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Diffusion-weighted magnetic resonance imaging of cervical cancer

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Background. Diffusion-weighted magnetic resonance imaging (DW–MRI) has been employed in the diagnostics of malignant tumors of abdomen and pelvis relatively recently. Nowadays, there exists a particular interest in adaptation DW–MRI for assessing the response of tumors to chemoradiaton therapy. The aim of our study was to compare the mean value of the apparent diffusion coefficient (ADC) in a healthy cervix, cancer-affected cervix and a cervix after chemoradiation therapy, as well as to identify the ADC range typical of cervical cancer.

Materials and methods. The study enrolled 108 female patients who underwent pelvic MRI in the Lithuanian University of Health Sciences Kaunas Clinics Hospital in 2008–2010. The study group consisted of 65 patients in whom cervical cancer had been clinically suspected and confirmed by biopsy before MRI examination. All these patients underwent pelvic MRI twice: before the chemoradiation therapy and 6 months after the therapy. The control group consisted of 43 patients in whom cervical cancer had been not suspected and MRI was performed because of other pelvic diseases.

Results. The mean ADC value of the study group ($0.658 \pm 0.118 \times 10^{-3}$ mm^2/s) was lower than of the control group ($1.171 \pm 0.143 \times 10^{-3}$ mm^2/s) ($t = 20.315$, $p = 0.03$). The ADC threshold value of 0.945×10^{-3} mm^2/s was defined, differentiating the cancer-affected cervical tissue from the normal. The mean ADC value of the patients who responded to chemoradiation therapy ($1.111 \pm 0.138 \times 10^{-3}$ mm^2/s) increased and in those who did not respond it remained lower ($0.733 \pm 0.073 \times 10^{-3}$ mm^2/s) ($t = 9.518$, $p = 0.04$). The ADC threshold value of 0.830×10^{-3} mm^2/s was defined, differentiating the residual tumor tissue from the healthy cervical tissue after chemoradiation therapy.

Conclusions. The ADC value in the case of cervical cancer was significantly lower than in the non-affected cervical tissue. The ADC value increases after effective chemoradiation therapy and becomes closer to the coefficient value of non-affected cervical tissue, but still remains lower. The 0.945×10^{-3} mm^2/s ADC threshold was detected while differentiating between cancer-affected and normal cervical tissues, while the ADC threshold was 0.830×10^{-3} mm^2/s when differentiating between residual tumor tissue and healthy cervical tissue after chemoradiation therapy at a high sensitivity and specificity.

Key words: diffusion-weighted magnetic resonance imaging, apparent diffusion coefficient, cervical cancer, chemoradiation therapy

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INTRODUCTION

Cervical cancer is one the most frequently diagnosed malignant diseases in females, affecting approximately 16 out of 100 000 women. It takes the third place in the world among female genital malignancies, following the uterine body and ovarian cancers. The morbidity of cervical cancer in Lithuania is one of the highest in the European Union (1–3).

The cervical cancer diagnosis is suspected according to the symptoms, results of clinical examinations, positive screening cytology results and is confirmed by biopsy. It is important to assess the extent of the disease before planning surgical treatment or chemoradiation therapy (4, 5). Magnetic resonance imaging (MRI) complements the clinical examination and is the optimal radiodiagnostic method for evaluating the spread of cervical cancer. This diagnostics helps to select more accurately the most appropriate treatment approach – an operation, radiation therapy or chemoradiation therapy – for each patient. MRI images visualize the cervical tumor, its spread to adjacent tissues and organs and metastases in the lymphatic nodes more clearly (6, 7). The examination evaluates the form of the tumor and its growth direction more precisely, thus improving the planning of radiation therapy. MRI examination methodology is also useful for assessing the efficiency of radiation or chemoradiation therapy and in the determination of tumor recurrence (6, 8).

Diffusion-weighted (DW) MRI is a relatively new technology. The principle of this examination is based on the diversity of the movement of water molecules in a biological tissue and is characterized by an apparent diffusion coefficient (ADC) (9, 10). Previously, DW–MRI was used exclusively for the analysis of brain diseases (stroke, trauma, epilepsy, depression, dementia or intoxication). The DW–MRI methodology has been employed in the diagnostics of abdomen and pelvis malignant tumors relatively recently (11, 12). Nowadays, there exists a particular interest in DW–MRI adaptation for assessing the response of tumors to chemoradiaton therapy (9, 13).

The aim of our study was to compare the mean value of ADC in a healthy cervix, cancer-affected cervix and cervix after chemoradiation therapy.

MATERIALS AND METHODS

The study enrolled 108 patients who underwent pelvic MRI examination in the Radiology Department of the Lithuanian University of Health Sciences Kaunas Clinics Hospital in the years 2008–2010. The study protocol was approved at the meeting of the Kaunas Regional Biomedical Research Ethics Committee (No. BE-2-52).

The study group consisted of 65 patients in whom cervical cancer had been clinically suspected and confirmed by biopsy before MRI examination. The mean age of the study group was 53.7 ± 5.3 years (range, 30–87). Histologically, the most frequent type was non-keratinizing squamous cell carcinomas – 35 (53.9%), followed by keratinizing squamous cell carcinomas (21, 32.3%), the least frequent type being adenocarcinomas (6, 9.2%) and other types of cervix malignant tumors (3, 4.6%). According to the histological grade, tumor differentiation was good for 8 (12.3%) subjects (G1), moderate for 44 (67.7%) (G2) and poor for 13 subjects (20.0%) (G3). The stage of the disease was defined according to the classification of the International Federation of Gynaecology and Obstetrics (FIGO, 2009). The IB stage was defined in 3 subjects (4.6%), IIA in 1 subject (1.5%), IIB in 41 subjects (63.1%), IIIA in 2 subjects (3.1%), IIIB in 15 subjects (23.1%), IVA in 2 subjects (3.1%) and IVB in 1 subject (1.5%). The patients of the study group underwent MRI twice: in the pretreatment evaluation of cervical cancer and 6 months after chemoradiation therapy. In 13 (20%) patients, residual tumor was found. No cervical tumor was detected in 52 (80%) women. MRI results were compared with the clinical examination data at the time of and 1.5 to 2 years after examination. The patient monitoring median was 704 days (1.95 years).

The control group consisted of 43 patients in whom cervical cancer was not suspected and MRI was performed because of other pelvic diseases. The mean age of the control group was 57.3 ± 5.5 years, ranging from 31 to 88 years. For these patients, MRI was performed only once. They had no cervical pathology. Uterus myomas were diagnosed in 16 patients (37.2%), ovarian cysts in 14 (32.6%), ovarian cystadenomas in 7 (16.3%), pelvic abscesses in 1 patient (2.3%), and no pathology was found in 5 patients (11.6%).

MRI examinations were performed using a 1.5 Tesla MRI scanner (Siemens Magnetom Avanto Syngo MR B 15), employing pelvic phased–array coils. Patients lay on their back, with hands raised above their heads, legs outstretched along the hip and knee joints. The examinations were carried out using the pelvic examination protocol. The first phase involved a native scan in T1W / TIRM, T1W / TSE and T2W / TSE sequences (Fig. 1). The second stage included a DW / EPI sequence using the *b* values of 50, 400 and 800 s/mm^2. The ADC maps were reconstructed from DW images (Fig. 2). The third phase consisted of T1W / TSE and T1W / SE / FS sequences using an intravenous contrast medium (Omniscan, Gadovist, Magnevist). A contrast medium was injected into the peripheral vein; the precise amount was calculated according to the patient's body weight: 1 ml product / 5 kg body weight or 15 ml / 75 kg.

The statistical data analysis was performed using the SPSS 15.0 for Windows and Microsoft Excel 2003 program. The Kolmogorov–Smirnov test was used to evaluate

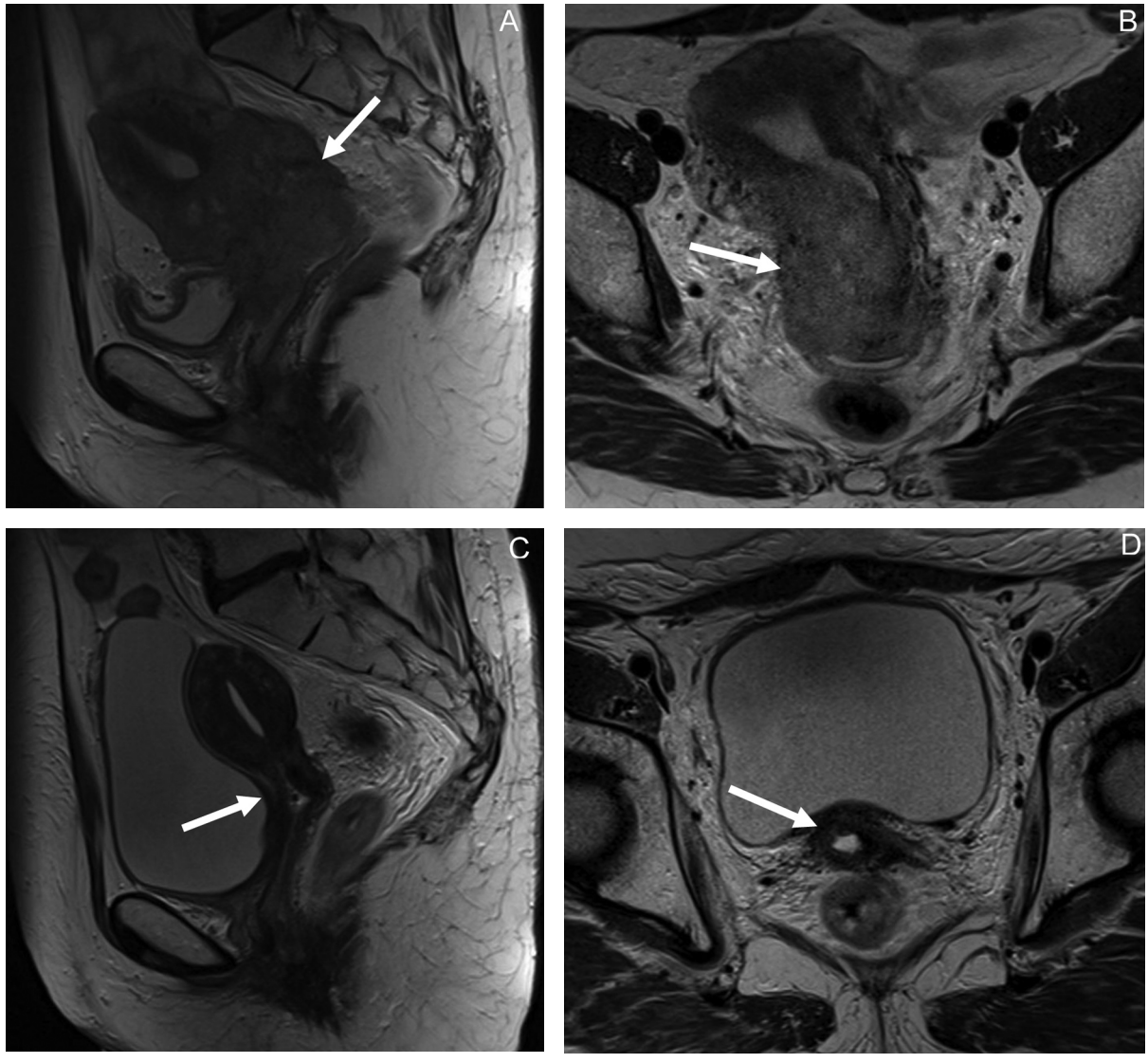

Fig. 1. 53-year-old woman. T2W / TSE sagittal (A) and axial (B) MR images show hyperintense tumor in the cervix (arrows). T2W / TSE sagittal (C) and axial (D) MR images show no tumor in the cervix after chemoradiation therapy (arrows)

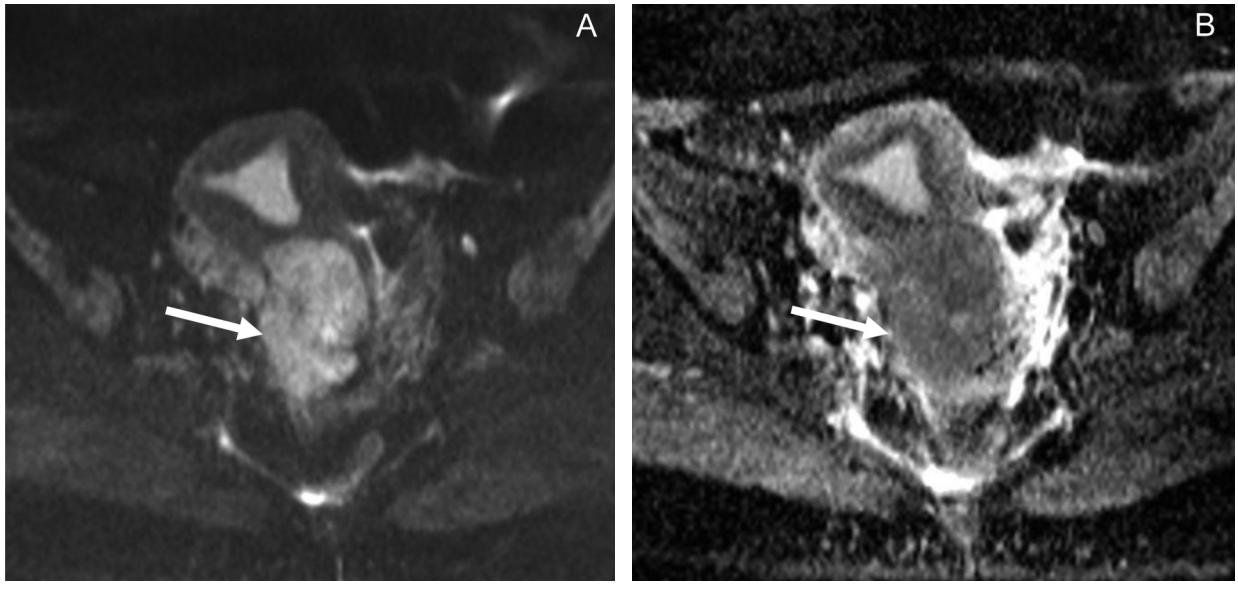

Fig. 2. Cervical cancer. A: DW–MRI (b value 400 s/mm^2) shows hyperintense tumor (arrow). B: Corresponding ADC is low (0.634×10^{-3} mm^2/s) (arrow)

the distribution of sample values in the study, control and other smaller groups. The Student criterion was used for the comparison of the mean ADC values. The receiver operating characteristic (ROC) curve was applied for determining the ADC threshold value between the cancer-affected and unaffected cervical tissues. The chosen level of statistical significance was $p < 0.05$.

RESULTS

The ADC of cervical tissues was calculated using the DW–MRI method for patients of both the study and the control groups. The mean ADC of the study group was $0.658 \pm 0.118 \times 10^{-3}$ mm^2/s, ranging from $0.325 \pm 0.150 \times 10^{-3}$ mm^2/s to $0.991 \pm 0.040 \times 10^{-3}$ mm^2/s, and the mean ADC of the control group was $1.171 \pm \pm 0.143 \times 10^{-3}$ mm^2/s, ranging from $0.940 \pm 0.090 \times 10^{-3}$ mm^2/s to $1.543 \pm 0.180 \times 10^{-3}$ mm^2/s. The Kolmogorov–Smirnov test showed a normal (Gaussian) distribution of sample values in both groups ($p = 0.200$ and $p = 0.066$). The mean ADC in the cervical cancer group was lower than in the control group. A statistically significant (substantial) difference was detected between the means of the compared samples ($t = 20.315$, $p = 0.03$) (Fig. 3).

The ADC threshold value of 0.945×10^{-3} mm^2/s was defined using the ROC curve differentiating the cancer-affected and the normal cervical tissues at the sensitivity of 98.0% and the specificity of 98.3% (Fig. 4).

The mean ADC of the patients who responded to chemoradiation therapy increased to $1.111 \pm 0.138 \times 10^{-3}$ mm^2/s,

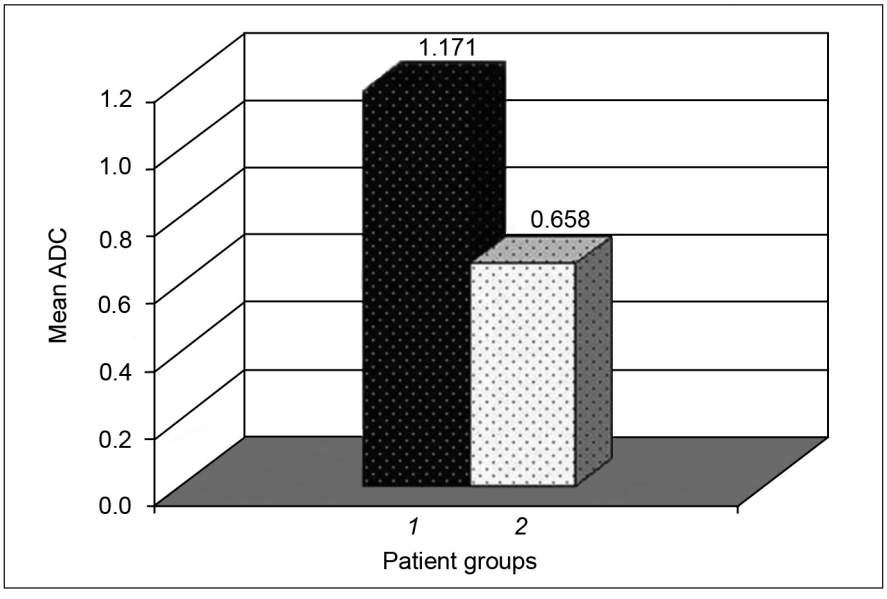

Fig. 3. Comparison of ADC values in the study and control groups ($t = 20.315$, $p = 0.03$). *1* – control, *2* – study

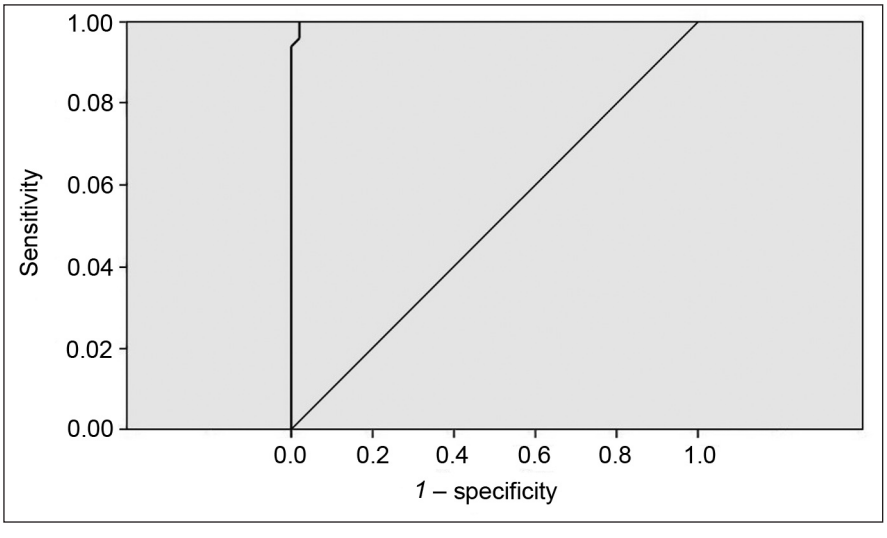

Fig. 4. The ROC curve of ADC values in the differentiation of cancer-affected and normal cervical tissue (area under the curve 0.999, $p < 0.01$)

and in patients who did not respond it remained lower – $0.733 \pm 0.073 \times 10^{-3}$ mm²/s. A comparison of the mean values of the groups of responders and non-responders revealed that the difference of the means between the groups was substantial (t = 9.158, p = 0.04). The difference among the responders before ($0.655 \pm 0.127 \times 10^{-3}$ mm²/s) and after ($1.111 \pm 0.138 \times 10^{-3}$ mm²/s) therapy was statistically significant (t = 19.214, p = 0.03). The mean ADC of non-responders after therapy increased slightly: from $0.658 \pm 0.079 \times 10^{-3}$ mm²/s up to $0.733 \pm 0.073 \times 10^{-3}$ mm²/s (t = 3.58, p = 0.02). The mean ADC of the control group was slightly higher than of the group of responders (t = 2.056, p = 0.03) and significantly higher than of the group of non-responders (t = 10.614, p = 0.04) (Fig. 5). A comparison of the mean ADC of responders and non-responders before the treatment showed no significant difference ($0.655 \pm 0.127 \times 10^{-3}$ and $0.658 \pm 0.079 \times 10^{-3}$ mm²/s, t = 0.59, p = 0.04).

The ADC threshold value of 0.830×10^{-3} mm²/s was defined using the ROC curve differentiating between the residual tumor tissue and the healthy cervical tissue after chemoradiation therapy at the sensitivity of 94.5% and the specificity of 100.0% (Fig. 6).

DISCUSSION

The DW-MRI method has been introduced to cancer diagnostics in the recent years, and this has widened the diagnostic possibilities of MRI. There are few researches in the world to involve the DW-MRI method for the assessment

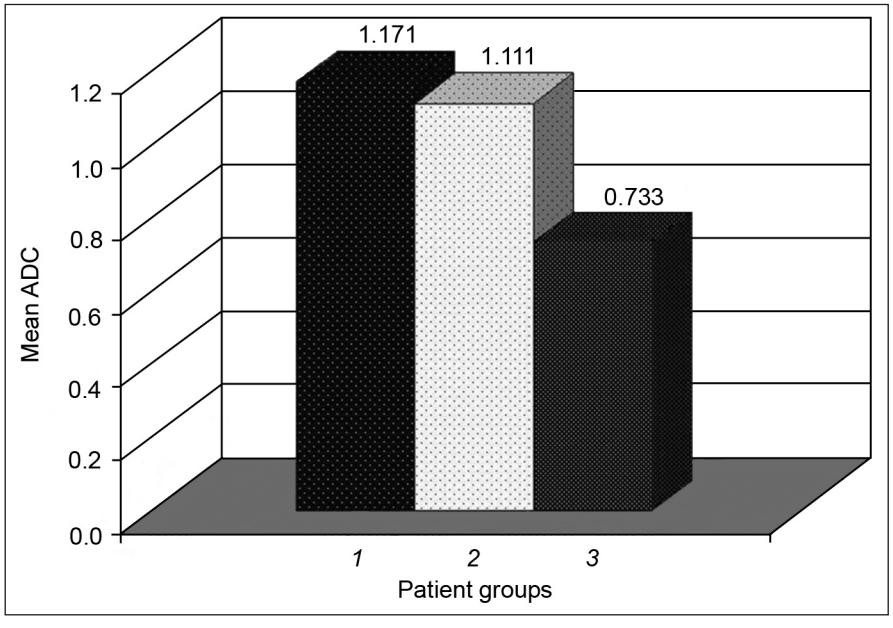

Fig. 5. Comparison of ADC values in the groups of responders, non-responders and control (t = 2.056, p = 0.03 and t = 10.614, p = 0.04). *1* – control, *2* – responders, *3* – non-responders

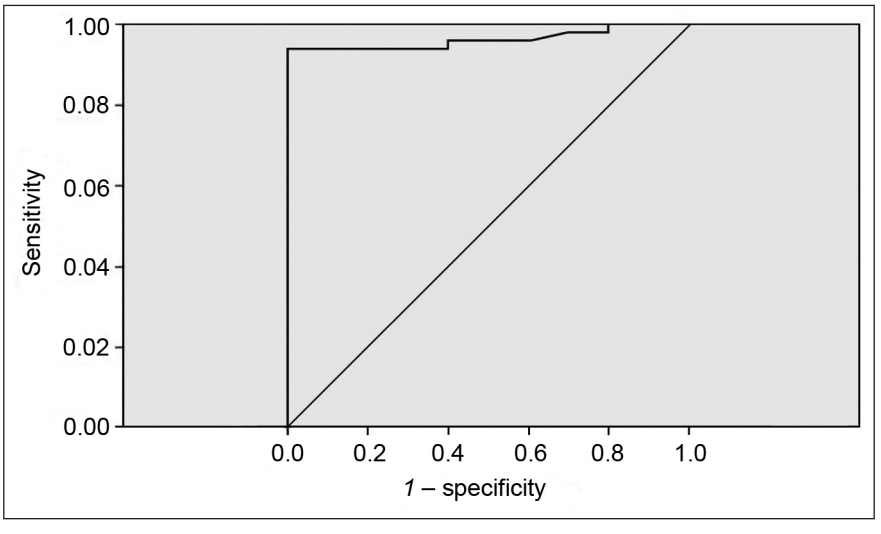

Fig. 6. The ROC curve of ADC values in assessing the efficiency of chemoradiation therapy (area under the curve 0.966, p < 0.01)

Table. **Review of studies in the field of cervical cancer DW–MRI diagnostics**

Author	Journal	Year of publication	Number of subjects		ADC ($\times 10^{-3}$ mm^2/s)	
			Study group	Control group	Cervical cancer	Normal cervix
S. Naganawa (14)	Eur Radiol.	2005	12	10	1.09 ± 0.20	1.79 ± 0.24
V. Zhang (15)	Ai Zheng	2007	20	16	0.97 ± 0.13	1.71 ± 0.14
H. D. Xue (16)	Clin Med Sci J.	2008	24	24	0.98 ± 0.17	1.73 ± 0.31
E. V. Charles-Edwards (17)	Radiology	2008	18	15	0.757 ± 0.110	1.331 ± 0.159
P. Z. McVeigh (18)	Eur Radiol.	2008	47	26	1.09 ± 0.20	2.09 ± 0.46
V. N. Harry (19)	Gynecol Oncol.	2008	20	–	ADC correlation with MRI response	
					ADC correlation with clinical response	
Y. Liu (20)	Clin Radiol.	2009	17	–	Pretreatment ADC of responders was lower than of non-responders	
Y. Liu (21)	J Comput Assist Tomogr.	2009	42	15	0.88 ± 0.15	1.50 ± 0.16
J. Chen (22)	Eur J Radiol.	2010	33	20	1.110 ± 0.175	1.593 ± 0.151
Y. B. Chen (23)	Abdom Imaging.	2010	26	30	0.98 ± 0.19	1.77 ± 0.23
G. S. Payne (24)	Gynecol Oncol.	2010	62	–	1.117 ± 0.183	1.724 ± 0.195

of cervical cancer (Table). Most of these studies involved a small number of patients (14–17, 19, 20, 22, 23). The first paper on this topic was published by Sh. Naganawa and co-authors in 2005 (14). Our study is the first to assess cervical cancer by employing the DW-MRI method in Lithuania; thus, its comparison with the data of Lithuanian authors is imposible.

To sum up, the ADC numeric value of cervical cancer is significantly lower than of the unaffected cervical tissue (14–18, 21–23). The differences between the ADC numerical values obtained in various clinical studies may be related to the MRI equipment, differences of the study protocols (b values of 50, 400, 800 s/mm^2 and b values of 0, 300, 600 s/mm^2) and the insufficient number of subjects in some groups. According to data of our investigation and of the cited studies, the ADC numerical value increases after an effective chemoradiation therapy; it becomes closer to the coefficient value of intact cervical tissue, but still remains lower (14, 15, 18–20, 22). Two of the cited studies compared the cervical ADC mean values of the responders and non-responders before and after chemoradiation therapy (18, 20). One of the studies found that the mean ADC value of responders before the treatment had been slightly lower than of non-responders (18). In the second clinical study, the cervical ADC mean value in responders before treatment was significantly lower than in partial responders (20). Literary sources explain this tendency by the fact that tumour tissues with high ADC numerical values are more necrotic. Such tissues are often more hypocsic, acidotic, poorly fed, thus their sensitivity to chemoradiation therapy is decreased (10–12). Other publications did not compare the above-mentioned mean ADC values (14, 15, 19, 22). Our study revealed no significant difference in the mean ADC values of responders and non-responders before the treatment. The reason could be the ADC measurement features: during the measurement, it was attempted to define the widest part of the cervical tumor, excluding ulceration and necrosis, so that the analyzed area would be prevented from fluid and air inclusions from the cervical canal (14, 18).

Three of the above-discussed clinical studies determined the ADC threshold value for differentiating cancer-damaged tissue with unaffected cervical tissue: it was 1.100×10^{-3} mm^2/s in the study of Charles-Edwards and co-authors (17), 1.359×10^{-3} mm^2/s in the work of Chen and colleagues (22), and 1.28×10^{-3} mm^2/s in the research of Chen et al. (23). In our study, the ADC threshold value for differentiating between cancer-affected and non-affected cervical tissues was 0.945×10^{-3} mm^2/s. The differences of the ADC threshold values in our research and the cited clinical trials may be dependent on the MRI equipment, test protocols and the insufficient number of patients in other groups (17, 22, 23). In addition, our study revealed 0.830×10^{-3} mm^2/s ADC threshold value differentiating residual tumor tissue and healthy tissue of the uterine cervix after chemoradiation therapy. The ADC value after chemoradiation therapy has been determined in none of the cited clinical studies.

CONCLUSIONS

1. The ADC value in case of cervical cancer was significantly lower than in the non-affected cervical tissue.

2. The ADC value increases after an effective chemoradiation therapy and becomes closer to the coefficient value of non-affected cervical tissue but still remains lower.

3. The ADC threshold of 0.945×10^{-3} mm^2/s was detected when differentiating between cancer-affected and normal cervical tissues, while the ADC threshold was 0.830×10^{-3} mm^2/s in the differentiation of residual tumor and healthy cervical tissues after chemoradiation therapy at a high sensitivity and specificity.

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GIMDOS KAKLELIO VĖŽIO DIFUZINĖS MAGNETINIO REZONANSO TOMOGRAFIJOS TYRIMAI

Santrauka

Įvadas. Difuzinė magnetinio rezonanso tomografija (DW–MRT) santykinai neseniai pradėta taikyti pilvo ir dubens piktybinių navikų diagnostikai. Šiuo metu ypač domimasi DW–MRT pritaikymu vertinant piktybinių navikų atsaką į chemospindulinį gydymą. Mūsų darbo tikslas buvo palyginti tariamojo difuzijos koeficiento (ADC) skaitinės reikšmės vidurkį sveikame gimdos kaklelyje, vėžio pažeistame ir po chemospindulinio gydymo, taip pat nustatyti gimdos kaklelio vėžiui būdingą ADC skaitinės reikšmės ribą.

Tyrimo medžiaga ir metodai. Tyrime dalyvavo 108 pacientės, kurioms 2008–2010 m. Lietuvos sveikatos mokslų universiteto (LSMU) ligoninės Kauno klinikose buvo atlikti dubens organų MRT tyrimai. Tiriamąją grupę sudarė 65 pacientės, kurioms gimdos kaklelio vėžys buvo kliniškai įtartas ir histologiškai patvirtintas prieš MRT tyrimą. Šios moterys MRT metodu buvo tirtos du kartus – prieš chemospindulinį gydymą ir praėjus 6 mėnesiams. Kontrolinę grupę sudarė 43 pacientės, kurioms gimdos kaklelio vėžys neįtartas, o MRT tyrimas buvo atliktas dėl kitų dubens organų ligų.

Rezultatai. Tiriamosios grupės ADC vidurkis ($0{,}658 \pm 0{,}118 \times \times 10^{-3}$ mm²/s) buvo mažesnis negu kontrolinės ($1{,}171 \pm 0{,}143 \times \times 10^{-3}$ mm²/s) grupės ($t = 20{,}315$, $p = 0{,}03$). Diferencijuojant vėžio pažeistą ir nepakitusį gimdos kaklelio audinį, nustatyta $0{,}945 \times 10^{-3}$ mm²/s ADC slenkstinė reikšmė. Pasveikusiųjų po chemospindulinio gydymo ADC vidurkis padidėjo ($1{,}111 \pm 0{,}138 \times 10^{-3}$ mm²/s), nepasveikusiųjų išliko mažesnis ($0{,}733 \pm 0{,}073 \times 10^{-3}$ mm²/s) ($t = 9{,}518$, $p = 0{,}04$). Nustatyta $0{,}830 \times 10^{-3}$ mm²/s ADC slenkstinė reikšmė diferencijuojant liekamąjį naviko audinį ir sveiką gimdos kaklelio audinį po chemospindulinio gydymo.

Išvados. ADC skaitinė reikšmė gimdos kaklelio vėžio atveju ženkliai mažesnė nei nepažeisto gimdos kaklelio audinio. Po efektyvaus chemospindulinio gydymo ji padidėja, tampa artima vėžio nepažeisto gimdos kaklelio audinio koeficiento reikšmei, bet vis tiek išlieka mažesnė. Diferencijuojant vėžio pažeistą ir nepakitusį gimdos kaklelio audinį nustatyta $0{,}945 \times 10^{-3}$ mm²/s, o diferencijuojant liekamąjį naviko audinį ir sveiką gimdos kaklelio audinį, apskaičiuota $0{,}830 \times 10^{-3}$ mm²/s ADC slenkstinė reikšmė, esant labai dideliam jautrumui ir specifiškumui.

Raktažodžiai: difuzinė magnetinio rezonanso tomografija, tariamasis difuzijos koeficientas, gimdos kaklelio vėžys, chemospindulinis gydymas