.628, respectively.

Survival outcomes

Locoregional recurrence-free survival

Locoregional recurrence was observed in 20 patients (8 local recurrences, 11 regional recurrences, and both in 1 patient). The 1 and 2-year LRFS rates were 75.0% and 70.4%, respectively (figure 1). N 2 - 3 were associated with poor LRFS in the univariate analysis (table 2). In multivariate analysis, N 2 - 3 was a significant independent predictor of LRFS (hazard ratio [HR]=4.47,

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confidence interval [CI]=1.43-14.0, p=0.0103) (table 3). MLR was not a significant prognostic factor of LRFS.

Progression-free survival

Cancer progression was observed in 27 patients, including 20 patients with locoregional recurrence and 7 patients with lung metastasis. The 1 and 2-year PFS rates were 64.5% and 57.8%, respectively (figure 2). N 2 - 3 were associated with poor PFS in the univariate analysis (table 2). In the multivariate analysis, N 2 - 3 was a significant independent predictor of PFS (hazard ratio [HR]=4.94, confidence interval [CI]=1.84-13.2, p<0.01) (table 3). MLR was not a significant prognostic factor of PFS.

Overall survival

19 patients died during the follow-up period, with 10 patients dying due to primary cancer. The 1 and 2-year OS rates were 85.3% and 70.8%, respectively. The lower MLR group had a longer OS (1 and 2-year OS of 96.0% and 76%, respectively) than the higher MLR group (1 and 2-year OS of 86.9% and 57.0%, respectively) (p=0.0326) (figure 3). A lower MLR was associated with a better OS in the univariate analysis (table 2). In multivariate analysis, a lower MLR was a significant independent predictor of OS (hazard ratio [HR]=0.305, confidence interval [CI]=0.102–0.916, p=0.034) (table 3).

Table 1. Characteristics of patients.

Characteristics	n (%)
Age, median[range],y	66 [38-87]
<70	44 (57.9)
≥70	32 (42.1)
Sex	
Male	68 (89.4)
Female	8 (10.6)
Smoking	
Yes	64 (84.2)
No	12 (15.8)
Drinking	
Yes	62 (81.5)
No	14 (18.5)
Primary	
Larynx	11 (14.5)
Oropharynx	25 (32.9)
Hypopharynx	40 (52.6)
T stage	
1-2	42 (55.5)
3-4	34 (44.5)
N stage	
0-1	34 (44.4)
2-3	42 (55.6)
Clinical stage	
I, II	18 (23.7)
III, IV	58 (76.3)
Radiotherapy	
IMRT	68 (89.4)
3DCRT	8 (10.6)
Chemotherapy	
Cisplatin	26 (34.2)
CBDCA+5-FU	21 (27.7)
Cetuximab	22 (28.9)
Others	7 (9.2)
Radiotherapy system	
TrueBeam	70 (92.1)
MHCL-15DP	6 (7.9)
MLR, median[range]	0.266 [0.1-1.0]

Table 2. Univariate analysis for locoregional-free survival, progression-free survival, and overall survival

	LRFS		PFS		OS	
Variable	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age (< vs. ≥ 70 years)	0.930(0.378-2.29)	0.875	1.03(0.468-2.26)	0.947	0.565(0.227-1.41)	0.219
Sex (male vs. female)	0.890(0.204-3.87)	0.876	1.31(0.309-5.57)	0.712	0.891(0.205-3.87)	0.877
Smoking (No vs. Yes)	1.00(0.289-3.47)	0.998	0.635(0.190-2.13)	0.461	0.251(0.033-1.88)	0.179
Drinking (No vs. Yes)	1.28(0.423-3.85)	0.665	1.10(0.413-2.91)	0.967	0.494(0.114-2.14)	0.346
T classification (T3-4 vs. T1-2)	0.658(0.262-1.65)	0.373	0.972(0.456-2.09)	0.662	0.870(0.349-2.17)	0.765
N classification (N2-3 vs. N0-1)	3.98(1.30-12.2)	0.016*	4.85(1.81-13.0)	<0.01*	1.58(0.622-4.03)	0.335
Clinical stage (III-IV vs. I-II)	5.78(0.772-43.4)	0.088	4.00(0.944-16.9)	0.060	1.02(0.338-3.08)	0.972
Treatment (CRT vs. BRT)	0.517(0.209-1.28)	0.154	0.763(0.345-1.69)	0.503	0.708(0.284-1.76)	0.458
MLR (< vs. ≥ cut-off)	0.582(0.237-1.43)	0.236	0.514(0.225-1.18)	0.116	0.345(0.109-0.975)	0.042*

Table 3. Multivariate analysis for locoregional-free survival, progression-free survival, and overall survival

Variable	HR (95% CI)	p
Locoregional free survival		
N stage (N2-3 vs. N0-1)	4.47 (1.43-14.0)	0.010*
Treatment (CRT vs. BRT)	0.440 (0.177-1.070)	0.076
Progression free survival		
N stage (N2-3 vs. N0-1)	4.94 (1.84-13.2)	<0.01*
MLR (< vs. ≥ cut-off)	0.495 (0.216-1.13)	0.096
Overall survival		
Smoking (No vs. Yes)	0.209 (0.027-1.56)	0.127
MLR (< vs. ≥ cut-off)	0.305 (0.102-0.916)	0.034*

HR: hazard ratio, CI: confidence interval, MLR: monocyte-to-lymphocyte ratio, BRT: bioradiotherapy, CRT: chemoradiotherapy

* Statistically significant

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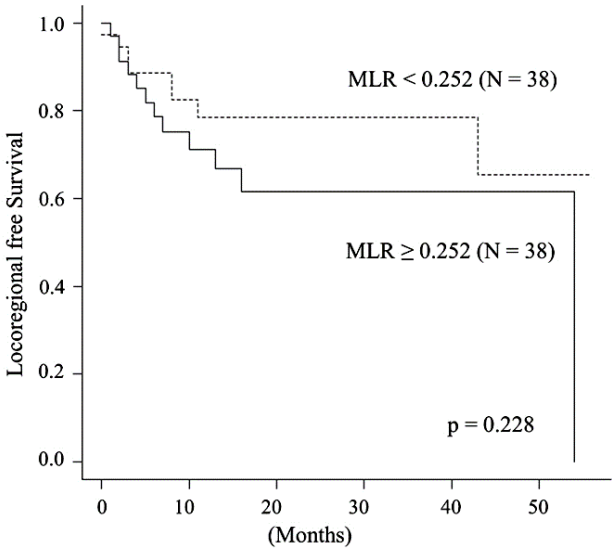

Figure 1. Kaplan-Meier curve for monocyte to lymphocyte ratio (MLR) on locoregional recurrence-free survival.

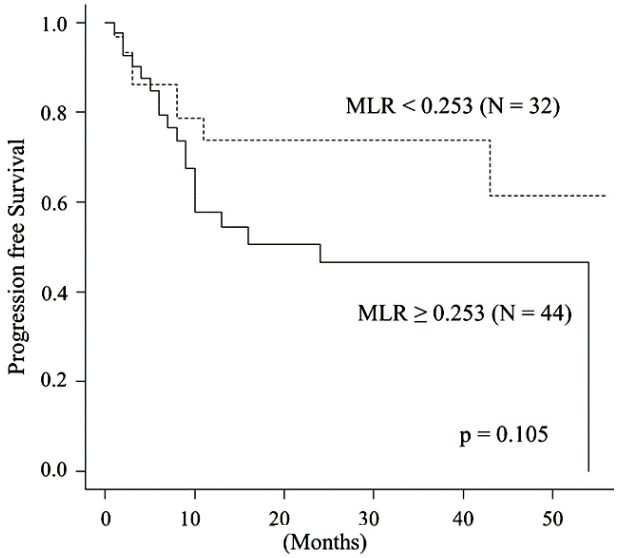

Figure 2. Kaplan-Meier curve for monocyte to lymphocyte ratio (MLR) on progression-free survival.

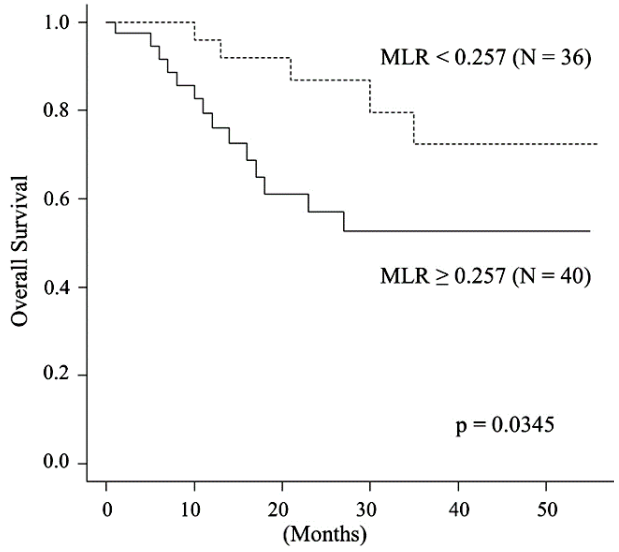

Figure 3. Kaplan-Meier curve for monocyte to lymphocyte ratio (MLR) on overall survival.

DISCUSSION

This study showed that MLR can be a prognostic factor in the CRT or BRT patient group, as well as in other HNC studies [16-20]. Systematic reviews have also shown that MLR is a prognostic factor for OS in HNC [22]. Since there is confounding between the N stage and clinical stage, in multivariate analysis performed without using the clinical stage, N stage was a significant prognostic factor for LRFS and PFS. The difference between CRT and BRT with respect to LRFS tended to be significant; this result was consistent with that reported the by Tang *et al.* [15]. Differences in treatment intensity may have influenced differences in LRFS. In addition, there is a possibility that the observation period in the study was short, which resulted in the absence of a significant difference in clinical stage or N stage with respect to OS.

It has been reported that monocytes act as tumour -associated macrophages (TAMs) in the tumour microenvironment promoting tumour growth and distant metastasis [23]. It is thought that an increase in the number of monocytes in the peripheral blood is correlated with an increased number of TAMs in the tumour microenvironment. Lymphocytes in the peripheral blood contain cytotoxic T cells that activate the immune system response against tumour cells and suppress tumour development [24]. Thus, an increase in monocytes and a decrease in lymphocytes, i.e., an increase in MLR, are beneficial to tumour cells. In that respect, MLR is considered to affect LRFS, PFS and OS; however, in this study only OS was significantly associated with MLR. Meanwhile, several studies have reported MLR as a predictor of diseases other than cancer. For example, it has been reported that MLR is a prognostic factor for haemodialysis patients [25], and a predictor for the occurrence of pneumonia in stroke patients [26]. These observations suggest that a high MLR value may not only influence death from cancer, but also death from other diseases. This is consistent with the finding of this study that only OS was significantly associated with MLR. In addition, MLR has been reported to be useful for predicting new onset of chronic nephritis [27] and for diagnosing knee osteoarthritis [28], suggesting a potential relationship between MLR and chronic inflammation. It has also been reported that chronic inflammation causes diseases such as type 2 diabetes and cardiovascular disease [29], and this may also have a negative impact on OS. Therefore, MLR may be more reflective of OS, rather than of LRFS or PFS. To distinguish between the effects of cancer and chronic inflammation on MLR, one possible approach would be to assess changes in MLR before and after treatment and compare them to tumour response to treatment and changes in tumour markers, as reported by Lin *et al.* [30].

Macrophages can be classified into tissue-resident macrophages (TRMs) and bone marrow-derived

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macrophages (BDMs) [31]. BDMs are the primary constituent of TAMs in advanced cancers [32]. However, the composition ratio of BDMs to TRMs in the tumour microenvironment changes depending on tumour progression [32]. For instance, in murine-derived pancreatic ductal adenocarcinomas, TRMs are the main constituent of the tumour microenvironment [9]. Therefore, the composition ratio of macrophages may differ depending on the histological type or staging of the tumour. This may affect the MLR cut-off value, as previous studies have reported cut-off values ranging between 0.18-0.44.

The limitations of this study are the small sample size and the single-centre retrospective design. Therefore, future multicentre prospective studies are needed to establish the usefulness of MLR as a prognostic indictor.

In conclusion, our data suggest that in HNSCC MLR is a useful prognostic predictor when patients treated with CRT or BRT are analysed together. Since the MLR is thought to reflect not only the tumour microenvironment but also the chronic inflammatory state, MLR may be more reflective of OS than of LRFS or PFS. Larger studies are needed to establish MLR as a prognosis indictor.

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***Ethnical statement*:** This study was approved by Institutional Review Board of Yamaguchi University Hospital (No.2020-094) and conducted according to the principles of the Declaration of Helsinki and its later amendments.

***Author contribution*:** HT and HT conceived the idea of the study. HT contributed to data analysis and interpretation. HT, TO, MK and YM contributed to draft and revise the manuscript. MM supervised the conduct of this study. All authors reviewed and approved the final manuscript.

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