Original Article

Clinical significance of mean corpuscular volume as a prognostic indicator of radiotherapy for locally advanced lung cancer: a retrospective cohort study

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Background: Although the prognosis of solid tumors is related to the mean corpuscular volume (MCV), which can roughly predict the prognosis of patients, its correlation with locally advanced lung cancer is still unclear. We evaluated the relationship between serum MCV levels and prognosis in patients before radiotherapy.

Methods: We retrospectively collected the age, sex, smoking history, TNM stage, ECOG score, hematocrit (HCT), MCV, mean corpuscular hemoglobin (MCH), and red blood cell distribution width-standard deviation (RDW-SD) of patients with locally advanced lung cancer who received chest radiotherapy from 2013 to 2017, and analyzed the relationship between this information and the overall survival (OS).

Results: Among all patients, 89 were male (79.5%), 23 were female (20.5%), 46 (41.1%) were older than 65 years, and 66 (58.9%) were younger than 65 years. Seventy-four patients had MCV <93.65 fL, 38 patients had MCV ≥93.65 fL, and the median follow-up period was 24 months. The patients with high T stage, high N stage, and high MCV had lower OS (P<0.05). In the Cox regression analysis, MCV [odds ratio (OR) =0.534, 95% confidence interval (CI): 0.349–0.818, P=0.01], T stage (OR =0.654, 95% CI: 0.440–0.972, P=0.04) and N stage (OR =0.545, 95% CI: 0.371–0.801, P=0.01) were predictors of prognosis.

Conclusions: In the clinical treatment of patients with locally advanced lung cancer, MCV can be used to roughly predict their survival time.

Keywords: Lung cancer; radiotherapy; prognostic factors; mean corpuscular volume (MCV); overall survival (OS)

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Introduction

Lung cancer is currently the most common cancer in China and the leading cause of cancer death (1). While the incidence and mortality of other cancers have declined, the incidence of lung cancer has gradually increased (2). About 30% of patients with non-small cell lung cancer are diagnosed with stage III disease, which is usually unresectable. Radiotherapy and concurrent radiotherapy have become the standard treatment for locally advanced lung cancer, but prognosis is poor, with a 5-year survival rate of ≈15–30% (3-5).

So far, traditional tumor-based histopathological risk factors such as tumor and lymph node stages, tumor differentiation, and resection margin status are the main

clinical prognostic factors but can only be determined from a biopsy. Furthermore, these factors are often influenced by neoadjuvant therapy. Therefore, additional prognostic indicators available preoperatively are urgently needed.

Recent findings suggest that mean corpuscular volume (MCV) is associated with prognosis in head and neck tumors, colorectal cancer, gastroesophageal adenocarcinoma, esophageal cancer, and liver cancer (6-10). Alcoholism can cause elevated MCV and folic acid deficiencies (11), and lung cancer is highly associated with alcohol and nicotine abuse (12). In addition, folic acid and vitamin B12 deficiencies, oxidative stress, and chemotherapy are known causes of elevated and/or altered MCV levels in cancer patients (10,13-16).

Currently, there is no research on the prognostic value of MCV in patients with locally advanced lung cancer, so we conducted a retrospective cohort study of patients with locally advanced lung cancer undergoing radiotherapy for the potential prognostic value of MCV. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1684/rc).

Methods

Patients

Patients with locally advanced lung cancer, including those clinically or pathologically diagnosed, who underwent intensity-modulated radiotherapy in the Department of Radiation Oncology at The First Affiliated Hospital of Shandong First Medical University between January 2013 and April 2017 were enrolled. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The First Affiliated Hospital of Shandong First Medical University (No. 2022-S607). Individual consent for this retrospective analysis was waived.

Eligible patients were: ≥18 years old, male or female, with locally advanced lung cancer confirmed by cytology or histology and without a history of malignant tumor, radiotherapy, serious cardiopulmonary, liver, or kidney disease, immune deficiency, or other complications. The hematological and routine biochemical results of the patients within 1 week prior to radiotherapy were collected, including red blood cells (RBC), white blood cells (WBC), platelets (PLT), hemoglobin (Hb), MCV, mean corpuscular hemoglobin (MCH), hematocrit (HCT), red blood cell distribution width index standard deviation value (RDW-SD) and RBC coefficient of variation (RDW-CV). In addition, basic tumor characteristics, including tumor-node-metastasis (TNM) stage and pathological type, and baseline information such as patient age, sex, smoking and drinking history, and ECOG score were collected.

A standardized monitoring protocol followed patients for at least 5 years with clinical assessments every 3 months. Data collected after radiotherapy included clinical assessment, laboratory tests, and whole body computed tomography. Evidence of recurrence was acquired from the patients' medical records. Overall survival (OS) was defined as the time from diagnosis to death from any cause or to the last follow-up.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA). The optimal cutoff value for each metric was selected using the subject receiver operating characteristic (ROC) curve, and the metrics were stratified. Survival curves were drawn using the Kaplan-Meier method; differences in survival were assessed using the log-rank test; multivariate analyses were performed using Cox proportional hazards models to assess the effect of prognostic factors on survival. $P<0.05$ was considered statistically significant.

Results

Patients' characteristics

A total of 112 patients with locally advanced lung cancer diagnosed between January 2012 and April 2017 were

Highlight box

Key findings

- MCV can roughly predict the survival time of patients with locally advanced lung cancer after radiotherapy.

What is known and what is new?

- MCV can predict the survival of many solid tumors.
- We found that MCV can predict the survival time of locally advanced lung cancer after radiotherapy.

What is the implication, and what should change now?

- High MCV is an unfavorable predictor of OS, which can be used to roughly predict its survival time.

Table 1 Basic physiological characteristics of patients with locally advanced lung cancer

Characteristics	Value (N=112)
Gender, n (%)	
Male	89 (79.5)
Female	23 (20.5)
Age, years, median [range]	62 [37–83]
Age, n (%)	
≥65 years	46 (41.1)
<65 years	66 (58.9)
History of smoking, n (%)	
Smoking	78 (69.6)
No smoking	34 (30.4)
Drinking history, n (%)	
Drinking	73 (65.2)
No drinking	39 (34.8)
T stage*, n (%)	
T1 + T2	63 (63.3)
T3 + T4	49 (43.8)
N stage*, n (%)	
N0 + N1 + N2	53 (47.3)
N3	59 (52.7)
ECOG score, n (%)	
0	56 (50.0)
1+2	56 (50.0)
Pathological type, n (%)	
Squamous cell carcinoma	42 (37.5)
Adenocarcinoma	41 (36.6)
Small cell lung cancer	29 (25.9)

*, according to the 7th AJCC/International Union against Cancer staging system. ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee for Cancer.

identified: 89 were male (79.5%), 23 (20.5%) were female, 46 (41.1%) were >65 years old, and 66 (58.9%) were ≤65 years old. The median follow-up period for the entire cohort was 24 months. The specific physiological and pathological characteristics of the patients are shown in *Table 1*, and the pretreatment clinicopathological parameters are shown in *Table 2*.

Table 2 Clinicopathological parameters before radiotherapy in patients with locally advanced lung cancer

Parameters	Mean ± SD
RBC ($\times10^{12}$/L)	4.1±0.69
WBC ($\times10^{9}$/L)	6.41±2.57
PLT ($\times10^{9}$/L)	226.82±84.28
Hb (g/L)	124.41±19.52
MCV (fL)	91.43±6.21
MCH (pg)	30.5±2.41
MCHC (g/L)	333.67±16.77
HCT	0.373±0.06
RDW-CV (%)	13.86±1.84
RDW-SD (fL)	48.68±20.52

MCV, mean red blood cell volume; MCHC, mean hemoglobin concentration; HCT, hematocrit; MCH, mean corpuscular hemoglobin; RDW-CV, red blood cell width CV; RDW-SD, red blood cell width SD value; CV, coefficient of variation; SD, standard deviation.

Relationship between pretreatment hematology and basic physiological characteristics and OS

To clarify whether hematologic indexes and basic physiological characteristics of the patients were related to OS, the correlation between the values obtained before radiotherapy and OS was analyzed. T stage, N stage, ECOG score, HCT, MCV, MCH, and RBC-SD were all negatively correlated with OS (P<0.05) (*Figure 1*).

Critical value of each parameter in patients with locally advanced lung cancer before radiotherapy

From the correlation analysis, the relevant parameters were included in the ROC curve analysis, and the optimal critical point of each index parameter was obtained. MCV area under the curve (AUC) =0.683, and the best cutoff value was 93.65 fL; HCT AUC =0.565, and the best cutoff value was 0.35; MCH AUC =0.692, and the best cutoff value was 31.15; RDW-SD AUC =0.64, and the best cutoff value was 48.75 (*Figure 2*).

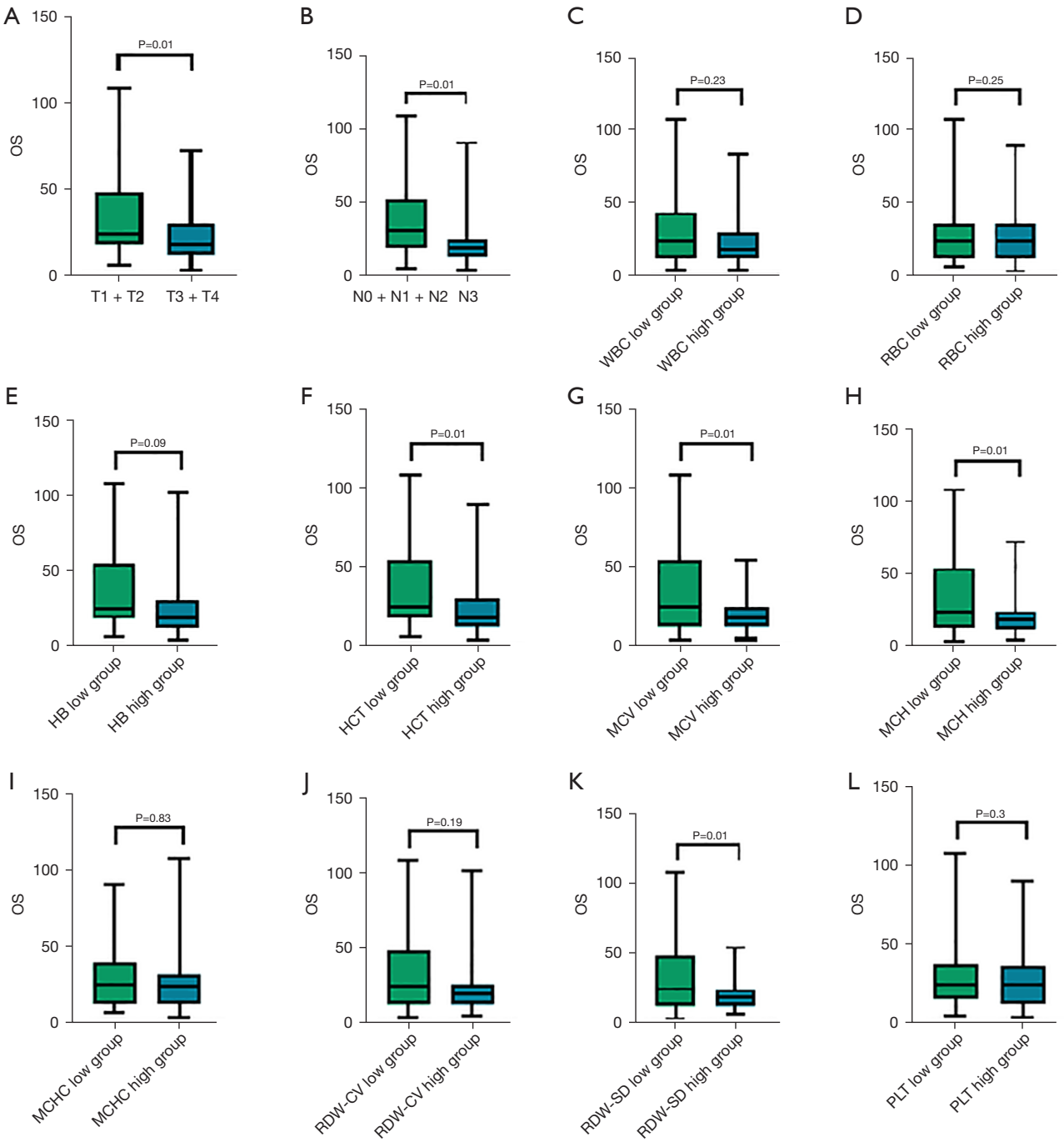

Figure 1 Correlation between high and low group parameters before radiotherapy and OS. (A-L) The correlation between high and low groups of parameters before radiotherapy and OS. Before radiotherapy, T stage, N stage, ECOG score, HCT, MCV, MCH, and RDW-SD were all negatively correlated with OS, P<0.05. OS, overall survival; WBC, white blood cells; RBC, red blood cells; HB, hemoglobin; HCT, hematocrit; MCV, mean red blood cell volume; MCH, mean corpuscular hemoglobin; MCHC, mean hemoglobin concentration; RDW-CV, red blood cell width CV; RDW-SD, red blood cell width SD value; CV, coefficient of variation; SD, standard deviation; PLT, platelet; ECOG, Eastern Cooperative Oncology Group.

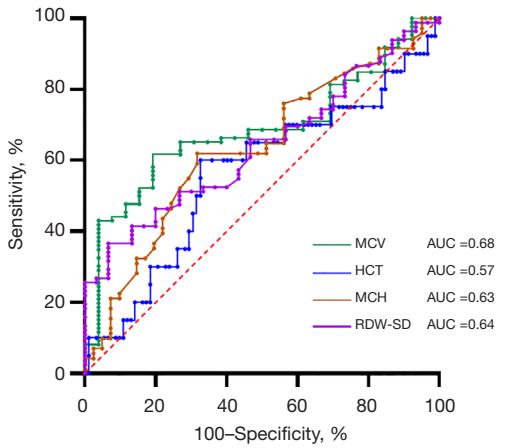

Figure 2 ROC curves of parameters and OS for all patients (n=112). The AUC was 0.68 (green line) for MCV, 0.57 (blue line) for HCT cells, 0.63 for MCH (brown line), and 0.64 for RDW-SD (purple line). AUC, area under the curve; MCV, mean red blood cell volume; HCT, hematocrit; MCH, mean corpuscular hemoglobin; RDW-SD, red blood cell width SD value; SD, standard deviation; ROC, receiver operating characteristic; OS, overall survival.

Correlation of parameters with OS

Kaplan-Meier survival analysis showed that the median OS of T1 + T2 patients was significantly better than that of T3 + T4 patients (24 *vs.* 18 months, P<0.01), and the median OS of N1 + N2 patients was significantly better than for N3 patients (30 *vs.* 18 months, P<0.01). Patients with MCV ≤93.65 fL had significantly better median OS than those with MCV >93.65 fL (24 *vs.* 18 months, P<0.01). The median OS of patients with HCT ≤0.35 was significantly better than that of patients with HCT >0.35 (24 *vs.* 18 months, P<0.01), the median OS of patients with MCH ≤31.15 was significantly better than that of patients with MCH >31.15 (24 *vs.* 18 months, P<0.01), and the median OS of patients with RDW-SD ≤48.75 was significantly better than that of patients with RDW-SD > 48.75 (24 *vs.* 18 months, P<0.01) (*Figure 3*).

Prognostic value of MCV

To investigate the prognostic impact of MCV on OS in

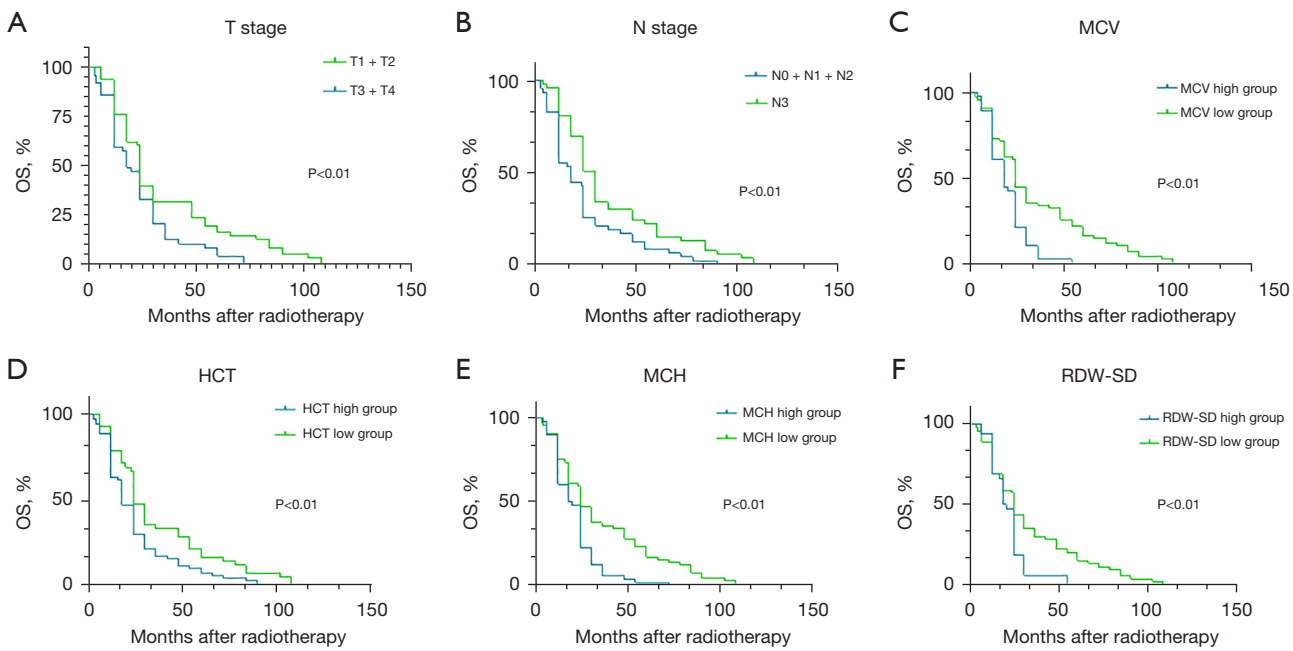

Figure 3 Stratified survival analysis for each parameter. Kaplan-Meier curve shows the overall survival of all patients with T stage (A), N stage (B), MCV (C), HCT (D), MCH (E), and RDW-SD (F) locally advanced lung cancer. OS, overall survival; MCV, mean red blood cell volume; HCT, hematocrit; MCH, mean corpuscular hemoglobin; RDW-SD, red blood cell width SD value; SD, standard deviation.

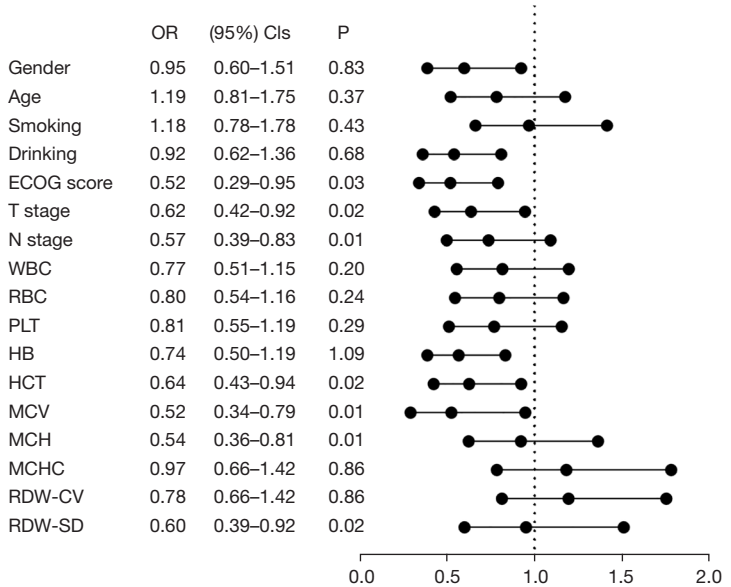

Figure 4 Univariate analysis of parameters and OS before radiotherapy. Based on univariate analysis of the relationship between OS and parameters, ECOG score, T staging, N staging, HCT, MCV, MCH, and RDW-SD were significantly correlated. ECOG, Eastern Cooperative Oncology Group; WBC, white blood cells; RBC, red blood cells; PLT, platelet; Hb, hemoglobin; HCT, hematocrit; MCV, mean red blood cell volume; MCH, mean corpuscular hemoglobin; MCHC, mean hemoglobin concentration; RDW-CV, red blood cell width CV; RDW-SD, red blood cell width SD value; CV, coefficient of variation; SD, standard deviation; OR, odds-ratio; CI, confidence interval; OS, overall survival.

Table 3 Univariate and multivariate analyses of clinical and pathological parameters for the prediction of overall survival

Factors	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
ECOG score	0.52	0.29–0.95	0.03			*
T stage	0.62	0.42–0.92	0.02	0.65	0.44–0.97	0.04
N stage	0.57	0.39–0.83	0.01	0.55	0.37–0.8	0.01
MCV	0.52	0.34–0.79	0.01	0.53	0.35–0.82	0.01
HCT	0.64	0.43–0.94	0.02			*
MCH	0.54	0.36–0.81	0.01			*
RDW-SD	0.62	0.39–0.92	0.02			*

*, not in the last step. OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; MCV, mean red blood cell volume; HCT, hematocrit; MCH, mean corpuscular hemoglobin; RDW-SD, red blood cell width SD value; SD, standard deviation.

patients with locally advanced lung cancer, we performed a Cox regression analysis. In the univariate analysis, ECOG score (P=0.03), T stage (P=0.02), N stage (P=0.01), MCV (P=0.01), HCT (P=0.02), MCHC (P=0.01), and RDW-SD (P=0.02) (*Figure 4*) were significant predictors and included in the multivariate analysis results showed that MCV [odds ratio (OR) =0.534, 95% confidence interval (CI): 0.349–0.818, P=0.01], T stage (OR =0.654, 95% CI: 0.440–0.972, P=0.04) and N stage (OR =0.545, 95% CI: 0.371–0.801, P=0.01) were prognostic factors. MCV was a prognostic factor among the pretreatment hematological indices, indicating that patients with pretreatment MCV level >93.6 fL had significantly shorter OS than those with MCV <93.6 fL (*Table 3*).

Discussion

In the present study, MCV was associated with OS of patients with locally advanced lung cancer undergoing radiotherapy, and a high MCV was a poor prognostic factor.

Currently, at present, the prognosis of locally advanced lung cancer mainly includes pathological type, pathological stage, molecular pathology, tumor location, treatment methods, patients' mental state, and lifestyle, among which the TNM stage is the most effective predictor of lung cancer survival rate. In this study, T stage, N stage, and MCV all had predictive effects on long-term survival in patients with locally advanced lung cancer before radiotherapy. However, precise TNM staging usually requires postoperative or biopsy pathological evaluation, making it hard to predict survival and determine the next treatment strategies for patients with inoperable locally advanced lung cancer. For such patients, other valid predictors are urgently needed.

MCV is a relatively stable blood index in healthy crowds, which mainly reflects the degree of anemia in patients. With the advent of automatic blood counts, more and more attention has been paid to the clinical significance of its increase or decrease in predicting disease progression. Except for being used to assist in the diagnosis of hematological diseases, MCV has been reported as clinically associated with tumors such as head and neck tumors, esophageal cancer, colorectal cancer, liver cancer, etc. and a high MCV is a poor predictor of long-term survival in patients with solid tumors (6-10,17,18).

In this study, we investigated the relationship between MCV and OS in patients with locally advanced lung cancer receiving radiotherapy. First, the best cutoff value of MCV was determined by ROC curve analysis, and it was 93.6 fL. Univariate and multivariate Cox regression analysis also showed that MCV is strongly associated with OS in these patients. Those with high MCV levels before treatment had significantly shorter OS than those with low MCV levels. Similarly, we found that both T and N stages were negatively correlated with OS, which concurred with the results of previous studies (6-10,17,18).

Our study of the relationship between MCV and locally advanced lung cancer found the high MCV level is a poor prognostic factor, however, we did not determine whether MCV plays a direct role in local recurrence and metastatic invasion. We hypothesize why a high MCV is a poor prognostic factor in patients with locally advanced lung cancer receiving radiotherapy.

First, MCV is an important marker of folate level, and folate deficiency usually causes an elevated MCV. Folic acid is an important carbon unit transfer carrier in human body, which plays an important role in DNA synthesis, replication, repair and methylation. Folic acid deficiency often leads to abnormal DNA methylation, which may be a bad predictor of the prognosis of lung cancer patients (19-21).

Furthermore, patients undergoing radiotherapy for lung cancer will experience loss of appetite, nausea, vomiting, dry mouth, and dry throat, resulting in poor dietary intake and reduced serum levels of Na^+, K^+, and other electrolytes, leading to a loss of osmotic pressure and a negative correlation with MCV level (22).

The MCV value is bound up with the HCT/L of blood and the number of RBCs/L of blood. The decrease of RBCs per unit volume involved in oxygen transport and metabolism may lead to the increase of MCV. Fewer RBCs will result in less oxygen available to the tumor, which will increase the proportion of hypoxic tumor cells. Hypoxia reduces the sensitivity of cells to radiation therapy, leading to a poor prognosis (21,23-25).

The current study has several limitations, despite repeated confirmation and calculation of our data and results. First, the number of patients was only 112, which may have led to erratic results due to small sample sizes. Secondly, this was a single-center retrospective study of patients in the same hospital, and its conclusions have not been validated by other centers. Hence, further prospective trials in multiple centers are needed to verify the reproducibility of these results in different populations. Several diseases that affect the MCV value, such as hypothyroidism, hematogic and hepatic diseases, were not screened, which could lead to selection bias. Furthermore, patients receiving concurrent chemoradiotherapy were included and represented 45.5% of the entire cohort. Concurrent chemoradiotherapy can act as an important confounding factor. Furthermore, this study was conducted over a considerable amount of time between 2012 and 2017, with historical biases regarding treatment strategies and radiotherapy management that may have determined prognostic outcomes. Despite these limitations, our findings may be clinically relevant for pre- and post-radiotherapy treatment or monitoring planning because MCV can be obtained by routine blood testing, which is readily available and inexpensive.

Conclusions

In patients with locally advanced lung cancer who received

radiotherapy, high MCV was an unfavorable predictor of OS. In the clinical treatment of patients with newly diagnosed locally advanced lung cancer, MCV can be used to roughly predict their survival time. For patients with a short-expected survival period, relatively conservative treatment methods can be adopted to shorten the radiotherapy cycle, thereby reducing the toxic and side effects of treatment. For those patients who are expected to survive long term, we can use more aggressive treatment to achieve the best results. We believe our findings will trigger many basic studies to elucidate the mechanisms behind them.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1684/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1684/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1684/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The First Affiliated Hospital of Shandong First Medical University (No. 2022-S607). Individual consent for this retrospective analysis was waived.

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