Evaluation Short-term Efficacy of Cervical Cancer Under Radiotherapy by Shear Wave Elastography: a Preliminary Study

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Evaluation short-term efficacy of cervical cancer under radiotherapy by shear wave elastography: a preliminary study

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ABSTRACT

Backgroud

To find a reliable, safe, convenient and low-cost imaging technology in evaluation of the short-term clinical efficacy of cervical cancer. Here, we performed a preliminary examination of the value of shear wave elastography (SWE) in assessing short-term efficacy of radiotherapy in cervical cancer.

Methods

In this study, we used SWE to measure the elastic modulus of cervical masses and healthy paracervical tissues and record the maximum elastic modulus (Emax) and the mean elastic modulus (Emean) in 46 patients with cervical cancer. The 46 patients who were naive to treatment were monitored at 5 time points. We divided those into sensitive and non-sensitive groups based on MRI in combination with RECIST1.1. The relative changes in the elastic modulus of the mass before and after radiotherapy were calculated in all patients. MRI was also combined with gynecological examinations to determine if any residual masses remained.

Results

In this study, 25 patients completed all 5 time points examinations showing the elastic modulus of the cervix decreased while healthy paracervical tissues first increased and then decreased. Then, all 46 patients underwent SWE at 3 time points: prior to radiotherapy, the 15th radiotherapy session, and at completed radiotherapy. The results revealed that the relative changes in cervical masses in the sensitive group were larger than that in the non-sensitive group ($P < 0.05$). We further discovered the Emax and the Emean of cervical tissues in the residual group were higher than that in the non-residual group (135.69 ± 35.18, 128.25 ± 35.55 vs 104.13 ± 20.19, 98.14 ± 18.9, respectively; $P < 0.05$), and the area under the curve (AUCs) of the receiver operating characteristic (ROC)were 0.770 and 0.767, respectively ($P < 0.05$).

Conclusions

SWE can be used to monitor changes in cervix and paracervical stiffness, and to assist in assessments of the efficacy of radiotherapy in cervical cancer.

KEYWORDS: cervical cancer; residual masses; efficacy; shear wave elastography

INTRODUCTION

Cervical cancer is the fourth most common malignant tumor in women worldwide, following breast cancer, colorectal cancer, and lung cancer [1]. As we all know, radiotherapy plays an irreplaceable role in cervical cancer. The effect of radiotherapy in early stage patients is similar to that of surgery, and the advanced stage is better than surgery [2]. Due to individual differences in sensitivity to different radiotherapy patients, so the effects are inconsistent [3]. However, in the era of personalized medicine, real-time monitoring and accurate assessment of efficacy play an essential role in determining future treatments.

At present, pelvic MRI plain scan and enhancement combined with the revised response-evaluation criteria in solid tumors (RECIST) 1.1 to assess efficacy in patients after radiochemotherapy [4]. However, MRI is not suitable for patients with allergy to contrast agents, poor kidney function, and metals in their bodies. In addition, MRI examination is relatively expensive, and it is not feasible to use MRI as the only curative effect method to evaluate efficacy of radiotherapy in cervical cancer. Due to ultrasound is *a* safe convenient and low-cost technology, so it has an irreplaceable position for gynecology. Strain elastography imaging could provide the information of stiffness that is complementary to the morphology and vascularity information provided by conventional sonographic examinations [5]. It has been used to detect and predict tumor response to concurrent chemo-radiotherapy in locally advanced cervical cancer [6-7]. But the strain elastography technology is limited to the technology based on the quasi-static deformation

of the medium and semi-quantitative method. Due to subjective error in the measurement process, so we need a new alternative technology.

SWE is a novel quantitative technique that can indicate tissue stiffness, and the Q-BOX in this system is used to measure the elastic modulus of the region of interest (ROI). The relationship between the elastic modulus and shear wave is $E = 3\rho c_S^2$, in which E is the elastic modulus (kPa), c is the shear-wave propagation speed (m/s), and ρ is tissue density (kg/m^3). The greater the elastic modulus, the higher the elasticity coefficient and the harder the tissue, which results in a red-color code. Conversely, the lower the elastic modulus, the softer the tissue, and the color code will be blue [8]. It is quantitative, operator independent, and more reproducible than static elastography, It has been widely used in the diagnosis and evaluation of treatment efficacy of liver fibrosis[9], thyroid cancer[10], breast cancer[11], and prostate cancer [12]. However, poorly was understood in the area of cervical cancer assessment using SWE. Thus, we performed a preliminary examination of the applicative value of real-time SWE in assessing fibrosis after radiotherapy, and the efficacy of radiotherapy in cervical cancer.

MATERIALS and METHODS

General information

Patients who additionally met the following criteria were prospectively enrolled from December 2017 to January 2019. The first 3 inclusion criteria were (1) KPS (Karnofsky) score ≥70, BMI ≥18.5,,and life expectancy ≥6 months; (2) pathologic confirmation of the diagnosis of cervical squamous cell carcinoma; and (3) successful completion of radiochemotherapy. The enrolled patients underwent concurrent radiochemotherapy

(extra-pelvic irradiation + 3-dimensional brachytherapy + concurrent chemotherapy ± adjuvant chemotherapy) at Xiangya Hospital's Department of Oncology. The total dose of whole extra-pelvic irradiation was 45–50 Gy (25–28 times, approximately 5 times per week), which was followed by 30 Gy of high-risk clinical target volume (HRCTV) radiotherapy (approximately 5 times). For the concurrent chemotherapy, cisplatin monotherapy (35–40 mg/m^2) was used; and for adjuvant chemotherapy, the standard TP regimen was used (i.e., liposomal paclitaxel [135–175 mg/m^2] + cisplatin [75 mg/m^2]). A final criterion was that (4) the patient must have completed B-mode ultrasonographic examinations before, during, and after radiotherapy as scheduled. The exclusion criteria were (1) poor SWE filling; (2) incomplete or non-continuous SWE data; and (3) patient's withdrawal during the treatment regimen due to an inability to tolerate side-effects or for other reasons. The workflow of the criteria listed above is depicted in Figure 1.

Equipment and scanning methods

This study was approved by the Ethics Committee of the Xiangya Hospital of Central South University, and all patients provided informed consent. All ultrasonographic examinations were performed by the same examiner (A.C.T.), who is skilled in gynecologic oncology. We used a fully digital color Doppler ultrasound diagnostic device from the French imaging company Aixplorer (SuperSonic Imaging, Aix-en-Provence, France). The device and protocol have been described by Bercoff et al. as generating a remote radiation force using focused ultrasonic beams (or "pushing beams"—a patented technology called Sonic Touch), with probes SE12-3 at frequencies of 3–12 MHz. Patients were instructed to empty their bladders and then assume a lithotomy position. First, a conventional 2-dimensional vaginal ultrasonographic examination was used to examine the size and

thickness of the cervix; and the echogenicity of the endometrium and myometrium, continuity of the cervical line, the presence of space-occupying lesions inside the cervix, size and morphology of these lesions, and relationship to the surrounding tissues. The uterine appendages were simultaneously examined for abnormalities; and color Doppler ultrasound was used thereafter to observe cervical blood flow. Finally, the probe was retracted to the external orifice of the cervix to gently touch the surface of the cervix without exerting any pressure. The device was switched to the elastic imaging mode to simultaneously display the 2-dimensional and elastic images (at a color-coding range of 0–150 kPa). The probe was gently moved to the median sagittal plane of the cervix and transverse plane of the middle segment of the cervix to confirm both the location and range of the defined ROI, and it was held in place for 3–5 s until the image was stable. The image was then frozen, and a quantitative analysis system (Q-BOX) was activated to measure the elastic modulus. The diameter of the Q-BOX was set to 5 mm and the reddest, brightest part of the cervix in the ROI and uninvaded paracervical tissues were selected as measurement sites. The measurement sites and their maximal and mean elastic modulus were recorded in kPa [13,14] Planned time-intervals between enhanced pelvic MRI examinations did not exceed 1 week.

Data acquisition and processing

Changes in the stiffness of the cervical mass and healthy paracervical tissues were monitored in 46 cervical cancer patients during the entire treatment period, with time-points as follows: 1 week before radiochemotherapy (before radiotherapy), 1–2 days before and after the 15^{th} radiotherapy session (during radiotherapy), when radiotherapy was completed (immediately after radiotherapy), the first adjuvant-chemotherapy cycle (1 month after

radiotherapy), and the fourth adjuvant chemotherapy (3 months after radiotherapy). Five measurements were completed on 25 patients, and a curve was plotted to monitor changes. The first 3 measurements were completed on the 46 patients and used to calculate the percentage change in the Emax and Emean of the mass before and after treatment, and the percentage change equaled the elastic modulus after treatment minus the elastic modulus before treatment/elastic modulus before treatment. Simultaneously, we combined MRI with RECIST 1.1 to assess efficacy in patients after radiochemotherapy [15]. Patients with CR and partial response (PR) were allocated to the sensitive group, while patients with stable disease (SD) or progressive disease (PD) were allocated to the non-sensitive group. We combined MRI with gynecologic examinations to record any residual masses that may have been present after radiochemotherapy; if any mass remained, it was designated to the residual group.

Statistical methods

We used SPSS 22.0 software for statistical analysis. Fisher's exact-probability test was used to compare differences between general indices, and an independent sample *t* test was used to compare differences in SWE values between the residual and non-residual groups. We used a paired *t* test to compare differences in SWE values at different time-points, and the Mann-Whitney *U* test was used to compare differences in the percentage change in parameters between the sensitive and non-sensitive groups. ROC curves were used to analyze the performance of the elastic modulus in assessing residual masses in cervical cancer patients. $P < 0.05$ was considered statistically significant.

RESULTS

171 ***SWE monitoring of the statuses of cervical squamous cell carcinoma and healthy***
172 ***paracervical tissues***

173 Forty-six patients were screened for enrollment in the this study (Table 1); of these, 21
174 refused a fourth or fifth evaluation, leaving 25 patients who were able to complete all
175 planned imaging evaluations. In 25 cervical cancer patients, the stiffness of the cervical
176 mass gradually decreased as treatment progressed, the Emax and Emean both showed a
177 decreasing trend (Figure 2a), and SWE images gradually changed from red to blue (Figure
178 3). The elastic modulus of healthy paracervical tissue stiffness increased first , then
179 decreased, and reached peak after radiotherapy (Figure2b). In addition, the differences in
180 SWE values of cervical masses during radiotherapy, immediately after radiotherapy, 1
181 month after radiotherapy, and 3 months after radiotherapy were statistically significant ($P <$
182 0.05).

183 **Table 1** Clinical and pathologic characteristics of 46 patients undergoing radiotherapy for
184 cervical cancer [*n* (%)]

Item	*Total (n=46)*	*Resist group (n = 34)*	*Non-resist group (n =12)*	P-*value*
Age (years)	54.09 ± 11.03	52.71 ± 11.82	58.00 ± 7.47	0.16*
FIGO stage†				
IB2	1 (2.2)	1 (2.9)	0 (0.0)	0.44‡
IIA1	1 (2.2)	0 (0.0)	1 (8.3)	
IIA2	3 (6.5)	2 (5.9)	1 (8.3)	
IIB	35 (76.1)	25 (73.5)	10 (83.3)	

IIIB	4 (8.7)	4 (11.8)	0 (0.0)	
IVA	2 (4.3)	2 (5.9)	0 (0.0)	
Concurrent chemotherapy				
Yes	44 (95.7)	33 (97.1)	11 (91.7)	0.46‡
No	2 (4.3)	1 (2.9)	1 (8.3)	
Adjuvant chemotherapy				
Yes	35 (76.1)	27 (79.4)	8 (66.7)	0.62‡
No	11 (23.9)	7 (20.6)	4 (33.3)	

Note: **T* test was used; †2009 staging was used; ‡Fisher's test was used

SWE determination of sensitive and non-sensitive groups after radiotherapy for cervical squamous cell carcinoma

Of the 46 patients who underwent radiochemotherapy, 26.09% (12/46) achieved CR, and 58.69% (27/46) achieved PR, so 84.78% (39/46) were treatment sensitive. In addition, 7 of 46 patients (13.22%) were not sensitive to treatment and showed SD. These results thus showed that 39 patients were sensitive (the sensitive group) and 7 (the non-sensitive group) were not. The relative changes of the Emax and Emean before and after treatment in the sensitive group were larger than in the non-sensitive group (0.33%, 0.31% vs. 0.17%, 0.17%, respectively; P = 0.015, 0.023) (Table 2).

Table2 Comparison of relative changes in shear-wave elastography (SWE) between treatment-sensitive and non-sensitive groups, comprising a total of 46 cervical cancer

198 patients [*M*, median]

	*Sensitive group (*n = *39)*	*Non-sensitive group (*n = *7)*	Z-*value*	P-*value*
Percentage change in maximal elastic modulus before and after treatment (%)	0.33	0.17	2.431	0.015
Percentage change in mean elastic modulus before and after treatment (%)	0.31	0.17	2.278	0.023

199

200

201 ***SWE determination of residual cervical masses***

202 We further used MRI and gynecologic examinations to determine whether any residual
203 masses were present after radiotherapy. Our results showed that 34 patients had residual
204 masses (residual group) and 12 (non-residual group) did not. The Emax and Emean of the
205 residual group were statistically higher than that of the non-residual group (135.69 kPa vs.
206 104.13 kPa, and 128.25 kPa vs. 98.14 kPa, $P < 0.05$) (Table 3). The ROC curve analysis
207 showed that the best cut-offs for the Emax and Emean upon ultrasonographic evaluation for
208 the detection of residual masses were 119.35 kPa and 121.3 kPa, respectively; AUC of
209 0.770 (95% confidence interval (CI), 0.630–0.909) and 0.767 (95% CI, 0.629–0.905),
210 sensitivity of 64.71% and 47.05%, specificity of 83.33% and 100%, and accuracy 69.57%

and 60.86%, respectively (Figure 4).

Table 3 Comparison of the elastic modulus between residual and non-residual groups after radiotherapy ($\bar{x} \pm s$)

	Residual group	*Non-residual group*	t-*value*	P-*value*
Maximum mass elastic modulus (kPa)	135.69 ± 35.18	104.13 ± 20.19	2.93	<0.01
Mean mass elastic modulus (kPa)	128.25 ± 35.55	98.14 ± 18.9	2.79	<0.01

DISCUSSION

In this study, SWE was used to measure the elastic modulus of cervical masses and healthy paracervical tissues in 46 cervical cancer patients. To the best of our knowledge, it is the first study to use SWE to explore the cervical short-term efficacy of radiotherapy in cervical cancer, which could be a reliable, safe, convenient and low-cost imaging technology in cervical cancer.

Monitoring efficacy is indispensable for determining future treatment regimens. In clinical practice, MRI cannot be used for monitoring real-time efficacy in patients because it is too time-consuming, expensive , having contraindications, and its contrast agent will affect the body. Gynecological examinations are useful in efficacy testing. However, such examinations are highly subjective, and biases are inevitable. SWE can directly and

quantitatively reflect tissue stiffness. In this study, we used this characteristic to monitor efficacy across the entire cervical cancer treatment period, and we found that the elastic modulus of the paracervical tissues peaked after radiotherapy finishing, which was thought to be caused by radiation fibrosis [16]. The elastic modulus of cervical masses has been demonstrated to diminish as treatment progresses, indicating that the stiffness of the masses was attenuated with treatment caused by the biologic characteristics of the tissue itself. Through effective treatment, tumor cell necrosis, apoptosis and dissolution are caused, and the stiffness of the tumor is reduced, until the normal cervical tissue is restored. Similar to the results of this study, Marangon et al. found that the tumor tissues after photothermal therapy softened significantly and decreased in volume, and the stiffness of untreated tumor tissues increased [17].

During the past decades, many researchers have demonstrated a commitment to finding new MRI sequences that provide more accurate and timely assessment of radiotherapeutic efficacy at an early stage. These sequences include diffusion-weighted MRI [18]and intravoxel incoherent motion MR imaging [19]. However, MRI is relatively costly and image analysis is complicated, which limits its clinical applications. In our study, we used the advantages of SWE (i.e., ease of operation and good repeatability), and found that the percentage change in the SWE elastic modulus before and after radiotherapy reflected a therapeutic efficacy for cervical cancer. The percentage changes of Emax and Emean in the sensitive group before vs. after treatment were all greater than in the non-sensitive group ($P < 0.05$), allowing SWE to be used to assess efficacy in patients. Our results were similar to those from a study in which MRI-SWI was used to assess efficacy in cervical cancer treatment [20]. In addition, the elastic modulus of the residual group after

radiotherapy was higher than that in the non-residual group ($P < 0.05$), which is consistent with the results of and Mabuchi et al [21]; and the differences in the area under the ROC curve were statistically significant ($P < 0.05$), such that when the mean threshold value was 127.15 kPa, the specificity was 100%. In this way, the SWE elastic modulus after radiotherapy could be used to determine the presence of residual masses after radiotherapy, which has significant implications for guiding subsequent treatment. SWE possesses several specific features that make it suitable for clinical practice, including 1) the creation of tissue disturbances that are operator independent, 2) the provision of a quantitative evaluation of the propagation of the shear-wave, and 3) the relatively long distance transmission of the stimulus.

However, our study also had some limitations. First, our sample consisted only of patients with squamous cell carcinoma, as we were unable to analyze the different pathologic types. Second, under the current conditions, the SWE images were affected by the location of the cervix, level of rectal filling, and urine in the bladder—causing insufficient filling in some images. Third, the measurement site of the paracervical tissues was not identical for each measurement, causing our results to lack comparability. Further standardization is thus required. Fourth, the efficacy time-points with respect to cervical cancer as assessed using SWE and MRI were the same, but this is difficult to achieve in actual clinical practice; we therefore attempted to control the timing of the 2 measurements to be within 1 week. Fifth, there were limitations in pathologic sampling after radiochemotherapy because there is currently no gold-standard control. Finally, the duration of the present study was short, and there was a lack of long-term follow-up data. Follow-ups therefore need to be continued to predict recurrence, and to carry out

differential diagnoses of fibrosis, residual lesions, and recurrence after radiochemotherapy.

CONCLUSION

The present study is the first to examine the preliminary applications of SWE to cervical cancer, and demonstrated that SWE constitutes a suitable technique for assessing the efficacy of cervical cancer treatment. This technique is intuitive, convenient, non-invasive, affordable, and with good repeatability. SWE can thus be used to monitor the changes in tumor masses during treatment, and it provides a novel method for predicting and assessing the efficacy of radiochemotherapy—with high clinical application value.

ABBREVIATIONS

SWE: Shear wave elastography

Emax: The maximum elastic modulus modulus

Emean: The mean elastic modulus

MRI: Magnetic resonance imaging

RECISTR: Response evaluation criteria in soli tumors

ROC: Receive operating characteristics curve

AUC: Area under the curve

FIGO: International federation of gynecology and obstetrics

ROI: Refined region of interest

CR: Complete response

PR: Partial response

SD: Stable disease

PD: Progressive disease

CI: Confidence interval

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Xiangya Hospital of Central South University, and all patients provided informed consent.The research design and methods are in accordance with the requirements of regulations and procedures regarding to human subject protection laws such as GCP and ICH-GCP.

Consent for publication

Not applicable.

Availability of data and materials

Availability of data and materials during the study are available from the corresponding author .

Competing interests

Not applicable.

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Authors' contributions

Manting Zeng and Hong Zhu is responsible for designing this study and writing the main manuscript; Yangying Zhou and Yu Zhang revised the manuscript; Jian Wang and Xuanxuan Li had roles in the acquisition data and interpretation of data; Ningbo Zhou and Xueying Long carried out the quality control of ultrasound & MR examinations and data analysis. All authors have read and approved the final manuscript.

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FIGURE LEGENDS

Figure 1 A flow chart diagrams with the study design of short-term efficacy

Figure 2 Changes in the elastic modulus of cervical masses (a) and healthy paracervical tissues (b) upon treatment of 25 cervical cancer patients.

Figure 3 Changes in the elastic modulus across the entire treatment period for 1 patient with stage-IIIB cervical squamous cell carcinoma. (a) Before radiotherapy, the maximal elastic modulus of the cervical mass was 234.8 kPa, and the majority of the region of interest (ROI) was red; the tumor mass occupying the cervix was stiff. (b) During radiotherapy, the maximal elastic modulus of the cervical mass was 209.1 kPa, and the ROI remained red. However, some portions of the ROI gradually changed to yellow and the mass diminished slightly, but the cervix was still stiff. (c) Immediately after radiotherapy, the maximal elastic modulus of the cervical mass was 167.6 kPa, the red area in the ROI was significantly smaller, the mass was smaller than it had been before, and the cervix had become softer. (d) One month after radiotherapy, the maximal elastic modulus of the cervical mass was 112.5 kPa, the red area in the ROI had disappeared, the mass had disappeared, and the tissue was hard. (e) Three months after radiotherapy, the maximal elastic modulus of the cervical mass was 96.6 kPa, the ROI was principally yellow and blue, the cervix had returned to its normal state, no mass was seen, and the cervix was soft.

Figure 4 Region of interest (ROI) curve with respect to the presence or absence of residual masses after radiotherapy, as determined by the elastic modulus.

Figures

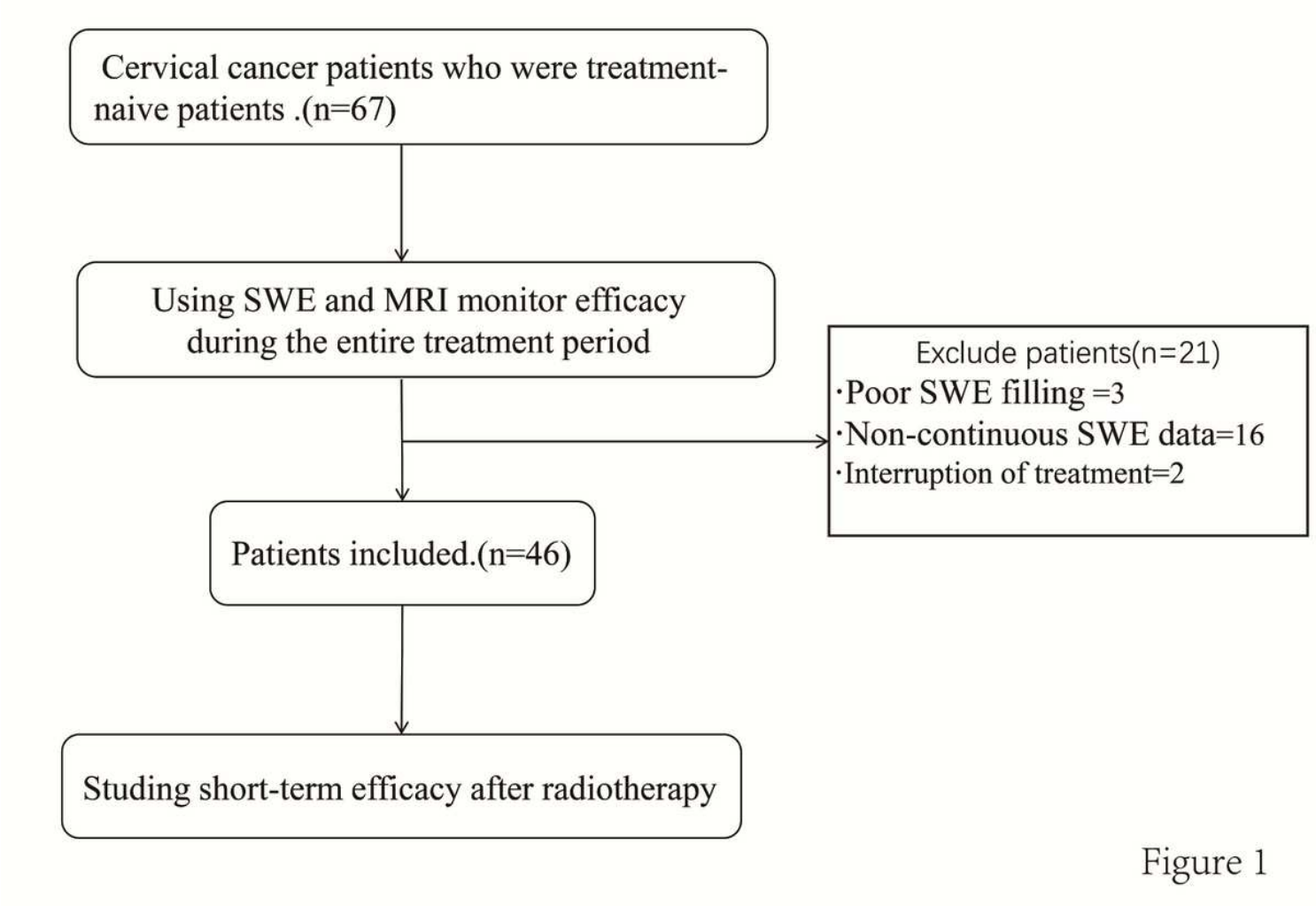

Figure 1

A flow chart diagrams with the study design of short-term efficacy

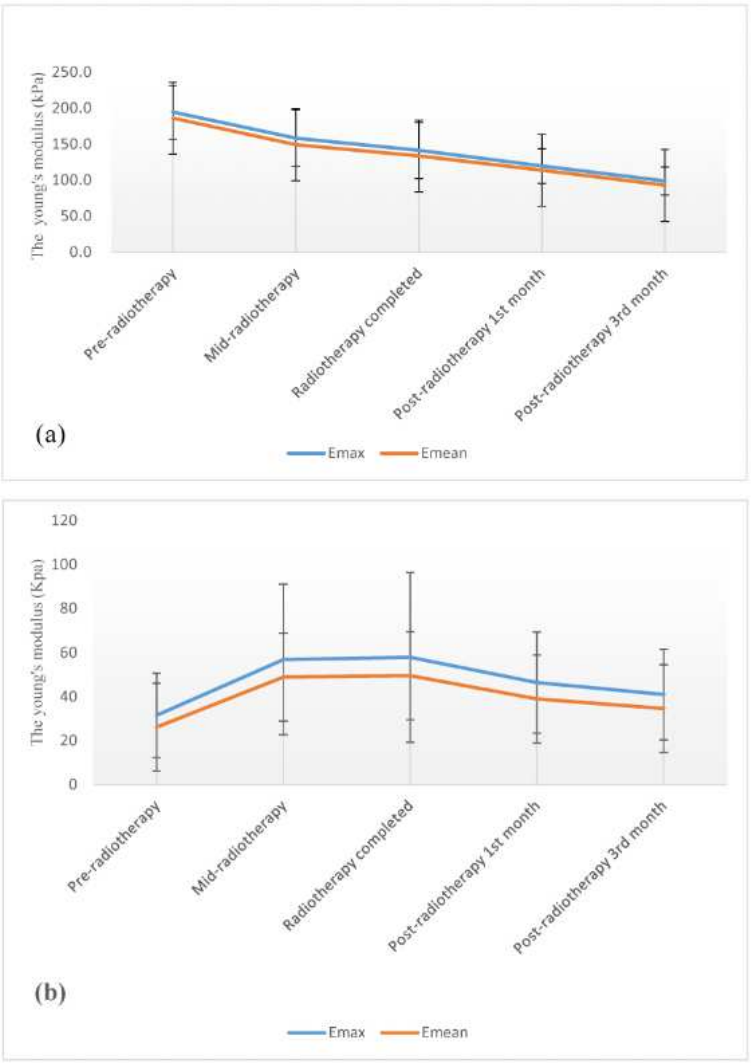

Fig. 2

Figure 2

Changes in the elastic modulus of cervical masses (a) and healthy paracervical tissues (b) upon treatment of 25 cervical cancer patients.

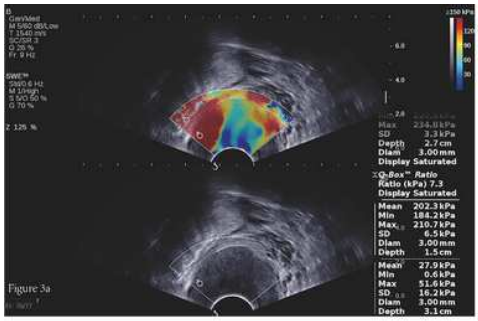

Figure 3a

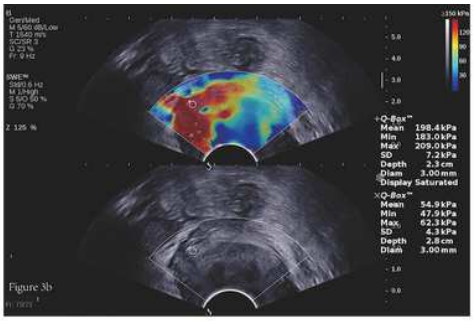

Figure 3b

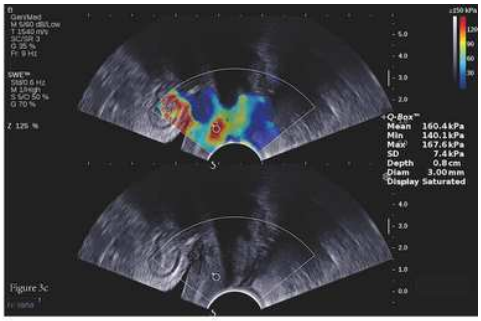

Figure 3c

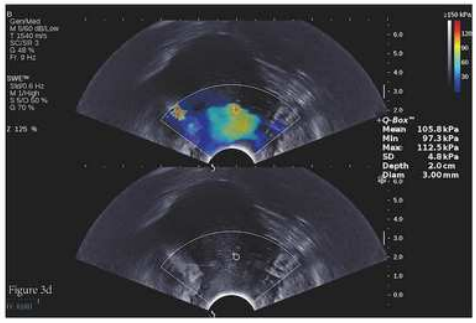

Figure 3d

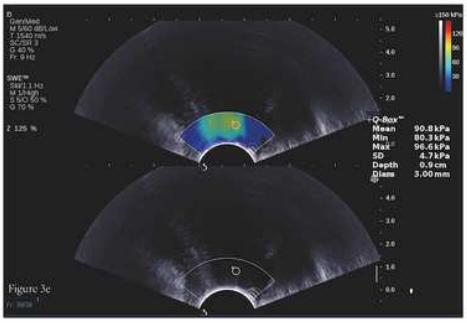

Figure 3e

Figure 3

Changes in the elastic modulus across the entire treatment period for 1 patient with stage-IIIB cervical squamous cell carcinoma. (a) Before radiotherapy, the maximal elastic modulus of the cervical mass was 234.8 kPa, and the majority of the region of interest (ROI) was red; the tumor mass occupying the cervix was stiff. (b) During radiotherapy, the maximal elastic modulus of the cervical mass was 209.1 kPa, and the ROI remained red. However, some portions of the ROI gradually changed to yellow and the mass diminished slightly, but the cervix was still stiff. (c) Immediately after radiotherapy, the maximal elastic modulus of the cervical mass was 167.6 kPa, the red area in the ROI was significantly smaller, the mass was smaller than it had been before, and the cervix had become softer. (d) One month after radiotherapy, the maximal elastic modulus of the cervical mass was 112.5 kPa, the red area in the ROI had disappeared, the mass had disappeared, and the tissue was hard. (e) Three months after radiotherapy, the maximal elastic modulus of the cervical mass was 96.6 kPa, the ROI was principally yellow and blue, the cervix had returned to its normal state, no mass was seen, and the cervix was soft.

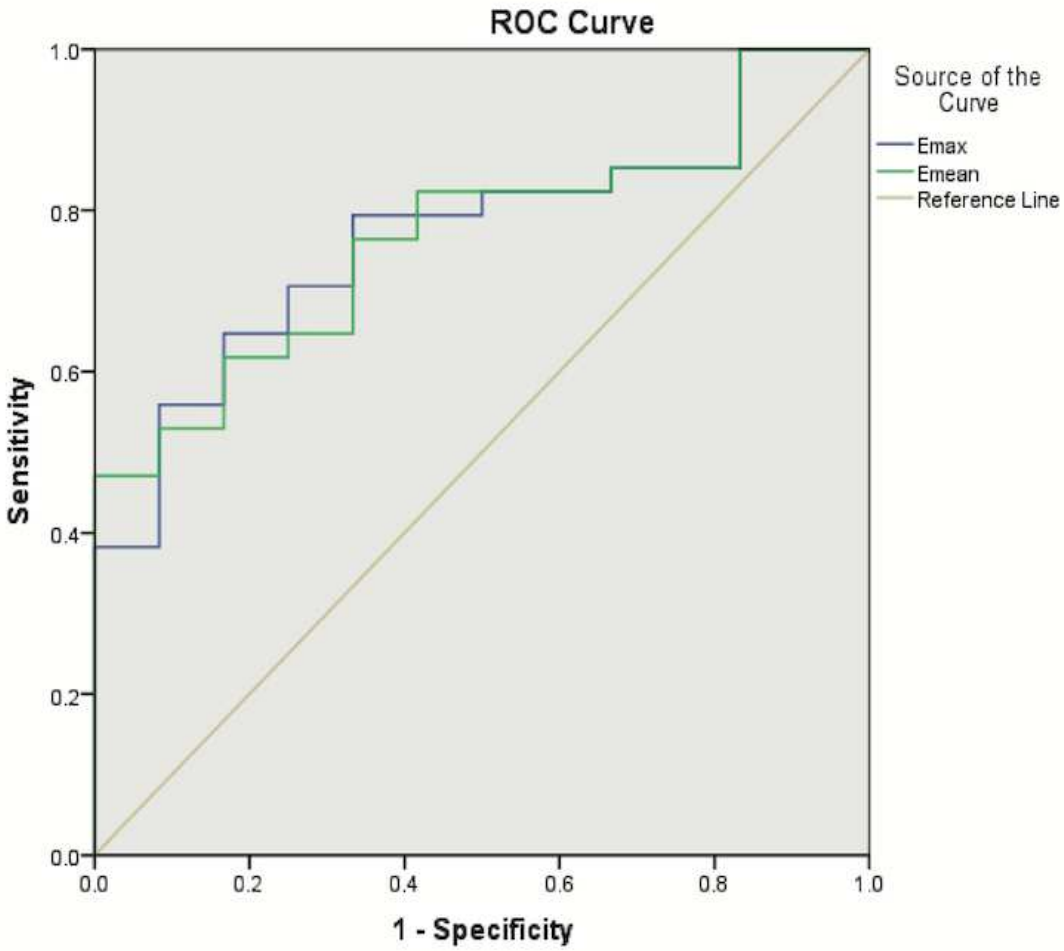

Fig. 4

Figure 4

Region of interest (ROI) curve with respect to the presence or absence of residual masses after radiotherapy, as determined by the elastic modulus.