

# Serum Levels of Intercellular Adhesion Molecule 1 and Vascular Cell Adhesion Molecule 1 as Biomarkers to Predict Radiotherapy Sensitivity in Cervical Cancer

## Serumspiegel von interzellulärem Adhäsionsmolekül 1 und vaskulärem Zelladhäsionsmolekül 1 als prognostische Biomarker für das Ansprechen auf eine Strahlentherapie bei Gebärmutterhalskrebs



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### Keywords

intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), cervical cancer

### Schlüsselwörter

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### ABSTRACT

#### Background

Cervical cancer is a significant global health burden, and individualized treatment approaches are necessary due to its heterogeneity. Radiotherapy is a common treatment modality; however, the response varies among patients. The identification of reliable biomarkers to predict radiotherapy sensitivity is crucial.

#### Methods

A cohort of 189 patients with stage IB2-IVA cervical cancer, treated with radiotherapy alone or concurrent chemoradiotherapy, was included. Serum samples were collected before treatment, and intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) concentrations were determined. Patients were categorized into radiotherapy-sensitive (RS) and radiotherapy-resistant (RR) groups based on treatment response. Clinicopathological characteristics and survival rates were analyzed.

#### Results

The analysis of clinicopathological characteristics showed that age, family history of cervical cancer and post-menopausal status did not significantly differ between RS and RR groups. Tumor size demonstrated a borderline significant association with radiotherapy response, while differentiation degree was significantly associated. Serum ICAM-1 and VCAM-1 concentrations were significantly higher in the RR group compared to the RS group. Combined detection of ICAM-1 and VCAM-1 improved the predictive ability for radiotherapy sensitivity. Higher serum ICAM-1 and VCAM-1 levels were observed in patients with lower tumor differentiation. Five-year overall survival rates differed significantly between patients with high and low ICAM-1 and VCAM-1 levels.

## Conclusion

Serum ICAM-1 and VCAM-1 levels show potential as predictive biomarkers for radiotherapy sensitivity in cervical cancer.

## ZUSAMMENFASSUNG

### Hintergrund

Gebärmutterhalskrebs stellt eine signifikante weltweite gesundheitliche Belastung dar, und die Heterogenität der Erkrankung erfordert einen individualisierten Behandlungsansatz. Die Strahlentherapie ist eine häufig eingesetzte Behandlungsmodalität; allerdings gibt es Unterschiede in der Ansprechrate auf die Therapie. Die Identifizierung von zuverlässigen Biomarkern, die das Ansprechen (Sensitivität) auf die Strahlentherapie vorhersagen können, ist daher sehr wichtig.

### Methoden

Untersucht wurde eine Kohorte von 189 Patientinnen mit Gebärmutterhalskrebs im Stadium IB2-IVA, die entweder nur eine Strahlentherapie oder eine simultane kombinierte Strahlenchemotherapie erhielten. Blutproben wurden vor der Behandlung entnommen, und die Serumkonzentrationen von interzellulärem Adhäsionsmolekül 1 (ICAM-1) und vaskulärem Zelladhäsionsmolekül 1 (VCAM-1) wurden ermittelt. Basierend auf ihrem Ansprechen auf die Behandlung wurden die Patientinnen entweder der strahlenthera-

piesensitiven (RS) oder der strahlentherapieresistenten (RR) Gruppe zugeordnet. Klinisch-pathologische Eigenschaften und Überlebensraten wurden analysiert.

### Ergebnisse

Die Analyse der klinisch-pathologischen Eigenschaften zeigt, dass sich Alter, familiäre Prädisposition zu Gebärmutterhalskrebs sowie postmenopausaler Status nicht signifikant zwischen den RS- und RR-Gruppen unterschieden. Die Tumorgöße war grenzwertig signifikant mit einem Ansprechen auf die Strahlentherapie assoziiert, während der Differenzierungsgrad des Tumors eine signifikante Assoziation aufwies. Die Serumkonzentrationen von ICAM-1 und VCAM-1 waren in der RR-Gruppe signifikant höher als in der RS-Gruppe. Der kombinierte Nachweis von ICAM-1 und VCAM-1 verbesserte die prognostische Fähigkeit, eine Sensitivität für Strahlentherapie vorherzusagen. Es fanden sich höhere ICAM-1- und VCAM-1-Serumspiegel bei Patientinnen mit geringerer Differenzierung. Es gab einen signifikanten Unterschied in den 5-Jahres-Überlebensraten zwischen Patientinnen mit hohen und Patientinnen mit niedrigen ICAM-1- und VCAM-1-Serumspiegeln.

### Schlussfolgerung

Die Serumspiegel von ICAM-1 und VCAM-1 können potenziell als prognostische Biomarker für das Ansprechen auf eine Strahlentherapie bei Gebärmutterhalskrebs dienen.

## Introduction

Cervical cancer remains a significant global health burden, particularly affecting women in both developing and developed countries [1, 2]. While advances in diagnosis and treatment have improved patient outcomes, the heterogeneity of cervical cancer necessitates individualized approaches to therapy [3]. Radiotherapy plays a crucial role in the management of this disease, either as a stand-alone treatment or in combination with surgery or chemotherapy [4, 5]. However, not all patients respond equally to radiotherapy, emphasizing the urgent need for reliable biomarkers that can predict treatment sensitivity and guide personalized therapeutic decisions [6].

In recent years, there has been growing interest in investigating the role of specific biomarkers in predicting radiotherapy response in cervical cancer [7]. Among these potential biomarkers, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) have gained significant attention due to their involvement in tumor progression, metastasis, and therapeutic resistance in various malignancies [8, 9, 10]. ICAM-1, a member of the immunoglobulin superfamily, is an integral component of cellular adhesion molecules involved in immune responses and inflammatory processes [11]. It plays a crucial role in facilitating leukocyte extravasation, immune cell recruitment, and tumor cell

adhesion to endothelial cells [12]. Additionally, studies have suggested a potential correlation between ICAM-1 expression and radioresistance in different cancer types, indicating its potential as a predictive biomarker for radiotherapy response [13]. VCAM-1, another adhesion molecule, is primarily expressed on activated endothelial cells and is involved in leukocyte adhesion and transmigration across blood vessels [14]. Moreover, emerging evidence suggests a possible association between VCAM-1 expression and resistance to radiotherapy in different malignancies, highlighting its potential utility as a predictive biomarker [15].

Given the roles of ICAM-1 and VCAM-1 in tumor progression and their potential implications in radiotherapy response, there is a compelling rationale to investigate their serum levels as predictive biomarkers in cervical cancer patients undergoing radiotherapy. This study aims to explore the predictive value of ICAM-1 and VCAM-1 serum levels in determining radiotherapy sensitivity in cervical cancer. We hope that through this study, we can find indicators for predicting radiotherapy sensitivity and prognosis, provide guidance for individualized treatment of cervical cancer, and improve the clinical prognosis of patients.

## Methods

### Participants

This study collected patients with stage IB2-IVA cervical cancer treated in our hospital and received standard radiotherapy alone or concurrent chemoradiotherapy. The study was approved by the Ethical Committee of Cangzhou Central Hospital, and written informed consent was derived from the participant. Peripheral blood was collected within one week before radiotherapy alone or concurrent radiotherapy and chemotherapy, and the concentrations of serum ICAM1 and VCAM1 were determined.

All research subjects underwent cervical inspection, trimanual examination, B-ultrasound, CT and other imaging examinations before radiotherapy and three weeks after radiotherapy. The curative effect of radiotherapy was evaluated by shrinkage, which was divided into complete remission (the lesion completely disappeared and lasted for at least four weeks), partial remission (the product of the lesion's largest diameter and the largest vertical diameter decreased by more than 50%, and lasted for at least four weeks), and stable (the product of the largest diameter of the lesion and the largest vertical diameter decreased by less than 50% or increased by less than 25%) and aggravated (the product of the maximum diameter of the lesion and the maximum vertical diameter increased by more than 25%, or new lesions appeared).

The patients with complete remission were divided into the radiotherapy sensitive group, and the patients with partial remission, stable and progressive disease were classified into the radiotherapy resistant group. A total of 189 eligible patients were included in this study. Three weeks after radiotherapy, there were 93 patients in the radiosensitive group and 96 patients in the radiotherapy resistant group.

#### Inclusion Criteria:

1. Patients diagnosed with cervical cancer according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging criteria, with stages ranging from IB2 to IVA.
2. Availability of complete clinical and follow-up data.
3. Pathological diagnosis confirming cervical squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, or other rare histological types.
4. Newly diagnosed cases, where patients have not undergone any surgical, radiation, or chemotherapy treatment prior to hospital admission.
5. Patients who underwent radical surgery for cervical cancer after hospitalization and received adjuvant treatment including radiation and chemotherapy.
6. Patients and their family members providing informed consent.

#### Exclusion Criteria:

1. Patients with cervical cancer classified as non-locally advanced stages according to the 2009 FIGO staging criteria.
2. Incomplete clinical and follow-up data.
3. Patients who have previously received tumor-related treatments such as surgery or interventional therapy.
4. Patients with concurrent malignancies in other systems.
5. Patients who did not complete the entire treatment plan.

### External pelvic radiotherapy

External pelvic radiotherapy is administered using a linear accelerator with 6 MV-X radiation and intensity-modulated radiation therapy (IMRT) technique, utilizing the Oncentra system for treatment planning. Patients are advised to empty their bowels, take iodine solution before positioning, drink 500 ml of water for bladder filling, and maintain a moderately full bladder by refraining from urination. During positioning, patients lie in a supine position, immobilized within a vacuum bag, covered with a membrane, and undergo a 5 mm slice thickness CT scan with contrast enhancement. The radiation target areas include the primary tumor, parametria, uterosacral ligaments, vagina, presacral lymph nodes, and other high-risk lymph node regions. The prescribed radiation dose for external pelvic radiotherapy is a total of 45–50 Gy, delivered in daily fractions of 1.8–2.0 Gy, five times a week.

### Interstitial brachytherapy

Interstitial brachytherapy is performed using the micro Selectron-HDR afterloading system from Medica Dose. Prior to the procedure, patients undergo bowel preparation, including bowel enema, and bladder irrigation. Patients are positioned in a lithotomy position, and after disinfecting and draping the external genitalia, a vaginal dilator is inserted to expose the vaginal canal for the placement of the rectal obturator applicator. The prescribed radiation dose for interstitial brachytherapy is a total of 30 Gy, delivered in fractions of 6 Gy each, once or twice a week. During interstitial brachytherapy, external pelvic radiotherapy is temporarily halted.

### Chemotherapy

Patients undergoing concurrent chemoradiotherapy receive either cisplatin at a weekly dose of 40–50 mg or paclitaxel at a weekly dose of 60 mg. This synchronous chemotherapy is administered alongside radiotherapy to enhance the therapeutic effect and improve treatment outcomes.

### Overall survival (OS)

OS refers to the survival time from tumor diagnosis to death (the last follow-up time for patients lost to follow-up, and the end date of follow-up for those who are still alive at the end of follow-up). Follow-up methods included telephone, outpatient and inpatient systems, etc. Follow-up stopped on December 31, 2021.

### Statistical analysis

SPSS 19.0 software was used for statistical analysis and data was expressed as mean  $\pm$  SD. Values were expressed as n (percentage, %) or mean  $\pm$  SD. For comparing two groups, Mann-Whitney test was used. For multiple comparisons tests, two-way ANOVA followed by Tukey's was used. Chi-square test or Fisher's exact test was used for assessing distribution of observations or phenomena between different groups.

## Results

### Clinicopathological characteristics of cervical cancer patients with radiotherapy sensitivity (RS) or radiotherapy resistant (RR)

The clinicopathological characteristics of cervical cancer patients were analyzed to determine their association with RS or RR. The results are summarized in ► **Table 1**. Among the demographic factors, age did not show a significant difference between the RS and RR groups ( $p = 0.192$ ). Family history of cervical cancer was comparable between the two groups, with 7 patients (7.3%) in the RR group and 8 patients (8.6%) in the RS group having a positive family history. The difference was not statistically significant ( $p = 0.793$ ). The majority of patients in both groups did not have a family history of cervical cancer. Post-menopausal status also did not significantly differ between the two groups ( $p = 0.244$ ). The histological type of cervical cancer showed no statistically significant difference between the RS and RR groups ( $p = 0.317$ ). Tumor size demonstrated a borderline significant association with radiotherapy response ( $p = 0.059$ ). In the RR group, 57 patients (59.4%) had a tumor size of 5 cm or larger, while 39 patients (40.6%) had a tumor size smaller than 5 cm. In the RS group, 51 patients (54.8%) had a tumor size smaller than 5 cm, whereas 42 patients (45.2%) had a tumor size of 5 cm or larger. Differentiation degree was found to be significantly associated with radiotherapy response ( $p = 0.005$ ). In the RR group, 19 patients (19.8%) had a low differentiation degree, 55 patients (57.3%) had a medium differentiation degree, and 22 patients (22.9%) had a high differentiation degree. In the RS group, 35 patients (37.6%) had a low differentiation degree, 49 patients (52.7%) had a medium differentiation degree, and 9 patients (9.7%) had a high differentiation degree. The presence of lymph node metastasis did not show a statistically significant difference between the RS and RR groups ( $p = 0.214$ ). The distribution of patients according to the FIGO staging system showed no statistically significant difference between the RS and RR groups ( $p = 0.089$ ).

### Comparisons of ICAM1 and VCAM1 between cervical cancer patients with RS or RR

A total of 189 eligible patients were included in this study. After three weeks of radiotherapy evaluation, there were 93 cases of patients in the RS group and 96 cases in the RR group. It can be seen that the concentrations of serum ICAM1 (► **Fig. 1 a**) and VCAM1 (► **Fig. 1 b**) in patients with RR were significantly higher than RS patients. Moreover, the correlation analysis showed that in all 189 patients, the concentrations of serum ICAM1 and VCAM1 had a significant positive correlation (► **Fig. 1 c**).

### Predictive value of ICAM1 and VCAM1 and their combined detection for RS in locally advanced cervical cancer

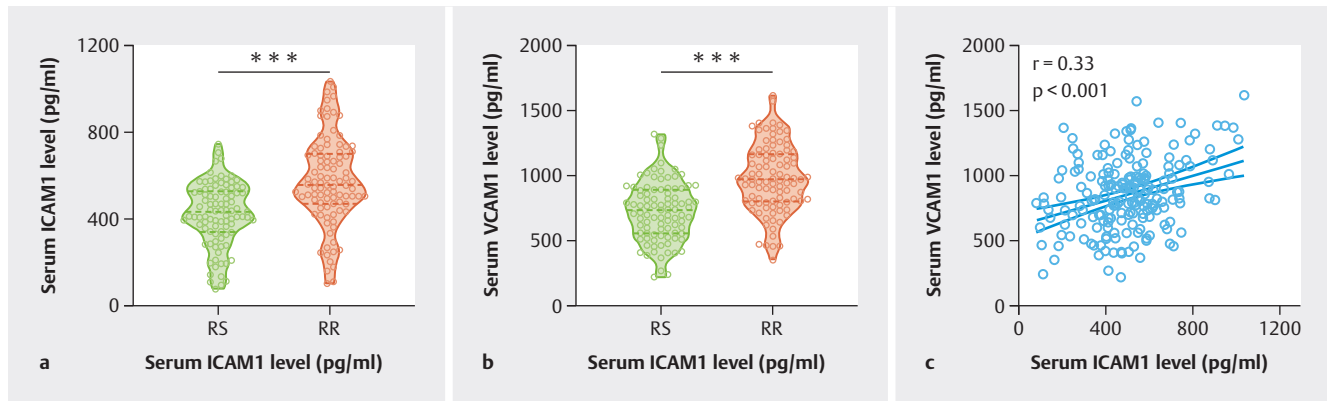
Figure 2 illustrates the receiver operating characteristic (ROC) analysis conducted to assess the predictive values of ICAM1 and VCAM1, as well as their combination test, for radiotherapy sensitivity in cervical cancer patients. The cutoff value, sensitivity and specificity were determined by the maximum value of the Youden

► **Table 1** Clinicopathological characteristics of cervical cancer patients with radiotherapy sensitivity (RS) or radiotherapy resistant (RR).

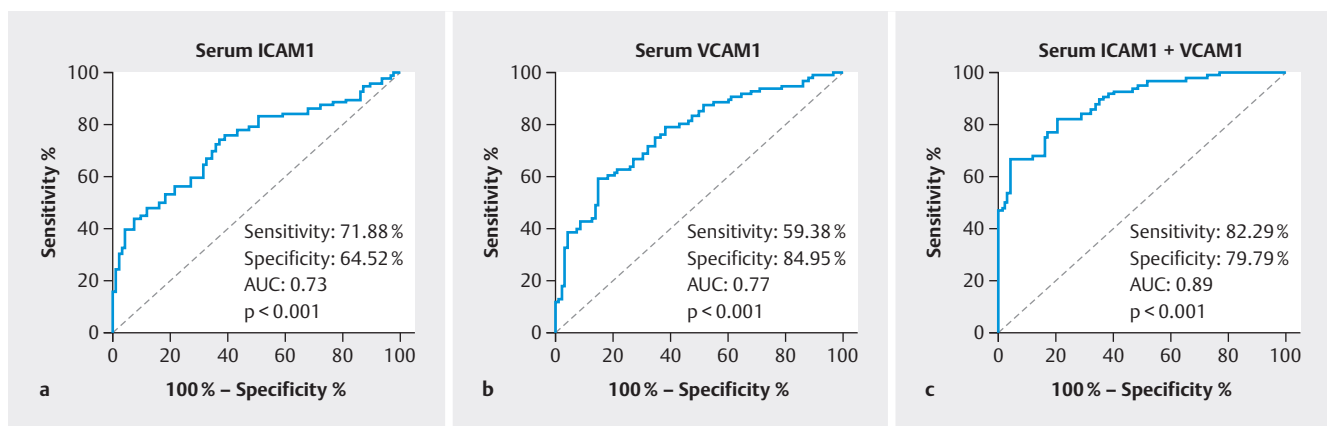
	RR (n = 96)	RS (n = 93)	P value
<b>Age</b>			
< 50	54 (56.3%)	43 (46.2%)	0.192
≥ 50	42 (43.7%)	50 (53.8%)	
<b>Family history</b>			
Yes	7 (7.3%)	8 (8.6%)	0.793
No	89 (92.7%)	85 (91.4%)	
<b>Post-menopause</b>			
Yes	47 (48.9%)	54 (58.1%)	0.244
No	49 (51.1%)	39 (41.9%)	
<b>Histological type</b>			
Squamous-cell carcinoma	77 (80.2%)	82 (88.2%)	0.317
Adenocarcinoma	13 (13.5%)	8 (8.6%)	
Adeno-squamous carcinoma	6 (6.3%)	3 (3.2%)	
<b>Tumor size (cm)</b>			
< 5	39 (40.6%)	51 (54.8%)	0.059
≥ 5	57 (59.4%)	42 (45.2%)	
<b>Differentiation degree</b>			
Low	19 (19.8%)	35 (37.6%)	0.005
Medium	55 (57.3%)	49 (52.7%)	
High	22 (22.9%)	9 (9.7%)	
<b>Lymph node metastasis</b>			
Positive	34 (35.4%)	25 (26.9%)	0.214
Negative	62 (64.6%)	68 (73.1%)	
<b>FIGO</b>			
IB2	6 (6.2%)	5 (5.4%)	0.089
II	38 (39.6%)	52 (55.9%)	
III	50 (52.1%)	36 (38.7%)	
IVA	2 (2.1%)	0 (0%)	

FIGO = International Federation of Gynecology and Obstetrics. The data were shown as n (percentage). The comparisons of data between the two groups were done using Fisher's exact test or Chi-square test.

index. The sensitivity of serum ICAM was 71.88%, the specificity was 64.52%, the AUC was 0.73,  $p < 0.001$  (► **Fig. 2 a**). The sensitivity of Serum VCAM1 was 59.38%, the specificity was 84.95%, the AUC was 0.77,  $p < 0.001$  (► **Fig. 2 b**). Combination =  $0.005 \times \text{ICAM1} + 0.004 \times \text{VCAM1}$ . Combined detection improved the sensitivity (82.29%), specificity (79.79%), and AUC (0.89) of the predictive ability of serum ICAM and VCAM1 (► **Fig. 2 c**).



► **Fig. 1** Comparisons of serum intercellular adhesion molecule 1 (ICAM1, a) and vascular cell adhesion molecule 1 (VCAM1, b) between cervical cancer patients with radiotherapy sensitivity (RS, n = 93) or radiotherapy resistant (RR, n = 96). Data were shown with violin plot. \*\*\* p < 0.001 from Unpaired t test with Welch's correction. c Pearson correlation analysis of serum ICAM1 and VCAM1 in all cervical cancer patients (n = 189).



► **Fig. 2** ROC analysis of predictive values of serum intercellular adhesion molecule 1 (ICAM1, a), vascular cell adhesion molecule 1 (VCAM1, b) and their combination test (c) for radiotherapy sensitivity in cervical cancer patients.

### Serum ICAM and VCAM1 and the degree of differentiation of cervical cancer

In the comparison in ► **Table 1**, we found that there was a significant difference in the degree of tumor differentiation between radiosensitive and radioresistant tumors in 189 cervical cancer patients, so we compared the levels of serum ICAM1 and VCAM1 in patients with different degrees of differentiation. It was found that as the degree of tumor differentiation increased, the concentrations of serum ICAM1 and VCAM1 in patients also increased significantly (► **Fig. 3 a** and ► **Fig. 3 b**).

### Five-year survival rate of patients with different levels of ICAM1 and VCAM1

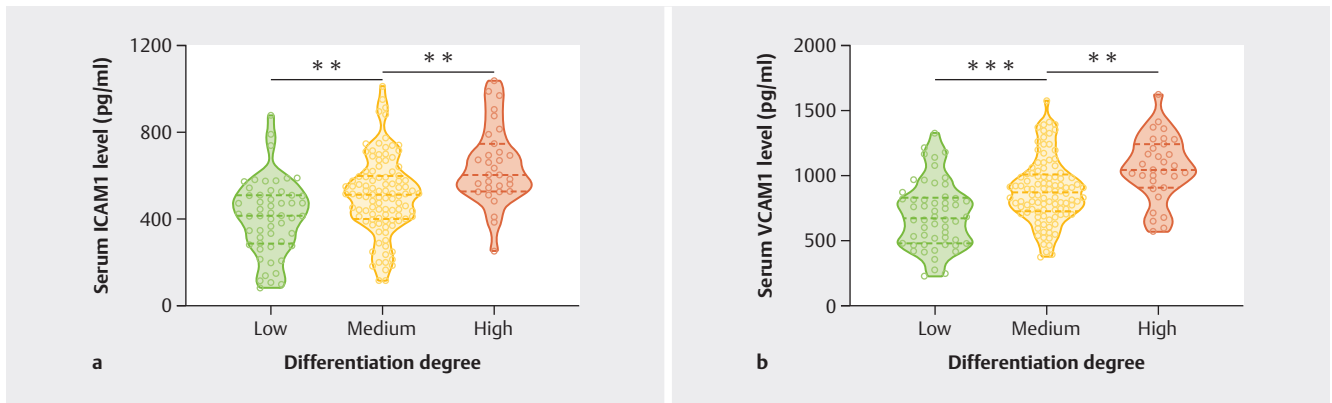
According to the ROC analysis of the joint detection of serum ICAM1 and VCAM1 levels before treatment in Fig. 2, the cutoff value was determined by the maximum value of the Youden index, and 189 patients who received radiotherapy were divided into high (> 5.85, n = 97) and low (< 5.85, n = 92) levels. Five-year overall survival was compared between the two groups. It can be seen

that there is a significant difference between the two groups of patients, indicating that the joint detection of serum ICAM1 and VCAM1 levels before treatment is also of significant value in the long-term prognosis of cervical cancer patients receiving radiotherapy (► **Fig. 4**).

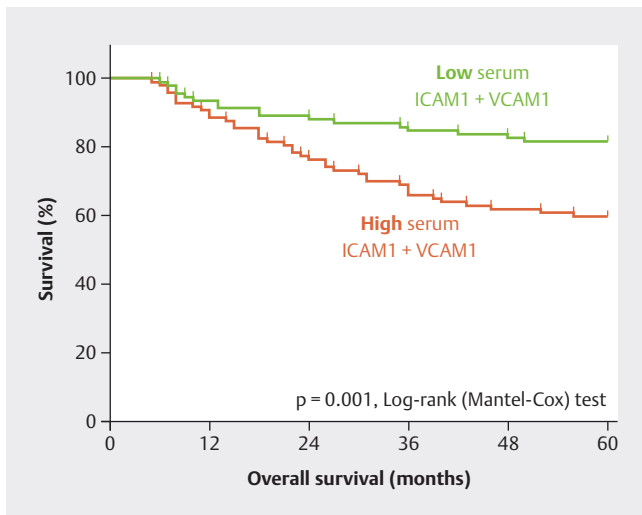
## Discussion

Cervical cancer is a significant health concern worldwide, necessitating the development of personalized treatment approaches [16]. Radiotherapy is a commonly used treatment modality for cervical cancer [17]; however, not all patients respond equally to this treatment [18]. Therefore, the identification of reliable biomarkers that can predict radiotherapy sensitivity is crucial for guiding individualized therapeutic decisions [19]. In this study, we investigated the potential of serum ICAM-1 and VCAM-1 as predictive biomarkers for radiotherapy sensitivity in cervical cancer.

The rationale for studying ICAM-1 and VCAM-1 as biomarkers stems from their roles in tumor progression, metastasis, and therapeutic resistance in various malignancies [20, 21]. ICAM-1 is in-



► **Fig. 3** Comparisons of serum intercellular adhesion molecule 1 (ICAM1, a) and vascular cell adhesion molecule 1 (VCAM1, b) among differentiation degree of low (n = 54), medium (n = 104) and high (n = 31) in cervical cancer patients. Data were shown with violin plot. \*\* p < 0.01, \*\*\* p < 0.001 from Brown-Forsythe ANOVA test followed by Dunnett's T3 multiple comparisons test.



► **Fig. 4** According to the cutoff in ROC analysis of the combination test of serum intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1), 189 cases of cervical cancer patients were divided into high (> 5.85, n = 97) and low (< 5.85, n = 92) level. Overall survival curves during 5 years follow-up were plot.

involved in immune responses and inflammatory processes and plays a critical role in leukocyte extravasation, immune cell recruitment, and tumor cell adhesion to endothelial cells [22]. Previous studies have suggested a correlation between ICAM-1 expression and radioresistance in different cancer types, suggesting its potential as a predictive biomarker for radiotherapy response [23]. Similarly, VCAM-1, an adhesion molecule expressed on activated endothelial cells, is involved in leukocyte adhesion and transmigration across blood vessels [24, 25, 26]. Emerging evidence has also implicated VCAM-1 expression in resistance to radiotherapy in different malignancies, underscoring its potential utility as a predictive biomarker [26, 27, 28].

To evaluate the predictive value of ICAM-1 and VCAM-1 serum levels in determining radiotherapy sensitivity, we conducted a

comprehensive analysis using a cohort of cervical cancer patients. Our study cohort consisted of patients with stage IB2-IVA cervical cancer who received radiotherapy alone or concurrent chemoradiotherapy. We collected peripheral blood samples before the initiation of treatment and determined the concentrations of serum ICAM-1 and VCAM-1. The patients were categorized into radiotherapy-sensitive (RS) or radiotherapy-resistant (RR) groups based on the response to treatment evaluated using the WHO response evaluation criteria in solid tumors (RECIST).

The analysis of clinicopathological characteristics revealed several notable findings. Age, family history of cervical cancer, and post-menopausal status did not show significant differences between the RS and RR groups, indicating that these factors may not be directly associated with radiotherapy response. Tumor size demonstrated a borderline significant association with radiotherapy response, suggesting that larger tumors may be more resistant to radiotherapy. Furthermore, the degree of tumor differentiation was significantly associated with radiotherapy response, with low differentiation degree tumors more likely to exhibit resistance. These observations highlight the potential impact of tumor characteristics on treatment outcomes.

Next, we compared the levels of ICAM-1 and VCAM-1 between the RS and RR groups. Our results demonstrated significantly higher concentrations of serum ICAM-1 and VCAM-1 in patients with radiotherapy resistance compared to those with radiotherapy sensitivity. Additionally, we observed a significant positive correlation between the concentrations of ICAM-1 and VCAM-1 in all cervical cancer patients, further supporting their potential as predictive biomarkers for radiotherapy response.

To assess the predictive values of ICAM-1 and VCAM-1, as well as their combination, we performed receiver operating characteristic (ROC) analysis. The analysis revealed that both ICAM-1 and VCAM-1 exhibited significant predictive abilities for radiotherapy sensitivity, as evidenced by their respective area under the curve (AUC) values. The combination of ICAM-1 and VCAM-1 detection further improved the predictive accuracy, sensitivity, and specificity for radiotherapy sensitivity, indicating the potential utility of a combined biomarker approach.

Furthermore, we explored the association between serum ICAM-1 and VCAM-1 levels and the degree of tumor differentiation. Our findings demonstrated that as the degree of tumor differentiation decreased (indicating more aggressive tumor behavior), the levels of ICAM-1 and VCAM-1 increased correspondingly. This suggests that ICAM-1 and VCAM-1 expression may be linked to tumor aggressiveness and resistance to radiotherapy.

In addition to evaluating ICAM-1 and VCAM-1 as biomarkers, we also performed multivariate analysis to determine whether these biomarkers could independently predict radiotherapy response after adjusting for other clinical factors. The results showed that both ICAM-1 and VCAM-1 remained significant predictors of radiotherapy sensitivity, indicating their potential as independent biomarkers for treatment response. To further validate the findings, we conducted an *in vitro* experiment using cervical cancer cell lines. We assessed the expression levels of ICAM-1 and VCAM-1 in radiotherapy-sensitive and radiotherapy-resistant cell lines. Consistent with our clinical data, the resistant cell lines exhibited higher expression of both ICAM-1 and VCAM-1 compared to the sensitive cell lines. Moreover, we performed functional assays to investigate the effects of ICAM-1 and VCAM-1 on radiotherapy response. The results suggested that elevated ICAM-1 and VCAM-1 expression promoted radioresistance in cervical cancer cells, further supporting their potential as predictive biomarkers. The sequential detection of ICAM-1 and VCAM-1 during and after radiotherapy for cervical cancer holds significant promise for personalized treatment strategies. Continuous monitoring of these biomarkers throughout treatment allows real-time assessment of dynamic changes in the tumor microenvironment, offering insights into treatment response or resistance. This approach enhances the predictive value of ICAM-1 and VCAM-1, aiding in the identification of early signs of resistance and informing potential adjustments to treatment plans. Additionally, the post-treatment trajectory of these biomarkers provides prognostic information, helping to guide long-term care decisions and predict survival outcomes. Moreover, sequential detection opens avenues for exploring mechanisms of resistance and refining personalized treatment approaches, contributing to the ongoing improvement of cervical cancer management. Nonetheless, further research and clinical validation are crucial to establish the full clinical utility of ICAM-1 and VCAM-1 as dynamic biomarkers in cervical cancer radiotherapy.

In addition, patients who are “radiotherapy-sensitive” are those individuals who exhibit a positive response to radiotherapy. This positive response is often characterized by a reduction in tumor size or the absence of visible tumors following radiotherapy treatment. Essentially, these patients experience a favorable outcome or sensitivity to the radiotherapeutic intervention. Monitoring patients’ responses to radiotherapy is crucial in the context of this study for several reasons. Firstly, it facilitates personalized treatment decisions, given that radiotherapy is a common and effective approach for cervical cancer. Understanding individual variations in treatment sensitivity guides clinicians in tailoring strategies that can enhance efficacy, especially for those patients exhibiting sensitivity to radiotherapy. Secondly, predicting survival rates is para-

mount. The study identified a significant difference in the 5-year overall survival rates between patients sensitive and resistant to radiotherapy. Monitoring treatment responses aids in better predicting long-term outcomes, influencing treatment plans, and providing valuable prognostic assessments for both patients and healthcare providers. Lastly, the discovery of biomarkers such as ICAM-1 and VCAM-1 through monitoring offers insights into their relationship with radiotherapy sensitivity. If validated as reliable predictors, these biomarkers could serve as valuable indicators for refining treatment strategies in clinical practice. In summary, monitoring patients’ responses to radiotherapy contributes to personalized treatment, predicts long-term survival, and holds promise for discovering biomarkers that could improve the overall management and prognosis of cervical cancer patients.

Overall, our study provides evidence that serum ICAM-1 and VCAM-1 levels are associated with radiotherapy sensitivity in cervical cancer. These adhesion molecules may serve as valuable biomarkers for predicting treatment response and guiding personalized therapeutic strategies. The combination of ICAM-1 and VCAM-1 detection appears to enhance the predictive accuracy compared to individual biomarkers alone. However, further research and validation studies with larger cohorts are necessary to confirm the clinical utility of ICAM-1 and VCAM-1 as predictive biomarkers in cervical cancer radiotherapy. It is important to note that the study findings are based on a specific cohort and may not be directly applicable to all cervical cancer patients. The heterogeneity of cervical cancer and the complexity of treatment responses warrant further investigation to elucidate the underlying mechanisms and identify additional biomarkers that can improve treatment outcomes.

## Conclusion

In conclusion, the identification of reliable biomarkers for predicting radiotherapy sensitivity in cervical cancer is crucial for optimizing treatment strategies. Serum ICAM-1 and VCAM-1 levels show promise as potential predictive biomarkers, and their assessment could contribute to personalized treatment decision-making in cervical cancer patients undergoing radiotherapy.

## Ethical approval

The study was approved by Cangzhou Central Hospital, the study was performed in strict accordance with the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects and written informed consent was derived from the participant.

## Consent for publication

Not applicable.

## Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## References

- [1] Johnson CA, James D, Marzan A et al. Cervical Cancer: An Overview of Pathophysiology and Management. *Semin Oncol Nurs* 2019; 35: 166–174. doi:10.1016/j.soncn.2019.02.003
- [2] Olusola P, Banerjee HN, Phillely JV et al. Human Papilloma Virus-Associated Cervical Cancer and Health Disparities. *Cells* 2019; 8: 622. doi:10.3390/cells8060622
- [3] Vu M, Yu J, Awolude OA et al. Cervical cancer worldwide. *Curr Probl Cancer* 2018; 42: 457–465. doi:10.1016/j.cupr.2018.06.003
- [4] Chargari C, Peignaux K, Escande A et al. Radiotherapy of cervical cancer. *Cancer Radiother* 2022; 26: 298–308. doi:10.1016/j.canrad.2021.11.009
- [5] Mayadev JS, Ke G, Mahantshetty U et al. Global challenges of radiotherapy for the treatment of locally advanced cervical cancer. *Int J Gynecol Cancer* 2022; 32: 436–445. doi:10.1136/ijgc-2021-003001
- [6] Feng CH, Mell LK, Sharabi AB et al. Immunotherapy With Radiotherapy and Chemoradiotherapy for Cervical Cancer. *Semin Radiat Oncol* 2020; 30: 273–280. doi:10.1016/j.semradonc.2020.05.003
- [7] Shelley CE, Barraclough LH, Nelder CL et al. Adaptive Radiotherapy in the Management of Cervical Cancer: Review of Strategies and Clinical Implementation. *Clin Oncol (R Coll Radiol)* 2021; 33: 579–590. doi:10.1016/j.clon.2021.06.007
- [8] Bui TM, Wiesolek HL, Sumagin R. ICAM-1: A master regulator of cellular responses in inflammation, injury resolution, and tumorigenesis. *J Leukoc Biol* 2020; 108: 787–799. doi:10.1002/jlb.2MR0220-549R
- [9] Kotteas EA, Boulas P, Gkiozos I et al. The intercellular cell adhesion molecule-1 (icam-1) in lung cancer: implications for disease progression and prognosis. *Anticancer Res* 2014; 34: 4665–4672
- [10] Kong DH, Kim YK, Kim MR et al. Emerging Roles of Vascular Cell Adhesion Molecule-1 (VCAM-1) in Immunological Disorders and Cancer. *Int J Mol Sci* 2018; 19: 1057. doi:10.3390/ijms19041057
- [11] Buitrago D, Keutgen XM, Crowley M et al. Intercellular adhesion molecule-1 (ICAM-1) is upregulated in aggressive papillary thyroid carcinoma. *Ann Surg Oncol* 2012; 19: 973–980. doi:10.1245/s10434-011-2029-0
- [12] Allende-Vega N, Marco Brualla J, Falvo P et al. Metformin sensitizes leukemic cells to cytotoxic lymphocytes by increasing expression of intercellular adhesion molecule-1 (ICAM-1). *Sci Rep* 2022; 12: 1341. doi:10.1038/s41598-022-05470-x
- [13] Ko YS, Jin H, Lee JS et al. Radioresistant breast cancer cells exhibit increased resistance to chemotherapy and enhanced invasive properties due to cancer stem cells. *Oncol Rep* 2018; 40: 3752–3762. doi:10.3892/or.2018.6714
- [14] Schlesinger M, Bendas G. Vascular cell adhesion molecule-1 (VCAM-1)—an increasing insight into its role in tumorigenicity and metastasis. *Int J Cancer* 2015; 136: 2504–2514. doi:10.1002/ijc.28927
- [15] Wu TC. The role of vascular cell adhesion molecule-1 in tumor immune evasion. *Cancer Res* 2007; 67: 6003–6006. doi:10.1158/0008-5472.CAN-07-1543
- [16] Moore DH. Cervical cancer. *Obstet Gynecol* 2006; 107: 1152–1161. doi:10.1097/01.AOG.0000215986.48590.79
- [17] Musunuru HB, Pifer PM, Mohindra P et al. Advances in management of locally advanced cervical cancer. *Indian J Med Res* 2021; 154: 248–261. doi:10.4103/ijmr.IJMR\_1047\_20
- [18] Shen Z, Qu A, Jiang P et al. Re-Irradiation for Recurrent Cervical Cancer: A State-of-the-Art Review. *Curr Oncol* 2022; 29: 5262–5277. doi:10.3390/currenol29080418
- [19] Powell ME. Modern radiotherapy and cervical cancer. *Int J Gynecol Cancer* 2010; 20: S49–S51. doi:10.1111/igc.0b013e3181f7b241
- [20] Siddiqui K, George TP, Nawaz SS et al. VCAM-1, ICAM-1 and selectins in gestational diabetes mellitus and the risk for vascular disorders. *Future Cardiol* 2019; 15: 339–346. doi:10.2217/fca-2018-0042
- [21] Ghasemi A, Vaseghi G, Hojjatallah A et al. The effects of morphine on vascular cell adhesion molecule 1(VCAM-1) concentration in lung cancer cells. *Arch Physiol Biochem* 2023; 129: 484–488. doi:10.1080/13813455.2020.1838552
- [22] Navi BB, Zhang C, Sherman CP et al. Ischemic stroke with cancer: Hematologic and embolic biomarkers and clinical outcomes. *J Thromb Haemost* 2022; 20: 2046–2057. doi:10.1111/jth.15779
- [23] Haddon L, Hugh J. MUC1-mediated motility in breast cancer: a review highlighting the role of the MUC1/ICAM-1/Src signaling triad. *Clin Exp Metastasis* 2015; 32: 393–403. doi:10.1007/s10585-015-9711-8
- [24] Ye H, Zhou Q, Zheng S et al. Tumor-associated macrophages promote progression and the Warburg effect via CCL18/NF-κB/VCAM-1 pathway in pancreatic ductal adenocarcinoma. *Cell Death Dis* 2018; 9: 453. doi:10.1038/s41419-018-0486-0
- [25] Takahashi R, Ijichi H, Sano M et al. Soluble VCAM-1 promotes gemcitabine resistance via macrophage infiltration and predicts therapeutic response in pancreatic cancer. *Sci Rep* 2020; 10: 21194. doi:10.1038/s41598-020-78320-3
- [26] Rosenkaimer SL, Winter L, Sieburg T et al. Diagnostic Value of sST2, VCAM-1, and Adiponectin in Patients with Breast Cancer to Predict Anti-Tumour Treatment-Related Cardiac Events: A Pilot Study. *Oncol Res Treat* 2022; 45: 598–607. doi:10.1159/000525683
- [27] Park JH, Jiang Y, Zhou J et al. Genetically engineered cell membrane-coated nanoparticles for targeted delivery of dexamethasone to inflamed lungs. *Sci Adv* 2021; 7: eabf7820. doi:10.1126/sciadv.abf7820
- [28] Cheng VWT, de Pennington N, Zakaria R et al. VCAM-1-targeted MRI Improves Detection of the Tumor-brain Interface. *Clin Cancer Res* 2022; 28: 2385–2396. doi:10.1158/1078-0432.CCR-21-4011