Original Article

The treatment response evaluation through the combination of contrast-enhanced ultrasound and squamous cell carcinoma antigen in cervical cancer

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Background: The evaluation of the treatment response after concurrent chemotherapy and radiotherapy (CCRT) for locally advanced cervical cancer is closely related to the formulation of treatment strategies. Magnetic resonance imaging (MRI) is a recommended method for efficacy evaluation; however, a unified consensus has not yet been reached on its use, and it has its limitations. This study aimed to evaluate the diagnostic value of a combination of contrast-enhanced ultrasound (CEUS) parameters and the squamous cell carcinoma antigen (SCC-Ag) to establish another efficient and feasible examination method.

Methods: The data of 94 patients with cervical cancer who underwent transvaginal contrast-enhanced ultrasound (TV-CEUS) from October 2020 to March 2023 were retrospectively collected. Based on the inclusion and exclusion criteria, 70 patients diagnosed with cervical squamous cell carcinoma (SCC) who underwent CCRT were selected for inclusion in the study. The patients were divided into the residual disease (RD) group (comprising 26 patients) and the complete response (CR) group (comprising 44 patients) according to the diagnostic standard. Data on the grayscale echogenicity, color Doppler flow imaging (CDFI), CEUS parameters, and the SCC-Ag of all the patients were collected by two experienced radiologists. Inter-observer reliability was assessed using the intraclass correlation coefficient (ICC). Receiver operating characteristic (ROC) curves were created based on the non-parametric *U*-test or *t*-test results for the two groups. Delong's test was used to compare the area under the curve (AUC) between different ROC curves. A subgroup analysis was conducted based on the patient's age, tumor diameter, and disease stage.

Results: The ICCs between the two observers ranged from 0.915 and 0.947. Hypervascular hyper-enhancement in the arterial phase, hypo-enhancement in the venous phase, and the SCC-Ag differed significantly between the RD and CR groups ($P<0.05$). The AUC of the ROC curve combining these indicators was 0.890 [95% confidence interval (CI): 0.792–0.989], which was higher than the AUC of any indicator alone ($P<0.05$). The subgroup analysis showed that the AUCs of the patients aged ≥53 and <53 years were 0.922 (95% CI: 0.816–1.00) and 0.896 (95% CI: 0.782–1.00), respectively, those of the patients with stage II, III, and IV were 0.881 (95% CI: 0.732–1.00), 0.955 (95% CI: 0.894–1.00), and 1.000

(95% CI: 1.00–1.00), respectively, and those of the patients with a tumor diameter ≤10 mm, 10 mm < tumor diameter (post) <20 mm, and tumor diameter (post) ≥20 mm were 0.976 (95% CI: 0.910–1.00), 0.883 (95% CI: 0.763–1.00), and 1.00 (95% CI: 1.00–1.00) respectively.

Conclusions: Transvaginal ultrasound (TVUS), TV-CEUS, and the SCC-Ag can be used in combination to evaluate the patient response to CCRT in locally advanced cervical SCC. This integrated approach enhanced the accuracy of the diagnosis of residual lesions and may be helpful in treatment plan optimization

Keywords: Cervical squamous cell carcinoma (cervical SCC); transvaginal contrast-enhanced ultrasound (TV-CEUS); squamous cell carcinoma antigen (SCC-Ag); treatment response; residual disease (RD)

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Introduction

Cervical cancer is the fourth most common malignant tumor worldwide, and represents a significant threat to women's health (1). Due to limited screening programs and atypical symptoms, some patients are diagnosed at advanced stages. Concurrent chemotherapy and radiotherapy (CCRT) is the recommended treatment for such patients. Previous studies have confirmed that the presence of tumor residue is an independent risk factor for cervical cancer recurrence and a poor prognosis (2-4).

Pelvic magnetic resonance imaging (MRI) is currently the preferred imaging modality for the preoperative staging and efficacy evaluation of cervical cancer, as its exceptional soft tissue contrast resolution enables it to distinguish between normal and cancerous tissues. However, there is currently no consensus as to its use in evaluating the treatment response of cervical cancer patients (5,6). Additionally, the availability of MRI resources for cancer patients may be limited worldwide. Thus, there is significant value in studying the diagnostic performance of alternative imaging methods, such as contrast-enhanced ultrasound (CEUS).

Transvaginal contrast-enhanced ultrasound (TV-CEUS) is a dynamic imaging technique that visualizes micro blood-flow perfusion patterns in tumors in real-time. It evaluates morphological changes in lesions using transvaginal ultrasound (TVUS). CEUS has been widely used in the diagnosis and treatment efficacy evaluation of tumors in the liver, kidney, and various other parts of the body (7-10). CEUS can be used to evaluate the perfusion and diffusion patterns of tumors in real time with a higher temporal resolution. Few studies have used US or CEUS in the preoperative diagnosis of cervical cancer, or assessed the changes in the perfusion parameters before and after neoadjuvant chemotherapy to predict therapeutic effects (11,12). The significant decrease in peak intensity after treatment may be associated with a better perfusion response (13). However, there is limited research on the correlation between CEUS and histological results following CCRT for cervical cancer.

A tumor associated protein called the squamous cell carcinoma antigen (SCC-Ag) has been reported to be positively correlated with the tumor activity status of cervical squamous cell carcinoma (SCC) patients (14). This study aimed to investigate the accuracy of a combination of TV-CEUS characteristic parameters and the clinical indicator SCC-Ag in evaluating the CCRT treatment response of patients with locally advanced cervical cancer. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-132/rc).

Methods

Patient selection

In total, 96 patients pathologically diagnosed with cervical cancer at Chongqing University Affiliated Cancer Hospital from October 2020 to March 2023 were retrospectively enrolled in this study. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have a primary clinical diagnosis of locally advanced cervical cancer [International Federation of Obstetrics and Gynecology (FIGO) IB3–IVA]; (II) have received complete CCRT, and have undergone pelvic MRI to evaluate the treatment response; and (III) have undergone a TV-CEUS evaluation examination 1 week

to 1 mouth after CCRT. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had malignant tumors of other origins; (II) had incomplete clinical data; and/or (III) did not meet the diagnostic standard. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Chongqing University Affiliated Cancer Hospital (No. 2023yxky05), and informed consent was obtained from all the patients.

Diagnostic standard

Residual disease (RD) was defined as the presence of tumor residue at the original tumor site of the cervix. Complete response (CR) was defined as the absence of tumor residue at the original tumor site of the cervix. RD was confirmed if either of the following criteria were met, while CR was only confirmed if neither of the following criteria were met:

(I) The patient had a diagnosis of RD based on TVUS-guided biopsy;
(II) The patient had local recurrence or metastasis during the 6–12-month CT/MRI follow-up period after receiving CCRT.

Implementation of TV-CEUS and puncture biopsy

Equipment and consumables

The Canon Aplio 800 ultrasound (US) diagnostic instrument and PVT-781VTE intracavity probe were used in both the TV-CEUS and puncture biopsy. The device parameters were uniformly set as follows: power: 6 MHz; frame rate: 10 frames per second (fps); mechanical index: 0.08; grayscale: 70; and dynamic range: 60. The US contrast agent was sulfur hexafluoride microbubble US contrast agent (Bracco, Italy), and the puncture biopsy used a puncture frame matched with the intracavity probe and an 18-G fully automatic biopsy needle (Bard, US).

TVUS and TV-CEUS evaluation process

Two radiologists with over 5 years of experience each in performing CEUS and diagnosing patients read the US images. The two radiologists were blinded to the patients' pathology and other clinical data. Based on the grayscale echogenicity of the cervical cancer residual lesions shown by TVUS, the lesions were classified as isoechoic, hypoechoic, or hyperechoic. Color Doppler flow imaging (CDFI) was then used to display the blood supply of the lesions. Combined with the International Ovarian Tumor Analysis (IOTA) nomenclature (15), the percentage and color hue of the vascularization in the lesion were subjectively evaluated. On the scale, 1 represented no color, 2 represented a minimal amount of color, 3 represented a moderate amount of color but less than 50%, and 4 represented an abundant amount of color (over 50%), while 4 was defined as hypervascular and 1–3 were defined as hypovascular. TV-CEUS was presented on a fixed screen using the dual image mode. Two dimensional (2D)-US was used as the monitoring image.

The operative process was as follows: contrast agent (1.5 mL) was injected through the antecubital vein, and 0.9% physiological saline (5 mL) was then quickly injected through the same venous channel. A dynamic video was recorded for at least 60 seconds for post-processing. The TV-CEUS perfusion mode was recorded as hyper-enhancement in the arterial phase and non-hyper enhancement in the arterial phase, while the washout mode was recorded as hypo-enhancement in the venous phase and non-hypo enhancement in the venous phase (*Figure 1*). When the visual evaluation results were unclear, quantitative analytic VueBox® software (Bracco, Italy) was applied to manually outline the regions of interest and control areas. The control areas were located at the surrounding tissues of the lesions. Time intensity curves were then the created and fitted. Consequently, objective and definite judgements for RD were made (*Figure 2*).

Collection of serum SCC-Ag

The serum SCC-Ag data were collected before and after CCRT, and the SCC-Ag reduction rate (SCCRR) was calculated using the following formula: SCCRR = (SCC-Agpre – SCC-Agpost) / SCC-Agpre × 100%.

Statistical analysis

The continuous variables are reported as the mean ± standard deviation (SD), or the median and interquartile range. The categorical variables are presented as the count and frequency. The continuous variables were analyzed using the Wilcoxon rank-sum *U*-test or the Student's *t*-test, while the categorical variables were analyzed using the χ^2 test or Fisher's exact test. Intraclass correlation coefficients (ICCs) were used to assess the inter-observer reliability of the US-related parameters, and an ICC >0.75 indicated good agreement. Receiver operating characteristic (ROC) curves were obtained for each parameter and the combined

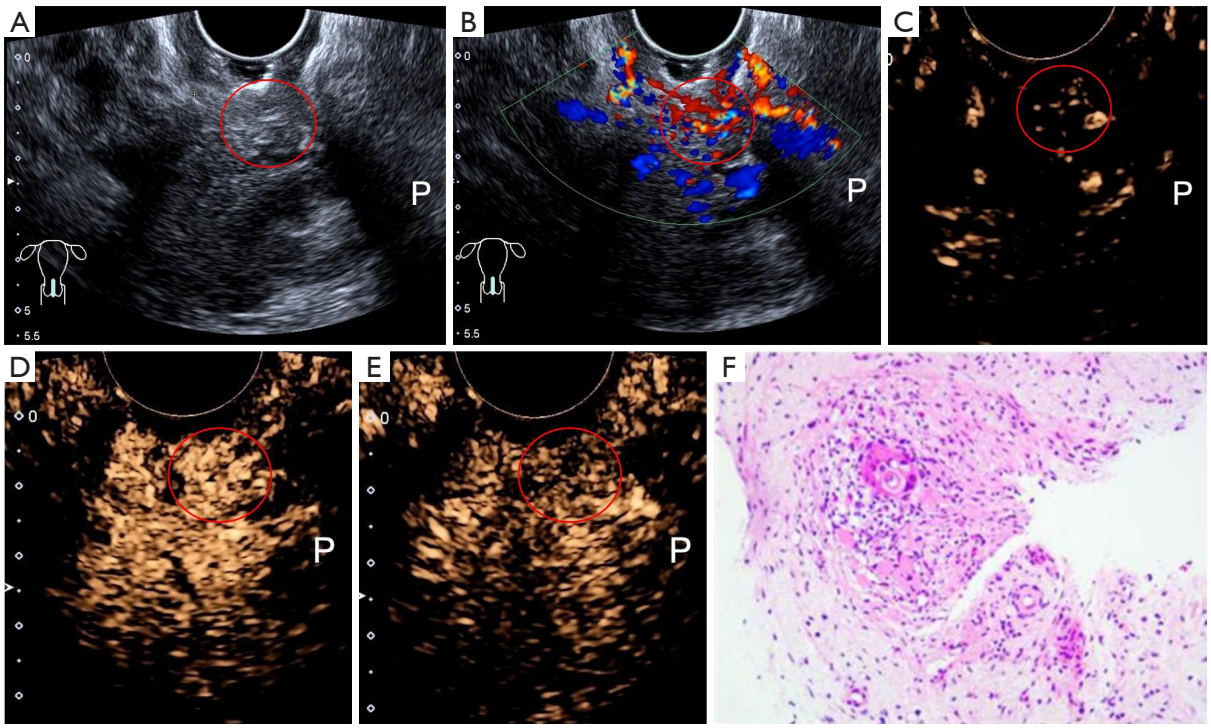

Figure 1 Scans of a 67-year-old female patient with cervical squamous cell carcinoma (phase IIIB FIGO staging). The circle represents the lesion area. (A) US showed isoechoicity in the cervix. (B) CDFI showed hypervascularity in the posterior wall of the lower cervical segment. (C) The early stage of the CEUS arterial phase. (D) CEUS of contrast agent perfusion at its peak. (E) The venous phase of CEUS. (F) Residual cervical squamous cell carcinoma through TV-CEUS guided biopsy (HE, ×200). P, posterior; FIGO, International Federation of Obstetrics and Gynecology; US, ultrasound; CDFI, color Doppler flow imaging; CEUS, contrast-enhanced ultrasound; TV-CEUS, transvaginal contrast-enhanced ultrasound; HE, hematoxylin-eosin staining.

parameters. The area under the curve (AUC) was used to evaluate diagnostic performance, and the AUCs were compared between various parameters and combined indicators using Delong's test. Subgroup analyses of the combined parameters were conducted according to the patient's age, International Federation of Obstetrics and Gynecology (FIGO) staging, and tumor diameters. A P value <0.05 (two-tailed) was considered statistically significant. All the statistical analyses were performed using SPSS 25.0 or R version 4.1.2 (The R Project for Statistical Computing; http://www.r-project.org/).

Results

Patients characteristics

A total of 94 cervical cancer patients underwent TV-CEUS evaluation of residual lesion activity, of whom 24 were excluded according to the exclusion criteria. Ultimately, 70 patients were included in the study and divided into the RD group (comprising 26 patients) and CR group (comprising 44 patients) according to the diagnostic standard. The study flowchart is presented in *Figure 3*. There were no statistically significant differences between the RD and CR groups in terms of the clinical baseline data, including the patient age, FIGO stage, whether the patient underwent staging surgery before treatment, and the residual tumor diameter (P=0.068, 0.482, 0.861, and 0.122, respectively) (*Table 1*).

Consistency analysis

In the evaluation of the TVUS and TV-CEUS parameters, the two radiologists independently described and documented the grayscale echogenicity, local vascularization, and CEUS characteristics. A consistency analysis of the correlation coefficients was conducted within the ICC group, and all the parameters showed good consistency (all ICCs >0.75) (*Table 2*).

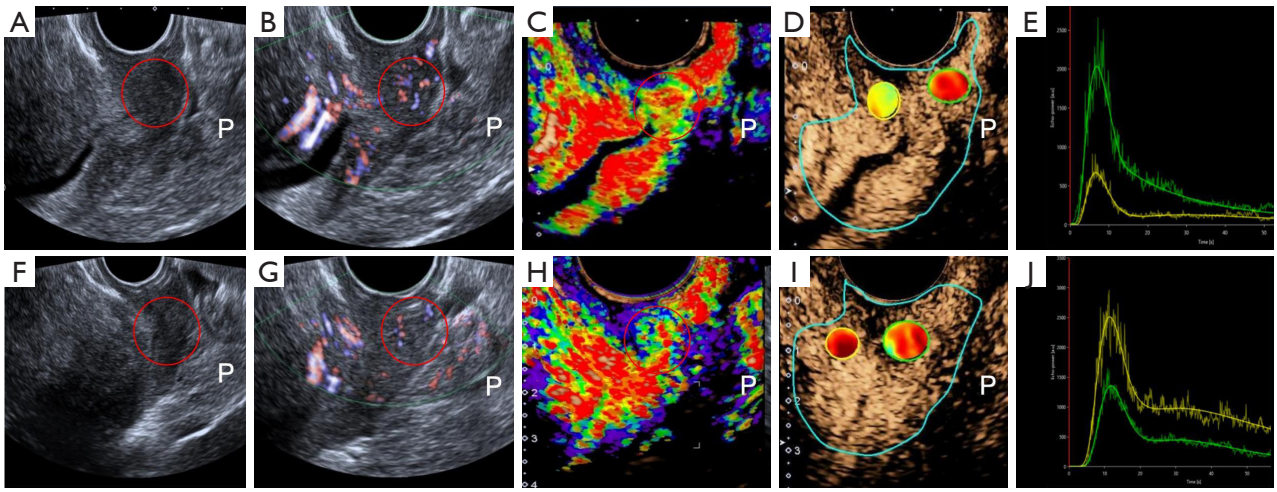

Figure 2 Scans of a 56-year-old female patient with cervical squamous cell carcinoma (phase IIIB FIGO staging). The circle represents the lesion area. (A) TVUS showed hypoechogenicity in the lower cervical segment. (B) ADF showed hypervascularoty. (C) CEUS time arrival imaging mode showed early hyper-enhancement. (D) Outline of the ROI; the green outlines indicate the lesion, and the yellow outlines indicate the control area. (E) The TIC. After operating TV-CEUS guided targeted puncture biopsy to confirm residual cervical cancer, the patient received an additional three-dimensional after loading treatment once (6 GY). The treatment response was re-evaluated using TV-CEUS (F-J). (F) TVUS showed an isoechoic lesion. (G) ADF showed hypovascularity. (H) CEUS time arrival imaging mode showed isochronic perfusion with the control area. (I) Outline of the ROI. (J) The TIC showed hypo-enhancement both in the arterial and venous phases. P, posterior; FIGO, International Federation of Obstetrics and Gynecology; TVUS, transvaginal ultrasound; ADF, advanced dynamic blood-flow technology; ROI, region of interest; TIC, time intensity curve; GY, Gray; TV-CEUS, transvaginal contrast-enhanced ultrasound; CEUS, contrast-enhanced ultrasound.

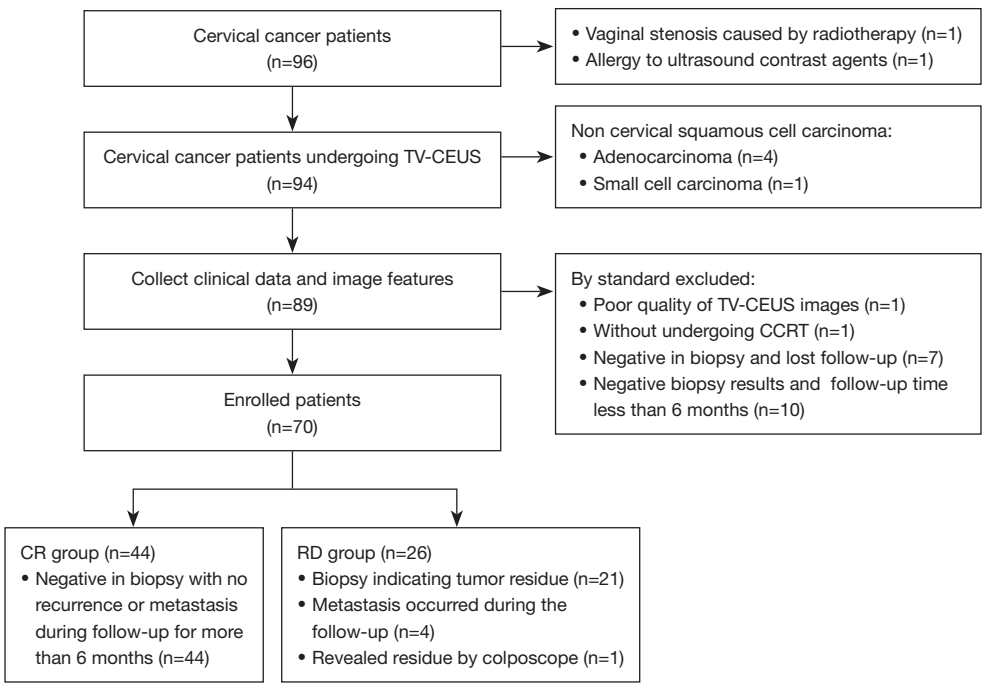

Figure 3 Patient screening process and grouping diagram. TV-CEUS, transvaginal contrast-enhanced ultrasound; CCRT, concurrent radiotherapy and chemotherapy; CR, complete response; RD, residual disease.

Table 1 Intergroup comparison of the clinical data, ultrasound imaging indicators, and the SCC-Ag in 70 patients with cervical squamous cell carcinoma

Items	RD group (n=26)	CR group (n=44)	Value†	P
Age (years)	58.08±9.29	54.41±7.13	–1.856	0.068
FIGO staging			4.483	0.482
IIA	1 (3.8)	0		
IIB	5 (19.2)	14 (31.8)		
IIIB	6 (23.1)	9 (20.5)		
IIIC	11 (42.3)	17 (38.6)		
IVA	2 (7.7)	4 (9.1)		
IVB	1 (3.8)	0		
Staging operation			0.031	0.861
No	16 (61.5)	28 (63.6)		
Yes	10 (38.5)	16 (36.4)		
TD (mm)	14.0 (11.00, 27.25)	13.5 (9.25, 19.75)	2.392	0.122
Grayscale echo_in_US			2.463	0.117
Isoechoic	6 (23.1)	16 (36.4)		
Hypoechoic	16 (61.5)	26 (59.1)		
hyperechoic	4 (15.4)	2 (4.5)		
Hypervascularity_in_US			10.394	0.001
No	10 (38.5)	34 (77.3)		
Yes	16 (61.5)	10 (22.7)		
Hyper_enhancement_in_CEUS_artery_phase			39.898	<0.001
No	3 (11.5)	39 (88.6)		
Yes	23 (88.5)	5 (11.4)		
Hypo_enhancement_in_CEUS_venous_phase			4.387	0.036
No	8 (30.8)	25 (56.8)		
Yes	18 (69.2)	19 (43.2)		
SCC-Ag_{pre} (ng/mL)	5.50 (1.93, 15.78)	5.15 (2.00, 11.43)	0.013	0.908
SCC-Ag_{post} (ng/mL)	1.55 (1.00, 2.35)	1.10 (0.73, 1.48)	5.464	0.019
SCCRR	0.69 (0, 0.89)	0.75 (0.29, 0.90)	0.714	0.398

†, the value includes *t*-value, x-value and u-value. Age follows a normal distribution, and is expressed as the mean ± standard deviation; TD, SCC-Ag_{pre}, SCC-Ag_{post} and SCCRR are expressed as the median and interquartile range; and the other values are expressed as examples and percentages. SCC_Ag, squamous cell carcinoma antigen; RD, residual disease; CR, complete response; FIGO, International Federation of Obstetrics and Gynecology; TD, tumor diameter; US, ultrasound; CEUS, contrast-enhanced ultrasound; SCC-Ag_{pre}, squamous cell carcinoma antigen; SCC-Ag_{post} pre-treatment, squamous cell carcinoma antigen post-treatment; SCCRR, SCC-Ag reduction rate.

The diagnostic ability of TVUS

The grayscale echo characteristics of cervical cancer after CCRT were described by TVUS. Among the patients, 22 (31.43%) had isoechoic lesions, 42 (60%) had hypoechoic lesions, and 6 (8.57%) had hyperechoic lesions. There was no statistically significant difference in the grayscale echo characteristics between the two groups (P=0.117). In the CDFI of the blood supply characteristics of the 70 lesions, 3 lesions scored 1, 25 lesions scored 2, 16 lesions scored 3, and 26 lesions scored 4.16. In the RD group, 16 (61.54%) cases showed hypervascularatization, while in the CR group, 34 (77.27%) cases showed hypovascularatization. The difference between the two groups was statistically significant (P<0.01). Based on this, it was evident that the residual cancer still exhibited a more abundant vascular framework than the surrounding normal or fibrotic tissues.

The diagnostic ability of TV-CEUS

Based on the above-mentioned research results, CEUS was further used to dynamically evaluate the blood-flow perfusion and diffusion characteristics of the suspected residual lesions. In this study, a total of 28 patients (23 in the RD group) showed hyper-enhancement in the arterial phase, of whom 15 showed uneven hyper-enhancement with small patches of no perfusion inside. Another 34 patients in the study showed iso-enhancement, 5 showed hypo-enhancement, and 3 showed non-enhancement. Among the 42 patients without the pattern of arterial phase hyper-enhancement, 39 (92.86%) patients were diagnosed with no residual cancer.

In terms of the CEUS diffusion characteristics, a total of 37 patients showed hypo-enhancement in the venous phase, of whom 18 were diagnosed with residual cancer. Among the remaining 33 patients without the pattern of hypo-enhancement in the venous phase, 25 were diagnosed with no residual lesions. The two characteristics of hyper-enhancement in the arterial phase and hypo-enhancement in the venous phase of CEUS differed significantly between the RD and CR groups (P<0.001, P=0.036), and their diagnostic efficacy is shown in *Table 3*.

Table 2 Consistency analysis of two radiologists in the TVUS and TV-CEUS parameter evaluation

Items	ICC	95% CI of ICC	
		Lower	Upper
Grayscale echo_in_US	0.947	0.918	0.966
Hypervascularity_in_US	0.915	0.869	0.946
Hyper_enhancement_in_CEUS_artery_phase	0.917	0.872	0.947
Hypo_enhancement_in_CEUS_venous_phase	0.920	0.877	0.949

TVUS, transvaginal ultrasound; TV-CEUS, transvaginal contrast-enhanced ultrasound; ICC, intraclass correlation coefficient; CI, confidence interval; US, ultrasound; CEUS, contrast-enhanced ultrasound.

The diagnostic ability of the SCC-Ag

In this study, there was no statistically significant difference in the SCC-Ag between the CR and RD groups before treatment (P=0.908). However, after CCRT, a statistically significant difference in the SCC-Ag was observed between the CR and RD groups (P=0.019) (*Table 1*). Based on the ROC curve analysis, the optimal value for using SCC-Ag_{post} to diagnose RD in this study was ≥1.55 ng/mL, with a diagnostic sensitivity and specificity of 50% and 79.5%, respectively.

Comparison of the diagnostic ability of the TVUS, TV-CEUS, and SCC-Ag indicators, and the combined indicator

Based on the above results, there were significant differences

Table 3 Diagnostic ability of different ultrasound features for residual cervical squamous cell carcinoma

Items	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Grayscale echo_in_US	76.92	36.36	41.67	72.73
Hypervascularity_in_US	61.54	77.27	61.54	77.27
Hyper_enhancement_in_CEUS_artery_phase	88.46	88.64	82.14	92.86
Hypo_enhancement_in_CEUS_venous_phase	69.23	56.82	48.65	75.76

US, ultrasound; CEUS, contrast-enhanced ultrasound.

Table 4 Diagnostic value of various ultrasound features and the SCC-Ag combined indicators in 70 patients with cervical squamous cell carcinoma

Items	AUC	95% CI	SE	Compared with the combined indicators	
				Z-value	P value
Hyper_enhancement_in_CEUS_artery_phase	0.886	0.796–0.975	0.046	0.186	0.852
Hypo_enhancement_in_CEUS_venous_phase	0.630	0.495–0.765	0.069	3.21	0.001
Hypervascularity_in_US	0.694	0.562–0.826	0.068	2.69	0.007
SCC_Ag_{post}	0.668	0.535–0.800	0.068	2.982	0.003
Combined indicators	0.890	0.792–0.989	0.050	–	–

SCC_Ag, squamous cell carcinoma antigen; AUC, area under the curve; SE, standard error; CI, confidence interval; US, ultrasound; CEUS, contrast-enhanced ultrasound.

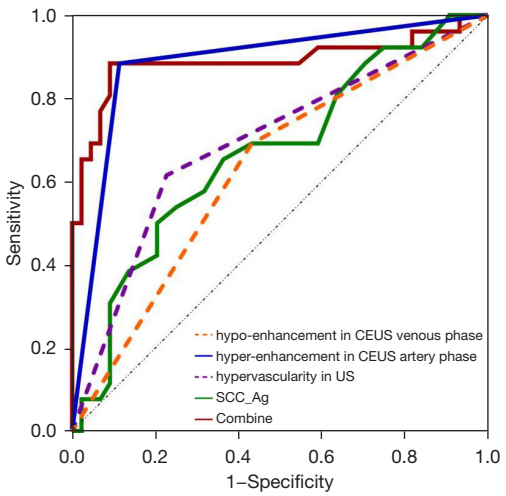

Figure 4 The ROC curves of residual cancer detected by hypervascularity in US, hyper-enhancement in the CEUS artery phase, hypo-enhancement in the CEUS venous phase, the SCC_Ag alone, and all the indicators combined. CEUS, contrast-enhanced ultrasound; US, ultrasound; SCC_Ag, squamous cell carcinoma antigen; ROC, receiver operating characteristic.

in the SCC-Ag, TVUS blood supply, TV-CEUS hyper-enhancement in the arterial phase, and TV-CEUS hypo-enhancement in the venous phase between the RD and CR groups. We compared and analyzed the diagnostic abilities of the above four indicators alone and combined to evaluate the residual activity of cervical cancer. The results indicated that the combined indicator had an increased diagnostic AUC value of 0.890, and there was a statistically significant difference between the AUC of the combined indicator and the AUCs of most indicators alone (*Table 4*, *Figure 4*).

Diagnostic ability of the combined indicator in various subgroups

Based on age, FIGO staging, and tumor diameter, a subgroup analysis was conducted to determine the ability of the combined indicator to detect residual cancer in each subgroup. As *Figure 5* shows, the AUC of patients aged ≥53 years was 0.922 [95% confidence interval (CI): 0.816–1.00], that of patients aged <53 years was 0.896 (95% CI: 0.782–1.00), that of patients with stage II was 0.881 (95% CI: 0.732–1.00), that of patients with stage III was 0.955 (95% CI: 0.894–1.00), that of patients with stage IV was 1.00 (95% CI: 1.00–1.00), that of patients with a tumor diameter ≤10 mm was 0.976 (95% CI: 0.910–1.00), that of patients with a 10 mm < tumor diameter (post) <20 mm was 0.883 (95% CI: 0.763–1.00), and that of patients with tumor diameter (post) ≥20 mm was 1.00 (95% CI: 1.00–1.00).

Discussion

CCRT is the main treatment method for locally advanced cervical cancer; however, unfortunately, CCRT is ineffective in 30–40% of patients (16). The main reasons for treatment failure in cervical patients are local uncontrolled and recurrent tumors, followed by lymph node metastasis and distant dissemination. Therefore, the effective and timely evaluation of the treatment response of cervical cancer patients is critical to ensure treatment efficacy and a favorable prognosis.

As changes in the overall structure and morphology of tumors occur later than the death of tumor cells, the use of the Response Evaluation Criteria in Solid Tumors (RECIST) alone for treatment evaluation cannot fully

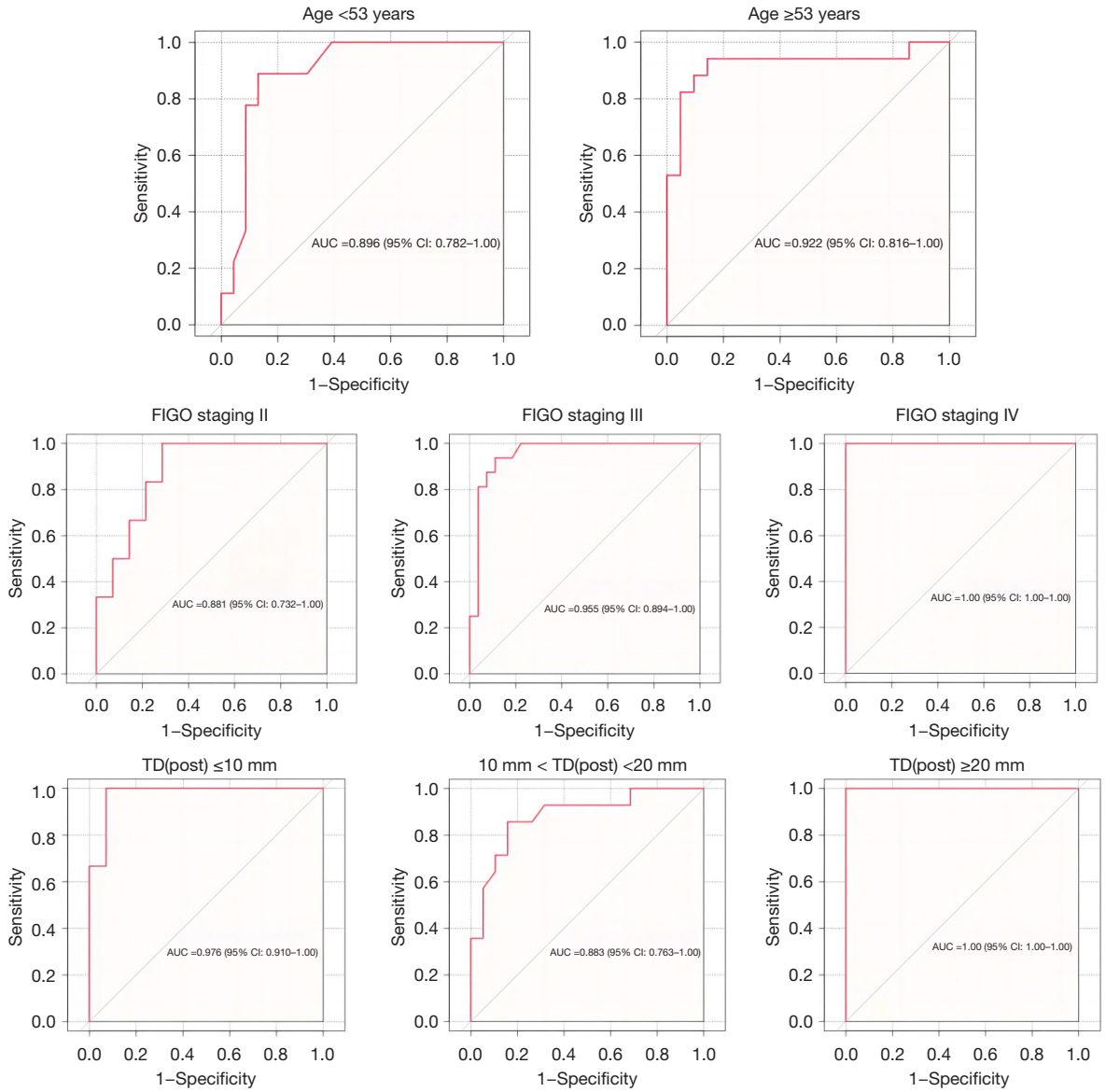

Figure 5 The ROC curves of residual cancer detected by the indicators combined for the age, FIGO staging, and tumor diameter subgroups. AUC, area under the curve; CI, confidence interval; FIGO, International Federation of Obstetrics and Gynecology; TD, tumor diameter; ROC, receiver operating characteristic.

reflect the therapeutic response after CCRT (17).

Pelvic MRI is an important method for CCRT response evaluation and is an important follow-up monitoring imaging modality in cervical cancer. It has high diagnostic efficacy. Indeed, the AUC of MRI in predicting treatment response after chemoradiotherapy or neoadjuvant chemotherapy has been reported to range from 0.701–0.998 (18-20). However, there is no global consensus on the use of pelvic MRI in CCRT treatment evaluation for locally advanced cervical cancer. Additionally, due to limited resources, high examination costs, and the inability of some patients to undergo MRI examinations because of claustrophobia, other effective and economic examination methods need to be established to evaluate the CCRT treatment response in locally advanced cervical cancer patients in clinical practice.

TV-CEUS is an imaging modality based on 2D-US that displays the anatomical structure of the lesion and

provides microvascular perfusion imaging of suspicious active residual tumors. TV-CEUS can be used to evaluate spatiotemporal changes in tumor microcirculation, and non-invasively assesses histopathological information related to perfusion patterns, and also has better diagnostic accuracy than CDFI (21,22). In this study, the AUC of hyper-enhancement in the CEUS artery phase was higher than hypervascularity in US (0.886 *vs.* 0.694).

Alcazar *et al.* compared the diagnostic ability of TVUS and MRI, and found that both TVUS and MRI had similar diagnostic performance for cervical cancer infiltration in the uterus (23). Testa *et al.* also found that 2D grayscale US and CDFI examinations had high efficiency in detecting residual lesions, with a sensitivity and specificity of 64.6% and 65%, and 87.1% and 21.4%, respectively (24).

In the present study, the diagnostic sensitivity and specificity of grayscale echogenic characteristics and CDFI were 76.92% and 61.54%, and 36.36% and 77.27%, respectively. One possible explanation for this result could be that the study samples predominantly had small residual tumor diameters (with a median tumor diameter of only 14 mm). Additionally, the fibrogenesis of normal tissue following radiotherapy also presented as hypoechogenicity, which could mimic the echogenicity of tumors, and thus result in lower diagnostic specificity for grayscale echogenic characteristics. CDFI examination is based on 2D grayscale US and can display low-speed blood flow using techniques to reduce blood-flow range and local amplification, thus achieving higher diagnostic efficiency than grayscale echogenic examinations.

Based on the abundance of blood vessels and lower vascular resistance in cervical cancer lesions, Juan *et al.* found that CEUS significantly improved the reliability of US in assessing tumor diameter (ICC: 0.672–0.735) and the accuracy of preoperative tumor staging (25). Zheng *et al.* also found that CEUS and MRI had good consistency in evaluating tumor size and local infiltration in cervical cancer (26). Moro *et al.* found that MRI-US fusion imaging improved the detection rate of residual lesions in locally advanced cervical cancer after neoadjuvant treatment (from 7/10 to 9/10), and the fusion also improved the consistency of MRI and US in detecting local and surrounding infiltration of the lesion (27). However, certain challenges hinder the widespread adoption of this fusion technology, including the need for expensive equipment and advanced technical expertise, the relatively time-consuming nature of the procedure, and its inability to provide real-time guidance for targeted puncture biopsies.

Based on previous research, the characteristic indicators of TV-CEUS in this study were hyper-enhancement in the arterial phase, and hypo-enhancement in the venous phase, and the AUC values of the diagnostic active residual lesions were 0.886 and 0.630, respectively. These are similar to the CEUS features that show early rapid enhancement and higher perfusion intensity in cervical cancer tissues than surrounding tissues in the arterial phase, and hypo-enhancement or iso-enhancement in the venous phase (28).

The SCC-Ag is a serological tumor marker in SCC in various organs, such as the cervix, lungs, esophagus, and neck. The SCC-Ag is also closely related to the progression of tumors; thus, measuring the SCC-Ag could help to monitor the treatment response and recurrence of cervical SCC. When the diagnostic threshold of the SCC-Ag was set to 1.5 ng/mL based on our hospital's testing indicators, there was a significant difference between the two groups (P=0.010). Our SCC-Ag indicator had a diagnostic sensitivity and specificity of 59.09% and 72.92%, respectively. Peng *et al.* set the diagnostic threshold of the SCC-Ag at 1.5 ng/mL (29), and reported a sensitivity and specificity of 87.3% and 57.6% for the diagnosis and detection of recurrent cervical cancer, respectively. Their diagnostic sensitivity was higher than that of this study, but their specificity was lower. The differences might result from the different sample sizes. Salvatici *et al.* (30) conducted regular follow-up examinations of serum SCC-Ag levels in 197 patients with early cervical SCC, and reported that 82.4% of patients in the SCC-Ag >1.5 ng/mL group experienced recurrence. The optimal cut-off values vary in each study; however, all the studies showed that patients with an above normal SCC-Ag level had a poor prognosis, thus confirming the prognostic value of the SCC-Ag. Chen *et al.* found that the SCC-Ag is an independent predictor of disease-free survival rate (31). In our study, while there was no statistically significant difference in the SCCRR between the CR group and the RD group (P=0.398), the SCCRR of the CR group was still higher than that of the RD group. We intend to conduct further research on the ability of the SCCRR to detect RD in the future with a larger sample size.

The combination of four indicators (i.e., hypervascularity in TVUS, hyper-enhancement in the TV-CEUS arterial phase, hypo-enhancement in the TV-CEUS venous phase, and an increased SCC-Ag level) increased the predictive AUC value of RD in locally advanced cervical cancer after CCRT to 0.890, which was higher than that of any of the indicators alone (which had AUC values of 0.890 *vs.*

0.694, 0.886, 0.630, and 0.668, respectively). There was no statistically significant difference between the combined AUC value and the AUC value for hyper-enhancement in the arterial phase of TV-CEUS. This might be because the early tissue background of the TV-CEUS in the arterial phase was clean, and there was no visual effect of other residual microbubbles, which increases the ability of radiologists to recognize this feature. This is also a key CEUS indicator for differentiating between benign and malignant tumors.

Previous research suggests that for postoperative residual lesions (<1 cm), the ability of TV-CEUS to detect residual lesions is even better than that of MRI (32). In the subgroup analysis of tumor diameter in our study, the AUC value for predicting RD with a tumor diameter ≤1 cm was 0.976, indicating that TV-CEUS had a high diagnostic ability to detect small residual lesions. As the number of cancer cells and malignancy level increase, the number of microvessels and arteriovenous communication flow rate inside the cancer lesions also increase (33). In our study, with the improvement of FIGO staging, the detection ability of the combined indicator for RD gradually increased. Its predicted AUC value increased from 0.881 in FIGO staging II to 1.00 in FIGO staging IV. However, there were only 7 cases of FIGO stage IV in this study, and thus further studies with larger sample sizes are needed in the future.

This research had a number of limitations. First, this was a retrospective study. The inter-observer consistency was high according to the ICC results; however, the feature extraction of US images in most cases depended on the visual evaluation of radiologists, which could have led to subjective results. Second, the sample size was small and the positive rate of suspected RD was low. This was due to the particularity of the research sample, and further research is needed to expand the research cycle and sample size. Third, due to the differences in blood circulation between individuals in TV-CEUS, a quantitative parameter analysis of CEUS was not performed. Fourth, there was no pre-treatment TV-CEUS, so there was no comparison of various imaging parameters before and after treatment.

Conclusions

In summary, TVUS, TV-CEUS, and the SCC-Ag can be used in combination to evaluate the CCRT response in locally advanced cervical SCC. This integrated approach enhanced the accuracy of the diagnosis of residual lesions and may be helpful in treatment plan optimization.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Chongqing University Affiliated Cancer Hospital (No. 2023yxky05), and informed consent was obtained from all the patients.

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