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ORIGINAL RESEARCH

High Mean Corpuscular Volume as a Predictor of Poor Overall Survival in Patients with Esophageal Cancer Receiving Concurrent Chemoradiotherapy

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Background: Increasing numbers of recent studies have demonstrated that high mean corpuscular volume (MCV) is a predictor of poor overall survival (OS) and therapeutic response in patients with solid tumors. The aim of the present study was to explore the association between high MCV and OS in patients with advanced esophageal cancer (EC) undergoing concurrent chemoradiotherapy.

Patients and Methods: Enrolled in this study were 249 patients with advanced EC who underwent concurrent chemoradiotherapy. Pre-treatment MCV values were collected in all patients and their correlations with OS and pathophysiological characteristics were analyzed. The chi-square test was used to explore the correlation between MCV and various clinical pathophysiological characteristics, and the prognostic significance of high MCV using Kaplan–Meier curves and the Cox proportional hazards model. All *P*-values were two-tailed and a *P*-value <0.05 was considered statistically significant.

Results: According to ROC curve analysis, the optimal cut-off value of MCV was 93.6 fL. The mean OS was 14.7 months in all 249 EC patients, 10.9 months in patients with MCV >93.6 fL, and 18.8 months in patients with MCV <93.6 fL; the difference is statistically significant (P<0.05). Chi-square test showed that the MCV value was correlated with the N stage of the tumor and the therapeutic effect, indicating that the higher the MCV was, the higher the T stage of the tumor and the worse the therapeutic effect would be (p=0.012 and p <0.01). Multivariate analysis showed that MCV (OR = 1.864, 95% CI: 1.439–2.415) was an independent prognostic factor for OS in EC patients.

Conclusion: High MCV is a poor predictor of OS in patients with advanced EC receiving concurrent chemoradiotherapy.

Keywords: esophageal cancer, mean corpuscular volume, concurrent chemoradiotherapy, predictors, overall survival

Introduction

Mean corpuscular volume (MCV) is one of the most common clinical hematological parameters. It refers to the mean volume of a single red blood cell in the human body. MCV is commonly used to assist in the diagnosis of hematological diseases; for instance, an increase in the mean red blood cell (RBC) volume is more common in large cell anemia, while a decrease in the mean RBC volume is more common in small cell anemia such as iron deficiency anemia and thalassemia. The predictive role of MCV in various solid tumors has received increasing attention in recent years. Motohiko Kato and his team reported that MCV was negatively correlated with the risk of advanced colorectal cancer (CRC).[1] Nagai et al considered

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preoperative MCV as a prognostic factor for CRC and reported that patients with lower MCV had better disease-free survival (DFS).[2] Dellapasqua et al showed that MCV was a predictor of advanced metastatic breast cancer.[3] Wang and her team reported that preoperative MCV was a predictive factor for patients with esophageal cancer (EC).[4] And in a previously published retrospective study, postoperative MCV was a predictor of esophageal cancer survival.[5] However, the correlation between MCV and overall survival (OS) after concurrent chemoradiotherapy in patients with advanced EC has not been reported.

Esophageal cancer is one of the most common global malignant tumors. According to the latest statistics, the incidence and mortality rates of EC rank the 7th and 6th in all malignant tumors, respectively. There will be about 580,000 new cases and 500,000 deaths around the world in 2018.[6] Esophageal squamous cell carcinoma (ESCC) accounts for about 90% EC and is the main pathological type.[7] The development of EC is very secretive and rapid. Most patients are already in the advanced stage and lose the opportunity of surgery at the time of diagnosis. At present, the standard treatment for inoperable EC patients is local radiotherapy combined with systemic chemotherapy.[8] According to statistics, about 80% patients with advanced EC received concurrent chemoradiotherapy. The Radiation Therapy Oncology Group (RTOG) 85–01 study reported that concurrent chemoradiotherapy could improve OS of patients with advanced unresectable EC, though the 5-year survival rate was still less than 30%.[9] However, OS varies significantly with individual patients who receive the same concurrent chemoradiotherapy regimen. It is therefore particularly important to predict the survival possibility of each patient after treatment so as to help clinicians plan individualized treatment options for the sake of achieving the optimal outcome for ESCC patients. Wen and his team showed that miRNA could predict the response to concurrent chemoradiotherapy in EC patients.[10] Butof et al reported that the pre-therapeutic tumor-to-blood Standardized Uptake Ratio (SUR) could predict the survival of EC patients.[11] Chi et al showed that TRIM24 was a potential predictor of survival in EC patients.[12] The research by Wen J et al suggested that pretreatment gene expression analysis could help predict the response to concurrent chemoradiotherapy in ESCC patients, thus facilitating individualized treatment of tumor patients.[13] However, the acquisition of these genes and factors requires accurate detection instruments and complex detection procedures, which are difficult to obtain in general hospitals. Given the previous studies on the predictive power of MCV in multiple solid tumors and the simplicity of MCV acquisition, our work aimed to investigate whether high MCV was a predictor of poor prognosis for patients with advanced EC receiving concurrent chemoradiotherapy.

Patients and Methods

Patient Selection

A total of 249 patients with advanced EC who received concurrent chemoradiotherapy in the first affiliated hospital of Wenzhou Medical University (Wenzhou, China) from 2013 to 2017 were enrolled in our study. Inclusion criteria are as follows: (1) patients aged 18–80 years; (2) patients with a histological diagnosis of ESCC; (3) ESCC patients who only received concurrent chemoradiotherapy after the diagnosis; (4) patients with no major blood diseases such as severe anemia, hypoproteinemia, malignant lymphoma and polycythemia eukaryotica at the time of diagnosis; (5) patients with complete follow-up data.

Data Acquisition

Hematological and routine biochemical indexes of all 249 patients were collected, including red RBC, white blood cell (WBC), platelet count, albumin (ALB), hemoglobin (Hb), RBC distribution width (RDW), MCV, hematocrit (HCT), carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC-Ag), and carbohydrate antigen (CA) 19–9. In addition, basic tumor characteristics including location, size, degree of tumor differentiation and lymph node (LN) metastasis, and the baseline information of the patients including age, gender, smoking index, drinking history and ECOG score were also collected.

Treatment Methods

All patients received three-dimensional (3D) conformal therapy combined with systemic chemotherapy. 95% PTVp and 95% PTVnd received 60Gy in 30 fractions (on work days; 2 Gy per fraction; over a 6-week cycle). After all patients received CT localization to fully understand the size and range of the tumor, the target area was delineated by the senior physicians from the department of radiotherapy and chemotherapy. The criteria for delineating the target area are as follows: gross tumor volume

(GTV), which refers to the primary esophageal lesion determined by the esophagogram display and/or the tumor size shown by esophagoscopy and/or intraventricular ultrasound combined with various imaging data; GTVnd, which refers to metastatic supraclavicular and paratracheal LN detected either by CT scan or palpation; and CTV, which refers to GTV, GTVnd and their LN drainage area and was placed around GTV and GTVnd for 0.8cm, put 3–5cm above and below GTV and GTVnd. PTV is the external radiation of 0.5–1cm on the basis of CTV, and the scope of PTV is appropriately released according to the specific situation of patients, so as to ensure that CTV can get the required prescription dose. The chemotherapy regimen for systemic chemotherapy was 5-Fu 750mg/m^2 combined with cisplatin 75mg/m^2 once every four weeks. The study was approved by the ethics committee of the first affiliated hospital of Wenzhou Medical University. As all the patients included in this retrospective study have died, we sought the consent of the patients' immediate family members or the authorized persons who signed the informed consent before treatment and signed the written informed consent before the study.

Assessment Strategies

The primary endpoint of the study was OS of the EC patients, which refers to the time from randomization to (any cause) death. The secondary endpoints were progression-free survival (PFS) and the objective response rate (ORR). PFS was defined as the time between the initiation of randomization and tumor progression (in any respect) or death (for any reason). ORR refers to the proportion of tumor shrinkage reaching a certain volume and remaining for a certain period of time, including the total number of patients with complete response (CR) and partial response (PR). According to Response Evaluation Criteria In Solid Tumor (RECIST), CR was defined as the disappearance of all target lesions, the occurrence of no new lesions, and the short diameter of all pathological lymph nodes (including target and non-target nodules) reduced to <10mm. PR was defined as reducing the sum of the diameters of target disease areas by at least 30% from baseline. OS was obtained by telephone interviews by the clinicians. PFS and ORR were obtained through outpatient and inpatient cases and imaging data at review to guarantee the objective authenticity of the evaluation endpoints.

Data Analysis

All statistical analyses were performed using the statistical package for social science software program version 22.0 (SPSS Inc., Chicago, IL, USA). The receiver operating characteristic (ROC) curve was used to determine the optimal diagnostic value of each indicator. Univariate COX regression was performed to identify factors associated with OS and PFS. Multivariate COX regression analysis was performed to determine adverse factors associated with OS and PFS. Chi-square test was used to analyze the differences in clinicopathological characteristics. Kaplan-meier method was used to draw the survival curve, and P value <0.05 was considered statistically significant.

Results

The follow-up period ranged from 2 to 77 months with a median of 11 months. Of the 249 EC patients, 46 were women and 203 were men, with a mean age of 65.8 years. Patients with cervical and upper thoracic EC were assigned to group Upper esophageal cancer (n=124), and those with middle and lower thoracic EC (n=125) to group Lower esophageal cancer. Similarly, patients with moderately and highly differentiated EC were assigned to well-differentiated group (n=180), and those with poorly differentiated EC to poor differentiated group (n=69). The specific physiopathological characteristics of the patients are shown in Table 1.

The mean MCV value of the 249 patients was 92.7 fL. According to the analysis of ROC curve, the area under the curve (AUC) was 0.733, and the optimal diagnostic value of MCV was 93.6 fL (Figure 1). Chi-square test was used to evaluate differences in the pathophysiological characteristics between the two groups of MCV patients. The results showed that the MCV value was correlated with the N stage of the tumor and the therapeutic effect, indicating that the higher the MCV was, the higher the T stage of the tumor and the worse the therapeutic effect would be ($p=0.012$ and $p < 0.01$). In the group with MCV < 93.6fL, 67 patients achieved effective remission, accounting for 26.9% of all participants. In the group with MCV> 93.6fL, only 51 patients achieved effective remission, accounting for 20.5% of the total subjects. However, no correlation was observed with other indicators, which may be related to the characteristics of the tumor (Table 2).

Univariate and multivariate cox analyses were used to explore whether MCV was an independent predictor of OS in

Table 1 Basic Physiological and Physiological Characteristics of 249 Patients

Characteristics	No. of People (%)
No of people	249
Sex	
Female	203
Male	46
Age	
Median	65.8 years old
Range	38–85 years old
65 years old or older	127
Under 65 years old	122
History of smoking	
Smoking	126
No smoking	123
Drinking history	
Drinking	124
No drinking	125
Differentiation	
Well differentiated	180
Poor differentiated	69
Tumor site	
Upper esophageal cancer	125
Lower esophageal cancer	124
Tumor length (cm)	
Median	4.8cm
Range	0.9–11.3cm
More than 5cm	123
Less than 5cm	126
Tumor width (cm)	
Median	3.6cm
Range	0.7–8.9cm
More than 4cm	116
Less than 4cm	133
T-staging	
T1+T2	86
T3+T4	163
N-staging	
N0	159
N1+N2	90
ECOG score	
0 Point	126
1 Point	82
2 Point	41

patients with advanced EC. Median OS for all ESCC patients was 14.7 months (95% CI 13.1–16.2 months). Univariate analysis showed that MCV, platelet count, the history of

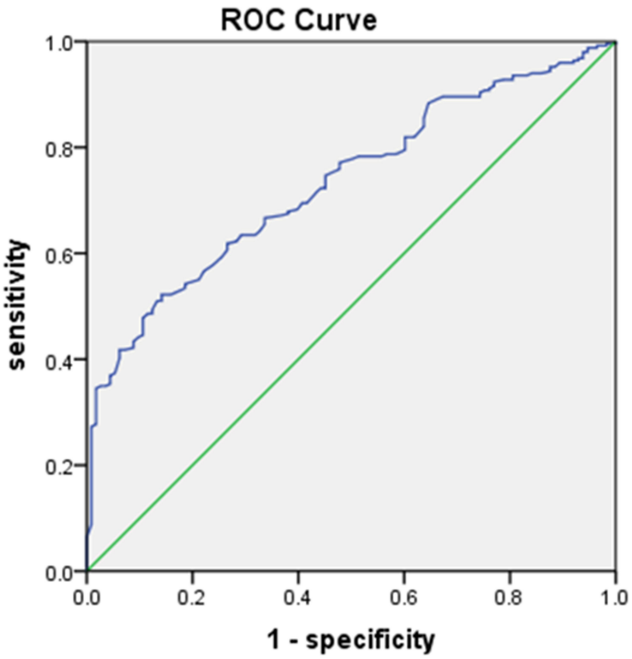

Figure 1 Receiver operating characteristic (ROC) curve plotted to check the value of a statistically significant variable in the COX regression model for MCV. According to ROC analysis, the areas under the curve of MCV was 0.733 and the optimal cutoff points was 93.6.

alcohol consumption, N stage, tumor width, and SCC-Ag were associated with OS of EC patients (Table 3). These factors were also observed to be associated with PFS. According to the multivariate survival analysis, MCV was an independent predictor of OS (Table 4), demonstrating that patients with a pretreatment MCV level>93.6 fL (the optimal diagnostic value for patients) had significantly shorter OS than those with a MCV level lower than 93.6 fL (median OS 10.9 months vs. 18.8 months; P<0.05) (Figure 2). These factors were also observed to be associated with the PFS. Patients who had a pretreatment MCV level>93.6 fL (the optimal diagnostic value for patients) had significantly shorter PFS than patients who had MCV level<93.6 fL (median Progress-Free Survival, 6.2 months vs. 13.5 months; P<0.05)(Figure 3).

Discussion

Esophageal cancer is one of the most common global malignant tumors. Currently available treatments for EC mainly include surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy.[14] Concurrent chemoradiotherapy is the main method for the treatment of advanced EC, and survival of such patients after concurrent chemoradiotherapy has always been a focus of concern and attention. At present, TNM staging is the most

Table 2 Univariate COX Regression Analysis of the Relationship Between Pathophysiological Parameters and Survival Time of Patients

Parameter	OR	95% CI	P
Sex	1.053	0.763–1.453	0.752
Age	1.082	0.843–1.390	0.536
Smoking history	1.227	0.953–1.580	0.112
Drinking history	1.308	1.015–1.688	0.038
Differentiation	0.881	0.667–1.165	0.374
Tumor site	0.933	0.724–1.202	0.592
Tumor length	1.182	0.920–1.517	0.191
Tumor width	1.396	1.082–1.801	0.010
T-staging	1.153	0.886–1.500	0.289
N-staging	1.531	1.174–1.997	0.002
ECOG score	1.166	0.833–1.633	0.371
Leukocyte	1.021	0.792–1.317	0.870
Erythrocyte	0.828	0.576–1.191	0.309
Platelet	1.297	1.003–1.678	0.047
Hemoglobin	0.967	0.693–1.349	0.842
Albumin	0.951	0.708–1.277	0.737
Hematocrit	0.996	0.771–1.286	0.974
MCV	1.966	1.525–2.536	<0.01
RDW	0.908	0.700–1.176	0.464
PCT	0.820	0.634–1.061	0.132
SCC	1.431	1.041–1.967	0.027
CA199	1.133	0.875–1.467	0.343
CEA	0.917	0.681–1.235	0.570

Table 3 Multivariate COX Regression Analysis of the Relationship Between Clinical Variables and Patient Survival

Parameter	OR	95% CI	P
Drinking history	1.290	0.997–1.669	0.052
Tumor width	1.249	0.964–1.620	0.093
N-staging	1.433	1.092–1.880	0.009
MCV	1.864	1.439–2.415	<0.01
Platelet	1.130	0.870–1.469	0.359
SCC	1.190	0.858–1.650	0.297

effective predictor for survival of EC patients.[15,16] However, there are significant differences in OS between patients with the same TNM staging receiving the same treatment. In addition, accurate TNM staging often requires postoperative pathological evaluation. It is therefore difficult to use TNM staging to predict survival and determine further treatment strategies for inoperable patients with advanced EC. Other effective predictors are required urgently for such patients.

MCV is a relatively stable blood indicator in healthy people. With the advent of automatic blood counting, the clinical significance of its increase and decrease in predicting a diseased condition has attracted increasing attention. In addition to being used to assist in the diagnosis of hematological diseases, the clinical significance of MCV has also been reported in other diseases. Solak et al reported a possible relationship between MCV and cardiovascular

Table 4 Relationship Between Pretreatment MCV and Clinicopathological Parameters in Patients with ESCC Who Received Concurrent Radiochemotherapy

Characteristic, n=204	MCV<93.6	MCV>93.6	P
Sex			
Female	23	23	
Male	95	108	0.745
Age			
<65 years old	59	63	
>65 years old	59	68	0.800
Smoking history			
Smoking	54	72	
No smoking	64	59	0.164
Drinking history			
Drinking	56	68	
No drinking	62	63	0.527
Tumor site			
Upper	62	63	
Lower	56	68	0.527
Differentiation			
Well	85	95	
Poor	33	36	0.522
Tumor length			
>5cm	55	68	
<5cm	63	63	0.447
Tumor width			
>4cm	51	65	
<4cm	67	66	0.373
T-staging			
T1+T2	45	41	
T3+T4	73	90	0.287
N-staging			
N0	85	74	
N1+N2	33	57	0.012
ECOG score			
0 Point	98	110	
1Point+2Point	20	21	0.866
Curative effect			
CR+PR	67	35	
SD+PD	51	96	<0.01

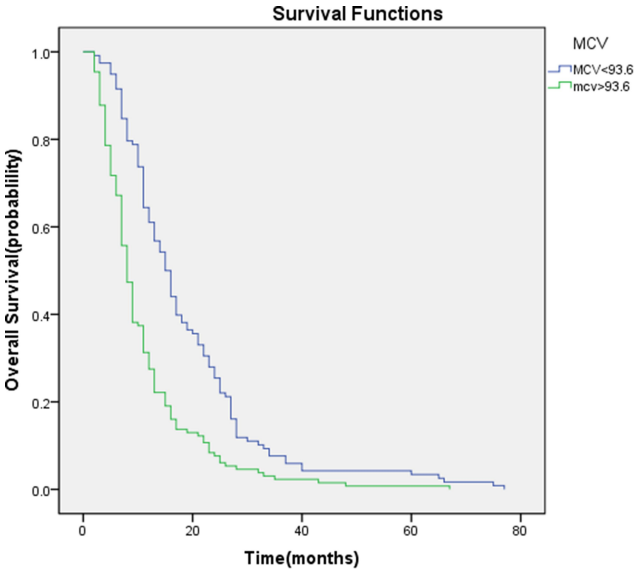

Figure 2 Kaplan-Meier survival curves for advanced esophageal cancer in different MCV groups. The blue curve represents the overall survival of the group with MCV <93.6 fL, while the green curve represents the overall survival of the group with MCV >93.6 fL. The mean survival time of patients in the group with MCV <93.6 fL was 10.9 months, while that of patients in the group with MCV >93.6 fL 18.8 months, P <0.05, indicating a significant difference between the two groups.

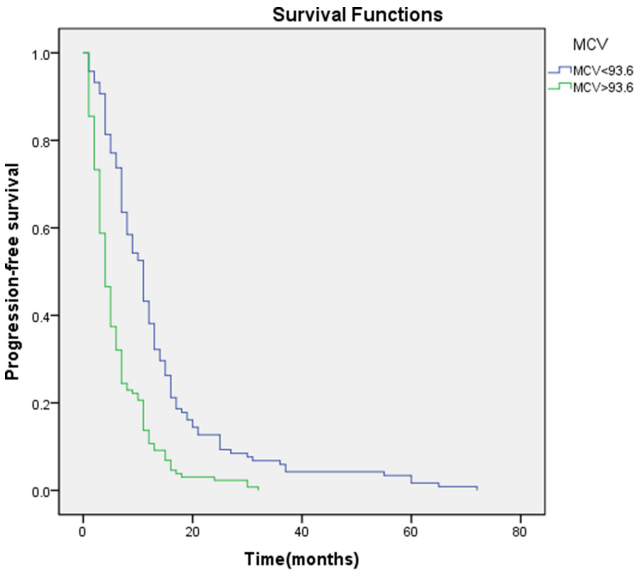

Figure 3 Kaplan-Meier survival curves describe the relationship between progression-free survival time and MCV in different groups. In the MCV <93.6 fL group, the mean progression-free survival time was 13.5 months. For MCV>93.6 fL, mean progression-free survival time was 6.2 months, P<0.05, indicating a significant difference between the two groups.

events in patients with chronic kidney disease.[17] Yoon et al reported that MCV could be used as an independent survival predictor for healthy populations.[18] Many other studies have also reported the relationship between MCV and survival of patients with solid tumors. Jomrich and his team found that high MCV was a poor prognostic factor for esophageal adenocarcinoma.[19] Qu and his team showed that MCV was associated with survival of patients with resectable non-small cell lung cancer (NSCLC).[20] Our study has demonstrated that high MCV is a poor predictor of survival in patients with advanced EC after concurrent chemoradiotherapy.

In this study, we analyzed the relationship between MCV and survival in patients with advanced EC who received radiotherapy and chemotherapy. First, we used the ROC curve to analyze and determine the optimal cutoff value of MCV, finding that the optimal cut-off value of MCV was 93.6 fL. Univariate and multivariate COX regression analyses showed that MCV was closely correlated with survival of the patients with advanced EC who received concurrent chemoradiotherapy. The analysis showed that OS of patients with a high level of MCV before treatment was significantly shorter than that of patients with a low-level MCV, showing a negative correlation between them. When we used PFS as a secondary endpoint, we obtained the same result. Meanwhile, the chi-square test analysis showed that MCV was related to the N stage of the patient and the therapeutic effect. This means that the size of MCV may be associated with lymph node metastasis.

Our study on the relationship between MCV and solid tumors have proved that high MCV is a poor prognostic factor but were unable to confirm whether MCV plays a direct role in local recurrence and metastatic invasion of tumors. We have several hypotheses as to why high MCV is a poor predictor of advanced EC. First, MCV is an important marker of the folate concentration in the body, and folate deficiency often leads to increased MCV. Folic acid, as an important carbon unit transfer carrier in the body, plays an indispensable role in DNA synthesis, replication, repair and methylation. Folate deficiency can lead to abnormal DNA methylation, which is a poor predictor of prognosis in EC patients.[21,22] Second, previous studies have shown that survival of EC patients is related to the individual's basic nutritional status.[23,24] Progressive dysphagia is the main clinical symptom of EC patients.[25] In patients with advanced esophageal cancer, reduced food intake reduces the serum concentration of Na+, K+ and other electrolytes, leading to the reduction in plasma crystal osmotic pressure. The size of MCV in the internal environment of the human body is negatively correlated with the osmotic pressure of plasma crystals, and decreased osmotic pressure of plasma crystals increases MCV.[26] Moreover, according to the definition of MCV, we can know that the size of MCV value is related to the

hematocrit per liter of blood and the number of RBCs per liter of blood. Increase in the MCV value may be due to the decrease of RBCs per unit volume of blood, and RBCs are involved in oxygen transport and metabolism of the body. The decrease in the number of RBCs will lead to a decrease in the amount of oxygen that the tumor tissue gets from the circulating blood, which will lead to a decrease in the total oxygen content in the tumor tissue and an increase in the proportion of hypoxic tumor cells. Hypoxia will lead to a decrease in the sensitivity of tumor cells to radiotherapy, which will greatly reduce the therapeutic effect and lead to poor prognosis.[27–30] Finally, drug resistance is likely to occur after the use of chemotherapy drugs. However, previous studies demonstrated that MCV was increased after the administration of capecitabine and other drugs, so whether high MCV is an insensitivity factor of chemotherapy and thus affects the prognosis of patients is also something that we need to explore.[31]

Although our data and results were confirmed and calculated repeatedly, this study has some limitations. Firstly, the number of patients in this study is only 249, which may lead to unstable results due to the small sample size. Secondly, because the study was a retrospective study, we could not control all possible risk factors of cancer patients, and our data were all from medical documents, and registration of these medical documents could not be completely accurate due to the busy clinical work. Therefore, when collecting patient data, our team hopes to reduce the error to the minimum after repeated verification and statistics by many people. Furthermore, it was a single-center retrospective study that included all patients from the same hospital, and its conclusions were not verified by other centers. Therefore, further prospective trials in multiple centers are required to confirm the repeatability of these results in heterogeneous populations. Finally, this study only demonstrated that high MCV was an adverse predictor for EC patients, but how to use specific MCV to judge patient survival in clinical practice requires further research and the establishment of a more systematic prediction model.

Conclusion

High mean corpuscular volume as a predictor of poor overall survival in patients with esophageal cancer receiving concurrent chemoradiotherapy. In our clinical treatment of newly diagnosed advanced esophageal cancer patients, we can use MCV to roughly predict their survival. For those patients whose survival is predicted to be short, we can adopt a relatively conservative treatment method to reduce the cycle of chemoradiotherapy, thus reducing the toxic side effects of chemotherapy on patients. And for those patients who predict long survival, we can use more aggressive treatment to achieve the best treatment results.

Abbreviations

MCV, mean corpuscular volume; OS, overall survival; EC, esophageal cancer; ROC curve, receiver operating characteristic curve; OR, odds ratio; CI, confidence interval; RBC, red blood cell; CRC, colorectal cancer; ESCC, esophageal squamous cell cancer; RTOG, Radiation Therapy Oncology Group; SUR, standardized Uptake Ratio; WBC, white blood cell; ALB, albumin; Hb, hemoglobin; RDW, Red Cell volume Distribution Width; HCT, hematocrit; CEA, carcinoembryonic antigen; SCC-Ag, squamous cell carcinoma antigen; CA19-9, carbohydrate antigen 19-9; LN, lymph node; CT, Computed Tomography; GTV, gross tumor volume; CTV, clinical target volume; PTV, Planning Target Volume; PFS, progression-free survival; ORR, objective response rate; CR, complete response; PR, partial response.

Ethics Approval and Consent to Participate

All the procedures followed were in accordance with the ethical guidelines of the Helsinki Declaration. The study protocol was approved by the Medical Ethical Committee of the First Affiliated Hospital of Wenzhou Medical University. All patients' family were given informed written consent.

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Disclosure

The authors declare that they have no competing interests.

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