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Research Paper

Systemic Inflammation Biomarkers Predict Survival in Patients of Early Stage Non-Small Cell Lung Cancer Treated With Stereotactic Ablative Radiotherapy - A Single Center Experience

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Abstract

Background: Increasing evidence indicates a relationship between systemic inflammation and survival following treatment in various tumors. However, the correlation of systematic inflammation with survival after stereotactic ablative radiotherapy (SABR) in early stage non-small cell lung cancer (NSCLC) has not been well established.

Patients and methods: We retrospectively analyzed patients with newly diagnosed early stage NSCLC treated with SABR in a single institution from 2011 to 2015. The neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte- monocyte ratio (LMR) were calculated as systemic inflammation biomarkers. Overall survival (OS) was the first end-point. Receiver operating characteristic (ROC) was used to determine cut-off points for OS. Univariate and multivariate Cox proportional hazards regression were used to investigate the potential factors associated with OS.

Results: In the 63 patients who were eligible for analysis. The median follow up after SBRT was 29.5 months (range 8-67 months) while the 3-year OS was 74.2%. Based on ROC analysis, optimal cut-off values of NLR, PLR, and LMR were 2.06, 199.55 and 4.0, respectively. Significant survival benefit was found in the NLR ≤2.06 group (p=0.028), PLR≤199.55 group (p=0.001), and LMR>4.0 group (p=0.046). Univariate analysis indicated that low NLR (p=0.011), low PLR (p=0.003), and high LMR (p=0.014) were correlated with improved survival. Multivariate analysis indicated that high PLR (p=0.033) and low LMR (p=0.046) were independent prognostic factors for poor survival.

Conclusions: In patients of early stage NSCLC who received SABR, pretreatment NLR, PLR, and LMR could be considered useful prognostic indicators of OS. These metrics may provide reliable and convenient predictors to identify patients who would benefit from SABR.

Key words: non-small cell lung cancer; neutrophil-lymphocyte ratio; platelet-lymphocyte ratio; lymphocyte-monocyte ratio; stereotactic ablative radiotherapy

Introduction

Lung cancer has become the most frequent cause of cancer death across the world, with NSCLC representing the most prevalent type [1, 2]. In the past few decades, much progress has been made in identifying and treating lung cancer. Though the 5-year OS for patients with locally advanced and

advanced stage NSCLC remains poor, patients with early stage (stage IA, IB or II) have the largest possibility of cure with advances in surgery resection and radiation therapy [3-5]. SABR, also called stereotactic body radiotherapy (SBRT) is an alternative therapy that is widely used in the management of early stage NSCLC. SABR has shown some success in treating patients who were either medically inoperable or refuse surgery [6]. For patients who were operable, SABR has also been investigated and demonstrated promising results [7]. As SABR becomes increasingly used, it is vitally important to select eligible patients that may benefit from this treatment protocol.

Systemic inflammation is the result of pro-inflammatory cytokine secretion by immune–related cells after the activation of immune system. Biomarkers indicative of inflammation, such as white cell counts and acute phase proteins, have been repeatedly demonstrated to have prognostic value [8, 9]. Over the last few decades, systemic inflammation has been revealed as both an etiologic factor and physiological response advanced cancer [10]. Recent findings have identified that cancer associated inflammation plays a critical role in the progression of different malignancies. Prognostic markers of systemic inflammation, including neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) are simple to derive, inexpensive, and have been evaluated and found to correlate with disease outcomes in multiple tumors [11, 12]. However, most of these studies focus primarily on surgery, chemotherapy and conventional radiotherapy, with very little emphasis placed on early stage NSCLC patients who received SABR.

The cost and relative ease of deriving NLR, PLR, and LMR measurements from complete blood count (CBC) make them attractive biomarker candidates. However, it is unknown whether these biomarker candidates have prognostic value for patients that have received SABR in early stage NSCLC. Thus, we investigated the relationship between systemic inflammation biomarkers and survival of early stage NSCLC patients treated with SABR.

Material and Methods

Patient population

This study was approved by the institutional review board of the Affiliated Cancer Hospital of Zhengzhou University. Clinical and treatment data of consecutive NSCLC patients who underwent SABR at our institution from 2011 to 2015 were retrospectively analyzed. The main inclusion criteria were: early stage diagnosis (T1-2N0M0), age ≥ 18 years, availability of CBC results prior to SABR, and no prior history of malignant tumors. Patients with metastatic lung cancer, small cell lung cancer, local-regional recurrence disease, or those receiving SABR with palliative intent were excluded. The reasons for the included patients who received SABR were: elderly, medically inoperable, refuse surgery.

Management

Prior to treatment, a computed tomography (CT) imaging of the thorax, magnetic resonance imaging of the brain, as well as blood samples were obtained. Pathologic diagnosis was conducted after voluntary biopsies. The 7th edition of the TNM classification for lung cancer by the IASLC (International Association for the Study of Lung Cancer) was used for tumor staging [13]. A written informed consent was obtained from each patient before treatment.

For treatment planning, all patients were immobilized with arms above head within a custom stereotactic frame in the supine position. A stimulation scan was conducted with a 16-slice CT scan for all patients (Brilliance CT, Big Bore, Philips Healthcare, Andover, MA), both 3-dimensional CT (3DCT) and 4-dimensional CT images (4DCT) were acquired. Moreover, 4DCT image datasets for 10 phase bins of the respiratory cycle were generated during free breathing [14]. The maximum intensity projection (MIP) dataset was calculated based on assigning the highest density value for each pixel throughout the 10 phases of 4DCT images [15]. Tumor volume delineation has been reported in our previous studies [16, 17]. The gross target volume (GTV) was delineated on the 3DCT images, the internal target volume (ITV) was contoured on the MIP datasets, and combined ITV was generated by combining of GTV and ITV. The planning target volume (PTV) was defined as the combined ITV plus a 5-mm isotropic expansion. Dosimetry required that the prescription dose cover 95% of the PTV. Both Exac Trac and cone-beam CT were performed to confirm the position of the target during daily setup. Volumetric modulated arc therapy technique was adopted (TureBeam SN1403 accelerator, Varian Medical Systems).

The SABR regimens were designed according to size and location of the tumors. The most used treatment protocols were: 48 Gy in 4 fractions for tumors with a maximum diameter less than 3 cm, 50 Gy in 5 factions and 55 Gy in 5 fractions for tumors larger than 3 cm in size. Patient follow up, including a clinical examination and computed tomography imaging, was typically scheduled every 3 months for

the first 2 years after the completion of treatment and every 6 months thereafter.

Statistical analysis

The following laboratory parameters were collected from the CBC 1-3 days before SABR: neutrophil count, lymphocyte count, platelet count, and monocyte count. NLR was calculated with dividing the neutrophil count by the lymphocyte count. PLR was calculated as the platelet count divided by the lymphocyte count; similarly, LMR was calculated by dividing the lymphocyte count to the monocyte count. OS was the primary endpoint and defined from the date of SABR to date of death, the last follow up. Survival analyses were evaluated via the Kaplan-Meier methodology; the log-rank test was used to detect potential differences. Receiver operating characteristic (ROC) analysis was applied to determine the optimal cut-off values of NLR, PLR and LMR for survival. These calculated values were used for subsequent Kaplan-Meier analysis. In order to assess different SABR fraction regimes on survival, we calculated the BED10 (biologically effective dose) according to the linear-quadratic equation. To identify potential prognostic factors, univariate and multivariate Cox proportional hazard regression models were analyzed. Spearman's-rho analysis was utilized to determine the correlation between systemic inflammation biomarkers and clinic-pathological features. Statistical analyses were calculated using the statistical package for social sciences (SPSS) version 20.0 (IBM Software Group, Chicago, USA). All statistical tests were two-sided, and the level of significance was set to 5% ($p < 0.05$) for all of the statistical analyses.

Results

Patient characteristics

There were 216 patients who treated with SABR in our institution. Under careful review, 63 patients met the inclusion criteria and were eligible for analysis. Median follow up time was 29.5 months (range, 8-67 months). Median age of the whole cohort was 73 years (range, 44-89 years). Most of the selected patients were men, the proportion of male individuals was about 77.8% whereas only 22.2% female patients were included. Pretreatment biopsy for histological diagnosis was available for 74.6% of individuals; the remaining patients refused to provide biopsies. The main characteristics of the selected patients are illustrated in **Table 1**.

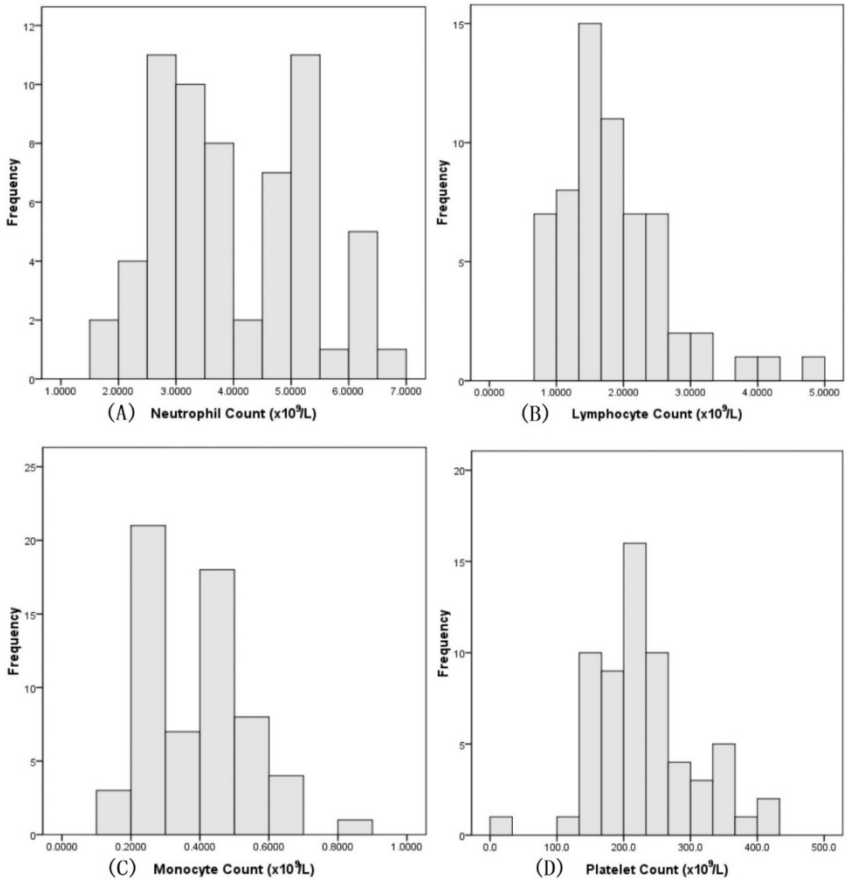

Figure 1. Pretreatment distribution of neutrophils, lymphocytes, monocytes, and platelets.

Laboratory values

Laboratory values of all included patients were available. The median neutrophil count was 3.96×10^9 cells/L (range: 1.80–6.87×109 cells/L). The median lymphocyte count was 1.85×10^9 cells/L (range: $0.68–4.77\times10^9$ cells/L). The median platelet count was 228.53×10^9 cells/L (range: $115.0–421.0\times10^9$ cells/L). The median monocyte count was 0.38×10^9 cells/L (range: 0.13–0.80 $\times10^9$ cells/L). Details are illustrated in **Figure 1**. Median NLR was 2.47 (range: 0.86–7.29), median PLR was 140.37 (range: 4.75–315.71), and median LMR was 5.25 (range: 1.33–11.14).

Survival analyses

ROC curves were calculated and the optimal cut-off values for NLR, PLR, and LMR were 2.06, 199.55, and 4.0, respectively. The 3-year OS of the entire cohort was 74.2%. Based on the cut-off points, patients were divided into two groups (low value group and high

value group). A NLR ≤ 2.06, a PLR ≤ 199.55, and a LMR > 4.0 optimally differentiated OS. We analyzed the two groups by Kaplan-Meier survival analysis, a high NLR (p=0.028; **Figure 2a**), a high PLR (p=0.001; **Figure 2b**) as well as a low LMR (p=0.046; **Figure 2c**) were associated with significantly decreased OS.

Table 1. Patients and disease characteristics.

Variable	Frequency
Patients (n)	63
Age (years)	
Mean	72.72±9.01
Median	73.00
Range	44-89
Sex (n)	
Women	14 (22.2%)
Men	49 (77.8%)
Smoke status	
Ex-smoker	10 (15.9%)
Current smoker	32 (50.8%)
Non-smoker	21 (33.3%)
Histology (n)	
Squamous cell carcinoma	25 (39.7%)
Adenocarcinoma	22 (34.9%)
Unknown	16 (25.4%)
Tumor stage (n)	
T1	44 (69.8%)
T2	19 (30.2%)
Radiotherapy (n)	
48 Gy in 4 factions	14 (22.2%)
50 Gy in 5 factions	25 (39.7%)
55 Gy in 5 factions	8 (12.7%)
Other factions	16 (25.4%)

Based on univariate analysis for OS, decreased NLR (P=0.011, hazard ratio [HR] = 1.489 [95% confidence interval (CI), 1.096-2.021]), elevated LMR (P=0.014, HR = 0.601 [95% CI, 0.402-0.900]), and decreased PLR (P=0.003, HR = 1.012 [95% CI, 1.004-1.019]) correlated with better OS (**Table 2**).

In order to determine the independent prognostic factors for OS, we also performed multivariate analyses by using Cox proportional hazard models. Decreased LMR (P=0.046, HR = 0.544 [95% CI, 0.299-0.989]), and elevated PLR (P=0.033, HR = 1.018 [95% CI, 1.001-1.034]) were correlated with poor OS (**Table 2**).

Correlations between Systemic inflammation biomarkers and clinic-pathological features

As illustrated in **Table 3**, the correlations between Systemic inflammation biomarkers and clinic-pathological features were also calculated using Spearman's-rho analysis. The following correlations achieved statistical significance ($p < 0.05$): NLR and gene mutation, NLR and smoke status, PLR and tumor stage, LMR and gene mutation, as well as LMR and smoke status. However, their correlation coefficients were too low, which suggests weak correlations.

Discussion

The present study demonstrates that Systemic inflammation biomarkers, as measured by NLR, PLR, and LMR, are correlated with survival in patients of early stage NSCLC who received SABR. Our results suggest that an elevated LMR (> 4.0) and a decreased PLR (≤ 199.55), were indicative of favorable independent prognostic factors for this patient population. In addition, our analysis also suggests that NLR, PLR, and LMR are weakly correlated with other clinical-pathologic features of early stage NSCLC patients who received SABR.

A century ago, the bilateral influence of inflammation and cancer was noticed by Rudolf Virchow [18]. In previous studies, the prognostic potential of systemic inflammation biomarkers was assessed in hematological cancers and various types of solid tumors. Hu et al conducted a retrospective study detailing a positive correlation between LMR and survival in operable NSCLC; the result indicated LMR was an effective prognostic factor [19]. The NLR has shown potential for use as a prognostic biomarker in patients of early stage NSCLC undergoing resection [20]. A systematic review by Guthrie has examined the clinical utility of the NLR and its association with patient outcomes in different kind of tumors; they found that the NLR could serve as an independent prognostic factor in patients undergoing surgery, neoadjuvant treatment followed by surgery, definitive chemoradiotherapy, and groups with inoperable tumors [21]. Lan et al recently reported the PLR as a good prognostic factor for OS in NSCLC patients undergoing radical lung cancer surgery [22]. However, the use of systemic inflammation biomarkers are not well characterized in patients with early stage NSCLC treated with SABR.

A single institution study by Shaverdian found an elevated pretreatment NLR and PLR independently predicted poor OS [23]. Likewise, a retrospective study by Cannon also indicated elevated NLR and PLR were associated with poor survival [24]. Giuliani et al demonstrated that NLR and LMR were independently correlated with OS in early stage NSCLC patients who were treated with SABR [25]. In the present work, we combined the NLR, PLR, and LMR metrics in order to analyze their collective contribution to OS. We calculated the cut-off value of NLR, PLR, and LMR to predict survival; the final outcomes were similar to Shaverdian's research insofar that our study suggests that an elevated pretreatment LMR, in conjunction with a decreased PLR and NLR were associated with better OS.

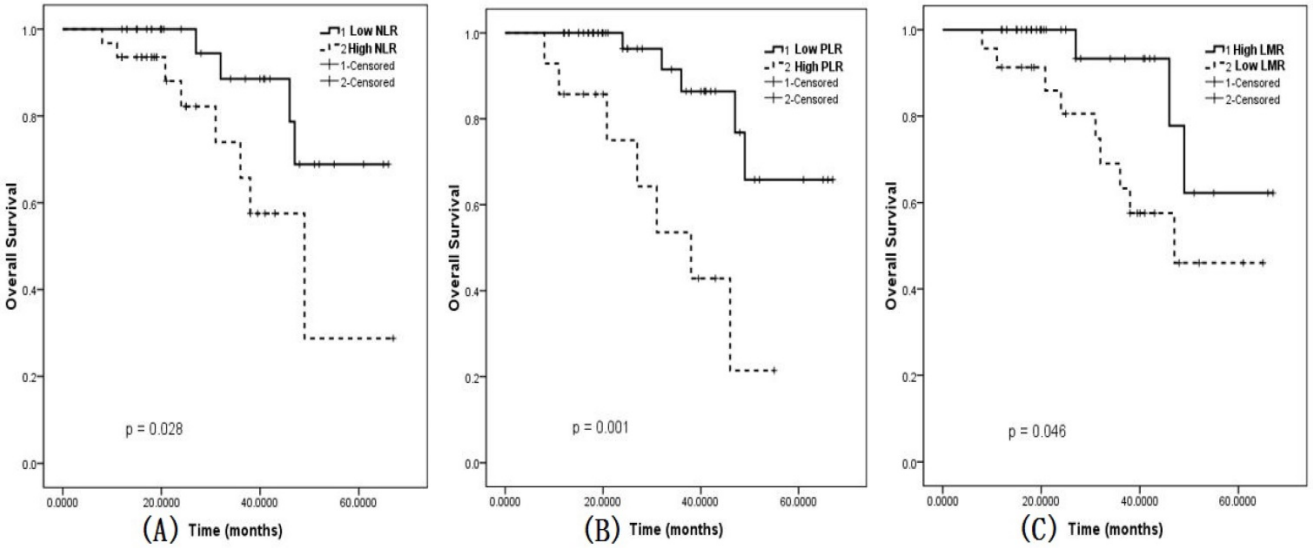

Figure 2. Overall survival in early stage patients. A: Survival based on neutrophil to lymphocyte ratio. Solid line-NLR≤2.06, dashed line-NLR>2.06. B: Survival based on platelet to lymphocyte ratio. Solid blue-PLR≤199.5, dashed green-PLR>199.5. C: Survival based on lymphocyte to monocyte ratio. Solid blue-PLR>4.0, dashed green-PLR≤4.0. Abbreviations: NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; LMR: lymphocyte- monocyte ratio.

Table 2. Cox proportional hazards regression for OS.

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P
Age (>65 vs ≤65)	1.047 (0.975-1.125)	0.203		
Sex (male vs female)	1.108 (0.299-4.100)	0.878		
Smoke status (yes vs no)	0.557 (0.164-1.895)	0.349		
Tumor stage (T1 vs T2)	2.402 (0.752-7.675)	0.139		
BED (>106Gy vs ≤106 Gy)	1.032 (0.958-1.113)	0.405		
NLR (>2.06 vs ≤2.06)	1.489 (1.096-2.021)	0.011		
PLR (>199.55 vs ≤199.55)	1.012 (1.004-1.019)	0.003	1.018 (1.001-1.034)	0.033
LMR (>4.0 vs ≤4.0)	0.601 (0.402-0.900)	0.014	0.544 (0.299-0.989)	0.046

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte- monocyte ratio. CI, confidence interval; HR, hazard ratio; BED, biological effective dose; OS, overall survival.

Table 3. Correlations between pretreatment immune parameters and clinic- pathological features.

Clinic-pathological features	NLR		PLR		LMR	
	Correlation coefficient	P	Correlation coefficient	P	Correlation coefficient	P
Age	-0.019	0.880	0.049	0.700	-0.192	0.132
Gene mutation	-0.262	0.038	-0.195	0.125	-0.339	0.007
Smoke status	-0.317	0.011	0.094	0.466	-0.360	0.004
Tumor stage	-0.107	0.406	0.289	0.022	-0.219	0.085
BED	-0.007	0.955	0.031	0.808	0.022	0.866

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte- monocyte ratio. BED, biological effective dose.

The immune system plays an important role in resisting or eradicating tumor formation and progression. Chronic inflammation induces several molecular cascades in cancer cells that facilitate immune cell evasion and tumor invasion [26]. Indeed, cancer incidence is increased when there are deficiencies in the development or function of CD8+ cytotoxic T lymphocytes and natural killer cells [27]. An elevated NLR, PLR, and a decreased LMR indicate systemic inflammation, which can lead to increased resting energy expenditure, hypoalbuminemia and malnutrition, eventually resulting in weight loss and tumor progression thereby leading to increased mortality [28, 29]. Other biomarkers such as transforming growth factor beta (TGF-β) are also involved in inflammation in cancer. Previous studies demonstrated that tumor cells could secreting TGF-β to inhibit the function of CD8+ cytotoxic T lymphocytes and natural killer cells [30].

Necroptosis is involved in the regulation of cancer. Radiotherapy can promote necroptosis of tumor cells. High dose radiation, such as SABR, could promote necroptosis through the caspase-3 signal pathway. Necroptotic cancer cells are capable of providing specific antigens and inflammatory stimuli for dendritic cells, while neutrophils, monocytes, and macrophages could produce pro-inflammatory cytokines and chemokines. Cytokine and chemokine production subsequently enhances antigen-presentation and T lymphocyte activation, thereby inducing anti-cancer immunity [31].

Mesenchymal stem cells (MSCs) are multipotent stromal cells that can differentiate into a variety of cell types. Chronic inflammation of the stroma could result in impairment of the immune system through an MSC dependent mechanism [32]. SABR could enhance MSC migration to the tumor microenvironment and generate pericytes, which

have been associated with local tumor recurrence, drug resistance, and passive immune evasion [33, 34].

Several researchers have shown the success of SABR as an effective, noninvasive treatment for patients with medically inoperable early stage NSCLC [35-38]. Findings from a retrospective study showed that the OS of SABR-treated NSCLC patients was 77% at 3 years [23]. Similarly, the 3-year OS reported by the Japanese Clinical Oncology Group 0403 trial was 76% [39]. In a propensity score-matched analysis by Verstegen, the 3-year OS of early stage NSCLC who received SABR was 79.6% [40]. The 3-year OS in the current study was similar to the above research. The combination of immunotherapy and SABR has been under investigation recently, as evidence showed synergy between immunotherapy and SABR in eliminating micrometastastatic disease [41, 42]. The NLR, PLR, and LMR metrics that are derived from CBC could be helpful in selecting the subset of early stage NSCLC patients who may benefit from SABR and its combination with immunotherapy.

There were some inherent limitations in our study. The present research was performed in a single medical center and only a small number of patients were included for analysis. The radiation doses received for the whole patient population were relatively uniform. Some patients also possessed additional medical co-morbidities such as coronary artery disease, which may influence systemic inflammation biomarkers and overall survival. Hence our findings should be interpreted with caution and need confirmation in larger prospective researches.

Conclusions

In conclusion, our data suggest that systemic inflammation biomarkers, including NLR, PLR, and LMR were correlated with OS in early stage NSCLC patients treated with SABR. The PLR and LMR could be regarded as useful independent prognostic factors in daily clinical practice. Future clinical trials based on larger populations are needed to determine the optimal cut-off values of NLR, PLR, and LMR.

Abbreviations

BED: biological effective dose; CBC: complete blood count; CI: confidence interval; CT: computed tomography; GTV: gross target volume; HR: hazard ratio; IASLC: International Association for the Study of Lung Cancer; ITV: internal target volume; LMR: lymphocyte- monocyte ratio; MIP: maximum intensity projection; MSC: Mesenchymal stem cell; NLR: neutrophil-lymphocyte ratio; NSCLC: non-small cell lung cancer; OS: overall survival; PLR: platelet-lymphocyte ratio; PTV: planning target volume; ROC: Receiver operating characteristic; SABR: stereotactic ablative radiotherapy; TGF-β: transforming growth factor beta.

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Competing Interests

The authors have declared that no competing interest exists.

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