Transvaginal doppler sonography for assessment the response to radiotherapy in locally advanced squamous cervical cancer: a preliminary study

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Abstract

Introduction: The place of sonography in the diagnostics and monitoring of cervical carcinoma remains controversial. Aim of the study is to assess the value of transvaginal sonography (TVS) and transvaginal color Doppler sonography (TVCD) for assessment of the effect of treatment in patients with locally advanced squamous cervical cancer.

Material and methods: Research included 18 patients with cervical cancer aged 36-72 year in FIGO stages II (11 patients) and III (7 patients) treated by radiotherapy. TVS and TVCD were performed: before the beginning of treatment (I), 3 days after radiotherapy (II), and 6 weeks after radiotherapy (III). The clinical course of disease in 6 months after treatment was evaluated.

Results: In each patients the volume of uterine cervix decreased after radiotherapy. The median values of RI were similar in each examinations. During 6 months of observation in 5 women out of 18 patients the progression of the cervical cancer was noted. Only in 2 out of 5 cases the progression was local, and in 3 patients distant metastases were found. In retrospective analysis we did not found statistically significant differences in results of sonographic examinations I, II, and III between patients with remission and progression of cervical cancer.

Conclusions: TVS is useful for estimation of uterine cervix during radiation therapy due to locally advanced cervical cancer, but its usefulness in prediction of progression of the cancer is rather low. The value of the assessment of RI in descending branches of uterine arteries in monitoring the treatment of the cervical cancer was not confirmed.

Key words: cervical cancer, radiotherapy monitoring, ultrasonography, color Doppler.

Introduction

Despite the screening programs targeting on early detection of cervical cancer, a substantial proportion of women are still diagnosed in advanced stage of the disease. In Poland in 2005 the number of diagnosed new cases

of invasive cervical cancer was 3263 (standardized coefficient 11.5/100 000) with the number of deaths 1796 (standardized coefficient 5.7/100 000) [1]. Besides the I and IIa cervical cancer, which are the subject to surgical treatment, in the remaining more advance stages the external beam irradiation, brachytherapy and chemotherapy are used [2, 3]. The overall, reported 5-year survival rates of patients treated with radiation alone are approximately 65 to 75% for FIGO stage II and 30 to 50% for FIGO stage III. The cure rates are strongly correlated with the size of the primary tumor and extend of regional involvement [4].

In the radical treatment of carcinoma of the uterine cervix external-beam radiation is used to treat central disease and to sterilize known or suspected regional lymph nodes metastases. The external-beam irradiation to the pelvis usually causes tumor partial regression. This improves the dose distribution of intracavitary radiation by shrinking endocervical disease. Some authors try to deemphasize the use of brachetherapy in patients with stage III disease. In their opinion the disease at the pelvic wall is considered to be beyond the reach of intracavitary therapy. However the significantly better survival rates for patients treated with a combination of external beam irradiation and brachytherapy was reported. The disease specific survival rate was 43% for patients treated with combined treatment and 21% for patients treated with external beam radiation alone [5, 6]. Five randomized phase III trials demonstrated significant survival benefit when compared the schedule of concurrent cisplatin based chemotherapy and irradiation with irradiation alone. These trials have shown that the use of concurrent radiochemotherapy results in a 30 to 50% decrease in the risk of death compared to radiotherapy alone [7-11].

For optimal effectiveness of radiotherapy in cervical cancer patients the monitoring during treatment which allows for doses modification, planning additional treatment and follow up is required [3]. Physical examination with its technical limitations, biopsy, ultrasound, MRI, and CT have been used to evaluate the response of cervical carcinoma to radiotherapy [2, 12]. The assessment of serum SCC and additionally CA125 levels as tumor markers can be used as well, but its specificity is rather low [13]. The use of MRI and CT is limited due to their costs, but the assessment of changes in uterine cervix volume in transvaginal sonography (TVS) can be very helpful.

Neo-vascularization through allowing the tumor growth is the indispensable factor of cancer spreading, metastasis, response to therapy, and survival [14, 15]. In malignant neoplasms vessels are deprived of smooth muscular coat and intense process of its formation is observed [15]. Since the gray scale sonography is an operator-dependent modality, detection of increased vascularity can be helpful for correct diagnosis. Based on these findings transvaginal color Doppler sonography (TVCD) has been used frequently in gynecological oncology in distinguishing between benign and malignant ovarian, endometrial and trophoblastic tumors. Neo-vascularization in malignant tumors is characterized by low resistance for blood flow, what is expressed by decreased values of resistive index (RI) [15]. In the literature the role of TVCD in cervical carcinoma remains still controversial [14-17].

The aim of the study was to analyze the usefulness of uterine cervix volume measurements in TVS and RI changes by TVCD in cervical branches of uterine arteries for monitoring the response on the radiation therapy, and to predict the 6-months course of neoplasmatic disease in patients with locally advanced squamous cervical carcinoma.

Material and methods

The prospective preliminary study comprised 18 patients with locally advanced squamous cervical cancer (FIGO stages IIB-IIIB, grade G1-G3). Median age was 49.6 ±7.1 years, range 36-72 years. All patients were treated with radiation therapy in Department of Gynecological Radiotherapy Copernicus Memorial Hospital of Lodz. In each case before study, physical examination, chest X-ray, ultrasound, and MRI were performed to assess clinical staging. Squamous cervical cancer was diagnosed in 11 women in clinical stage IIB (G1 – 4 cases, G2 – 5 cases, G3 – 2 cases) and in 7 women in clinical stage IIIB (G1 – 0 cases, G2 – 5 cases, G3 – 2 cases) (Table I).

All patients were treated according to homogeneous Department of Gynaecological Radiotherapy' in-house protocol. Preliminary treatment volume localization was done using simulator. Geometric centre of treatment fields as well as projecting lateral laser beams were marked on patients skin with tattoos. The planning CT scans were sent to Medical Physics Department, where treatment volumes as well as critical organs and radiation dose were defined using "Eclipse Variant" computer planning system. Patients underwent external beam and intracavitary irradiation with concurrent cisplatin based chemotherapy. In all cases the high-energy (15 MV) anterior and posterior fields were used to treat entire pelvic contents. The superior border was placed at the L4-L5 interspace. The inferior border was usually placed at the inferior border of the obturator foramen, and at least 4 cm below the lowest extend of cervical disease. The lateral borders were defined 1.5 cm lateral to the bony margins of the true pelvis. The dose of 44 Gy was delivered using external

beam irradiation. Afterwards 5 HDR fractions of 7.0 Gy each were applicated to the total dose of 80 Gy at the Point A. The dose to critical normal tissue was 80% or less of the dose to the paracentral reference point. The chemotherapy was begun on day 1 of the irradiation. Forty mg/m^2 of cisplatin by intravenous infusion was administrated every week during radiotherapy course.

The study protocol covered in each patient three TVS and TVCD examinations. The first examination (I) was carried out before the beginning of radiotherapy. The following two examinations were carried out 3 days after completion of treatment protocol (II) and after 6 weeks (III), to evaluate radiation – induced changes in cervical morphology, as well as in vascular blood flow in cervical branches of uterine arteries. TVS was performed with the guidance of the 5 MHz endocavitary Siemens Ellegra probe (advanced, Germany) with the assessment of organs situated in pelvis minor and particularly the estimation of uterine cervix (three dimensions in axes x-y-z). During performing the measurements of uterine cervix the markers were situated in following sites: to determine the longitudinal (A) dimension in the internal orifice and in the external orifice of cervical canal, for defining the transversal (B) and sagittal (C) dimension- on the most external points of the cervical cross-section. For calculating volume of uterine cervix the mathematical formula: V = 4/3 π A/2 B/2 C/2 = 0.5233 A B C was used. After gray scale study TVCD was activated to evaluate RI in the small descending branches of uterine arteries on the level of the internal orifice of cervical canal. The sonographic data were correlated with the effects of treatment.

The results of measurements of uterine cervix volume in TVS and RI in TVCD in examinations I, II, and III were compared, and correlated with the treatment results in patients in 6 months. Statistical analysis was made by means of CSS Statistica (Statsoft Inc., Tulsa, OK.,USA). Comparisons between groups were performed using the Student's *t*-test. A p value < 0.05 was considered significant.

Results

The median value of cervical volume in the group of all 18 patients diminished significantly after the completion of radiation therapy in relation to its volume before treatment (Table II). The median cervical volume 3 days after completion of treatment protocol was similar to that 6 weeks after. No statistically significant correlations between median RI values in consecutive examinations were found (Table II). The exact data are presented in Table I.

In spite of the sonographic and clinical reduction of uterine cervix volume in all patients 6 weeks

Table I. Clinical and morphological parameters of the study group

No	Histopathology	S	G	After 6 months	Volume I [cm^3]	Volume II [cm^3]	Volume III [cm^3]	RI I	RI II	RI III
1	Squamous	IIIB	2	Remission	3.65	2.75	2.08	0.59	0.41	0.68
2	Squamous	IIB	1	Remission	1.87	0.84	0.58	0.89	0.82	0.83
3	Squamous	IIIB	2	Remission	4.72	4.11	2.37	0.77	0.89	0.71
4	Squamous	IIB	1	Remission	1.10	0.46	0.44	0.76	0.58	0.76
5	Squamous	IIB	1	Remission	1.62	0.54	0.57	0.41	0.44	0.59
6	Squamous	IIB	2	Remission	1.37	1.40	0.71	0.58	0.47	0.67
7	Squamous	IIIB	3	Progression	4.77	1.14	1.05	0.48	0.39	0.49
8	Squamous	IIB	2	Remission	1.81	0.44	0.49	0.71	0.84	0.63
9	Squamous	IIB	3	Remission	2.24	1.30	1.09	0.97	0.85	0.71
10	Squamous	IIB	1	Remission	1.19	0.79	0.42	0.36	0.44	0.48
11	Squamous	IIB	3	Progression	3.11	3.03	1.82	0.58	0.39	0.55
12	Squamous	IIIB	2	Progression	7.60	1.68	2.10	0.47	0.51	0.81
13	Squamous	IIB	2	Remission	3.76	2.52	1.85	0.89	0.84	0.66
14	Squamous	IIB	2	Remission	3.56	3.07	0.87	0.78	0.86	0.71
15	Squamous	IIIB	3	Progression	4.26	1.84	2.25	0.51	0.42	0.63
16	Squamous	IIB	2	Progression	2.91	0.88	2.13	0.84	0.79	0.44
17	Squamous	IIIB	2	Remission	6.41	5.21	4.76	0.90	0.58	0.70
18	Squamous	IIIB	2	Remission	7.59	2.16	1.98	0.76	0.71	0.76

Table II. Median cervical volume by TVS and median RI by TVCD in patients with locally advanced cervical cancer

TVS and TVCD	Volume [cm³]	*p*	RI, X ± SD	*p*
Before treatment	3.53 ±2.07	I-II, $p < 0.01$	0.68 ±0.18	I-II, ns
Three days after completion treatment	1.90 ±1.34	I-III, $p < 0.001$	0.63 ±0.20	I-III, ns
Six weeks after completion treatment	1.53 ±1.08	II-III, ns	0.67 ±0.17	II-III, ns

Table III. Median cervical volume by TVS in patients with remission and progression of the cervical cancer

Median cervical volume by TVS	Remission ($n = 13$)	Progression ($n = 5$)	*p*
Before treatment	3.15 ±2.07	4.53 ±1.88	ns
Three days after completion treatment	1.97 ±1.51	1.71 ±0.83	ns
Six weeks after completion treatment	1.40 ±1.23	1.87 ±0.48	ns

Table IV. Median values of RI in cervical branches of uterine arteries by TVCD in patients with remission and progression of the cervical cancer

Median values of RI by TVCD	Remission ($n = 13$)	Progression ($n = 5$)	*p*
Before treatment	0.72 ±0.19	0.57 ±0.15	ns
Three days after completion treatment	0.67 ±0.19	0.50 ±0.17	ns
Six weeks after completion treatment	0.68 ±0.08	0.58 ±0.14	ns

after completion of radiation therapy in relation to its volume before treatment, during 6 months observation, in 5 out of 18 cases the progression of cervical cancer was observed ($p < 0.02$). The progression of the disease was noted: in 2 patients with cervical cancer initially diagnosed in FIGO stage II (G2 – 1 case and G3 – 1 case), and in 3 patients with cervical cancer initially diagnosed in FIGO stage III (G2 – 1 case and G3 – 2 cases) (Table I).

The median values of the cervical volume, as well as of RI, in examinations I, II, and III when compared 2 subgroups patients: with remission and with progression of the cervical cancer were similar (ns) (Tables III, IV).

Discussion

Nowadays, the principal role for the assessment of neoplasmatic infiltration in cervical cancer possesses MRI [2, 12]. Despite the consensus, that MRI is the most effective imaging method due to its superiority with soft tissue contrast and anatomical detail with multiplanar imaging in cervical cancer staging, detecting residual tumors and fibrosis [2], it is not widely used due to its cost [16]. Ultrasonography – the most widespread imaging method in gynecological oncology, is much less expensive than MRI. The place of transabdominal sonography (TAS), TVS and TVCD in the diagnostics and monitoring of cervical carcinoma remains still controversial [12, 17, 18].

Our results suggest, that TVS is helpful for estimation of the neoplasmatic infiltration extent, due to the possible assessment of the dimensions and echography of uterine cervix. Beside of clinical examinations, ultrasonography – commonly transvaginal and transabdominal, could be a simple and noninvasive expression of the efficacy of applied treatment [19, 20]. In cases with the lack of changes in cervix volume during therapy of cervical cancer, which can suggest the non-effective treatment, it indicates on the necessity of precise diagnosis, and in some cases – on the necessity of treatment modification.

According to Kerimoğlu *et al*., if the residual cervical tumor or local recurrence could not be visualized due to inexperience of the sonographer or low image quality of grey scale TVS, RI value by TVCD can be helpful to make the diagnosis correct, and to precise assess the extent of neoplastic infiltration [16]. It is postulated, that the estimation of RI can be useful in the monitoring of treatment results as well [18, 20]. In analyzed group of patients the decrease of uterine cervix volume in TVS was observed, however the changes did not correspond with changes of RI in descending branches of uterine arteries measured on the level of internal orifice of uterine cervix canal by TVCD. We did not observed in consecutive examinations the increase of RI values due to radiotherapy, which could be caused by angiofibrosis, the clot forming and embolism, and by shrinkage of vascular walls, which provides in consequence to their stenosis and occlusion of vessels [14, 21].

Our results confirm the data from the literature, that the assessment of RI by TVCD in locally advanced cervical cancer should be made rather in vessels forming on the way of neovascularization in the neoplasm in central and peripheral zones of the cervical tumor, than in the branches of uterine arteries [16, 22]. It was confirmed by Tepper *et al*., who used TVCD to measure RI and the pattern of flow in small vessels from uterine cervix. He reported the RI value ≤ 0.573 had an 81% sensitivity and 93% specificity for the diagnosis of cervical cancer [23]. Similar results were

published by Carter, who confirmed in the group of 32 patients with invasive cervical cancer and 34 patients with benign cervical lesions the intracervical RI lower (0.62) in malignant tumors compared to patients with benign lesions (0.71) [17]. Alcazar *et al*. [24] found, that cervical cancer with complete response to therapy has initially a lower mean number of vessels and higher RI values compared to partial responders, and similar results were published by Kerimoğlu *et al*. [16]. Greco *et al*. confirmed the value of RI measurement in monitoring the response to neoadjuvant chemotherapy in locally advanced cervical cancer patients [18].

Unfortunately, the local control of squamous cervical carcinoma by TVS and TVCD in some cases is not sufficient to early diagnose the progression of the disease [24], what is confirmed in our study. The reason for the decreased sensitivity of TVS in the detection of progressed disease are often distant metastases of cervical cancer. It was confirmed by us, because only in 2 cases out of 5 patients with progression of cervical cancer, it was local recurrences, and in 3 cases the cancer metastasized into distant organs (kidney – 1 case, retroperitoneal lymphatic nodes – 2 cases). Small number of patients in our study causes, that the results cannot be generalized on the whole population, and further study in needed. According to another authors and based on our results, it is obvious to recommend to patients with history of the cancer necessity of systematic control by specialists in gynecological oncology in multidisciplinary oncology centers due to silent character of cervical cancer recurrences [2, 3, 21].

In conclusion:

1) TVS is useful for estimation of uterine cervix during radiation therapy due to locally advanced cervical cancer, but its usefulness in prediction of progression of the cancer is rather low;
2) the value of the assessment of RI in descending branches of uterine arteries in monitoring the treatment of the cervical cancer was not confirmed;
3) small number of patients does not allow for generalize the results to the whole population.

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