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ORIGINAL RESEARCH

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Analysis of clinicopathological factors affecting the chemoradiotherapy sensitivity in advanced cervical squamous cell carcinoma treated

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Abstract

The average 5-year overall survival (OS) rate of locally advanced cervical cancer (LACC) is unsatisfactory, this study was to investigate the clinical factors of chemoradiotherapy resistance in cervical cancer after chemoradiation and to improve the efficacy. A total of 965 LACC patients treated with radical chemoradiotherapy, the patients were categorized into two groups: chemoradiotherapy-resistant and chemoradiotherapy-sensitive. The survival curve and survival rate were drawn by Kaplan-Meier method using the R language package. Log-rank test was applied to analyze the difference in the survival rate among the different groups, while COX regression models and logistic regression were applied to analyze the clinical factors affecting prognosis. The 5-year survival rate of the radiotherapy-sensitive group was approximately 40% higher than that of the radiotherapy-resistant group. Univariate analysis revealed that chemoradiotherapy sensitivity, tumor diameter, lymph node metastasis, hemoglobin levels, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and total radiotherapy time were prognostic factors for overall survival (OS) and progression-free survival (PFS). Multivariate analysis revealed that chemoradiotherapy sensitivity, age, PLR, and total radiotherapy time >8 weeks were independent prognostic factors for OS and PFS. The main clinical factors that contributed to the difference in the 5-year survival rate included the tumor stage, hemoglobin level, NLR, lymph node metastasis, and total radiotherapy time factors. Prognostic factors analyses revealed that OS and PFS affecting the efficacy of chemoradiotherapy for advanced cervical squamous cell carcinoma were associated with multiple clinical factors, and that chemoradiotherapy sensitivity, age, and PLR were independent prognostic factors for OS and PFS.

Keywords

Chemoradiotherapy; Cervical squamous cell carcinoma; Prognostic factors; Sensitivity

1. Introduction

Cervical cancer is the most common gynaecological cancer in China, 135,000 new cases of cervical cancer are reported every year. The latest statistics showed that 106,000 new incident cases were reported in 2018 [1]. Approximately 2/3rd of all patients affected by cervical cancer are in their advanced stage at the time of diagnosis.

According to the International Federation of Gynecology and Obstetrics stage (FIGO), stage IIB–IVA cervical cancer is defined as LACC. Approximately 75% of the pathological types of cervical cancers are squamous cell carcinoma. The current standard of treatment is radical concurrent chemoradiotherapy (CCRT). By the CCRT treatment, the average 5-year overall survival (OS) rate was 40–50%, 29%–38% of the failures were uncontrolled and recurrent, and the 5-year survival rate of patients with recurrence tumor was only 3.8–13.0% [2]. Therefore, to find the risk factors of uncontrolled or recurrent cervical squamous cell carcinoma patients after CCRT can understand the characteristics of the disease and guide the treatment plan to improve the prognosis of these patients.

In this restrospective study, we collected data of locally advanced squamous cervical cancer (LASCC) after CCRT over the past 9 years, and analyzed the survival rate and prognostic factors, and to do further research.

2. Materials and methods

2.1 Patients

Between January 2007 and September 2015, 965 patients with LASCC diagnosed for the first time and then treated with radical chemoradiotherapy were collected at the Department of Gynecology and Oncology of Guangxi Medical University Affiliated Tumor Hospital and department of Oncology of the affiliated Hospital of Southwest Medical University. The patients were categorized into two groups [3]: chemoradiotherapy sensitive group (RT-sensitive group: the tumor disappeared 6 months after chemoradiotherapy: The cervix had recovered or atrophied with smooth surface, with uniform texture and normal hardness, parametrium was no residual disease.) and chemoradiotherapy resistant group (RT-resistant group: There were residual disease or found new lesions within 6 months after chemoradiotherapy.).

2.2 Inclusion and exclusion criteria

2.2.1 The following were the inclusion criteria for the study subjects

(1) The pathological was squamous cell carcinoma;
(2) First time of diagnosis;
(3) 18–80 years old;
(4) ≥IIB stage, as staged by FIGO1995 and FIGO2009, and no distant metastasis confirmed;
(5) Eastern Cooperative Oncology Group (ECOG) score: 0–2;
(6) Patients with radical radiotherapy, including external beam radiotherapy (EBRT) and brachytherapy (BT);
(7) Patients with complete information cases and follow-up data;

2.2.2 The following were the exclusion criteria for the study subjects

(1) Other pathological types of cervical cancer;
(2) Patients with recurrence or distant metastasis;
(3) Patients who did not complete the radiotherapy, including those who have not received brachytherapy, or those who did not reach radical radiotherapy dose;
(4) Patients who had undergone treatment-related surgery for cervical cancer, including those who had undergone lymph node dissection before chemoradiotherapy, but excluding those who received interventional therapy to stop bleeding.

2.3 Treatment method

2.3.1 EBRT

All patients were treated by the pelvis with dose of 45–50 Gy with a daily fraction of 1.8–2 Gy/5 weeks with 6-MV photon beams. The dose for patients with lymph node metastasis could be raised to 60–70 Gy. Three technique types of radiotherapy could be selected. Anterior-posterior fields or four-field box technique. The upper border of pelvic field was at the L4 and L5 intespace and the lower border was the lower margin of symphysis pubis. The lateral borders were anterior superior spine. Center shield radiotherapy was performed, depending on tumor shrinkage after 30 to 40 Gy had been delivered. Three-dimensional radiotherapy (3DRT) and intensity-modulated radiotherapy (IMRT).

2.3.2 BT

All patients underernt high-dose rate brachycherapy with 192-iridium remote afterloading system. Fletcher-Suitapplicators consisting of uterine tandem and pairovoids or interstitial applicators were used. The prescription dose of two-dimensional radiotherapy is 30 Gy in 5 fractions or 28 Gy in 4 fractions. The biological effective dose to point A was ≥70 Gy. For those using three-dimensional technology, the treatment dose of the high-risk clinical volume (HR-CTV) was ≥70–85 Gy.

2.3.3 Chemotherapy

Whether and how the combination chemotherapy can be administered depended on the patient's situation, are detailed below:

(1) Radiotherapy alone: The above-mentioned radiotherapy methods were used alone.

(2) Concurrent chemoradiotherapy: Platinum-based chemotherapy was administered intravenously weekly or every 3 weeks or platinum-based 2-drug every 3 weeks.

(3) Adjuvant chemotherapy: It included the administration of neoadjuvant chemotherapy before radiotherapy and adjuvant chemotherapy after radiotherapy. Presently, whether to administer adjuvant chemotherapy remains controversial, with no standard chemotherapy regimen established yet. In this study, all platinum-based combination were incorporated, with a focus on the cycle of chemotherapy.

2.4 Follow-up

The follow-up deadline was December 2016. The main item for consideration during the follow-up included the hospitalization number, name, age, FIGO stage, tumor diameter, hemoglobin (Hb) before treatment, NLR before treatment, PLR before treatment, prior lymph node metastasis, total radiotherapy time, radiotherapy method used, radiotherapy dose, chemotherapy regimen and course, efficacy at the end of radiotherapy, OS (the time interval from the beginning of treatment to death or the end of follow-up), and PFS (the interval from the beginning of treatment to the end of tumor progression or follow-up).

2.5 Statistical analysis

All data were analyzed by the R language 3.4.3 Software (https://CRAN.R-project.org/package=survival). The Chi-square test was applied to evaluate the enumeration data, and the rank sum test was used for the measurement data. Logistic regression was applied to analyze the clinical factors that affected the sensitivity of chemoradiotherapy. The critical values of NLR and PLR were determined by the Receiver Operating Characteristic (ROC) curve method. For OS and PFS, the Kaplan-Meier method was employed to draw the survival curve and determine the survival rate, while the log-rank test was applied to examine the difference in the survival rate among the different groups. Univariate and multivariate regression analyses of clinical factors affecting OS and PFS were performed using COX regression models. All data were analyzed by two-sided test, with $p < 0.05$ considered to indicate statistical difference.

TABLE 1. General characteristics of the study subjects.

Clinical features	RT sensitive (n = 738)	RT resistant (n = 227)	*p*-value
Age (yr)	53.09 (9.50)	52.40 (10.06)	0.438
Status (example, %)			
alive	574 (77.81)	73 (32.24)	<0.001
death	164 (22.23)	154 (67.82)	
OS (mon)	49.62 (28.43)	27.13 (28.34)	<0.001
PFS (mon)	48.49 (28.30)	31.86 (29.30)	<0.001
Stage (example, %)			
IIB–IIIA	180 (24.44)	39 (17.18)	0.025
≥IIIA	557 (75.47)	187 (82.73)	
Tumor diameter (example, %)			
≤4 cm	227 (37.76)	63 (33.72)	0.298
>4 cm	372 (62.14)	124 (66.38)	
Hb (mean (SD), g/L)	109.40 (19.92)	104.80 (22.15)	0.004
NLR (mean (SD))	3.03 (1.92)	3.45 (2.43)	0.019
PLR (mean (SD))	182.90 (97.10)	196.70 (108.95)	0.158
LN (example, %)			
no metastasis	423 (66.04)	100 (49.78)	<0.001
metastasis	218 (34.96)	101 (50.22)	
TR (%)			
≤8 wk	295 (40.61)	69 (30.47)	0.011
>8 wk	441 (59.39)	156 (69.53)	
CCRT (wk)	3.63 (1.82)	3.43 (2.04)	0.253
AT (wk)	1.54 (1.60)	1.52 (1.53)	0.659
Hospital			
GuangXi	582 (78.86)	187 (82.37)	0.263
XiNan	155 (21.14)	40 (17.63)	

Note: RT: radiotherapy; SD: standard deviation; OS: overall survival; PFS: progression free survival; Hb: hemoglobin; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; LN: lymph node; TR: total time of radiotherapy; CCRT: concurrent radiotherapy; AT: adjuvant chemotherapy; yr: year; mon: month; wk: week.

3. Results

3.1 Patients characteristics

All 965 patients were followed up, which included 769 cases at the Guangxi Medical University Affiliated Tumor Hospital and 195 cases at the affiliated Hospital of Southwest Medical University. Among these patients, 73 were lost to follow-up, and the rate of loss to follow-up was 18%. Table 1 shows the clinicopathological characteristics of the 965 patients included in this study. The ratio of RT-sensitive group (n = 738) and RT-resistant group (n = 227) was 3.25%, while the RT-sensitive group accounted for 23.52% of all patients. The mortality rate of the RT-sensitive group and the RT-resistant group were 22.23% and 67.82%, respectively ($p < 0.001$). The OS and PFS in RT-sensitive group was about 22 months and 16 months longer than that in RT-resistant group, respectively ($p < 0.001$).

3.2 Factors affecting sensitivity to chemoradiotherapy

Univariate analysis revealed that concurrent chemoradiotherapy increased the sensitivity of chemoradiotherapy by approximately 37% compared with radiotherapy alone (OR, 0.63 (0.42–0.96, $p = 0.027$)). Patients with a later tumor stage ≥IIIB stage showed reduced sensitivity to chemoradiotherapy when compared with patients with IIB–IIIA by approximately 1.55 times (1.55 (1.07–2.30, $p = 0.025$)). Patients with lymph node metastasis showed decreased sensitivity to chemoradiotherapy by 1.96 times (1.96 (1.42–2.70, $p < 0.001$)), and those who received radiotherapy for >8 weeks showed reduced sensitivity to chemoradiotherapy by approximately 1.51 times (1.51 (1.10–2.09, $p = 0.011$)). Multivariate analysis revealed that the total radiotherapy time >8 weeks was an independent influencing factor that reduced the sensitivity of chemoradiotherapy by approximately 2.11 times (2.11 (1.16–3.96, $p = 0.017$)). The other factors included age, tumor

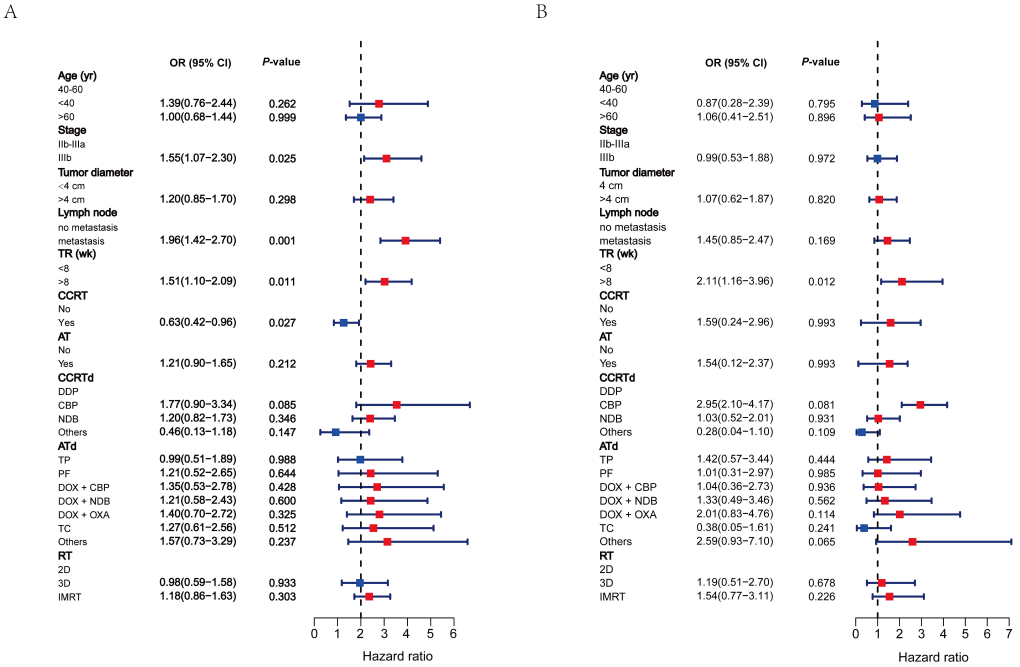

FIGURE 1. Univariate and multivariate analysis of chemoradiotherapy sensitivity. (A) Forest plot of univariate analysis in chemoradiotherapy sensitivity. (B) Forest plot of multivariate analysis in chemoradiotherapy sensitivity. OR: odds ratio; RT: radiotherapy; LN: lymph node; TR: total time of radiotherapy; CCRT: concurrent radiotherapy; AT: adjuvant chemotherapy; CCRTd: concurrent radiotherapy drugs; ATd: adjuvant chemotherapy drugs; DDP: cisplatin; CBP: carboplatin; NDB: nedaplatin; OXA: oxaliplatin; TAX: taxol; TP: paclitaxel + cisplatin; DOX: docetaxel; PF: cisplatin + fluorouracil; TC: paclitaxel + carboplatin; 2D: conventional radiotherapy; 3D: appropriate radiotherapy; IMRT: intensity modulated radiotherapy.

stage, chemotherapeutic drugs, and even different synchronous chemotherapeutic drugs, decision to use adjuvant chemotherapy and different adjuvant chemotherapeutic drugs. The use of improved technique of radiotherapy showed no statistical difference between the univariate and multivariate analyses of influencing factors related to chemoradiotherapy sensitivity (Table 2, Fig. 1).

3.3 The cut-off value of NLR and PLR for predicting efficacy

The ROC curve was drawn considering NLR and PLR before treatment as test variables and the treatment efficacy as the state variables. The maximum value of the sum of sensitivity and specificity was the cut-off value. The cut-off value of NLR for predicting the efficacy of chemoradiotherapy was 2.91, the sensitivity was 0.505, and specificity was 0.610. The area under the curve was 0.561. The cut-off value of PLR for predicting the efficacy of chemoradiotherapy was 174.8, the sensitivity was 0.498, and specificity was 0.587. The area under the curve was 0.531 (Fig. 2). ROC curve indicated the presence of no diagnostic value. Despite the differences in the NLR and PLR between chemoradiotherapy sensitive and resistant groups (Fig. 2), it is not enough to become predictors.

3.4 Survival analyses

At the end of the follow-up period, 647 of the 965 patients were alive. Based on the survival outcomes, the 3-year survival rates of the chemoradiotherapy sensitive and resistant groups were 90.02% and 54.08%, respectively, and the respective 5-year survival rates were 79.09% and 42.03%. The 5-year survival rate of the chemoradiotherapy sensitive group was approximately 40% higher than that of the RT-resistant group ($p < 0.01$). The survival rate in the chemoradiotherapy sensitive group was significantly higher than that in the RT-resistant group (Fig. 3A,B).

Owing to the large age span of the statistical data, a stratified analysis of different ages was performed, which revealed differences in the survival rates among different chemoradiotherapy sensitive groups in the same age group, but there was no significant difference among the different ages in the same group (Fig. 3C,D).

3.5 Clinical factors affecting chemoradiotherapy OS

There was no significant difference in overall survival between the two hospitals. Univariate analysis revealed that sensitivity to chemoradiotherapy, tumor diameter, hemoglobin, NLR, PLR, and lymph node metastasis were the influencing factors of OS, while age, tumor stage, times of concurrent chemotherapy, and the times of adjuvant chemotherapy did not factors affect the OS. Multivariate analysis revealed that sensitivity to chemoradiotherapy, tumor diameter, NLR, PLR, and the total time of radiotherapy acted as independent factors affecting OS, while the hemoglobin level and lymph node metastasis did not.

The results indicated that sensitivity to chemoradiotherapy can serve as an independent prognostic index, while the risk of death in the RT-resistant group was 6.48-times greater than that in the chemoradiotherapy sensitive group (HR = 6.48, 95%

TABLE 2. Analysis of clinical factors affecting the sensitivity of chemoradiotherapy.

Clinical factors	RT sensitive (example, %)	RT resistant (example, %)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (yr)						
40–60	542 (73.44)	163 (71.81)				
<40	43 (5.83)	18 (7.93)	1.39 (0.76–2.44)	0.262	0.87 (0.28–2.39)	0.795
>60	153 (20.73)	46 (20.26)	1.00 (0.68–1.44)	0.999	1.06 (0.41–2.51)	0.896
Stage						
IIb–IIIa	180 (24.42)	39 (17.26)	Ref		Ref	
≥IIIb	557 (75.58)	187 (82.74)	1.55 (1.07–2.30)	0.025	0.99 (0.53–1.88)	0.972
Tumor diameter						
≤4 cm	227 (37.89)	63 (33.68)	Ref		Ref	
>4 cm	372 (62.11)	124 (66.32)	1.20 (0.85–1.70)	0.298	1.07 (0.62–1.87)	0.820
Lymph node						
no metastasis	423 (66.00)	100 (49.75)	Ref		Ref	
metastasis	218 (34.00)	101 (50.25)	1.96 (1.42–2.70)	<0.001	1.45 (0.85–2.47)	0.169
TR (wk)						
≤8	295 (40.18)	69 (30.66)	Ref		Ref	
>8	441 (59.92)	156 (69.34)	1.51 (1.10–2.09)	0.011	2.11 (1.16–3.96)	0.012
CCRT						
No	85 (11.53)	39 (17.18)				
Yes	653 (88.47)	188 (82.82)	0.63 (0.42–0.96)	0.027	1.59 (0.24–2.96)	0.993
AT						
No	324 (43.90)	89 (39.21)				
Yes	414 (56.10)	138 (60.79)	1.21 (0.90–1.65)	0.212	1.54 (0.12–2.37)	0.993
CCRTd						
DDP	424 (65.33)	116 (61.70)				
CBP	31 (4.77)	15 (7.98)	1.77 (0.90–3.34,)	0.085	2.95 (2.10–4.17)	0.081
NDB	162 (25.96)	53 (28.19)	1.20 (0.82–1.73)	0.346	1.03 (0.52–2.01)	0.931
Others	32 (4.93)	4 (2.12)	0.46 (0.13–1.18)	0.147	0.28 (0.04–1.10)	0.109
ATd						
TP	127 (31.96)	35 (26.27)	0.99 (0.51–1.89)	0.988	1.42 (0.57–3.44)	0.444
PF	62 (15.13)	17 (12.75)	1.21 (0.52–2.65)	0.644	1.01 (0.31–2.97)	0.985
DOX + CBP	30 (7.32)	10 (7.54)	1.35 (0.63–2.78)	0.428	1.04 (0.36–2.83)	0.936
DOX + NDB	35 (8.47)	13 (9.75)	1.21 (0.58–2.43)	0.600	1.33 (0.49–3.46)	0.562
DOX + OXA	42 (10.21)	14 (10.52)	1.40 (0.70–2.72)	0.325	2.01 (0.83–4.76)	0.114
TC	40 (9.79)	14 (10.52)	1.27 (0.61–2.56)	0.512	0.38 (0.05–1.61)	0.241
Others	30 (7.32)	13 (9.74)	1.57 (0.73–3.29)	0.237	2.59 (0.93–7.10)	0.065
RT						
2D	343 (47.31)	99 (44.19)				
3D	92 (12.69)	26 (11.61)	0.98 (0.59–1.58)	0.933	1.19 (0.51–2.70)	0.678
IMRT	290 (40.00)	99 (44.19)	1.18 (0.86–1.63)	0.303	1.54 (0.77–3.11)	0.226

Note: RT: radiotherapy; CI: confidence interval; OR: odds ratio; CI: confidence interval; TR: total time of radiotherapy; CCRT: concurrent radiotherapy; AT: adjuvant chemotherapy; CCRTd: concurrent radiotherapy drugs; DDP: cisplatin; CBP: carboplatin; NDB: nedaplatin; OXA: oxaliplatin; ATd: adjuvant chemotherapy drugs; TP: paclitaxel + cisplatin; PF: cisplatin + fluorouracil; DOX: docetaxel; TC: paclitaxel + carboplatin; RT: radiotherapy; 2D: conventional radiotherapy; 3D: appropriate radiotherapy; IMRT: intensity modulated radiotherapy; yr: year; wk: week.

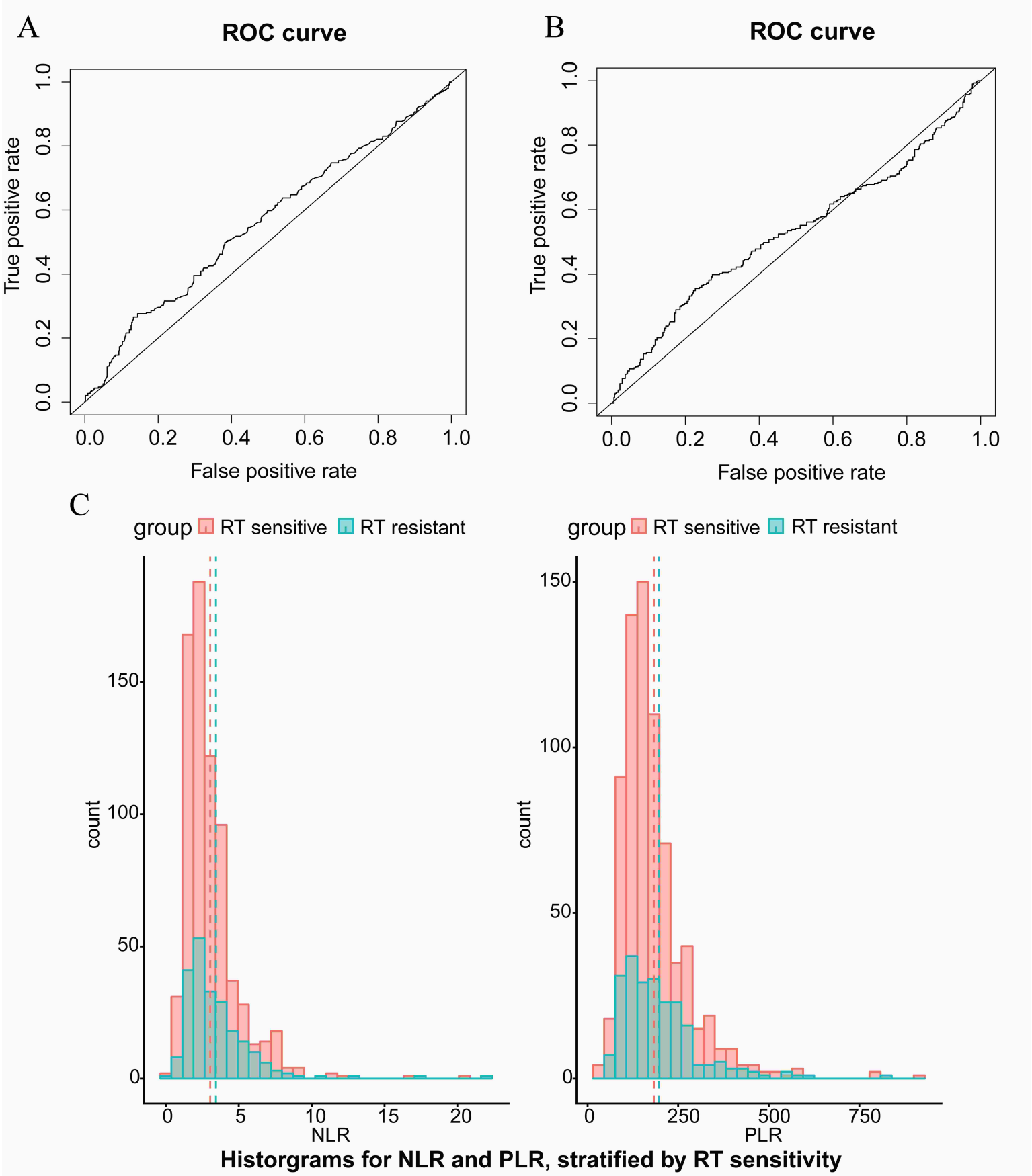

FIGURE 2. NLR and PLR for predicting efficacy. (A) ROC curve predicting the prognostic value of NLR. (B) ROC curve predicting the prognostic value of PLR. (C) Histograms of NLR and PLR in the radiotherapy sensitive and resistant groups. ROC: receiver operating characteristic; RT: radiotherapy; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio.

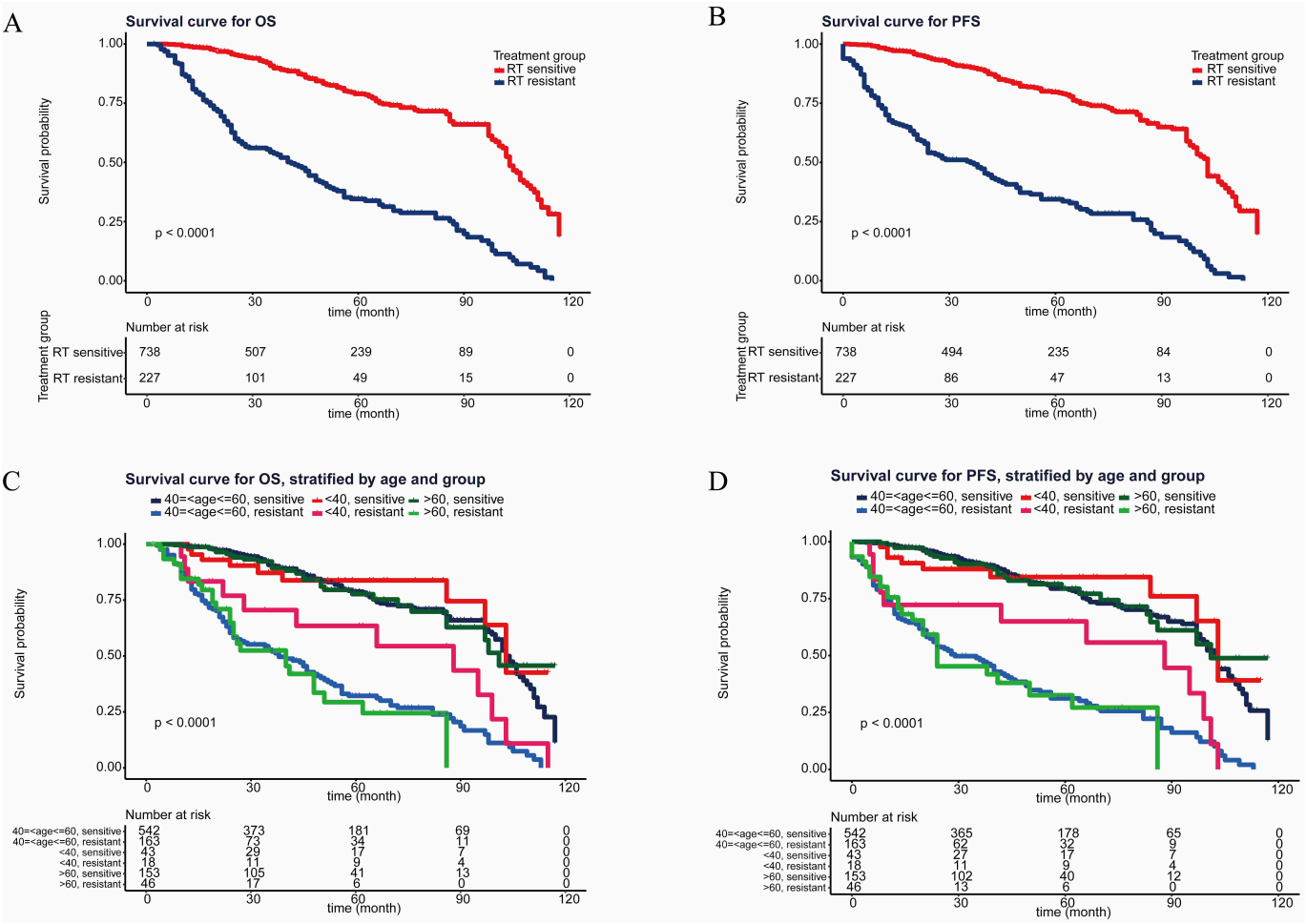

FIGURE 3. Survival analyses in the radiosensitive group and radioresistant group. (A) Survival curves of overall survival in the radiosensitive group and radioresistant groups. (B) Survival curves of progression-free survival in the radiosensitive and radioresistant groups. (C) Survival curves of overall survival in the radiosensitive and radioresistant groups stratified by age. (D) Survival curves of progression-free survival in the radiosensitive and radioresistant groups stratified by age.
OS: overall survival; RT: radiotherapy; PFS: progression-free survival.

CI = 4.7–8.95, $p < 0.001$). Tumor diameter also served as an independent prognostic indicator. The risk of tumor diameter >4 cm was 1.59-times greater than that of <4 cm (HR = 1.598, 95% CI = 1.15–2.20, $p = 0.005$). For every 1% increase in NLR, the risk level increased by 8% (HR = 1.08, 95% CI = 1.01–1.15, $p = 0.028$). For every 0.2% increase in PLR, the corresponding risk increased by 0.2% (HR = 1.002, 95% CI = 1.000–1.004, $p = 0.005$). When compared with patients whose total time of radiotherapy was ≤8 weeks, the risk to patients with a total time of radiotherapy >8 weeks was 1.53-times higher (HR = 1.53, 95% CI = 1.10–2.14, $p = 0.012$) (Fig. 4, Table 3).

3.6 Clinical risk factors of chemoradiotherapy PFS

The influence of clinical factors on PFS was found to be similar to that on OS, with no significant difference between the results of two hospitals. Univariate analysis revealed that the sensitivity to chemoradiotherapy, tumor diameter, hemoglobin, NLR, PLR and lymph node metastasis were the influencing factors of PFS, while age, tumor stage, simultaneous chemotherapy, and adjuvant chemotherapy did not affect the PFS. Multivariate analysis revealed that sensitivity to chemoradiotherapy, tumor diameter, NLR, PLR, and the total time of radiotherapy were independent factors affecting PFS, while the hemoglobin level and lymph node metastasis were not.

Based on our results, sensitivity to chemoradiotherapy served as an independent index, while the risk course of death in the RT-resistant group was 7.18-times greater than that in the chemoradiotherapy sensitive group (HR = 7.18,95% CI = 5.35–9.64, $p < 0.001$). Tumor diameter also acted as an independent prognostic indicator, with the risk of tumor diameter >4 cm being 1.52-times greater than that of <4 cm (HR = 1.52, 95% CI = 1.10–2.10, $p = 0.011$). For every 1% increase in NLR, the corresponding risk level increased by 7% (HR = 1.07, 95% CI = 1.00–1.15, $p = 0.036$). For every 0.2% increase in PLR, the corresponding risk increased by 0.2% (HR = 1.003, 95% CI = 1.002–1.004, $p = 0.009$). When compared with patients with total radiotherapy time ≤8 weeks, the risk of patients with a total radiotherapy time >8 weeks was 1.54-times higher (HR = 1.54, 95% CI = 1.11–2.16, $p = 0.011$) (Fig. 4, Table 4).

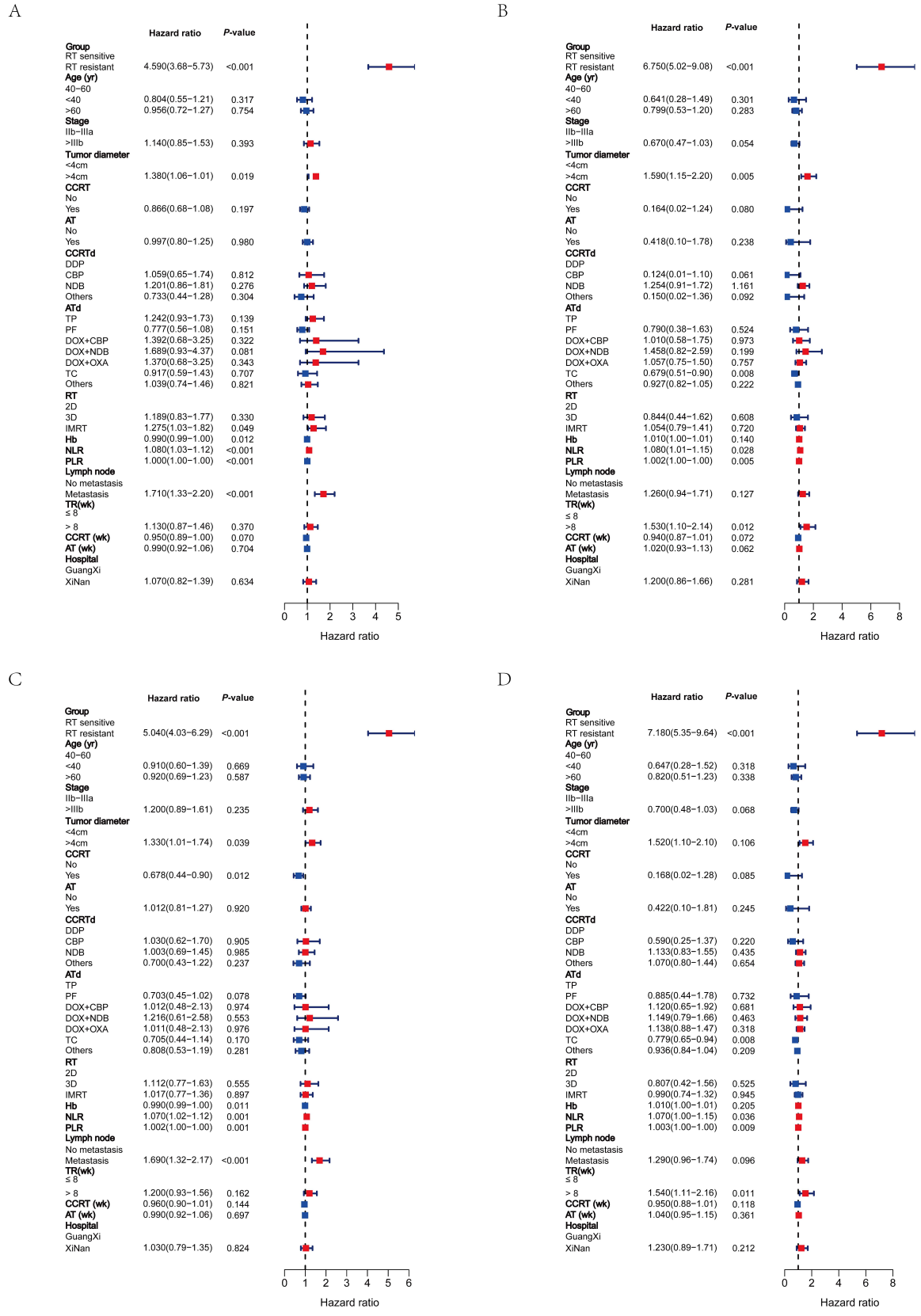

FIGURE 4. Univariate and multivariate analysis in OS and PFS. (A) Forest plot of univariate analysis in OS; (B) Forest plot of multivariate analysis in OS. (C) Forest plot of univariate analysis in PFS. (D) Forest plot of multivariate analysis in PFS. CCRT: concurrent radiotherapy; AT: adjuvant chemotherapy; CCRTd: concurrent radiotherapy drugs; DDP: cisplatin; CBP: carboplatin; NDB: nedaplatin; ATd: adjuvant chemotherapy drugs; TP: paclitaxel + cisplatin; PF: cisplatin + fluorouracil; DOX: docetaxel; CBP: carboplatin; NDB: nedaplatin; OXA: oxaliplatin; TC: paclitaxel + carboplatin; RT: radiotherapy; 2D: conventional radiotherapy; 3D: appropriate radiotherapy; IMRT: intensity modulated radiotherapy; Hb: hemoglobin; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; TR: total time of radiotherapy; CCRT: concurrent radiotherapy.

TABLE 3. Analysis of clinical factors affecting chemoradiotherapy OS.

Clinical factors	Number of cases (example)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Group					
RT sensitive	738	Ref	<0.001	Ref	<0.001
RT resistant	227	4.590 (3.68–5.73)		6.750 (5.02–9.08)	
Age (yr)	965	1.000 (0.99–1.01)	0.802	1.010 (0.99–1.03)	0.274
40–60	705	Ref		Ref	
<40	61	0.804 (0.55–1.21)	0.317	0.641 (0.28–1.49)	0.301
>60	199	0.956 (0.70–1.27)	0.754	0.799 (0.53–1.20)	0.283
Stage					
IIb–IIIa	219	Ref	0.393	Ref	0.054
≥IIIb	746	1.140 (0.85–1.53)		0.670 (0.47–1.03)	
Tumor diameter					
≤4 cm	290	Ref	0.019	Ref	0.005
>4 cm	496	1.380 (1.06–1.01)		1.590 (1.15–2.20)	
CCRT					
No	124	Ref		Ref	
Yes	841	0.866 (0.68–1.08)	0.197	0.164 (0.02–1.24)	0.080
AT					
No	413	Ref		Ref	
Yes	552	0.997 (0.80–1.25)	0.980	0.418 (0.10–1.78)	0.238
CCRTd					
DDP	540				
CBP	46	1.059 (0.65–1.74)	0.812	0.124 (0.01–1.10)	0.061
NDB	215	1.201 (0.86–1.81)	0.276	1.254 (0.91–1.72)	0.161
Others	36	0.733 (0.44–1.28)	0.304	0.150 (0.02–1.36)	0.092
ATd					
TP	162	1.242 (0.93–1.73)	0.139		
PF	79	0.777 (0.56–1.08)	0.151	0.790 (0.38–1.63)	0.524
DOX + CBP	40	1.392 (0.68–3.25)	0.322	1.010 (0.58–1.75)	0.973
DOX + NDB	48	1.689 (0.93–4.37)	0.081	1.458 (0.82–2.59)	0.199
DOX + OXA	56	1.370 (0.68–3.17)	0.343	1.057 (0.75–1.50)	0.757
TC	54	0.917 (0.59–1.43)	0.707	0.679 (0.51–0.90)	0.008
Others	104	1.039 (0.74–1.46)	0.821	0.927 (0.82–1.05)	0.222
RT					
2D	442				
3D	118	1.189 (0.83–1.77)	0.330	0.844 (0.44–1.62)	0.608
IMRT	389	1.275 (1.03–1.82)	0.049	1.054 (0.79–1.41)	0.720
Hb	965	0.990 (0.99–1.00)	0.012	1.010 (1.00–1.01)	0.140
NLR	965	1.080 (1.03–1.12)	<0.001	1.080 (1.01–1.15)	0.028
PLR	965	1.000 (1.00–1.00)	<0.001	1.002 (1.00–1.00)	0.005
Lymph node					
No metastasis	523	Ref	<0.001	Ref	0.127
Metastasis	312	1.710 (1.33–2.20)		1.260 (0.94–1.71)	
TR (wk)					
≤8	367	Ref	0.370	Ref	0.012
>8	599	1.130 (0.87–1.46)		1.530 (1.10–2.14)	
CCRT (wk)	965	0.950 (0.89–1.00)	0.070	0.940 (0.87–1.01)	0.072
AT (wk)	965	0.990 (0.92–1.06)	0.704	1.020 (0.93–1.13)	0.062
Hospital					
GuangXi	770	Ref	0.634	Ref	0.281
XiNan	195	1.070 (0.82–1.39)		1.200 (0.86–1.66)	

Note: HR: hazard rate; CI: confidence interval; RT: radiotherapy; CCRTd: concurrent radiotherapy drugs; DDP: cisplatin; CBP: carboplatin; NDB: nedaplatin; ATd: adjuvant chemotherapy drugs; TP: paclitaxel + cisplatin; PF: cisplatin + fluorouracil; DOX: docetaxel; TC: paclitaxel + carboplatin; 2D: conventional radiotherapy; 3D: appropriate radiotherapy; IMRT: intensity modulated radiotherapy; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; TR: total time of radiotherapy; CCRT: concurrent radiotherapy; AT: adjuvant chemotherapy; Hb: hemoglobin; OXA: oxaliplatin; yr: year; wk: week.

TABLE 4. Analysis of the clinical factors affecting chemoradiotherapy PFS.

Clinical factors	Number of cases (example)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Group					
RT sensitive	738	Ref	<0.001	Ref	<0.001
RT resistant	227	5.040 (4.03–6.29)		7.180 (5.35–9.64)	
Age	965	1.000 (0.99–1.01)	0.920	1.010 (0.99–1.03)	0.028
40–60	705	Ref		Ref	
<40	61	0.910 (0.60–1.39)	0.669	0.647 (0.28–1.52)	0.318
>60	199	0.920 (0.69–1.23)	0.587	0.820 (0.51–1.23)	0.338
Stage					
IIb–IIIa	219	Ref	0.235	Ref	0.068
≥IIIb	746	1.200 (0.89–1.61)		0.700 (0.48–1.03)	
Tumor diameter					
≤4 cm	290	Ref	0.039	Ref	0.106
>4 cm	496	1.330 (1.01–1.74)		1.520 (1.10–2.10)	
CCRT					
No	124				
Yes	841	0.678 (0.44–0.90)	0.012	0.168 (0.02–1.28)	0.085
AT					
No	413				
Yes	552	1.012 (0.81–1.27)	0.920	0.422 (0.10–1.81)	0.245
CCRTd					
DDP	540				
CBP	46	1.030 (0.62–1.70)	0.905	0.590 (0.25–1.37)	0.220
NDB	215	1.003 (0.69–1.45)	0.985	1.133 (0.83–1.55)	0.435
Others	36	0.700 (0.43–1.22)	0.237	1.070 (0.80–1.44)	0.654
ATd					
TP	162				
PF	79	0.703 (0.45–1.02)	0.078	0.885 (0.44–1.78)	0.732
DOX + CBP	40	1.012 (0.48–2.13)	0.974	1.120 (0.65–1.92)	0.681
DOX + NDB	48	1.216 (0.61–2.58)	0.553	1.149 (0.79–1.66)	0.463
DOX + OXA	56	1.011 (0.48–2.13)	0.976	1.138 (0.88–1.47)	0.318
TC	54	0.705 (0.44–1.14)	0.170	0.779 (0.65–0.94)	0.008
Others	104	0.808 (0.53–1.19)	0.281	0.936 (0.84–1.04)	0.209
RT					
2D	442				
3D	118	1.112 (0.77–1.63)	0.555	0.807 (0.42–1.56)	0.525
IMRT	389	1.017 (0.77–1.36)	0.897	0.990 (0.74–1.32)	0.945
HB	965	0.990 (0.99–1.00)	0.011	1.010 (1.00–1.01)	0.205
NLR	965	1.070 (1.02–1.12)	0.001	1.070 (1.00–1.15)	0.036
PLR	965	1.002 (1.00–1.00)	0.001	1.003 (1.00–1.00)	0.009
Lymph node					
no metastasis	523	Ref	<0.001	Ref	0.096
metastasis	312	1.690 (1.32–2.17)		1.290 (0.96–1.74)	
TR (wk)					
≤8	367	Ref	0.162	Ref	0.011
>8	599	1.200 (0.93–1.56)		1.540 (1.11–2.16)	
CCRT (wk)	965	0.960 (0.90–1.01)	0.144	0.950 (0.88–1.01)	0.118
AT (wk)	965	0.990 (0.92–1.06)	0.697	1.040 (0.95–1.15)	0.361
Hospital	738				
GuangXi	227	Ref	0.824	Ref	0.212
XiNan	195	1.030 (0.79–1.35)		1.230 (0.89–1.71)	

Note: HR: hazard rate; CI: confidence interval; RT: radiotherapy; CCRTd: concurrent radiotherapy drugs; DDP: cisplatin; CBP: carboplatin; NDB: nedaplatin; ATd: adjuvant chemotherapy drugs; TP: paclitaxel + cisplatin; PF: cisplatin + fluorouracil; DOX: docetaxel; TC: paclitaxel + carboplatin; 2D: conventional radiotherapy; 3D: appropriate radiotherapy; IMRT: intensity modulated radiotherapy; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; TR: total time of radiotherapy; CCRT: concurrent radiotherapy; AT: adjuvant chemotherapy; OXA: oxaliplatin; yr: year; wk: week.

4. Discussion

4.1 Effect of chemoradiotherapy sensitivity on survival

Based on our study results, the 5-year survival rate of the chemoradiotherapy sensitive group was approximately 40% greater than that of the RT-resistant group. Chemoradiotherapy sensitivity had a significant influence on the OS and PFS and can hence be used as an independent prognostic index to determine the curative effect of locally advanced cervical squamous cell carcinoma. In this study, the patients were categorized into the chemoradiotherapy resistant and chemoradiotherapy sensitive groups. There were differences in the tumor stage, hemoglobin level before radiotherapy, NLR value before radiotherapy, lymph node metastasis, and the total time of radiotherapy between the 2 groups. However, there was no significant difference in terms of age, tumor diameter, PLR value, the number of courses of concurrent chemotherapy and the number of courses of adjuvant chemotherapy between the 2 groups. The analysis of the factors affecting the sensitivity to chemoradiotherapy indicated that only patients treated with radiotherapy alone, of late tumor stage, with lymph node metastasis and the total time of radiotherapy >8 weeks were unfavorable factors affecting reduction in sensitivity to chemoradiotherapy. However, multivariate analysis revealed that only the total time of radiotherapy of >8 weeks acted as an independent factor.

Some articles on uncontrolled recurrence of advanced cervical squamous cell carcinoma obtained conclusions similar to ours. For instance, Chen [4] reported that lymph node metastasis and low hemoglobin level before treatment acted as uncontrolled risk factors for tumor recurrence. There was no difference in the tumor diameter between chemoradiotheraphy-sensitive and-resistant groups. However, most of the past literature did not conform to these results [5]. In this study, the proportion of tumor diameter ≥4 cm in the chemoradiotherapy sensitive and resistant groups was similar. This observation may be attributed to the subjectivity of the doctor to judge the tumor diameter and decide on the use of imaging for examination; therefore, the presumed size was different from the actual size one. The average course of concurrent chemotherapy between the two groups was approximately 1.5. Nevertheless, concerns such as whether this was related to the choice of chemotherapeutic drugs, the general condition of patients, complications, and other such factors warrant further in-depth and detailed research.

4.2 Effect of age on the efficacy of chemoradiotherapy

According to the latest epidemiological survey report on the incidence of cervical cancer in China, the victims of cervical cancer tended to be younger, of peak age 45–49 years [6]. Cervical cancer patients aged <35 years are usually considered to have young cervical cancer. However, according to the clinical data acquired in this study, there were only 27 patients aged <35 years, accounting for 2.8% of all cases (27/965). This finding may be related to the fact that the pathological type of the patients selected was squamous cell carcinoma and that young patients are relatively more likely to have non-squamous cell carcinoma [7]. Among the younger patients, the proportion of cervical adenocarcinoma and neuroendocrine carcinoma was higher, with a tendency of increasing incidence. These patients were also prone to lymph node and distant metastases, with a poor therapeutic response [8]. In a study by Chen *et al.* [9], the older the patient at the time of diagnosis the poorer was the prognosis. However, the present results were comparable to those of most literature, implying no correlation between age and survival rate. The results of Liu [10] suggested no difference in the OS and PFS, albeit there was a significant difference in the number of cases between the two groups of patients aged >40 years (n = 90) and <40 years (n = 8). Sturdza [11] also revealed that age was not related to prognosis. OS from 35 to 70 years was 14.5 months. OS for patients aged >70 years was 10 months, and for those <35 years, it was 9 months. This observation may be attributed to the age grouping and that some patients had recurrence or metastasis, which resulted in a bias. Combining our result with those reported in the literature, age may not be an independent prognostic factor for patients with advanced cervical squamous cell carcinoma treated with chemoradiotherapy.

4.3 Effect of clinical stage on chemoradiotherapy efficacy

Indeed, the clinical stage is directly related to the curative effect. In fact, the clinical stage reflects the severity of the disease to a certain extent, making it an independent factor of prognosis. The earlier the clinical stage, the higher is the 5-year survival rate. Binbin *et al.* [12] found that 5 years after concurrent chemoradiotherapy, the OS and PFS of patients at stage IIB were 75.9% and 71.7% and of those at stage ≥III were 52.9% and 42.8%, respectively. A Korean study [13] found that the 5-year survival rates after concurrent chemoradiotherapy was 71.5% for patients at stage IIB, 44.9% for patients at stage III, and 20.9% for patients at stage IVA. In our study, univariate and multivariate analyses revealed that staging affected the OS after chemoradiotherapy for advanced cervical squamous cell carcinoma, but staging did not affect the PFS. This observation may be attributed to the fact that the specimens in the study were at stage >III, accounting for approximately 77.2%. Moreover, the staging of the tumor depended on the doctor's gynecological examination experience and showed a certain degree of subjectivity. Differences in the technical level and equipment may have also influenced staging.

4.4 Effect of tumor diameter on chemoradiotherapy efficacy

In the early stage of cervical cancer, Tovanabutra *et al.* [14] demonstrated that the tumor size was an independent factor affecting the prognosis of patients, similar to that in our study. Univariate analysis revealed that the tumor diameter affected the OS and PFS, while multivariate analysis revealed that the tumor diameter affected OS. Research by Teh *et al.* [15] revealed that tumor diameter acted as an independent prognostic factor for the efficacy of concurrent chemoradiotherapy in advanced cervical squamous cell carcinoma. In patients

with tumor diameter ≥4 cm and <4 cm, the 5-year OS was 86.3% and 59.3%, respectively, while the 5-year tumor-free survival stage (DFS) was 55.3% and 69.3%, respectively. However, we noted that the tumor diameter did not act as an independent influencing factor in multivariate analyses. Moreover, the analysis of the tumor diameter was partially derived from the CT scans and may have had some errors. Some studies [16] have reported that the 5-year OS of tumor diameter >4 cm and <4 cm was 63% and 75%, respectively, while the local recurrence-free survival (LRFS) was 44% and 60%, respectively, with no difference in the results between the 2 groups. On the other hand, multivariate analyses did not suggest it to be an independent factor affecting prognosis. However, Endo *et al.* [17] analyzed the prognostic factors of patients with advanced cervical cancer treated with concurrent chemoradiotherapy, and found that both univariate and multivariate analyses revealed a 2.3-fold increased risk for tumor diameter ≥6 cm, indicating an association with poor prognosis.

Based on the above mentioned analysis, the tumor diameter of 4 cm in advanced cervical squamous cell carcinoma can act as an independent factor affecting tumor recurrence or uncontrolled recurrence, but it may be an independent factor for prognosis. For advanced cervical squamous cell carcinoma, setting the standard of tumor diameter at 6 cm may be an independent factor affecting prognosis, which raises the question of whether the standard should be defined as other sizes, warranting further discussion.

4.5 Effect of lymph node metastasis on chemoradiotherapy efficacy

Lymph node metastasis of cervical cancer has been recognized as the main independent factor affecting the prognosis of patients with cervical cancer. For early cervical cancer, postoperative lymph node metastasis is considered as the criterion of postoperative high-risk factor, requiring treatment with concurrent chemoradiotherapy. A domestic study revealed that lymph node metastasis is an independent risk factor for uncontrolled recurrence in patients with advanced cervical cancer after chemoradiotherapy [12]. Another study showed that the lymph node status affected the OS and DFS, while the 3-year OS of patients with lymph node metastasis decreased from 92.8% to 81.7%, while the survival time without distant metastasis decreased from 92.7% to 79.3% [18]. The same result was obtained by other foreign studies [19–21]. For instance, Endo *et al.* [17] reported that pelvic lymph node enlargement is an independent factor that affects prognosis, irrespective of univariate or multivariate analysis. In the present study, the latest FIGO2018 staging of cervical cancer [22] was applied to separate the patients with lymph node metastasis at IIIC stage to emphasize the importance of treatment choice and efficacy evaluation for lymph node metastasis. Our univariate analysis exhibited a correlation between lymph node metastasis and prognosis, although multivariate analyses revealed that lymph node metastasis is not an independent prognostic factor. This observation may be attributed to the lack of precise assessment regarding the existence of lymph node metastasis arising from issues related to the financial status of the patient, imaging technology, recognition of lymph node metastasis by medical staff and others such factors.

4.6 Effect of anemia on chemoradiotherapy efficacy

The study of advanced II and III stage cervical cancer at the Cancer Hospital Chinese Academy of Medical Sciences revealed that the 5-year survival rate of patients with hemoglobin level <80 g/L before radiotherapy was approximately 20% and 30% lower than that of patients with hemoglobin level 80–100 g/L and ≥120 g/L, respectively. Moreover, increasing number of studies [20, 23] have revealed that anemia can significantly reduce the efficacy of chemoradiotherapy in advanced cervical cancer. It is therefore considered that hemoglobin level <110 g/L is one of the factors of distant metastasis and an independent prognostic factor affecting prognosis, albeit it remains controversial as to which type of prognostic index hemoglobin serves as an independent prognostic factor. Teh *et al.* [15] analyzed the efficacy of concurrent chemoradiotherapy for locally advanced cervical cancer. Univariate and multivariate analyses revealed that hemoglobin level <100 g/L is an independent prognostic factor for OS, but not for DFS. Moreover, Gennigens *et al.* [24] reported that hemoglobin level <100 g/L is an independent prognostic factor for DFS as per a multivariate analysis. Our study revealed that the average hemoglobin level in the chemoradiotherapy sensitive and resistant groups were 109.4 ± 19.9 and 104.8 ± 22.1 g/L, respectively, with statistically significant differences between the two. Thus, it can be inferred that the hemoglobin level affects chemoradiotherapy sensitivity.

In this study, the results of univariate analysis implied that the hemoglobin level is associated with OS and PFS, albeit it acted as an independent prognostic factor for OS and PFS in multivariate analyses. Several scholars advocate that patients with cervical cancer should actively improve their anemia before undertaking radical radiotherapy to increase the sensitivity of their tumor cells to radiotherapy as well as to improve the effect of radiotherapy. However, establishing the uniform clinical standard of hemoglobin (100 g/L or 110 g/L) warrants further clinical research.

4.7 Effect of NLR and PLR on chemoradiotherapy efficacy

Presently, most related studies are focused on the relationship between early cervical cancer and the surgical outcome. Most studies suggest that the increase of NLR and PLR may indicate lymph node metastasis. Some past studies report that high NLR is associated with PFS and OS [25, 26], and there are no correlation reports among high NLR, PFS and OS [27, 28]. Moreover, it seems that high PLR is not associated with PFS and OS, and is hence a prognostic factor [27]. Some studies also suggest that high PLR is associated with PFS and OS [25, 29, 30]. Overall, the conclusions of different studies are mixed and hence controversial.

Furthermore, there are disagreement regarding the efficacy of NLR and PLR in the terms of treatment of cervical cancer. Lee *et al.* [31] analyzed the efficacy of chemoradiotherapy in cervical squamous cell carcinoma, and found that patients with high NLR before treatment had a larger tumor diameter,

late tumor stage, greater lymph node metastasis and low CR rate after treatment. Univariate and multivariate analyses also showed that high NLR before treatment was an adverse prognostic factor for PFS and OS. Nakamura *et al.* [32] analyzed the efficacy of second-line chemotherapy in patients with recurrent cervical cancer after chemoradiotherapy and found no correlation between NLR and survival time before treatment. In fact, PLR was related to the survival time in univariate and multivariate analyses. Further in-depth study by Tas *et al.* [33] revealed that NLR and PLR were evidently increased before and after cervical cancer invasion, albeit their correlational analysis indicated that PLR was associated with invasion but not NLR.

The present study results suggest that both NLR and PLR are correlated with sensitivity to chemoradiotherapy and that an increase of NLR and PLR may be related to resistance to chemoradiotherapy, although the result of ROC curve indicated that the AUC was approximately 0.5, which was not different from that of another study [34]. Therefore, predicting the curative effect has little significance as a clinical diagnosis, and it is of more clinical significance to add other indexes and establish a predictive model that provides the diagnosis rate of prognosis. Thus, NLR and PLR are prognostic factors of OS and PFS. There is a great divergence in the efficacy of NLR and PLR in the treatment of cervical cancer, warranting further clinical studies.

4.8 Effect of the total time of radiotherapy on the chemoradiotherapy efficacy

The total time of radiotherapy has been an important factor in the prognosis of cervical cancer after radiotherapy. The present study clarified whether the total time of radiotherapy was >8 weeks, and showed a correlation between the sensitive and resistant group. In the analysis of the effect on the prognosis, multiple factors indicated that the total time of radiotherapy >8 weeks was an independent factor for OS and PFS in advanced cervical squamous cell carcinoma.

However, the established total time of 6–8 weeks of radiotherapy was based on the results of simple radiotherapy. For advanced cervical cancer treated with concurrent chemoradiotherapy, the total time of radiotherapy may change. Liu *et al.* [16] showed that >6 weeks was not a prognostic factor in cervical cancer LRFS, distance metastasis free survival (DMFS), DFS, and OS, and that prolonging the treatment time did not increase the mortality of distant failure and distant metastasis. According to Song *et al.* [35], the total treatment time was 68 days (9–10 weeks), but the total radiotherapy time was <8 weeks, while the 3-year pelvic recurrence rate was 9%, which was 20% for >8 weeks, indicating statistical significance. However, the 3-year distant metastasis rate was 28% and 26%, respectively, and the 3-year mortality rate was 26% and 29%, respectively, indicating no statistical difference. Multivariate analysis results also suggested the significance of pelvic recurrence; the OS and distant metastasis failure rate did not increase in advanced cervical squamous cell carcinoma, which may be related to chemotherapy. However, concurrent chemotherapy did not counteract the tumor cell proliferation caused by prolonged tumor time, hence it is imperative that the total radiotherapy should be completed within 8 weeks to improve the local control rate.

We acknowledge that there are some limitations to this study, mostly related to the retrospective nature of the review and patients lost to follow-up. The reason for the latter is not death of the patient, rather there are other reasons, which makes it necessary to classify the loss of follow-up as survival.

5. Conclusions

In summary, we conducted retrospective analyses of data of patients with locally advanced cervical squamous cell carcinoma who were treated with chemoradiotherapy for 9 years. Our result demonstrated a significant difference in the 5-year survival rate between the chemoradiotherapy sensitive and resistant groups. The main clinical factors that affected the chemoradiotherapy sensitivity included tumor stage, lymph node metastasis and the total time of radiotherapy. The analysis of prognostic factors of these patients revealed that sensitivity to chemoradiotherapy, tumor diameter, NLR, PLR, and the total time of radiotherapy were independent prognostic factors of OS and PFS.

ABBREVIATIONS

AT: adjuvant chemotherapy; ATd: adjuvant chemotherapy drugs; BT: brachytherapy; CBP: carboplatin; CCRT: concurrent radiotherapy; CCRTd: concurrent radiotherapy drugs; DDP: cisplatin; DFS: tumor-free survival stage; DOX: docetaxel; ECOG: Eastern Cooperative Oncology Group; EBRT: external beam radiotherapy; FIGO: international federation of gynecology and obstetrics stage; Hb: hemoglobin; HR-CTV: the high-risk clinical volume; IMRT: intensity modulated radiotherapy; LACC: locally advanced cervical cancer; LASCC: locally advanced squamous cervical cancer; LN: lymph node; LRFS: local recurrence-free survival; NDB: nedaplatin; NLR: neutrophil to lymphocyte ratio; OS: overall survival; PF: cisplatin + fluorouracil; PFS: progression free survival; PLR: platelet to lymphocyte ratio; RT: radiotherapy; TC: paclitaxel + carboplatin; TP: paclitaxel + cisplatin; TR: Total time of radiotherapy; 3DRT: Three-dimensional radiotherapy.

AVAILABILITY OF DATA AND MATERIALS

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

ZHZ—designed the study, acquired the data. SXX and MTX—analyzed the data. ZHZ and QD—wrote the manuscript. FKD, HJJ, ZMY, XW, MXL, QLW, JL and ZGX—provided critical review. YSZ, JS and LL—critically revised the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed consent was obtained from all participants. The study was approved by the hospital ethical committee (Ethics Committee of Affiliated Hospital of Southwest Medical University, ethics number: KY2021035). All methods were carried out in accordance with relevant guidelines and regulations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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