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Original Article

Multimodal magnetic resonance imaging for staging diagnosis and assessment of radiotherapy efficacy in cervical carcinoma

Xia Wu[1], Weiqing Wang[2], Zhenfeng Zhu[1], Yanping Lu[1], Longxian Gai[1], Yuhua Li[1], Xuejian Liu[1]

Departments of [1]Oncology, [2]Radiology, People's Hospital of Linyi Economic and Technological Development Zone, Linyi City, Shandong Province, China

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Abstract: Objective: To investigate the functions of multimodal magnetic resonance imaging (MRI) in diagnosis of cervical carcinoma and assessment of radiotherapy efficacy. Methods: A total of 396 patients with cervical carcinoma who received assessment by multimodal MRI or color Doppler ultrasonography in People's Hospital of Linyi Economic and Technological Development Zone from October 2010 to October 2016 were recruited in this study. The patients were assigned to receive multimodal MRI (multimodal MRI group, n=201) or color Doppler ultrasonography (color Doppler ultrasonography group, n=195) according to the imaging tools used. Senior radiologists from the Imaging Department of People's Hospital of Linyi Economic and Technological Development Zone reviewed the images of cervical carcinoma in a double-blind manner, analyzed the results, and evaluated the effect of presence or absence of enhancement on multimodal MRI. Results: The diagnostic accordance rates of multimodal MRI for detecting cervical carcinoma of Stage 0, I, and II in patients were higher than those of color Doppler ultrasonography (all $P<0.05$), though the corresponding rates for detecting Stage III and IV were insignificantly different (both $P>0.05$). The overall sensitivity of multimodal MRI in assessing the stages of cervical carcinoma was 94.6%, and the specificity was 92.8%. By contrast, the overall sensitivity of color Doppler ultrasonography in assessing the stages of cervical carcinoma was 83.4%, and the specificity was 82.6%. The overall sensitivity and specificity were remarkably different between multimodal MRI and color Doppler ultrasonography (both $P<0.05$). In the receiver operating characteristic (ROC) curve analysis, the area under the multimodal MRI curve was significantly greater than that under the color Doppler ultrasonography curve, and the sensitivity and specificity were substantially higher than those with color Doppler ultrasonography (both $P<0.05$). There was a considerable correlation between presence/absence of tumor enhancement area on multimodal MRI scans and tumor reduction rate ($r=0.649$, $P<0.01$), which was significantly correlated with efficacy of radiotherapy ($r=0.679$, $P<0.01$). Conclusion: Multimodal MRI is of great value in assessing the stages of cervical carcinoma, and it is also useful in the assessment of radiotherapy efficacy. Thus, it is worth wide use in clinical practice.

Keywords: Multimodal multimodal magnetic resonance imaging, cervical carcinoma, color Doppler ultrasonography, FIGO staging, receiver operating characteristic curve

Introduction

Cervical carcinoma is the most common malignant tumor among all the malignancies in women [1, 2]. The disease results in 19.32% of deaths from cancers in women [3]. The general onset age ranges from 30 to 50 years old, and cervical carcinoma is more prevalent with the population between 40 and 60 years old. Few patients with cervical carcinoma are under the age of 20 years. Nevertheless, according to the statistical data reported by Scarsbrook et al., in recent years, the patients with cervical carcinoma shows a trend of younger age, as increasing patients with cervical carcinoma are merely approximately 23 years old [4]. This problem has attracted much attention from relevant experts worldwide. Given the trend of younger onset age, high morbidity and mortality and the poor prognosis of cervical carcinoma, it is paramount to find optimum methods for accurate stage diagnosis and efficacy assessment.

Currently, there are no simple methods with high accuracy and sensitivity for diagnosis of cervical carcinoma. It is still diagnosed by traditional techniques such as cervical biopsy and cervicoscopy. Cervical carcinoma in patients is almost at the advanced stage at the time of confirmation. Iturre et al. held that the promotion of imaging of cervical carcinoma contributes to improved efficiency of clinical work and treatment [5]. With the development of imaging diagnostic technology, various tools, including ultrasounds, CT and magnetic resonance imaging (MRI), have been used in the diagnosis of cervical carcinoma; however, the above three imaging tools still have such defects as unavailability of all-round localization of cervical carcinoma and high misdiagnosis rates [6]. Atri et al. argued that ultrasound is ineffective in identifying early cervical carcinoma, and CT and MRI uses are debatable in assessing the stages of cervical carcinoma [7]. MRI is characterized by high resolution, non-invasion and multi-sequence imaging; thus, it is widely regarded as the best imaging tool for adjuvant diagnosis of caners [8, 9]. In recent years, the emerging multimodal MRI functions well in diagnosis and treatment of brain tumors, lymphoma involving in the central nervous system, and prostate cancer [10]. However, few reports are implicated in the staging and evaluation of cervical carcinoma. As multimodal MRI has been used as an adjuvant tool for staging of most major cancers in People's Hospital of Linyi Economic and Technological Development Zone for half a year, we are so skilled in its operation and imaging judgement that we are able to independently discriminate and diagnose the stages and subtypes of most cancers. Therefore, the purpose of this study was to find a simpler, more accurate and better method for clinical staging and evaluation of cervical carcinoma, and bring some insights into clinical practice.

Materials and methods

Patient enrollment and randomization

All the patients and their families gave written informed consent. This study got approval from the Ethics Committee of People's Hospital of Linyi Economic and Technological Development Zone. Between October 2010 and October 2016, 396 patients with cervical carcinoma admitted to People's Hospital of Linyi Economic and Technological Development Zone were enrolled in this study. The enrolled patients had a mean age of 43.2±11.5 years and clinical characteristics which met the clinical manifestations of cervical carcinoma, and had received no previous relevant treatment in other hospitals. Patients were excluded if they were unwilling to follow the examination, refused to treat in People's Hospital of Linyi Economic and Technological Development Zone, or had disabled limbs, genetic disease or other tumors except for cervical carcinoma. We recruited the patients in strict accordance with the above mentioned inclusion and exclusion criteria. Moreover, every step in operating the two instruments was taken with the assistance of the special engineers from the suppliers. Strict regulation of the operating procedures and double-blind design minimized the contingency in this study and improved its reliability. The patients willingly chose examination tools of multimodal MRI or color Doppler ultrasounds. As a result, 201 patients were assigned to receive multimodal MRI (multimodal MRI group), whereas 195 patients were assigned to undergo color Doppler ultrasonography (color Doppler ultrasonography group).

Examination methods and procedures

Multimodal MRI examination: The multimodal MRI examination was performed with the use of the superconducting MRI system MAGNETOM Skyra 3.0T (SIEMENS, Germany). The conventional non-contrast MRI included the following parameters: SE-T1WI, TR600ms, TE11ms, TSE-T2WI, TR6500ms, and TE83ms. The median sagittal section was an oblique median sagittal section parallel to the long axis of the uterus. In the DWI, one single acquisition EPI sequence was used, with total acquisition time of 3 minutes and 11 seconds. The relevant parameters were 340 * 340 mm of FOV, 256 * 256 of matrix, 5 mm of slice thickness, and 20% slice thickness of slice spacing. In the DCR-MRI scanning, the FLASH-3D VIBE-FS sequence was used with the following parameters: 300 mm * 340 mm of FOV, 256 * 256 of matrix, 2 mm of slice thickness, 20% of slice thickness of slice spacing, for one single excitation. There were a total of 28 phases, with each phase lasting 20 seconds. At the end of the first phase, Gd-DTPA (20 mL) was injected intravenously into the dorsum of the hand of the patient at a speed of 3 mL/s. Normal saline (15 mL) was injected at the same speed as previously described, and consecutive 2-28 phases were performed 20 s later. Four senior radiologists from the Imaging Department in People's Hospital of Linyi Economic and Technological Development Zone reviewed the images in a double-blind manner and assessed the cancer stages in 201 patients with cervical carcinoma based on the International Federation of Gynaecology and Obstetrics (FIGO) staging system for cervical carcinoma. Multimodal MRI examination was performed at 1 week before the initial radiotherapy and 1 month after the end of the radiotherapy, followed by assessment of the efficacy of radiotherapy.

Color Doppler ultrasonography: Color Doppler ultrasonography was performed using ACUSON * 700 color Doppler ultrasonic diagnostic instruments (SIEMENS, Germany). The patients in the color Doppler ultrasonography group were well matched in baseline characteristics with those in the multimodal MRI group before examination, with the abdominal probe frequency of 3.0-6.0 MHz, the negative probe frequency of 4.0-8.0 MHz, and the superficial small organ probe frequency of 5.0-10.0 MHz. Likewise, the four senior radiologists from the Imaging Department in People's Hospital of Linyi Economic and Technological Development Zone were also requested to review the images in a double-blind manner and assessed the cancer stages in 195 patients with cervical carcinoma based on the FIGO staging system for cervical carcinoma.

Radiotherapy techniques and efficacy evaluation

Radiotherapy for cervical carcinoma, a combination of radiotherapy *in vitro* and intracavitary radiotherapy, primarily involves in pelvic lymph node drainage regions, whole uterus, bilateral appendages, cancer and adjacent cancer tissues. External pelvic radiotherapy included 45-50 Gy, 180-200 cGy/F, and after-loading therapy included 25-30 Gy and 500 cGy for twice a week. One month after radiotherapy, multimodal MRI was applied to evaluate the efficacy of radiotherapy (The efficacy of radiotherapy was adjudicated based on the tumor reduction rates, with complete disappearance of lesions defined as full recovery, and the tumor reduction rate of over 90% as residual tumor).

Outcome measures

The four senior radiologists from the Imaging Department in People's Hospital of Linyi Economic and Technological Development Zone were requested to review the images in a double-blind manner and assess the stages of cervical carcinoma in accordance with the FIGO staging system for cervical carcinoma. It was mainly involved in observing the lesion size, infiltration of cancer tissue and the lymph node metastasis. The T1WI + T2WI images were observed first, followed by T1WI + T2WI + DWI images, and finally the T1WI + T2WI + DWI + DCE-MRI images. Subsequently, all the images were analyzed, and the stages of cervical carcinoma were judged in combination with the FIGO staging system [11]. The result of assessment was compared with that of the pathological examination (golden standard). Likewise, during the efficacy evaluation, the correlation of the assessment results with the efficacy of radiotherapy was explored based on presence/absence of enhancement on the multimodal MRI.

Statistical analysis

The results of the study were analyzed with the use of the SPSS statistical software (Asia Analytics Formerly SPSS, China), version 22.0, and the plot of ROC curves was constructed. Measurement data were expressed as mean ± sd, and the independent samples t-test were used for comparisons of measurement data. Count data were described as rates, and the chi-squire tests were applied to compare count data. Spersman correlation analysis was utilized for correlation analysis. $P<0.05$ was deemed as statistically significant.

Results

Clinical and baseline characteristics of patients

In accordance with the pathological biopsy of the lesions and the staging classifications and clinical practice guidelines jointly formulated by the FIGO and the International Gynecologic Cancer Society (IGCS), cervical carcinoma of Stage 0 was confirmed in 76 patients, Stage I in 97 patients, Stage II in 112 patients, Stage III in 72 patients, and Stage IV in 39 patients [12]. Among them, cervical carcinoma of Stage 0

Table 1. Clinical and baseline characteristics of 396 patients (n, %)

Variables	Color Doppler ultrasonography group (n, %)	Multimodal MRI group (n, %)	P
Total case	201 (100.0)	195 (100.0)	
Age			0.671
<30	17 (8.5)	12 (6.2)	
≥30, <50	136 (67.7)	134 (68.7)	
≥50	48 (23.9)	49 (25.1)	
Nationality			0.713
Han	187 (93.0)	176 (90.3)	
Others	14 (7.0)	19 (9.7)	
Residence			0.642
Urban	127 (63.2)	132 (67.7)	
Rural	74 (36.8)	63 (32.3)	
Education			0.582
Illiterate	79 (39.3)	78 (40.0)	
Primary school	51 (25.4)	57 (29.2)	
Middle School	42 (20.9)	36 (18.5)	
University	29 (14.4)	24 (12.3)	
Drinking			0.693
Never	39 (19.4)	35 (17.9)	
Occasional	101 (50.2)	98 (50.3)	
Frequent	61 (30.3)	62 (31.8)	
FIGO stage			0.531
0	37 (18.4)	39 (20.0)	
I	48 (23.9)	49 (25.1)	
II	57 (28.4)	55 (28.2)	
III	38 (18.9)	34 (17.4)	
IV	21 (10.4)	18 (9.2)	

Note: MRI, magnetic resonance imaging.

Table 2. Diagnostic accordance rates of cervical carcinoma stages by multimodal MRI and color Doppler ultrasonography (%)

Stage	Color Doppler ultrasonography	Multimodal MRI	X^2	P
Stage 0	94.6	82.1	5.72	0.019
Stage I	97.9	85.7	5.16	0.021
Stage II	98.2	85.5	6.21	0.012
Stage III	100.0	97.1	4.87	0.281
Stage IV	100.0	94.4	5.95	0.162

Note: MRI, magnetic resonance imaging.

was reported in 37 patients, Stage I in 48 patients, Stage II in 57 patients, Stage III in 38 patients, and Stage IV in 21 patients in the multimodal MRI group; Stage 0 was reported in 39 patients, Stage I in 49 patients, Stage II in 55 patients, Stage III in 34 patients, and Stage IV in 18 patients in the color Doppler ultrasonography group. The baseline and clinical characteristics including age, nationality, residence, education levels, drinking and FIGO staging were generally well-balanced among the patients in both groups (all P>0.05). The baseline characteristics of the patients were detailed in **Table 1**.

Assessment of stages of cervical carcinoma by multimodal MRI and color Doppler ultrasonography

The diagnostic accordance rates of Stage 0, I and II of cervical carcinoma among patients with multimodal MRI were higher than those of the patients with color Doppler ultrasonography (all P<0.05); but the corresponding rates of Stage III and IV were insignificantly different (both P>0.05). According to multimodal MRI examination, 35 patients had cervical carcinoma of Stage 0, 47 had Stage I, 56 had Stage II, 38 had Stage III, and 21 had Stage IV; 4 cases of cervical carcinoma was undetected, with 2 cases of Stage 0, and 1 case of Stage I and 1 case of Stage II. On color Doppler ultrasonography, 32 patients had cervical carcinoma of Stage 0, 42 had Stage I, 47 had Stage II, 33 had Stage III and 17 had Stage IV; 24 cases of cervical carcinoma was undetected, with 7 cases of Stage 0, and 7 case of Stage I, 8 cases of Stage II, 1 case of Stage III, and 1 case of Stage IV (**Table 2**).

Sensitivity and specificity of multimodal MRI and color Doppler ultrasonography for assessment of stages of cervical carcinoma

The sensitivity and specificity of multimodal MRI for detecting cervical carcinoma of Stage 0 were 92.4% and 93.6%, respectively; 92.5% and 91.3% for detecting cervical carcinoma of Stage I; 94.7% and 93.5% for detecting stage II. The sensitivity and specificity of color Doppler ultrasonography for detecting cervical carcinoma of Stage 0 were 81.3% and 81.2%, respectively; 81.5% and 82.7% for detecting Stage I, 82.9% and 81.8% for Stage II. Multimodal MRI and color Doppler ultrasonography were remarkably different in the sensitivity and specificity for detecting cervical carcinoma of Stage 0, I, and II (all P<0.05), but slightly different in the sensitivity and specifici-

Table 3. Sensitivity and specificity of multimodal MRI and Color Doppler ultrasonography (%)

Stage	Multimodal MRI		Color Doppler ultrasonography		*P	#P
	Sensitivity	Specificity	Sensitivity	Specificity		
Stage 0	92.4	93.6	81.3	81.2	0.015	0.011
Stage I	92.5	91.3	81.5	82.7	0.023	0.017
Stage II	94.7	93.5	82.9	81.8	0.017	0.021
Stage III	91.6	92.1	88.5	89.3	0.068	0.065
Stage IV	93.4	92.3	87.4	87.8	0.071	0.078
Total	94.6	92.8	83.4	82.6	0.014	0.019

Note: *P, comparison in sensitivity between multimodal MRI and color Doppler ultrasonography; #P, comparison in specificity between multimodal MRI and color Doppler ultrasonography. MRI, magnetic resonance imaging.

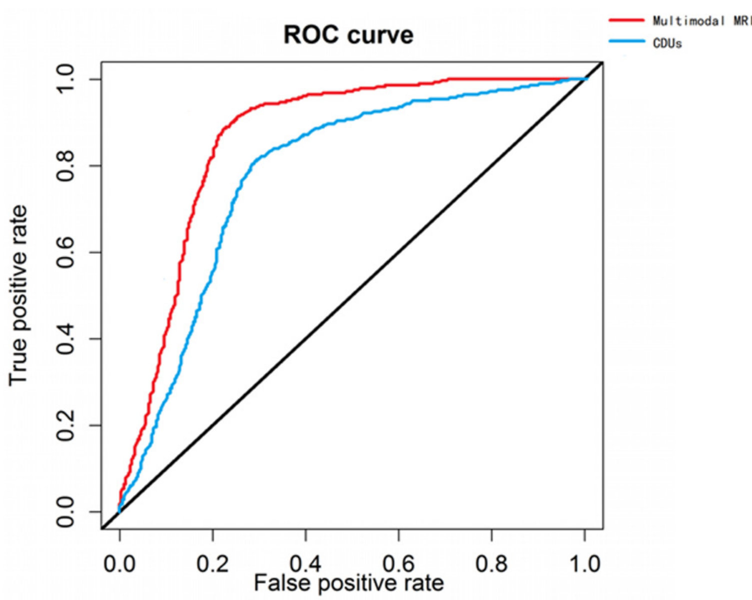

Figure 1. ROC curves of multimodal MRI and color Doppler ultrasonography. The area (0.874) under the multimodal MRI curve was remarkably greater than that (0.713) under the color Doppler ultrasonography curve (P=0.012). MRI, magnetic resonance imaging; ROC, receiver operating characteristic.

ty for detecting cervical carcinoma of Stage III, and IV (both P>0.05, **Table 3**). The overall sensitivity of multimodal MRI was 94.6% and its overall specificity was 92.8%; the over sensitivity of color Doppler ultrasonography was 83.4% and its overall specificity was 82.6%. Multimodal MRI and color Doppler ultrasonography were greatly different in the overall sensitivity and specificity (both P<0.05). In the ROC curve analysis, the area under the multimodal MRI curve was sustainably larger than that under the color Doppler ultrasonography curve (P=0.012; **Figure 1**).

Efficacy of radiotherapy assessed by multimodal MRI

The tumor size of the patients with cervical carcinoma was approximately 48-492 cm^3 before radiotherapy. After radiotherapy, 158 patients had a tumor reduction rate of over 87%, with 14 cases of residual tumor, and 144 cases of recovery. At the end of the entire course of radiotherapy, the tumor signals disappeared in 144 patients, the tumor signals were still observed in 43 patients, and weaker tumor signals in 14 patients. The presence/absence of enhancement on multimodal MRI was strongly correlated with the tumor reduction rates (r=0.649, P<0.01) and the efficacy of radiotherapy (r=0.679, P<0.01; **Table 4**).

Discussion

When it comes to diagnosis of cervical carcinoma, multimodal MRI is much more accurate in detecting early cervical carcinoma than color Doppler ultrasonography (P<0.05), but the two tools were insignificantly different in the accuracy of detecting moderate or advanced cervical carcinoma (P>0.05). This is mainly attributable to the fact that images of early cervical carcinoma were strikingly different from those of advanced cervical carcinoma. The size of lesions and the infiltration area of early cervical carcinoma are relatively smaller. The multimodal MRI sequences are superior to color Doppler ultrasonography in detecting the above two aspects. The findings in the study by Hoogendam et al. were consistent with ours [13]. Lu et al. also reported the superiority of multimodal MRI to spiral CT in the diagnosis of cervical carcinoma. Early diagnosis and treatment are always essential to diagnosis of cancers, especially diagnosis of malignancies. The ability of multimodal MRI to

Table 4. Efficacy of radiotherapy assessed by multimodal MRI in patients with cervical carcinoma

Tumor reduction rate (%)	Case	Absence of tumor enhancement	Presence of tumor enhancement	r	P
<87	43	1	42	0.649	0.004
≥87	158	156	2		
Recovery	144	144	0	0.679	0.003
Residual	14	11	3		

Note: MRI, magnetic resonance imaging.

improve the diagnostic rate of early cancers is undoubtedly its great advantage. Additionally, multimodal MRI is superior to color Doppler ultrasonography in the sensitivity and specificity for detecting cervical carcinoma of Stage 0, I, and II [14]. Due to its small lesion size and infiltration area, early carcinoma is susceptible to be ignored, leading to mis-judgement or misdiagnosis. The difficulties of early staging lie in the small lesions, undetectable metastasis of early lymph node, superficial muscularis invasion and fewer cervical invasions. On color Doppler ultrasonography, the interfaces of endometrium, the binding domain and muscularis are unclear and irregular; by contrast, with the features of all-round, multiple levels and sequences, and enhanced imaging, multimodal MRI allows a comprehensive judgement and observation of the lesions [15]. The results of the study by Nemoto et al. indicated that the application of multiple imaging tools significantly improved the sensitivity, specificity and accuracy in diagnosis of cervical carcinoma [16]. It is undeniable that the method is merely constrained to scientific research, and few patients are willing to accept multiple examinations for the same disease by various imaging tools, considering the social reality and the actual doctor-patient relationship. Moreover, the imaging examination is costly, and it will cost more in combined examinations. In this way, it is difficult for the patients to accept. In our current study, the accuracy, sensitivity and specificity for diagnosis of moderate or advanced cervical carcinoma were insignificantly different between multimodal MRI and color Doppler ultrasonography (all P>0.05). For cervical carcinoma of Stage III and IV, the images revealed overt characteristics and a wide range of diffusion of the lesions. In this case, Stage III and IV are relatively simpler to diagnose than Stage 0, I and II in terms of the images. What's more, there are no strict requirements for the functions, sensitivity and specificity of the instruments for diagnosis of Stage III and IV. Therefore, the above two adjuvant diagnostic instruments are slightly different in this aspect. The overall sensitivity and specificity of multimodal MRI are remarkably higher than those of color Doppler ultrasonography. Multimodal MRI is characteristic of multiple parameters and sequences, as well as multi-level imaging [17, 18]. Additionally, its tissue resolution and parenchyma contrast ratio are higher than those of other instruments. In the diagnosis of cervical carcinoma, multimodal MRI provides a clear and comprehensive vision of anatomical structure of the surrounding tissue and characteristics of the signals. The infiltration of cervical carcinoma is correlated with its pathological types and the degree of differentiation [19, 20]. All this fundamentally improves the accuracy, sensitivity and specificity of multimodal MRI for locating and qualifying cervical carcinoma.

Furthermore, as multimodal MRI is strongly correlated with the efficacy of radiotherapy for cervical carcinoma, it is a preferred tool for assessing the efficacy of radiotherapy for management of cervical carcinoma. The radio-sensitivity of the tumor tissue is a decisive factor for the efficacy of radiotherapy. The radio-sensitivity is variable at different stages of tumor treatment [21, 22]. The T1W1, T2W1 and enhanced sequences of multimodal MRI allow a clear differentiation of the signals of normal tissue and those of lesion tissue, and play key roles in judging whether there is any residual in tumor tissue. In our current study, when the tumor reduction rate was less than 87%, tumor enhancement was present in 1 patient. This might be due to the metastasis of cervical carcinoma in the patient who had not dieted following the doctor's advice before examination; in such case, the images were blurred, which affects the judgement of the radiologists from People's Hospital of Linyi Economic and Technological Development Zone. When the tumor reduction rate reached 87%, tumor enhancement was present in 2 patients, which might be attributed to the hyperplasia of granulation tissue in the examined regions, and the presence of false positive results induced by vascular regulatory dysfunction in the patients. Furthermore, tumor enhancement was present in 3 patients with residual tumor, and all of them were caused by the hyperplasia of granulation tissues, and showed a trend of recurrence. Incidentally, multimodal MRI convincingly suggested that the patients might have recurrent cancer. Nevertheless, the occurrence of the anomalies had no effects on the sensitivity and specificity of multimodal MRI.

There are still some limitations in our current study. Merely 396 patients were enrolled in this study, so it was not a study with a large sample size and the results of this study might be occasional. Moreover, the tools for imaging used in this study were not the most advanced, so the results of our analyses might be different from what reported by others, though we had tried our best to avoid any errors caused by human factors.

In conclusion, multimodal MRI has integrated the advantages of various sequences of MRI. As a result, it is superior to the common color Doppler ultrasonography in the diagnosis of cervical carcinoma. Moreover, it is of value for assessing the stages of cervical carcinoma as it is conductive in clinical detection of cervical carcinoma. It is also useful in evaluating the efficacy of radiotherapy. Therefore, it is worthy of extensive use in clinical practice.

Disclosure of conflict of interest

None.

Address correspondence to: Xuejian Liu, Department of Oncology, People's Hospital of Linyi Economic and Technological Development Zone, No. 117 Huaxia Road, Economical and Technological Development Zone, Linyi City 276023, Shandong Province, China. Tel: +86-0539-8769202; Fax: +86-0539-8769202; E-mail: liuxuejian110@126.com

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