CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Prognostic value of pretreatment circulating neutrophils, monocytes, and lymphocytes on outcomes in lung stereotactic body radiotherapy

M. Giuliani MBBS,* L.R. Sampson MA,* O. Wong BSc,* J. Gay BSc,* L.W. Le MSc,† B.C.J. Cho MD,* A. Brade MD,* A. Sun MD,* A. Bezjak MD,* and A.J. Hope MD*

ABSTRACT

Purpose In the present study, we determined the association of pretreatment circulating neutrophils, monocytes, and lymphocytes with clinical outcomes after lung stereotactic body radiotherapy (SBRT).

Methods All patients with primary lung cancer and with a complete blood count within 3 months of lung SBRT from 2005 to 2012 were included. Overall survival (OS) was calculated using the Kaplan–Meier method. Factors associated with OS were investigated using univariable and multivariable Cox proportional hazards regression. Fine–Gray competing risk regression was performed to test the association of the neutrophil:lymphocyte (NLR) and monocyte:lymphocyte (MLR) ratios with two types of failure: disease-related failure and death, and death unrelated to disease.

Results Of the 299 SBRT patients identified, 122 were eligible for analysis. The median and range of the NLR and MLR were 3.0 (0.3–22.0) and 0.4 (0.1–1.9) respectively. On multivariable analysis, sex ($p = 0.02$), T stage ($p = 0.04$), and NLR ($p < 0.01$) were associated with OS. On multivariable analysis, T stage ($p < 0.01$) and MLR ($p < 0.01$) were associated with disease-related failure; MLR ($p = 0.03$), NLR ($p < 0.01$), and SBRT dose of 48 Gy in 4 fractions ($p = 0.03$) and 54 Gy or 60 Gy in 3 fractions ($p = 0.02$) were associated with disease-unrelated death. Median survival was 4.3 years in the NLR≤3 group (95% confidence interval: 3.5 to not reached) and 2.5 years in the NLR>3 group (95% confidence interval: 1.7 to 4.8; $p < 0.01$).

Conclusions In lung SBRT patients, NLR and MLR are independently associated with OS and disease-unrelated death. If validated, NLR and MLR could help to identify patients who would benefit most from SBRT.

Key Words SBRT, SABR, neutrophils, lymphocytes, monocytes, hemoglobin, outcomes

Curr Oncol. 2016 Aug;23(4):e362-e368 www.current-oncology.com

INTRODUCTION

Stereotactic body radiotherapy (SBRT)—also called stereotactic ablative radiotherapy (SABR)—has become the standard of care for patients diagnosed with early-stage non-small-cell lung carcinoma (NSCLC) who are medically inoperable or who refuse surgery[1]. Stereotactic body radiotherapy also has been explored in patients who are operable[2]. The technique can be used in patients of advanced age and with significant medical comorbidities, demonstrating good clinical outcomes and minimal toxicity[3]. As SBRT becomes readily available, selecting patients who will benefit from treatment in the setting of advanced medical comorbidities is an increasing clinical challenge[4].

Given the advanced age of and prevalence of comorbidities in patients who commonly receive SBRT for NSCLC, clinical selection metrics that are minimally invasive and readily available are most appropriate. Increasing evidence suggests that circulating levels of neutrophils, monocytes, and lymphocytes are associated with variable tumour control and survival in tumour sites, including

Correspondence to: Meredith E. Giuliani, Department of Radiation Oncology, 5th Floor, Princess Margaret Cancer Centre, 610 University Avenue, Toronto, Ontario M5G 2M9. E-mail: meredith.giuliani@rmp.uhn.on.ca ■ **DOI:** http://dx.doi.org/10.3747/co.23.3051

head-and-neck cancer[5], ovarian cancer[6], colorectal cancer[7], and cervical cancer[a]. A recent meta-analysis of 13,964 patients participating in twenty-six studies demonstrated that elevated platelet:lymphocyte ratio (PLR) is a negative predictor for overall survival (OS) with a hazard ratio of 1.60 [95% confidence interval (CI): 1.35 to 1.90; $p < 0.01$)[8]. High neutrophil:lymphocyte ratio (NLR) has also been shown to have poor prognostic implications in patients with chronic medical conditions such as coronary artery disease[9] and end-stage renal disease[10]. Utilizing prognostic indicators obtained from a complete blood count (CBC) to inform decision-making in patients with early-stage lung cancer considering SBRT is attractive, given that it is readily obtained, minimally invasive, and low cost.

The purpose of the present study was to determine the association of pre-treatment circulating neutrophils, monocytes, and lymphocytes with clinical outcomes after lung SBRT in patients with early-stage NSCLC.

METHODS

Patient Selection

Patients with clinical T1–2N0M0 NSCLC who had received lung SBRT at our institution from January 2005 to January 2012 and who had CBC results within the 3 months before the start of SBRT were included[5,11]. Clinical and treatment data were abstracted from a prospective database that contains information on patient demographics, treatment, toxicities, patterns of recurrence, and cause of death. Patients with multiple courses of radiotherapy, metastatic lung tumours, or multiple synchronous primaries were excluded. The study was conducted with research ethics board approval.

In most cases, computed tomography (CT) imaging of the thorax, combined positron-emission tomography and CT imaging, and brain magnetic resonance imaging or CT imaging were used for pre-SBRT staging. The pathologic diagnosis was obtained where possible. Patients were treated according to the institutional SBRT protocol, mostly with 1 of 3 dose regimens: 48 Gy in 4 fractions (12 Gy per fraction delivered every other day) for peripheral tumours 3 cm or less in size, 54 Gy or 60 Gy in 3 fractions (without inhomogeneity correction; 18 Gy per fraction delivered every other day) for peripheral tumours larger than 3 cm in size, or 60 Gy in 8 fractions (7.5 Gy per fraction delivered once daily) for central tumours[3]. Patient follow-up included chest radiography 6 weeks after SBRT, followed by CT imaging of the thorax at 3, 6, 12, 18, and 24 months, and then annually thereafter.

Statistical Analyses

The OS was calculated from date of radiation to date of death (from any cause) or was censored at the last follow-up date. The association of the NLR and the monocyte:lymphocyte ratio (MLR) with OS was investigated using univariable and multivariable Cox proportional hazards regression. To further investigate any effect of those ratios, a competing risks analysis was carried out. The study considered two types of failure: failure type 1 (disease-related failure, including local, regional, or distant failure and death from disease) and failure type 2 (disease-unrelated death with no local, regional, or distant failure). Fine–Gray competing risk regression was performed to test the associations of NLR and MLR with the two types of failure. For the purposes of the foregoing analyses, NLR, MLR, and PLR were treated as continuous variables.

Before all multivariable analyses, a stepwise variable selection procedure was performed, and variables at $p \leq 0.10$ were included in the final multivariable analysis. The NLR and MLR, as the variables of interest, were included in all multivariable results regardless of statistical significance. The log-rank and Gray tests were used to compare the Kaplan–Meier estimates of OS and the cumulative incidence functions of the two failure types, using the median NLR (3.0) as the cut-off value.

RESULTS

Of the 299 SBRT patients identified, 122 patients who had a CBC within the 3 months before SBRT were eligible for the analysis. Of those 122 patients, 47 had their CBC within 1 month before and 75 had their CBC 1–3 months before SBRT. Median age in the group was 75 ± 9 years, and 62 of the patients (51%) were women. In 52 patients (43%), histology was adenocarcinoma; in 23 (19%), it was squamous cell carcinoma; in 19 (16%), it was NSCLC; and in 28 (23%), no pathologic diagnosis was made. The tumour in 91 patients (75%) was clinical stage T1, and in 31 (25%), it was T2. The SBRT dose in 28 patients (23%) was 54 Gy or 60 Gy in 3 fractions; in 72 (59%), it was 48 Gy in 4 fractions; and in 22 (18%) it was 60 Gy in 8 fractions. Based on the Radiation Therapy Oncology Group 0236 definition, 9 tumours (7%) were central.

Median neutrophil count at baseline was 4.5×10^9/L (range: 1.0–12.0×10^9/L). Median lymphocyte count was 2.0×10^9/L (range: 0–12.0×10^9/L), and median hemoglobin was 132.4 g/L (range: 71.0–178.0 g/L; Figure 1). Median NLR was 3.0 (range: 0.3–22.0), and median MLR was 0.4 (range: 0.1–1.9). Table I summarizes the demographic details of the patients.

In this cohort, 9 local failures (4 biopsy-proven), 16 regional failures, and 23 distant failures occurred. Median follow-up duration was 26.9 months (range: 1.3–99.3 months) for all patients and 32.6 months (range: 12.2–99.3 months) for patients still alive at last follow-up. Median OS duration was 43.7 months (95% CI: 29.7 to 57.0 months).

On multivariable analysis, female sex ($p = 0.02$), NLR ($p < 0.01$), and T stage ($p = 0.04$) were associated with better OS (Table II). Median OS was 4.3 years (95% CI: 3.5 years to not reached) in the group of patients with a NLR equal to or below the median (≤3, "low NLR"); it was 2.5 years (95% CI: 1.7 to 4.8 years) in the group with a NLR above the median (>3, "high NLR"). The 3-year survival rate was 66.2% for the low NLR group (95% CI: 55.5% to 79.1%) and 41.2% for the high NLR group (95% CI: 28.3% to 59.9%; $p < 0.01$; Figure 2).

On multivariable analysis, T stage ($p < 0.01$) and MLR ($p < 0.01$) were associated with disease-related failure, and NLR ($p < 0.01$), MLR ($p = 0.03$), and SBRT doses of 48 Gy in 4

[a] Glickman R, Chaudary N, Pintilie M, *et al.* Neutrophils modulate response to radiation and chemotherapy in locally advanced cervical cancer. Presented at: The Canadian Association of Radiation Oncology 28th Annual Scientific Meeting; St. John's, NL; 25–28 August 2014.

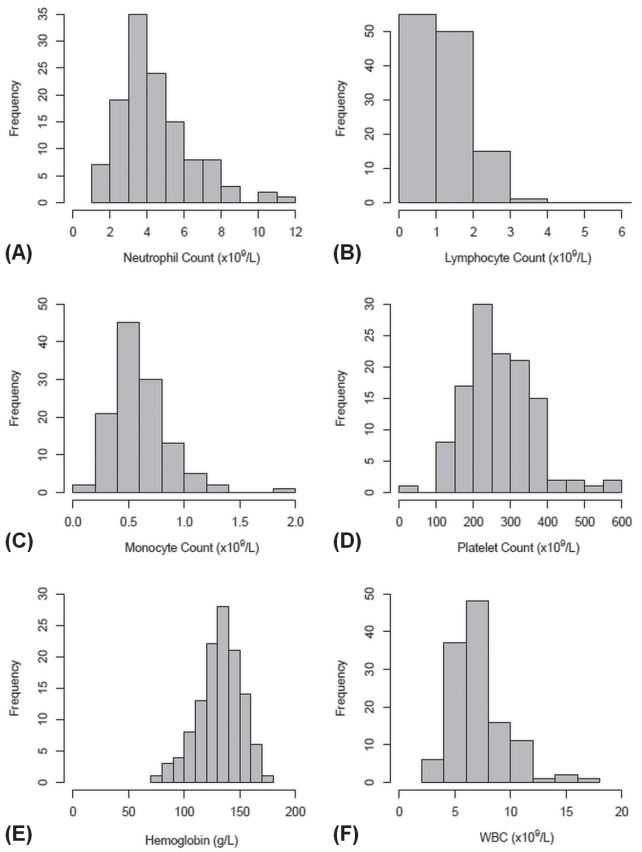

FIGURE 1 Pre-treatment distribution of neutrophils, lymphocytes, monocytes, platelets, hemoglobin, and white blood cells (WBC).

TABLE I Patient demographics and characteristics

Variable	Frequency
Patients (*n*)	122
Age (years)	
Mean	74.6±9.2
Median	76
Range	48–90
Sex [*n* (%)]	
Women	62 (50.8)
Men	60 (49.2)
Histology [*n* (%)]	
Adenocarcinoma	52 (42.6)
Non-small-cell lung cancer	19 (15.6)
Squamous	23 (18.9)
No pathologic diagnosis	28 (23.0)
Tumour stage [*n* (%)]	
T1	91 (74.6)
T2	31 (25.4)
Pulmonary function	
FEV[a] (L)	
Mean	1.5±0.6
Median	1.4
Range	0.5–3.1
Baseline %FEV[a]	
Mean	68.4±26.0
Median	67.5
Range	7.0–143.0
DLCO (L)	
Mean	13.1±4.8
Median	12.5
Range	0.9–26.1
Baseline %DLCO	
Mean	62.8±19.2
Median	62.0
Range	22.0–113.0
Radiotherapy [*n* (%)]	
54 Gy in 3 factions or 60 Gy in 3 factions	28 (23.0)
48 Gy in 4 factions	72 (59.0)
60 Gy in 8 factions	22 (18.0)
ECOG PS [*n* (%)]	
0	37 (30.3)
1	55 (45.1)
2	27 (22.1)
3	3 (2.5)
Baseline neutrophils (×10⁹/L)	
Mean	4.9±2.0
Median	4.5
Range	1.0–12.0
Baseline lymphocytes (×10⁹/L)	
Mean	1.8±1.2
Median	2.0
Range	0–12.0
Neutrophil:lymphocyte ratio	
Mean	3.5±2.5
Median	3.0
Range	0.3–22.0
Baseline white blood cells (×10⁹/L)	
Mean	7.6±2.5
Median	7.0
Range	2.0–17.0
Baseline hemoglobin (g/L)	
Mean	132.2±19.8
Median	133.5
Range	71.0–178.0
Baseline platelets (×10⁹/L)	
Mean	271.3±93.5
Median	265.0
Range	20.0–580.0
Platelet:lymphocyte ratio	
Mean	184.8±99.7
Median	158
Range	19.9–58.0
Baseline monocytes (×10⁹/L)	
Mean	0.6±0.3
Median	0.6
Range	0.1–1.9
Monocyte:lymphocyte ratio	
Mean	0.4±0.2
Median	0.4
Range	0.1–1.9

FEV = forced expiratory volume; DLCO = diffusing capacity of the lungs for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; PS = performance status.

TABLE II Cox proportional hazards regression for overall survival

Variable	Univariable			Multivariable[a]		
	HR	95% CL	*p* Value	HR	95% CL	*p* Value
Age	1.00	0.97, 1.02	0.99			
Female sex	0.49	0.30, 0.82	0.006	0.54	0.32, 0.91	0.02
Histology			0.07			
Adenocarcinoma	0.50	0.27, 0.96	0.04			
Non-small-cell lung cancer	0.74	0.35, 1.57	0.43			
No pathology	0.41	0.20, 0.88	0.02			
Squamous	—	—	—			
Tumour stage T2	1.66	0.98, 2.83	0.06	1.75	1.01, 3.02	0.04
ECOG performance status			0.09			
0	0.46	0.22, 0.94	0.03			
1	0.85	0.48, 1.50	0.57			
2–3	—	—	—			
Radiotherapy			0.13			
48 Gy in 4 factions	0.85	0.41, 1.78	0.67			
54 Gy in 3 factions or 60 Gy in 3 factions	1.47	0.69, 3.11	0.32			
60 Gy in 8 factions	—	—	—			
Neutrophils	1.16	1.02, 1.31	0.02			
Lymphocytes	0.93	0.72, 1.20	0.58			
Neutrophil:lymphocyte ratio	1.26	1.13, 1.41	<0.0001	1.22	1.08, 1.38	0.001
White blood cells	1.09	0.99, 1.20	0.09			
Hemoglobin	0.98	0.97	1.00, 0.02	0.99	0.97, 1.00	0.06
Platelets[b]	1.00	1.00, 1.01	0.20			
Platelet:lymphocyte ratio[b]	1.04	1.01, 1.07	0.004			
Monocytes	1.67	0.68, 4.11	0.26			
Monocyte:lymphocyte ratio	2.4	1.12, 5.17	0.02			
Baseline %FEV1	1.00	0.99, 1.01	0.70			
Baseline %DLCO	1.00	0.99, 1.01	0.61			

[a] A stepwise variable selection was performed, and variables with $p \leq 0.10$ were included in the multivariable result.
[b] Per 10-unit increase in platelets or platelet:lymphocyte ratio.
HR = hazard ratio; CL = confidence limits; ECOG = Eastern Cooperative Oncology Group; FEV1 = forced expiratory volume in 1 second; DLCO = diffusing capacity of the lungs for carbon monoxide.

fractions ($p = 0.03$) and 54 Gy or 60 Gy in 3 fractions ($p = 0.02$) were associated with disease-unrelated death (Table III). The 3-year cumulative incidences of disease-unrelated death were 14.4% (95% CI: 5.5% to 23.4%) in the low NLR group and 38.6% (95% CI: 23.4% to 53.8%) in the high NLR group ($p < 0.01$, Figure 3).

DISCUSSION

Our data demonstrate that NLR and MLR are associated with both OS and disease-unrelated death in patients treated with lung SBRT. Patients receiving SBRT are likely to achieve NSCLC control and to die of other causes. Consideration of comorbid diseases such as chronic obstructive pulmonary disease (COPD) is as relevant as tumour factors are in clinical decision-making for this patient population. The evidence suggests that withholding SBRT from elderly patients with advanced COPD is not justified[12] and that there is no known lower limit for pulmonary function[13]. In the context of patients with previous COPD diagnoses undergoing SBRT in increasing numbers, the implications of NLR and MLR in chronic disease are as important as are their roles in cancer prognosis.

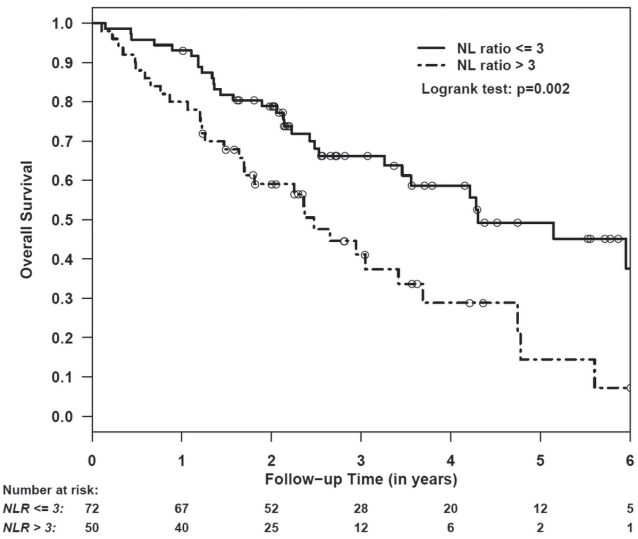

FIGURE 2 Kaplan–Meier curves for overall survival by neutrophil:lymphocyte (NL) ratio (NLR).

TABLE III Fine–Gray competing risk regression for disease-related failure (type 1) and disease-unrelated death (type 2)

Variable	Event type 1[a]						Event type 2[b]					
	Univariable			Multivariable			Univariable			Multivariable		
	HR	95% CL	*p* Value	HR	95% CL	*p* Value	HR	95% CL	*p* Value	HR	95% CL	*p* Value
Age	0.99	0.95, 1.03	0.45				1.02	0.99, 1.05	0.18			
Female sex	0.69	0.36, 1.32	0.26				0.50	0.26, 0.95	0.03			
Histology			0.34						0.12			
Adenocarcinoma	1.36	0.54, 3.42	0.51				0.42	0.19, 0.94	0.03			
Non-small-cell lung cancer	1.51	0.49, 4.67	0.47				0.42	0.16, 1.15	0.09			
No pathology	0.60	0.18, 1.95	0.39				0.47	0.19, 1.13	0.09			
Squamous	—	—	—				—	—	—			
Tumour stage T2	2.71	1.38, 5.32	0.004	3.18	1.45, 7.00	0.004	0.65	0.29, 1.47	0.3			
ECOG performance status			0.93						0.23			
0	1.15	0.46, 2.85	0.77				0.46	0.19, 1.12	0.09			
1	1.18	0.50, 2.80	0.71				0.70	0.34, 1.46	0.34			
2–3	—	—	—				—	—	—			
Radiotherapy			0.09						0.12			0.07
48 Gy in 4 factions	0.44	0.19, .01	0.05				3.42	0.81, 14.43	0.09	5.58	1.16, 26.89	0.03
54 Gy in 3 factions or 60 Gy in 3 factions	0.86	0.33, 2.22	0.75				4.46	1.04, 19.09	0.04	6.19	1.33, 28.83	0.02
60 Gy in 8 factions	—	—	—				—	—	—	—	—	—
Neutrophils	0.97	0.78, 1.21	0.8				1.13	0.96, 1.32	0.15			
Lymphocytes	1.03	0.86, 1.24	0.72				0.90	0.45, 1.80	0.77			
Neutrophil:lymphocyte ratio	0.88	0.70, 1.11	0.27	1.11	0.97, 1.28	0.13	1.26	1.09, 1.45	0.001	1.31	1.16, 1.49	<0.0001
White blood cells	1.00	0.86, 1.17	0.96				1.06	0.95, 1.19	0.31			
Hemoglobin	0.99	0.98, 1.01	0.29				0.99	0.98, 1.01	0.54			
Platelets[c]	1.01	0.97, 1.04	0.71				1.01	0.96, 1.06	0.69			
Platelet:lymphocyte ratio[c]	0.97	0.94, 1.01	0.15				1.06	1.02, 1.09	0.002			
Monocytes	0.24	0.05, 2.25	0.26				3.44	1.12, 10.50	0.03			
Monocyte:lymphocyte ratio	0.05	0.01, 0.33	0.002	0.02	0.001, 0.23	0.003	15.6	3.95, 61.90	<0.0001	5.67	1.15, 27.88	0.03
Baseline %FEV1	1.01	1.00, 1.02	0.17				1.00	0.99, 1.01	0.89			
Baseline %DLCO	1.01	0.99, 1.02	0.47				1.01	0.99, 1.02	0.40			

[a] Disease-related failures, including local, regional, or distant failure and died of disease.
[b] Disease-unrelated death.
[c] Per 10-unit increase in platelets or platelet:lymphocyte ratio.
HR = hazard ratio; CL = confidence limits; ECOG = Eastern Cooperative Oncology Group; FEV1 = forced expiratory volume in 1 second; DLCO = diffusing capacity of the lungs for carbon monoxide.

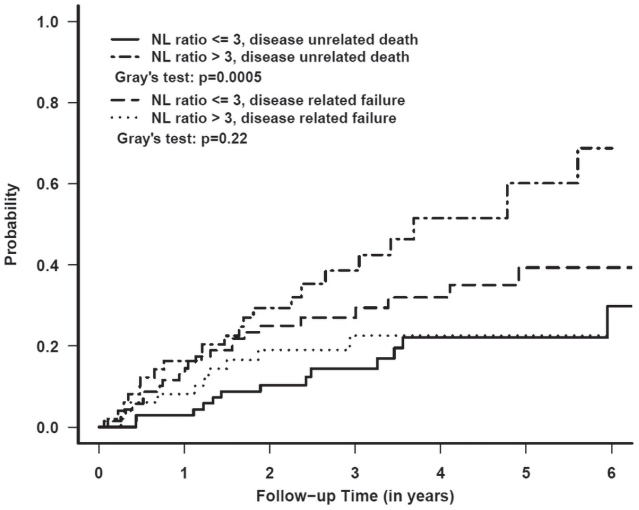

FIGURE 3 Cumulative incidence of disease-unrelated deaths and disease-related failure. NL = neutrophils:lymphocytes.

The NLR is associated with a number of chronic and comorbid conditions in this patient population, including COPD, smoking, and vascular disease, and the NLR has been shown to be significantly higher in patients with COPD than in healthy control subjects[14]. During acute exacerbation of COPD, a further increase in NLR was demonstrated compared with the stable period in the same patients[14]. There is evidence that smoking has an effect on neutrophil count and inflammatory response markers, independent of genetic background and environmental variables[15]. Finally, an elevated NLR has also been shown to be associated with mortality in patients which coronary artery disease[16].

The question therefore remains whether NLR is predictive of survival because of the tumour itself, because of an underlying poor medical status of the patient, or because of some interplay between the two. Until a better understanding of the association between NLR and NSCLC outcomes emerges, the NLR could be used to inform decision-making in patients with early-stage lung cancer considering SBRT. Such patients, whose survival will be determined by their other comorbidities, could potentially be spared unnecessary treatment for their lung cancer.

Cells of myeloid and lymphoid lineages might have different biologic effects on tumour progression, metastasis, and response to radiation therapy[17,18]. In a 2015 study of pre-treatment neutrophils, monocytes, and lymphocytes in oropharyngeal cancer, Huang *et al.*[5] demonstrate that higher circulating myeloid cells (for example, neutrophils and monocytes) independently predict inferior OS and recurrence-free survival after chemoradiotherapy. Preclinical data suggest the presence of an interaction between lymphocytes and myeloid cells in regulating pro-tumour activity compared with antitumour activity in solid tumours, and B and T lymphocytes might play a role in regulating multiple pro-tumour properties of myeloid cells[19,20]. Evidence suggests that neutrophils and monocytes are recruited to tumours during radiation therapy and promote vasculogenesis, offsetting the effectiveness of treatment and ultimately negatively influencing treatment outcomes[21–23]. The degree to which that hypothesis is relevant in situations such as SBRT, with its high dose per fraction, remains to be explored.

The NLR has been shown to be predictive of OS and progression-free survival in patients with small-cell lung cancer[24]. Reports in patients with other chronic diseases have shown that NLR is predictive of survival[10,16]. To our knowledge, the present study represents the largest series of SBRT patients reported with respect to this topic to date; it is also the first to include MLR in the analyses. A previous study of 59 patients showed an association of NLR and PLR with survival, and PLR was associated with an increased risk of nonlocal failure[11]. The univariate regression analyses in that study demonstrated that OS was associated with NLR and PLR only when the latter variables were coded categorically; the association became statistically nonsignificant when NLR and PLR were tested as continuous variables[11]. Using multivariate analyses, we demonstrated that low NLR and MLR are independently predictive of OS and that high ratios are associated with disease-unrelated death. On univariate analysis, the PLR was found to be significantly associated with OS and disease-unrelated death, but not with disease-related failure. Together, both datasets confirm the importance of NLR in NSCLC outcomes, and our data convey the importance of MLR in addition to NLR.

The NLR and MLR are simple, inexpensive, and reliable tests, and are thus clinically useful. Their application is still unclear, because NLR and MLR might not be consistent with tumour-specific markers. Comorbid inflammatory conditions and steroid treatments can confound results. Some authors recommend that these ratios be assessed with other inflammatory markers such as C-reactive protein, red cell distribution width, and erythrocyte sedimentation rate[25,26]. Validation remains an ongoing consideration because numerous articles have reported on NLR and MLR using different cut-off levels[27–30].

Our study has several limitations. First, the limited number of disease failures could represent a lack of power to determine any associations of NLR and MLR with disease-related outcomes such as local failure or disease-specific survival. In addition, as in many series about SBRT, confirming cause of death is challenging. Many patients have significant medical comorbidities, and death related to previously undiagnosed recurrence or related-to-treatment toxicity might not be identified in the face of sudden death in the presence of significant cardiac, pulmonary, or other chronic comorbidities. Future prospective studies to evaluate the effects of chronic versus acute SBRT on NLR and MLR are needed. Because high-dose radiation has been shown to alter cells associated with pro- and antitumour immunity[31], investigating the interplay between dose and these cell ratios is also justified. Finally, CBC within 3 months of SBRT, as chosen for the present study, is consistent with other radiotherapy analyses of NLR and MLR[5,11]; however, the degree to which neutrophils, monocytes, and lymphocytes can change within that time period is not known.

CONCLUSIONS

The NLR and MLR are independently correlated with OS and disease-unrelated death in patients treated with SBRT for early-stage primary lung cancer. If validated, NLR and MLR could help to identify patients who would benefit most from SBRT and other interventions.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: AJH and MG have received travel funding from Elekta, and AB has received funding from Elekta for SBRT database support.

AUTHOR AFFILIATIONS

*Department of Radiation Oncology and †Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON.

REFERENCES

1. Dahele M, Brade A, Pearson S, Bezjak A. Stereotactic radiation therapy for inoperable, early-stage non-small-cell lung cancer. *CMAJ* 2009;180:1326–8.
2. Chang JY, Senan S, Paul MA, *et al.* Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015;16:630–7.
3. Timmerman R, Paulus R, Galvin J, *et al.* Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070–6.
4. Boily G, Filion E, Rakovich G, *et al.* on behalf of the Comité de l'évolution des pratiques en oncologie. Stereotactic ablative radiation therapy for the treatment of early-stage non-small-cell lung cancer: CEPO review and recommendations. *J Thorac Oncol* 2015;10:872–82.
5. Huang SH, Waldron JN, Milosevic M, *et al.* Prognostic value of pretreatment circulating neutrophils, monocytes, and lymphocytes in oropharyngeal cancer stratified by human papillomavirus status. *Cancer* 2015;121:545–55.
6. Asher V, Lee J, Innamaa A, Bali A. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. *Clin Transl Oncol* 2011;13:499–503.
7. Kwon HC, Kim SH, Oh SY, *et al.* Clinical significance of preoperative neutrophil–lymphocyte versus platelet–lymphocyte ratio in patients with operable colorectal cancer. *Biomarkers* 2012;17:216–22.
8. Zhou X, Du Y, Huang Z, *et al.* Prognostic value of PLR in various cancers: a meta-analysis. *PloS One* 2014;9:e101119.
9. Prajapati JH, Sahoo S, Nikam T, Shah KH, Maheriya B, Parmar M. Association of high density lipoprotein with platelet to lymphocyte and neutrophil to lymphocyte ratios in coronary artery disease patients. *J Lipids* 2014;2014:686791.
10. Turkmen K, Ozcicek F, Ozcicek A, Akbas EM, Erdur FM, Tonbul HZ. The relationship between neutrophil-to-lymphocyte ratio and vascular calcification in end-stage renal disease patients. *Hemodial Int* 2014;18:47–53.
11. Cannon NA, Meyer J, Iyengar P, *et al.* Neutrophil–lymphocyte and platelet–lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non-small-cell lung cancer. *J Thorac Oncol* 2015;10:280–5.
12. Louie AV, Rodrigues G, Hannouf M, *et al.* Withholding stereotactic radiotherapy in elderly patients with stage I non–small cell lung cancer and co-existing COPD is not justified: outcomes of a Markov model analysis. *Radiother Oncol* 2011;99:161–5.
13. Guckenberger M, Klement RJ, Kestin LL, *et al.* Lack of a dose-effect relationship for pulmonary function changes after stereotactic body radiation therapy for early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013;85:1074–81.
14. Gunay E, Sarinc Ulasli S, Akar O, *et al.* Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: a retrospective study. *Inflammation* 2014;37:374–80.
15. Andreoli C, Bassi A, Gregg EO, Nunziata A, Puntoni R, Corsini E. Effects of cigarette smoking on circulating leukocytes and plasma cytokines in monozygotic twins. *Clin Chem Lab Med* 2015;53:57–64.
16. Duffy BK, Gurm HS, Rajagopal V, Gupta R, Ellis SG, Bhatt DL. Usefulness of an elevated neutrophil to lymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention. *Am J Cardiol* 2006;97:993–6.
17. Donskov F. Immunomonitoring and prognostic relevance of neutrophils in clinical trials. *Semin Cancer Biol* 2013;23:200–7.
18. Dumitru CA, Lang S, Brandau S. Modulation of neutrophil granulocytes in the tumor microenvironment: mechanisms and consequences for tumor progression. *Semin Cancer Biol* 2013;23:141–8.
19. DeNardo DG, Andreu P, Coussens LM. Interactions between lymphocytes and myeloid cells regulate pro- versus antitumour immunity. *Cancer Metastasis Rev* 2010;29:309–16.
20. Ruffell B, DeNardo DG, Affara NI, Coussens LM. Lymphocytes in cancer development: polarization towards pro-tumor immunity. *Cytokine Growth Factor Rev* 2010;21:3–10.
21. Kozin SV, Kamoun WS, Huang Y, Dawson MR, Jain RK, Duda DG. Recruitment of myeloid but not endothelial precursor cells facilitates tumor regrowth after local irradiation. *Cancer Res* 2010;70:5679–85.
22. Ahn GO, Brown JM. Influence of bone marrow-derived hematopoietic cells on the tumor response to radiotherapy: experimental models and clinical perspectives. *Cell Cycle* 2009;8:970–6.
23. Ng WL, Huang Q, Liu X, Zimmerman M, Li F, Li CY. Molecular mechanisms involved in tumor repopulation after radiotherapy. *Transl Cancer Res* 2013;2:442–8.
24. Kang MH, Go SI, Song HN, *et al.* The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer. *Br J Cancer* 2014;111:452–60.
25. Nakamura T, Matsumine A, Matsubara T, Asanuma K, Uchida A, Sudo A. The combined use of the neutrophil-lymphocyte ratio and C-reactive protein level as prognostic predictors in adult patients with soft tissue sarcoma. *J Surg Oncol* 2013;108:481–5.
26. Yalcinkaya E, Bugan B, Celik M, Yasar S, Gursoy E. Neutrophil lymphocyte ratio should be assessed together with other inflammatory markers and confounding factors. *Eur Rev Med Pharmacol Sci* 2013;17:2410.
27. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. *Oncology* 2007;73:215–20.
28. Kishi Y, Kopetz S, Chun YS, Palavecino M, Abdalla EK, Vauthey JN. Blood neutrophil-to-lymphocyte ratio predicts survival in patients with colorectal liver metastases treated with systemic chemotherapy. *Ann Surg Oncol* 2009;16:614–22.
29. Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. *Br J Cancer* 2011;104:1288–95.
30. Stotz M, Gerger A, Eisner F, *et al.* Increased neutrophil–lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. *Br J Cancer* 2013;109:416–21.
31. Demaria S, Formenti SC. Role of T lymphocytes in tumor response to radiotherapy. *Front Oncol* 2012;2:95.