

Evaluation of radiotherapy response of cervical carcinoma with gray scale and color Doppler ultrasonography: resistive index correlation with magnetic resonance findings

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PURPOSE

To investigate the role of the resistive index measured with transvaginal color Doppler ultrasonography (TVCDUS) for assessing the radiotherapy response of cervical carcinoma and to compare it with magnetic resonance findings.

MATERIALS AND METHODS

A total of 13 patients with advanced stage cervical carcinoma (>IIA) underwent magnetic resonance imaging (MRI) and TVCDUS exams 6 months prior to and 6 months after radiotherapy. Pre- and post-treatment resistive indices obtained from the central and peripheral zones of the tumor were compared. These values were also compared with MRI findings and resistive indices obtained from the control group.

RESULTS

Tumoral masses could be visualized in all patients with B-mode TVCDUS prior to the treatment. Resistive indices before and after treatment were 0.20-0.82 (mean: 0.52 ± 0.15), and 0.70-0.99 (mean: 0.81 ± 0.14), respectively. Eleven out of 13 patients responded to the treatment completely and no mass was detected in MRI and TVCDUS. Investigations were performed in areas with flow within the tumor-free cervix. A residual mass was noted in 2 patients with MRI and TVCDUS. There was a statistically significant difference between complete response to the treatment and increased resistive indices ($P = 0.001$). In 2 patients with residual masses, no increase in resistive indices was detected. The mean resistive index of the control group was 0.65 ± 13 and the difference was statistically significant compared to the resistive indices of the patients prior to the treatment.

CONCLUSION

Since there was a significant correlation between the MRI findings and resistive indices, the spectral parameters obtained with TVCDUS were a good alternative to such an expensive modality as MRI in the evaluation of the response of cervical cancer to the treatment.

Key words: • cervix carcinoma • response to therapy
• color Doppler ultrasound

Cervical carcinoma is the third most common gynecological malignancy in developed countries after endometrial and ovarian cancer. Gynecological examination and biopsy is the mainstay for the diagnosis. "Federation Internationale de Gynecologie et d'Obstetrique" (FIGO) criteria are used for staging of cervical carcinoma, but it is also known that FIGO has a misdiagnosis rate of 25%- 35% (misstaging/under or over staging) when it is correlated with a histological examination. Nowadays, magnetic resonance imaging (MRI) is becoming a routine imaging tool for staging and therapy planning due to its radiation-free nature and high soft tissue resolution (1-3).

The size and extension of the tumor, cell type, invasion of the vascular space, and lymph node metastasis are accepted prognostic factors for cervical carcinoma. The vascularity of the tumor, which was first mentioned by Folkman, is also a prognostic factor (4, 5). Neo-vascularization has effects on growth of the tumor, potential for metastasis, response to therapy, and survival (6-10). Based on this finding, color Doppler ultrasonography (CDUS) has been used frequently in distinguishing benign and malignant tumors in ovarian, endometrial, and gestational trophoblastic tumors, and to evaluate neo-vascularization (11, 12). There are cervical carcinoma studies using CDUS to determine the pattern of flow and resistive indices. CDUS is accepted as a diagnostic tool for the visualization of angiogenesis in vivo and the detection of different flow features, as well as the response of the tumor to therapy (6).

Teper et al. used transvaginal color Doppler ultrasound (TVCDUS) to measure the resistive index (RI) and the pattern of flow in 16 patients with cervical carcinoma. They reported that an RI value ≤ 0.573 had an 81% sensitivity and 93% specificity for the diagnosis of cervical carcinoma (9).

External radiotherapy, brachytherapy, and chemotherapy, including cisplatin, are used as a combination therapy in advanced stages of cervical carcinoma (stage IIB and above) (13). Since parametrial invasion is an indication for surgery and extracervical invasion is an indication for repeat radiotherapy, it is important to evaluate the regression of the tumor after therapy to plan additional treatment and follow-up. It is well-known that a pelvic physical examination is no longer reliable for the evaluation of the response to therapy. Despite the fact that MRI and computed tomography (CT) have high accuracy for the diagnosis and evaluation of the response to therapy, they have been found to be expensive and hardly reproducible (9). This is the reason why some investigators focused on CDUS as an alternative and simpler diagnostic tool than MRI for the follow-up of cervical cancer.

In this study, our aim was to compare and correlate the findings of MRI to the RI measured by TVCDUS in assessing the response of tumors to the radiotherapy.

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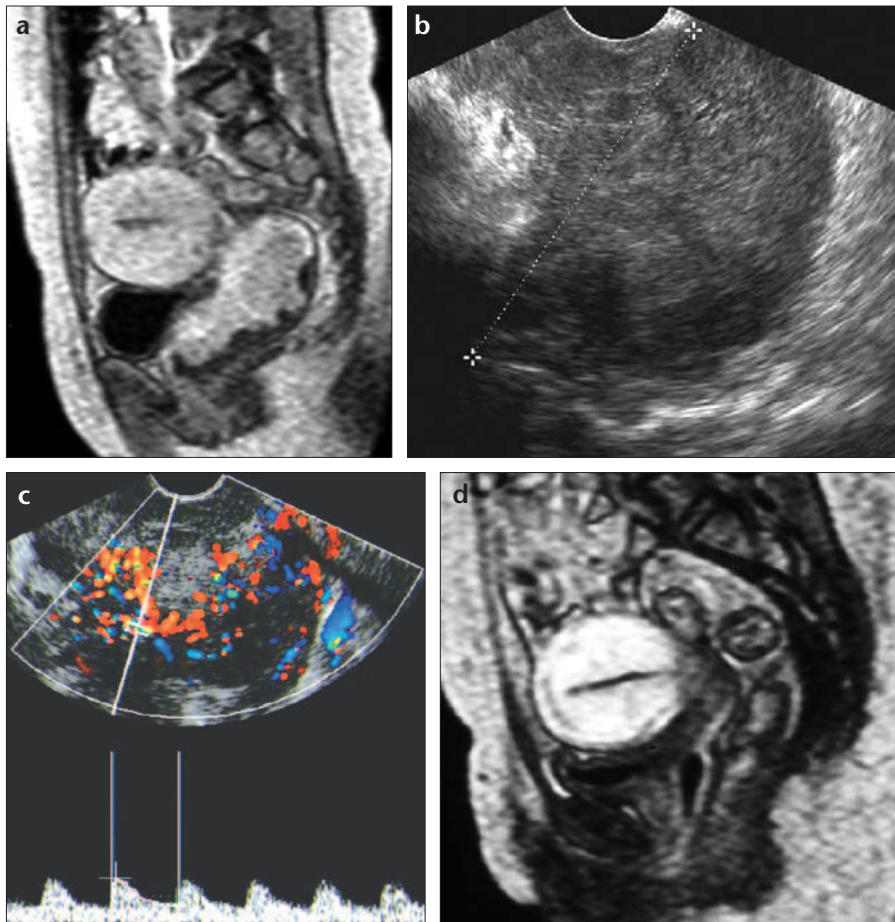


Figure 1 a-d. A 47-year-old female with stage IIIB cervical carcinoma. **a.** Sagittal T1-weighted MRI with fat saturation reveals the cervical mass filling the endocervix and vaginal canal. It demonstrates heterogeneous enhancement after administration of intravenous contrast. **b.** Transvaginal gray-scale sonographic image shows the lesion as a hypoechoic mass. **c.** Transvaginal color Doppler ultrasound demonstrates the increased vascularity of the lesion as well as the spectra with high diastolic flow, which refers to decreased resistance of the tumor to blood flow. **d.** Post-therapy control MRI examination, including sagittal T1-weighted image obtained after administration of IV contrast, displays no enhancement of the cervix, which is diminished in size, despite the homogenous enhancement of the myometrium.

Materials and methods

The study included 47 patients diagnosed with cervical cancer, who were prospectively evaluated for staging and determination of prognostic factors by abdominopelvic MRI between October 2000 and October 2002. Thirteen of them received radiotherapy because of the advanced stage of their cancer, and of those, 2 also received chemotherapy. Both 6 months before and 6 months after radiotherapy, the 13 patients with advanced stage carcinoma received TVCDUS examinations within 48 hours after MRI examinations.

MRIs were obtained with a Philips Intera 0.5 T (upgraded to 17mT gradients) system with a body wrap around coil. T2-weighted turbo spin-echo images were obtained in the sagittal and

oblique axial planes before and after vaginal contrast administration. Scan parameters for T2 weighted sequences were: TR/TE: 5200/100; turbo factor: 19; 4 signals acquired; matrix: 256 x 256; section thickness: 5 mm for axial and 8 mm and for the sagittal planes, with a 1 mm gap; FOV: approximately 350 mm; acquisition time: 2 min 11 sec for oblique transverse and 3 min 38 sec for the sagittal planes. T1 weighted turbo spin echo images in the transverse plane were obtained: TR/TE: 500/10; turbo factor: 4; 3 signals acquired; matrix: 256 x 256; section thickness: 8mm with a 2 mm gap; FOV: approximately 350 mm. Dynamic contrast enhanced MRI in the sagittal plane was performed with gradient echo technique: TR/TE: 155/4.5; time of inver-



Figure 2. Post-contrast sagittal T1-weighted image with fat saturation demonstrates the atrophic cervix, which appears hypointense relative to myometrium.

sion: 80 msec; 1 signal acquired; matrix: 256 x 512; FOV: 415 mm; slice thickness: 8 mm with an 0.8 mm gap; acquisition time: 37 sec. Data acquisition began 15 sec after the initiation of rapid manual IV injection of a bolus of gadopentetate dimeglumine (0.1mol/l per kilogram of body weight) (Magnevist, Berlex Laboratories, Wayne, NJ). Three consecutive scans were obtained with 5-7 sec breath hold interval. Dynamic contrast-enhanced scans in the sagittal plane were used primarily to evaluate corpus, vaginal, bladder, or rectal invasion. According to our routine protocol, 0.1 mmol/kg Gd- DTPA was used for the IV contrast. For vaginal contrast, barium sulphate was used in order to increase the viscosity of the intravaginal contrast. It was diluted to 40% with saline and 60 cc of the mixture was slowly infused into the vagina through a Foley catheter until extravasation of the contrast was seen. All patients were informed about the vaginal contrast.

The MRIs were evaluated by 2 radiologists for tumor size and invasion of the vagina, parametrium, pelvic sidewall, bladder, and rectum, as well as lymph node and distant metastases. The MRI-based staging was performed according to modified FIGO staging. The sizes of the tumors were noted in 3 orthogonal planes. For vaginal invasion, the thickness and the enhancement pattern of the wall was examined. For parametrial invasion, the destruction of the hypointense stromal ring surrounding the cervix and the contour irregularity

between the tumor and the parametrial tissues were evaluated. Full response was ascribed if no residual tumor was detected. Partial response was ascribed as $\geq 50\%$ tumor diameter decrease.

All sonographic examinations were performed by the same radiologist who was blind to MRI exam results. TVUS was performed with the guidance of a 5 MHz endocavitary Siemens Ellegra probe (advanced, Germany). After each patient was placed in the pelvic exam position, the probe was inserted gently into the vagina and then cervix and adnexal regions were scanned. The size, echogenicity, and extension of the tumor, and infiltration of the surrounding structures were examined. After gray scale study, CDUS was activated to evaluate vascularity. The sampling rate ranged from 2 kHz to 32 kHz and the color Doppler sensitivity was set to slow velocities.

As the vascularity was noted at the central portion or at the wall of the cervical channel invaded by the tumor, pulse CDUS was activated for the spectral examination and the RI was calculated. When the patient had full response to the therapy, with no tumoral lesion visualized, the entire cervix was scanned and an examina-

tion was performed at the vascular areas with flow. Additionally, 14 women who underwent routine TVUS with unremarkable results were selected as the control group to compare their RI values found in CDUS examinations of their cervixes.

Results

According to the MRI staging criteria, 6 patients (46%) had stage IIB, one patient (8%) IIA, 2 (15%) had IIIB, and 4 (31%) of the patients had stage IVB disease prior to treatment (Table 1, Figure 1a). Among the patients with stage IVB disease, 1 demonstrated invasion of the bladder and the other 3 patients had findings of invasion of the rectum on MRI. Only invasion of the bladder was diagnosed histologically, but invasion of the rectum was not confirmed in rectoscopy and was concluded as overall in all 3 patients. Although MRI overcalled the invasion of the rectum, the treatment protocol of those 3 patients did not change due to associated parametrial invasion. In 4 patients, the entire cervix was seen as hypoechoic and enlarged in TVUS prior to radiotherapy, which was compatible with diffuse involvement (Figure 1b). In the remaining 9 patients, hypoechoic neo-

plastic masses, as well as normal cervical tissue, were identified.

All patients were evaluated by CDUS for vascularity prior to radiotherapy. The RI ranged between 0.20 and 0.82 (mean = 0.5246 ± 0.15) in the cervical cancer group (Table 2). On spectral ultrasound examination, blood flow with low resistance was predominantly seen (Figure 1c). The control group was randomly selected among healthy women with a normal TVUS. RI values obtained from the cervix of the control group ranged between 0.56 and 0.74 (mean = 0.652 ± 0.13), and the difference between the RI values of the healthy women and the patients with cervical tumors was statistically significant (Mann Whitney test, $p = 0.005$).

After radiotherapy, MRI demonstrated full response in all but 2 patients. Full response was ascribed if the following conditions were observed; no focal lesion in the region of the cervix in any of the MRI series, no early (before uterine myometrium) contrast enhancement detected in the cervix, no lymphadenopathy. The cervixes of the patients with full response were very atrophic and 100% smaller in size (Figures 1d and 2). In 2 patients, MRI

Table 1. Ages, histopathological diagnosis, and MRI stages of patients with known clinical stages.

Number	Age	Histological type	Treatment	Clinical stage	MRI stage	Pre-RT diameter (cm) AP x CC x TR	Post-RT diameter (cm) AP x CC x TR
1	66	Squamous	RT	IIB	IIB	4x7x4.8	0
2	61	Squamous	RT	IB1	IVA	4x5x3.2	0
3	56	Squamous	RT	IIB	IIB	8x6x5	0
4	57	Squamous	RT	IVA	IVA	7x3x4.8	0
5	47	Squamous	RT	IIB	IIIB	3x4x4	0
6	54	Squamous	RT	IIB	IIA	4.5x5.5x3	0
7	63	Squamous	RT	IIB	IIB	6x5x8	0
8	54	Squamous	RT	IIB	IVA	5x7x4.5	0
9*	36	Squamous	RT	IIB	IIB	5x5x4	0.8x1x1.6
10*	47	Squamous	RT	IIB	IIB	5x6x4.8	1x1.5x1.6
11	52	Squamous	RT	IB2	IIIB	5.5x4x3.6	0
12	45	Squamous	RT	IIB	IIB	6x10x8	0
13	38	Squamous	RT	IIB	IVA	6x6x6.4	0

*: Patients with residual tumors
RT: Radiation therapy
cm: centimeters
AP x CC x TR: anteroposterior x cranio-caudal x transverse

Table 2. RI values before and after radiotherapy.

Number	Pre RT RI	Post RT RI	Control group RI
1	0.49	0.97	0.58
2	0.70	0.82	0.56
3	0.20	0.71	0.58
4	0.53	0.99	0.62
5	0.50	0.66	0.73
6	0.42	0.96	0.71
7	0.47	0.83	0.59
8	0.82	0.71	0.62
9*	0.67	0.70	0.73
10*	0.52	0.53	0.74
11	0.42	0.97	0.69
12	0.57	0.88	0.61
13	0.51	0.77	0.72

*: Patients with residual tumors
Pre-RT: Prior to radiation therapy
Post-RT: After radiation therapy
RI: Resistive indices

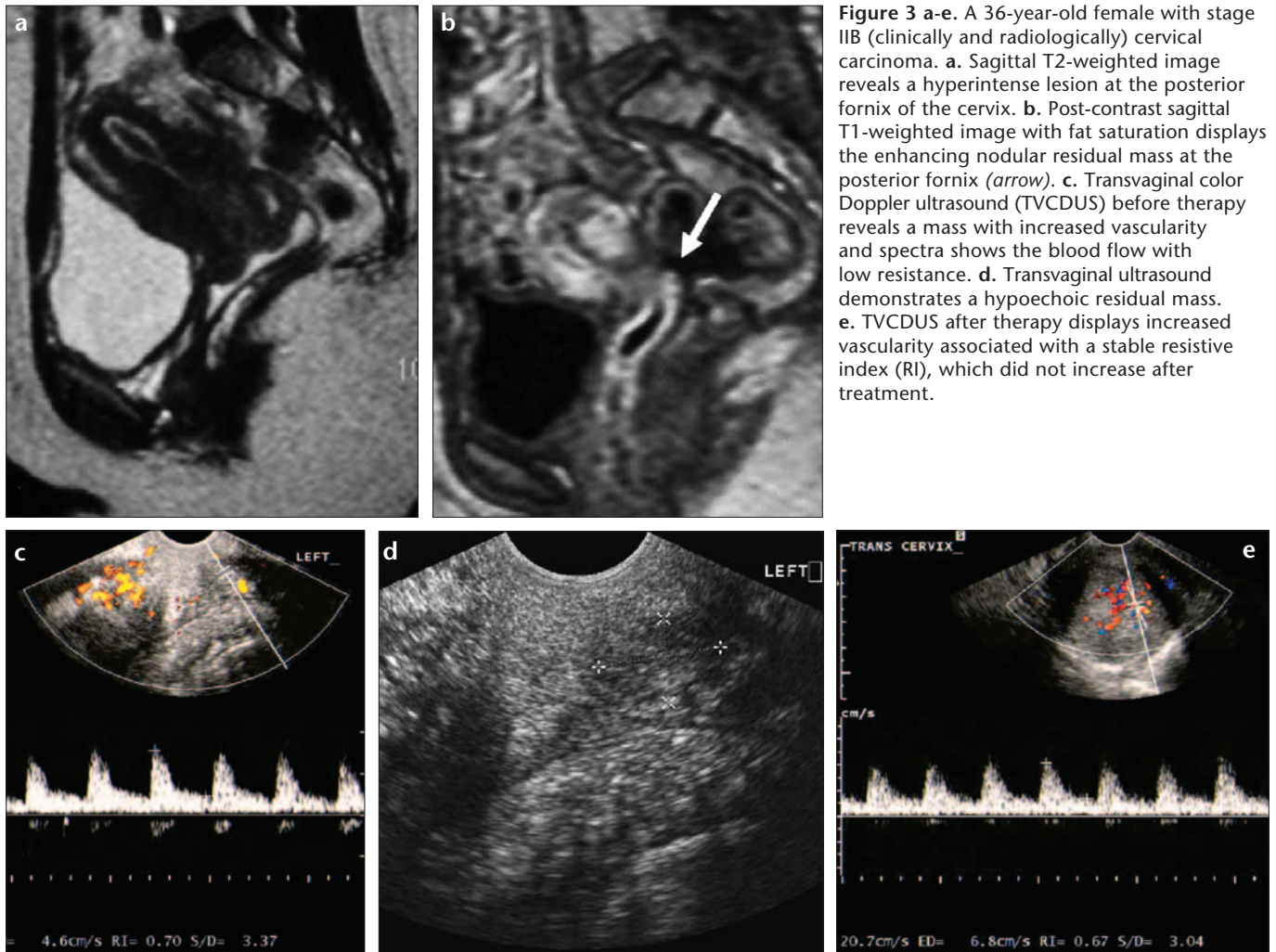


Figure 3 a-e. A 36-year-old female with stage IIB (clinically and radiologically) cervical carcinoma. **a.** Sagittal T2-weighted image reveals a hyperintense lesion at the posterior fornix of the cervix. **b.** Post-contrast sagittal T1-weighted image with fat saturation displays the enhancing nodular residual mass at the posterior fornix (arrow). **c.** Transvaginal color Doppler ultrasound (TVCDUS) before therapy reveals a mass with increased vascularity and spectra shows the blood flow with low resistance. **d.** Transvaginal ultrasound demonstrates a hypoechoic residual mass. **e.** TVCDUS after therapy displays increased vascularity associated with a stable resistive index (RI), which did not increase after treatment.

showed early enhancement in the cervix at the posterior fornix, representing residual masses. The hypoechoic residual tumoral tissue was also identified with TVUS in 2 patients. The hypoechoic tumoral tissue was easily differentiated from the atrophic cervical tissue and RIs did not increase in these patients (Figures 3 and 4).

On spectral study, RI values after therapy ranged from 0.70 to 0.99 (mean = 0.81 ± 0.14) in patients with full response and the difference between the pre- and post-radiotherapy values was statistically significant according to the Mann Whitney U test ($p < 0.05$) (Table 2). The RI values after radiotherapy were higher than the pre-treatment values for the patients with full response. The RI of one patient with full response and 2 patients with residual masses did not increase after therapy.

When we accept the RI cutoff value of 0.573 (equal or smaller demonstrates

carcinoma), our study showed 76% sensitivity and 92% specificity to diagnose cervical carcinoma. Furthermore, MRI and TVUS showed 100% correlation in the evaluation of the residual masses and the response to therapy.

Discussion

Neo-adjuvant chemotherapy and preoperative radiotherapy are the new strategies for therapy of locally advanced cervical carcinoma in order to prevent local recurrence and distant metastases (14, 15). Post-treatment tumor regression evaluation is so important that patients whose parametria are devoid of the tumor should be led to surgery and patients who have extra cervical invasion should receive additional chemotherapy and/or radiotherapy.

Physical examination, biopsy, ultrasound, CT, and MRI have been used to evaluate the response of cervical carcinoma to therapy. Physical exami-

nation has some technical limitations due to intratumoral necrosis and fibrosis within the cervix. CT or physical examination may not distinguish the residual tumor from the postoperative fibrosis or from the inflammatory reactions due to radiation therapy (13-15). Despite the consensus that MRI is the most effective imaging modality due to its superiority with soft tissue contrast and anatomical detail with multiplanar imaging in detecting residual tumors and fibrosis, and in staging, is not widely used due to its cost and limited availability (16-18).

Cheng et al. reported that the characteristics of blood flow signals and vascularity index in cervical carcinoma detected by CDUS were beneficial to in vivo assessment of global tumor angiogenesis (7, 19, 20). Tepper et al. reported that the resistive indices obtained from the cervix of healthy women (0.643) were higher than the patients with cervical carcinoma (0.493). They

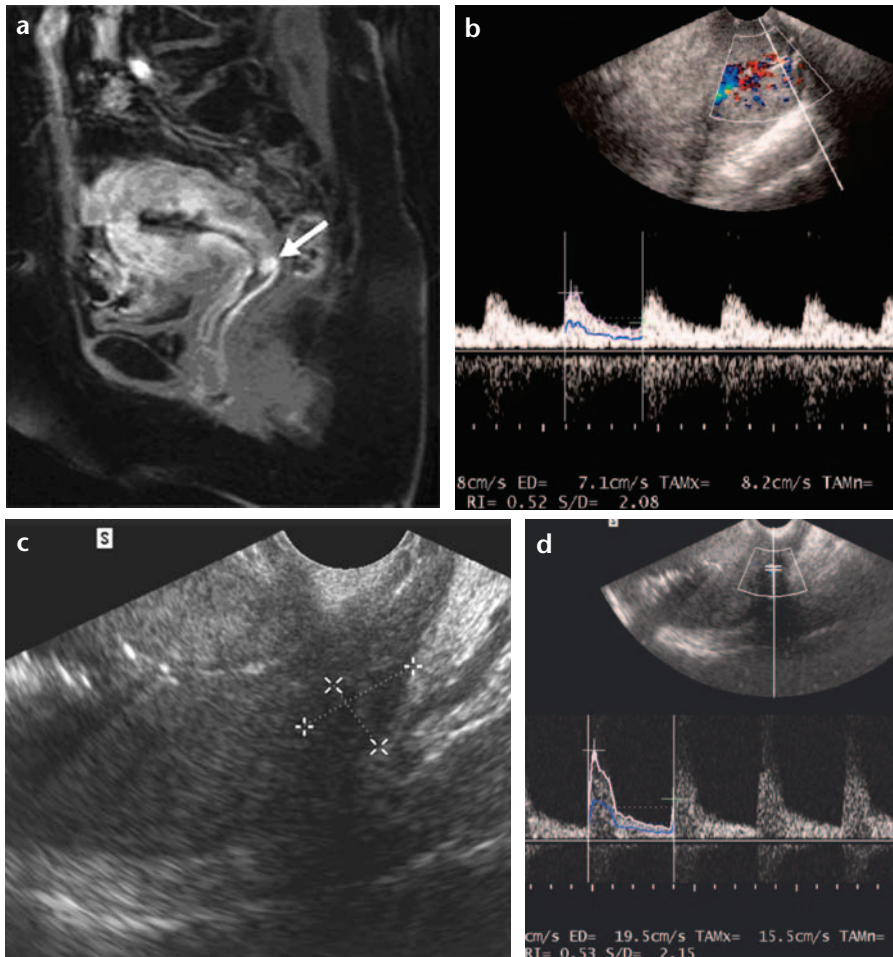


Figure 4 a-d. A 47-year-old female with stage IIB cervical carcinoma. **a.** Post-contrast sagittal T1-weighted image with fat saturation assesses the residual tumor at the posterior fornix of the cervix after radiotherapy. **b.** Transvaginal color Doppler ultrasound (TVCDUS) demonstrates a hypervascular lesion associated with a blood flow showing a low resistive index (RI). **c.** After therapy, a hypoechoic residual tumor is seen with transvaginal ultrasound. **d.** TVCDUS shows persistent increased vascularity and a stable RI.

concluded that if an RI was ≤ 0.573 , it had 81% sensitivity and 93% specificity for the diagnosis of cervical carcinoma (11). In our study, mean pre-radiotherapy RI value was 0.524 and it was lower than 0.573 in 10 patients. Alcazar et al. demonstrated that cervical carcinomas with increased vascularity had lower RI values. They found that tumors with complete response to therapy had a lower mean number of vessels and higher RI values compared to partial responders (6, 21).

Testa et al. studied color score, peak systolic velocities (PSV), and RI values according to the size of the tumor and found that a significantly higher color score, lower RI, and higher PSV were associated with tumor diameters ≥ 4 cm compared to the smaller tumor group (22). Since all cervical tumors in our study were > 4 cm in diameter,

we could not evaluate the relationship between tumor size and RI values and vascularity.

We could not study the predictive value of the RI on prognosis because the range of RI values were so broad and the number of patients with residua was not sufficient. There was no significant difference between initial RI values of the patients with residual masses and the patients with full response; therefore, it is not accurate to talk about a cutoff value of RI to predict the response of cervical carcinoma to therapy.

In our prospective study, we evaluated the RI before and after therapy to determine the response to treatment. Our results clearly showed that all patients with full response, except one, had significantly increased RI values after therapy. Moreover, nei-

ther of the 2 patients with residual masses showed a significant increase in RI values after therapy. If a residual tumor could not be visualized due to inexperience of the sonographer or low image quality of gray scale US, RI values would be helpful for suspecting a residual tumor. Although we were able to visualize residual masses as suspicious thickening in 2 patients with gray scale TVUS, TVCDUS provided additional information in terms of vascularity and RI. Since the gray scale sonography is an operator-dependent modality, detection of increased vascularity and measurement of the RI is more reliable. We observed that the cervix becomes thinner due to fibrosis and atrophy, so any area with different echogenicity could represent a residual mass. In order to standardize these findings, spectra and RI measurements of a vessel using CDUS would be easier and more accurate. MRI is also used to visualize the extensions of tumors and residual masses. Since it is expensive, it is preferred for selected cases. As our study demonstrated, CDUS can be an alternative diagnostic tool to MRI in determining residual masses.

Sironi et al. evaluated the response of cervical tumors to chemotherapy in 21 patients with MRI and compared the MRI findings to histological findings. The hyperintense areas in the cervixes of 16 patients corresponded to residual masses in histological examinations. The areas demonstrating low intensity were consistent with necrosis and hemosiderin deposits (24). Manfredi et al. performed MRI in 18 patients with cervical carcinoma prior to and 4 weeks after therapy (chemotherapy and radiotherapy) and were able to identify full response in 12 patients with MRI with an accuracy of 78%, utilizing transverse T1 and sagittal T2 weighted images. They defined the hyperintense areas within the cervixes associated with mass effect on T2 weighted images as a finding of residual masses. However, they commented that the hyperintense areas without any mass effect could represent a small residual mass, or hyperplasia or necrosis of cervical glands (15).

Okada et al. revealed that hyperintense foci on T2-weighted images within the cervix after therapy represent cancer cells with varying degrees of degeneration and necrotic

tissues; however, hypointense foci on T2-weighted images correspond to a small number of degenerated cancer cells (24). On the other hand, there are studies in which differentiation of the residua from the edema and necrosis by T2 weighted images was not possible (25). Mary et al. reported that combined data, including the tumor volume, which is calculated on T2-weighted images, and the dynamic enhancement pattern, allows more accurate prediction of treatment response in patients with advanced cervical cancer. Yamano et al. confirmed that a dynamic MRI exam is more valuable and reliable for evaluation of the response of cervical carcinoma to therapy (18, 26).

We performed dynamic exams in addition to T2 weighted images in order to evaluate residual and recurrent masses. In 2 patients, we observed contrast enhanced areas within the cervix before uterine myometrial enhancement and considered these residual masses; however, on T2-weighted images, the residual masses could not be identified. TVUS also revealed these areas as hypoechoic residual masses.

Studies including the comparison of CDUS and histology, as well as the comparison of MRI and histology have been reported (15, 27), however, to the best of our knowledge, this is the first study to assess tumor response after therapy with both TVCDUS and MRI. One limitation of our study is that although both TVCDUS and MRI exams had a very good correlation, following therapy, none of our patients had histological confirmation. One patient in whom MRI detected a residual mass presented with metastasis to the femur 2 months after MRI. Because of the small size of the residual tumor and the maximal radiotherapy dose already being delivered, oncologists decided to give adjuvant chemotherapy without having a biopsy. This patient was then lost to follow-up.

CDUS is a valuable diagnostic study to determine the vascularity and flow patterns of cervical tumors and to distinguish malignancy from normal cervical tissue. Although larger series of patients are needed, the RI and vascular score were helpful in monitoring the efficacy of the therapy. The major

limitations of our study were the small group of patients with residual masses and the lack of histological confirmation. Although the results would be more accurate with a larger group, we can still recommend TVCDUS as an alternative to MRI for monitoring the response of cervical tumors to therapy.

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