ORIGINAL ARTICLE

UDC: 616-073.75::616-006-07
DOI: https://doi.org/10.2298/VSP190726102B

Diffusion-weighted magnetic resonance imaging in evaluating malignant lymph node invasion in patients with female genital neoplasms

Magnetnorezonantna sekvenca difuzionog kretanja u proceni metastatske invazije limfnih čvorova kod malignih tumora ženskih polnih organa

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Abstract

Background/Aim. Functional imaging, including diffusion-weighted magnetic resonance imaging (DWI MRI) and apparent diffusion coefficient (ADC) map, provides promising results in discrimination benign from malignant pelvic and inguinal lymph nodes in patients with gynecological malignancies. The aim of the study was to assess diagnostic performances of DWI in differentiation between benign and malignant pelvic and inguinal lymph nodes in patients with gynecological malignancies. **Methods.** The prospective clinical study was conducted at the Clinical Center of Vojvodina, Serbia, from 2013 to 2016, comprising 80 patients with malignant gynecological tumors. Preoperatively, all patients underwent MRI examination, followed by standard surgical treatment with complete pelvic and/or inguinal lymphadenectomy. A combination of ADC value criteria and size-based criteria yields MRI the following diagnostic performances in discrimination between benign and malignant lymph nodes: sensitivity 95%, specificity 92%, overall accuracy 92.5%, positive predictive value 46%, and negative predictive value 99.6%. Histopathological examination of surgically removed material and lymph nodes separated in pelvic and inguinal anatomic groups was performed after the surgery. **Results.** A total of 2,320 lymph nodes were mapped and histopathologically examined in 80 patients included in the study. Metastases in lymph nodes were histopathologically confirmed in 28 (35%) patients. Measured ADC values were significantly lower in metastatic (mean ± standard deviation (SD), ADC: $0.8725 \times 10^{-3} \pm 0.0125 \times 10^{-3}$ mm^2/s) than benign lymph nodes (mean ± SD, ADC: $1.116 \times 10^{-3} \pm 0.1848 \times 10^{-3}$ mm^2/s; $p = 0.001$). If ADC value of 0.860×10^{-3} mm^2/s was determined as a cut-off value for discrimination between benign and malignant lymph nodes, DWI sensitivity was 89%, specificity 85%, and overall accuracy was 86%, positive predictive values 30%, and negative predictive value 99%. **Conclusion.** DWI MRI sequence is a fast, simple, non-invasive method that aids significantly to MRI diagnostic performances in discrimination between benign and malignant pelvic and inguinal lymph nodes.

Key words:
diagnosis, differential; diffusion magnetic resonance imaging; genital neoplasms, female; lymph nodes; lymphatic metastasis; magnetic resonance imaging.

Apstrakt

Uvod/Cilj. Funkcionalna radiološka dijagnostika, uključujući i magnentnorezonantnu sekvencu difuzionog kretanja (*diffusion-weighted magnetic resonance imaging* – DWIMRI) i iz nje izvedenu mapu očiglednog koeficijenta difuzije – *apparent diffusion coefficient* (ADC), daju obećavajuće rezultate u mogućnosti razlikovanja benignih od maligno izmenjenih limfnih čvorova male karlice i ingvinuma kod bolesnica sa malignim tumorima ženskih polnih organa. Cilj rada bio je da se procene dijagnostičke osobine DWI u razlikovanju benigno- od maligno-izmenjenih pelvičnih i ingvinalnih limfnih čvorova kod bolesnica sa ginekološkim malignim oboljenjima. **Metode.** Prospektivnom kliničkom studijom, sprovedenom u Kliničkom centru Vojvodine, u periodu od 2013. do 2016. godine, obuhvaćeno je 80 bolesnica sa malignim tumorima ženskih polnih organa. Svim bolesnicama je preoperativno učinjen magnetnorezonantni pregled male karlice, uz naknadno sprovedeno standardno hirurško lečenje po protokolu hirurškog lečenja za dato maligno ginekološko oboljenje sa karličnom i/ili ingvinalnom limfadenektomijom. Na osnovu definisanog modela koji kombinuje kriterijum ADC vrednosti sa kriterijumom veličine, MRI ima sledeće dijagnostičke performanse za

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razlikovanje maligno- od benigno- izmenjenih limfnih čvorova: senzitivnost od 95%, specifičnost od 92%, sveukupnu tačnost od 92,5%, pozitivnu prediktivnu vrednost od 46% i negativnu prediktivnu vrednost od 99.6%. Postoperativno je izvršena patohistološka analiza hirurški uklonjenih materijala i limfnih čvorova razdvojenih po anatomskim grupama u karlici i ingvinalnoj regiji. **Rezultati.** Ukupno 2 320 limfnih čvorova mapirano je i patohistološki pregledano kod 80 bolesnica. Metastaze u limfnim čvorovima patohistološki su verifikovane kod 28 (35%) bolesnica. Izmerena ADC vrednost bila je značajno niža kod metastatski izmenjenih limfnih čvorova [srednja vrednost (SV) ± standardna devijacija (SD), ADC: 0,8725 × 10^{-3} mm²/s ± 0,0125 × 10^{-3} mm²/s] u poredjenju sa limfnim čvorovima koji nisu bili metastatski izmenjeni (SV ± SD, ADC: 1,116 × 10^{-3} mm²/s ± 0,1848 × 10^{-3} mm²/s; p = 0,001). Za ADC vrednost od 0,860 × 10^{-3} mm²/s, kao kritičnu vrednost za razlikovanje metastatskih od limfnih čvorova koji nisu bili metastatski izmenjeni, senzitivnost DWI MR iznosila je 89%, specifičnost 85%, ukupna tačnost 86%, pozitivna prediktivna vrednost 30%, a negativna prediktivna vrednost 99%. **Zaključak.** Magnentnorezonantna sekvenca difuzionog kretanja je brza, jednostavna, neinvazivna metoda koja značajno doprinosi dijagnostičkim mogućnostima magnetne rezonance u razlikovanju benigno- od maligno-izmenjenih limfnih čvorova male karlice i ingvinuma.

Ključne reči:
dijagnoza, diferencijalna; magnenta rezonanca, difuziona; polni organi, ženski; limfne žlezde; neoplazme, limfna metastaza; magnetna rezonanca, snimanje.

Introduction

Malignant gynecological tumors are among the leading causes of morbidity and mortality among women, both in Serbia and worldwide [1, 2]. The presence of lymph node metastases has a significant impact on tumor staging, as well as treatment planning and prognosis. When evaluating lymphatic metastases by radiological studies, it is very important to be familiar with the potential localization of metastases, the probability of metastases in particular groups of lymph nodes depending on the primary tumor, and with the impact that the lymphatic metastases have on the stage and treatment of the disease.

The most common typical lymphatic pathways of malignant gynecological tumors spread are superficial inguinal, pelvic, and paraaortic pathways.

Imaging is an integral part of the strategy in planning optimal treatment of gynecological cancer [3]. Computed tomography (CT) and magnetic resonance imaging (MRI) are the golden standard of imaging nodal status in these patients, mostly relying on short lymph node axis diameter as discriminating criteria. However, both modalities have low sensitivity in detecting pelvic lymph node metastases [4]. The combination of functional and morphological imaging yields better precision in the detection of lymph node involvement [5].

Due to technical development, diffusion-weighted imaging (DWI) and derived apparent diffusion coefficient (ADC) have been refined and shortened and thus incorporated in routine MRI protocols. Restriction of water molecules' diffusion is directly proportional to tissue cellularity [6]. Such restriction of diffusion is primarily seen in malignant tumors, hypercellular metastases, and fibrosis, where a higher number of cells with an intact cellular wall is present compared to normal tissue [7].

The aim of the study was to determine the diagnostic performance of DWI in detecting pelvic and inguinal lymph nodes in patients with malignant gynecological tumors.

Methods

The prospective clinical study was conducted from 2013 to 2016 at the Center for Radiology, Clinic for Gynecology and Obstetrics and Department of Pathology, Clinical Center of Vojvodina in Novi Sad, Serbia and comprised 80 patients with malignant vulvar, vaginal, cervical, uterine, and ovarian tumors.

Staging of the disease was based on the histopathological assessment of complete surgical specimen, including examination of removed lymph nodes, based on the International Federation of Gynecology and Obstetrics (FIGO) classification.

Preoperatively, all patients underwent pelvic MRI at the Center for Radiology, Clinical Center of Vojvodina within 30 days prior to the surgery. All examinations were performed on a 1.5 T General Electric Signa HDx machine using a phased array coil and routine protocols for pelvic MRI (Table 1).

Table 1

Routine protocol for pelvic magnetic resonance imaging (MRI)

Sequence	T1 weighted	T2 weighted	T2 weighted	Diffusion weighted
Type	fast spin echo	fast spin echo	fast spin echo	spin echo planar imaging
Plane	axial	axial	sagittal	axial
TR [ms]	460	2,640	3,560	10,760
TE [ms]	12.9	99.3	103.9	78.3
Slice thickness [mm]	5	5	5	5
FOV [cm]	30 × 30	30 × 30	33 × 33	30 × 30
Matrix	320 × 224	320 × 224	384 × 256	82 × 128
NEX	4	4	2	8
b value [s/mm²]	–	–	–	800; 1,200

TR – repetition time; TE – time to echo; FOV – field-of-view; NEX – number of excitations.

Based on a defined model which combines criteria of ADC values with size criteria, MRI has the following diagnostic performances in discriminating malignant and benign lymph nodes: sensitivity 95%, specificity 92%, overall accuracy 92.5%, positive predictive value (PPV) 46%, and negative predictive value (NPV) 99.6%. Depending on the type of the tumor, additional sequences were added, including thin-sliced T2W sequences perpendicular to the long axis of the cervix or uterine body, axial T1W tomograms with fat saturation, coronal T2W as well as biplanar and dynamic postcontrast tomograms. A corresponding ADC map was calculated for each patient. Qualitative analysis of signal intensity on DWI and quantitative analysis of ADC values were performed using the lowest measured ADC value. Using the receiver operating characteristic (ROC) curve analysis, the following threshold values were used for determining metastatic invasion of lymph nodes: short axis (S) > 7.75 mm; long axis (L) > 10 mm; L/S ratio ≤ 1.23 and minimal ADC ≤ 0.860 × 10^{-3} mm^2/s.

All patients underwent standard surgical treatment depending on the type and stage of the tumor, including pelvic and/or inguinal lymphadenectomy.

Postoperatively, histopathological analysis of the surgical specimen was performed, with special emphasis on the lymph node group and position.

Statistical analysis was performed using Statsoft Statistica 10 software package (StatSoft, Inc. Tulsa, Oklahoma, USA).

Results

The study comprised 80 women, aged 32–79 years [mean age 57.35, standard deviation (SD) ± 9.99], with histologically verified gynecological tumor: 3 (3.75%) patients with vulvar, 1 (1.25%) patient with vaginal, 32 (40%) cervical, 30 (37.5%) with the uterine body, and 14 (17.5%) with malignant ovarian tumor.

A total of 2,320 lymph nodes were mapped and histologically examined in 80 patients. Lymph nodes metastases were verified in 28 (35%) patients.

In 28 (35%) patients with positive lymph nodes, 152 (27.28%) out of 557 lymph nodes were metastatic (Figure 1).

Pelvic lymph nodes metastases were observed in 2 (7.14%) patients with vulvar cancer, 11 (39.28%) patients with cervical cancer, 9 (32.14%) patients with uterine body tumors, and 6 (21.42%) patients with malignant ovarian tumors (Figure 2).

The distribution of metastases in relation to pelvic lymph nodes is shown in Table 2.

The period between preoperative pelvic MRI and surgery was 1–22 days (mean ± SD: 10.48 ± 2.7).

There was no statistically significant difference between the S of of lymph nodes with metastatic invasion (mean ± SD: 8.3 ± 5.4 mm, range 4.5–30 mm) and lymph nodes with no metastatic invasion (mean ± SD: 6.3 ± 1.5 mm, range: 4.5–9.6 mm; p = 0.191).

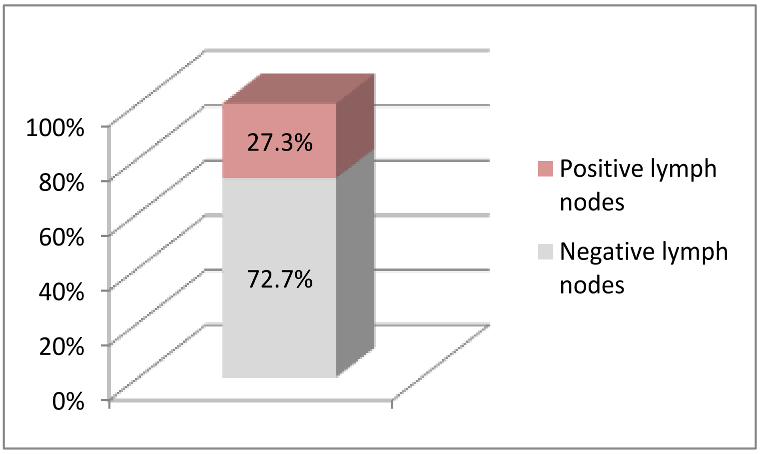

Fig. 1 – Ratio of positive and negative lymph nodes in 28 patients with verified metastases in pelvic lymph nodes.

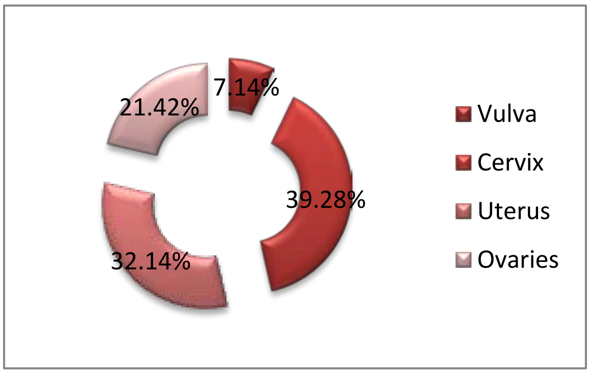

Fig. 2 – Distribution of positive lymph nodes in relation to primary tumor localization.

Table 2

Distribution of metastases in relation to pelvic lymph nodes

Tumor localization	Group of pelvic lymph nodes						
	parametrial	obturator	external iliac	internal iliac	common iliac	inguinal	total
Vulva	0	0	0	0	0	8 (5.26)	8 (5.26)
Cervix	8 (5.26)	23 (15.13)	16 (10.52)	13 (8.55)	5 (3.28)	0	65 (42.77)
Uterine body	0	14 (9.21)	16 (10.53)	14 (9.21)	2 (1.31)	0	46 (30.26)
Ovary	0	11 (7.23)	8 (5.26)	9 (5.92)	5 (3.28)	0	33 (21.71)
Total	8 (5.26)	48 (31.58)	40 (26.32)	36 (23.68)	12 (7.90)	8 (5.26)	152 (100)

All values are expressed as number (percentage).

There was no statistically significant difference between the L of lymph nodes with metastatic invasion (mean ± SD: 12.6 ± 6.1 mm, range: 8–35 mm) and lymph nodes with no metastatic invasion (mean ± SD: 11.3 ± 2.6 mm, range: 7.1–17.9 mm; $p = 0.419$).

Measured ADC value was significantly lower in metastatic lymph nodes (mean ± SD: $0.8725 \times 10^{-3} \pm 0.0125 \times 10^{3}$ mm^2/s) compared to lymph nodes with no metastatic invasion (mean ± SD: $1.116 \times 10^{-3} \pm 0.1848 \times 10^{-3}$ mm^2/s; $p = 0.001$) (Figures 3–5).

The area under the ROC curve for differentiation between metastatic and benign lymph nodes was presented with a value of 0.901 [standard error 0.022; 95 % confidence interval (CI), 0.857–0.937] (Figure 6). ADC value of 0.860×10^{-3} mm^2/s was derived from the ROC curve as a threshold value for distinction between metastatic and benign lymph nodes (Figure 7). In other words, the lymph node with ADC value $\leq 0.860 \times 10^{-3}$ mm^2/s was regarded as metastatic.

With the calculated threshold value from the ROC curve, lesion-based sensitivity was 89%, specificity 85%, and overall accuracy was 86%.

MRI performances were significantly better for minimal ADC values compared to all size-based criteria ($p = 0.001$ for minimal ADC value compared to all other criteria). Since the area under the ROC curve was larger for minimal ADC values than for all other criteria, minimal ADC value was used as a representative index for differentiation between metastatic and non-metastatic lymph nodes. The comparison of diagnostic performance of MRI based on ADC values and size criteria is shown in Table 3.

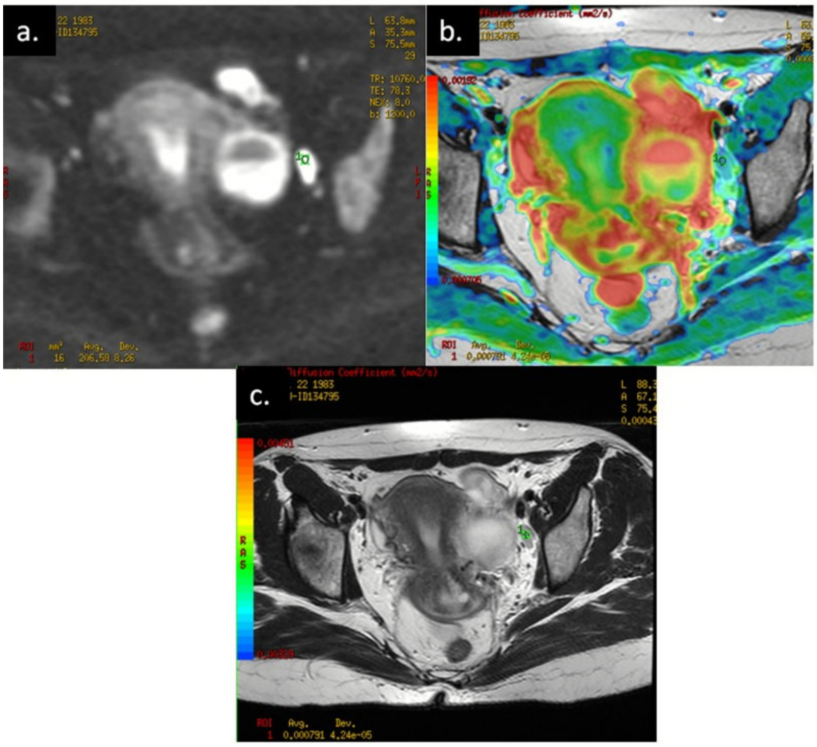

Fig. 3 – A 33-year-old-patient with serous cystadenocarcinoma of the left ovary, the International Federation Gynecology and Obstetrics (FIGO) stage IIIC. Metastatic enlarged external iliac lymph node with restricted diffusion: a) axial high b-value diffusion-weighted imaging (DWI); b) fusion of apparent diffusion coefficient (ADC) map and axial T2W; c) axial T2W.

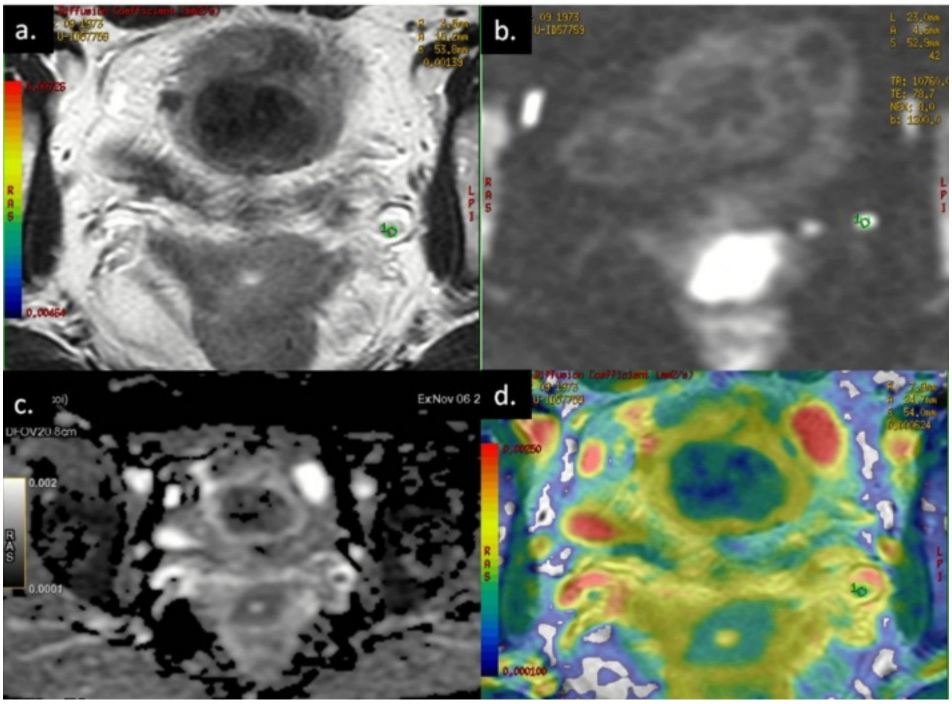

Fig. 4 – A 43-year-old-patient with squamocellular cervical cancer, FIGO IIB stage. Parametrial lymph node sized 5 mm, with restricted diffusion and histological confirmation of metastatic involvement: a) axial T2W; b) axial high b-value DWI; c) ADC map; d) fusion of ADC map and axial T2W.
For abbreviations see Figure 3.

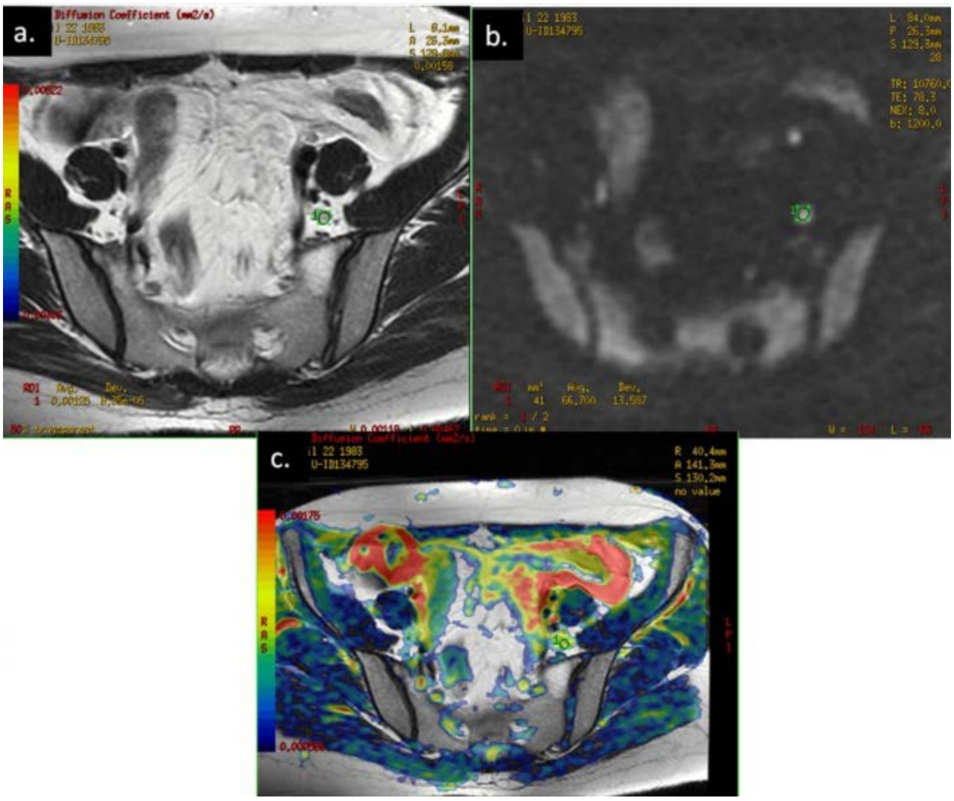

Fig. 5 – A 63-year-old patient with endometrial cancer FIGO IC stage. Normal-sized left common iliac lymph node, with high signal intensity on DWI, but with high ADC values (1.25×10^{-3} mm^2/s) and histopathology confirmed reactive lymph node: a) axial T2W; b) axial high b-value DWI; c) fusion of ADC map and axial T2W.
For abbreviations see Figure 3.

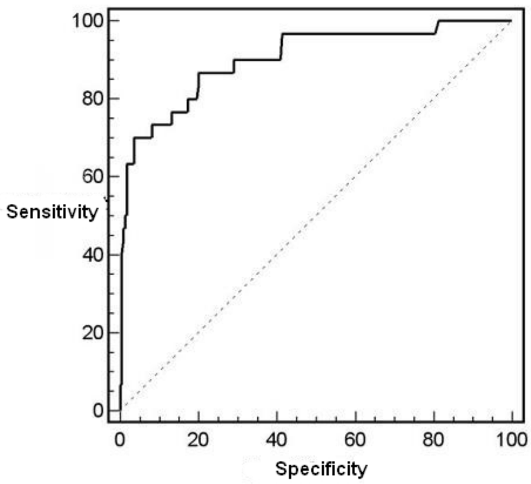

Fig. 6 – Receiver operating characteristic (ROC) curve for apparent diffusion coefficient (ADC) values in discriminating between malignant and benign lymph nodes.

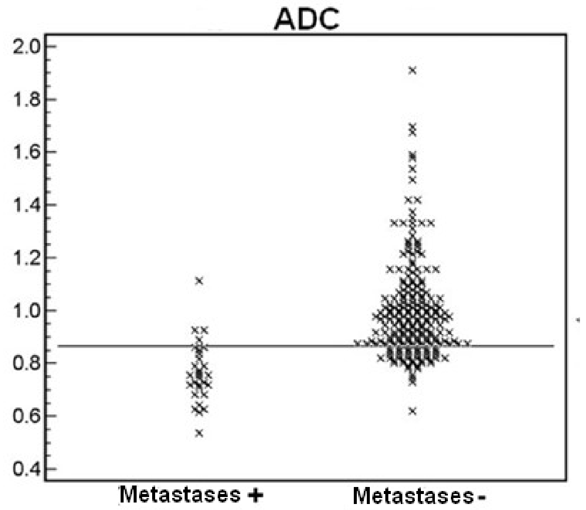

Fig. 7 – Apparent diffusion coefficient (ADC) values of metastatic and benign lymph nodes.

Table 3

Comparison of diagnostic performance of MRI based on ADC values and size criteria

Parameter (%)	Minimal ADC	Short-axis (S) diameter	Long-axis (L) diameter	Long to short axis criteria (L/S ratio)
Sensitivity	89	55	73	52
Specificity	85	74	66	73
PPV	30	13	13	12
NPV	99	96	97	96
Overall accuracy	86	73	67	72

MRI – magnetic resonance imaging; ADC – apparent diffusion coefficient; PPV – positive predictive value; NPV – negative predictive value.

ROC curves of different predictive models which combine the following criteria: ADC values alone, in combination with size criteria and size criteria alone, are shown in Figure 8. A model which combines ADC and size criteria is more accurate in detecting lymph node metastases compared to the other two models.

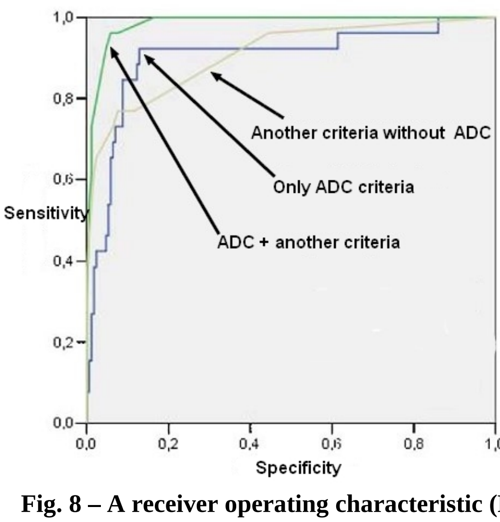

Fig. 8 – A receiver operating characteristic (ROC) curves of different predictive models which include apparent diffusion coefficient (ADC) values and size criteria, alone or in combination.

Discussion

Conventional imaging methods cannot discriminate normal from metastatic lymph nodes with satisfactory precision, especially when normal in size. Therefore, numerous studies have been conducted worldwide searching for diagnostic methods or a combination of methods that could discriminate benign from malignant lymph nodes, being minimally invasive, cheap, easily available, and simple. The method which satisfies all these criteria and yields promising results is DWI.

Up to date, several studies have been done analyzing the role of DWI in discriminating benign from malignant lymph nodes [8–13]. However, the conclusions of these studies differ a lot, leading to the need for more research on the topic.

Traditional lymph node size criterion used in clinical practice defines lymph nodes with short axis larger than 10 mm as probable metastases. However, researchers showed that this criterion is imprecise [14–18], which was confirmed in our study. A high number of false-negative results is explained by a high percentage of positive lymph nodes smaller than 10 mm on histopathological examination and microscopic metastases that are beyond the possibility of recognition by conventional imaging modalities.

Our study confirmed that ADC values of metastatic lymph nodes (mean ± SD: 0.8725 × 10^{-3} mm^2/s ± 0.0125 ×

10^{-3} mm^2/s) were statistically significantly lower than benign (mean ± SD: 1.116 × 10^{-3} mm^2/s ± 0.1848 × 10^{-3} mm^2/s; p = 0.001), which is in concordance with the results of other similar studies [10, 11, 19].

In our study, diagnostic performances of MRI were significantly better for minimal ADC value compared to all size-based criteria (p = 0.001 for minimal ADC value compared to all other criteria), which is similar to the results of other authors [12].

We analyzed the correlation of ADC values and different size criteria on conventional T2W tomograms with histopathological reports as a reference standard. It was shown that minimal ADC values were significantly lower in metastatic lymph nodes compared to benign ones. The sensitivity, specificity, and overall accuracy of DWI, *ie*, minimal ADC values, in the detection of positive lymph nodes, were significantly higher compared to size criteria (S and L, S to L ratio). These results suggest that DWI can enhance visualization and detection of metastatic lymph nodes with a short diameter above 5 mm in patients with malignant gynecological tumors. Good diagnostic performance of DWI is based on its ability to obtain functional information regarding active microstructural changes within a lymph node, which occur before alterations of size. Thus, diagnosis based on ADC criteria overcomes the main limitation of size-based criteria in detecting metastases in normal-sized lymph nodes.

The S on MRI is routinely used for detecting metastases in lymph nodes. Although the first studies indicated a promising detection [18, 20], two recent prospective studies that compared S of 9 mm or 10 mm in correlation with histopathological findings showed low sensitivity of 30% and 36%, despite high specificity of 93% and 97% [21, 22]. Besides low accuracy, another problem with S criteria is the lack of consensus on optimal "cut-off" value for discriminating metastatic from benign lymph nodes. Although most authors used a S diameter of 10 mm as a "cut-off" value, some advocated the size of 9 mm or 8 mm [19, 22, 23]. As the S diameter of many metastatic lymph nodes can range from 8 mm to 10 mm, even the smallest (1 mm) changes in size criteria can lead to significant changes in sensitivity and specificity. Some authors examined the L diameter of the lymph node or shape by calculating the L/S ratio based on which they assessed the lymph node status [4, 24, 25]. Our results, which show unsatisfactory diagnostic accuracy for these two criteria, indicate that these strategies can be used with limitations.

Studies with strict "lesion-by-lesion" comparison of imaging and histopathological findings showed poor sensitivity of CT (24%), MRI (29%), and even position emission tomography (PET)-CT (58%) [26]. Such limited sensitivity is mainly based on inaccurate detection of small metastatic lymph nodes based on size criteria, which is imprecise [12, 27, 28]. Moreover, even the standard uptake value of PET-CT is unsatisfactory when metastatic lymph nodes are of small dimensions [22, 29, 30]. Regarding these limitations, ADC values are favorable compared to CT, conventional MRI, and PET-CT because ADC measurements are relatively independent of the size of the lesions as long as the surface of the lymph node allows precise region of interest (ROI) placement.

Since the area under the ROC curve was higher for minimal ADC value compared to all size criteria, minimal ADC value was used as a representative index for differentiation metastatic from benign lymph nodes. We compared ROC curves of different predictive models that include the following criteria: ADC value alone, in combination with size criteria, and size criteria alone. The model combining ADC value and size criteria is more efficient in detecting malignant lymph nodes compared to the other two models. The combination of ADC value and size criteria improves the sensitivity of MRI from 89% to 95%, specificity from 85% to 92%, overall accuracy from 86% to 92.5%, PPV from 30% to 46%, and NPV from 99% to 99.6%. The model comprising only ADC values criteria has equally good diagnostic performances as the model that includes other MRI criteria.

Conclusion

Size criterion, widely used in clinical radiology for discrimination between malignant and benign lymph nodes, is insufficiently precise. The study confirmed a high positive correlation between preoperative assessment of metastatic invasion of pelvic and inguinal lymph nodes in patients with malignant genital tumors by DWI and postoperative histopathological examination. Using a cut-off ADC value of 0.860 × 10^{-3} mm^2/s, the sensitivity of MRI DWI in detecting metastatic pelvic lymph nodes was 89%, and specificity 85%. The combination of ADC values and morphological criteria is the most precise predictor of metastatic infiltration of pelvic lymph nodes in patients with malignant genital tumors. DWI sequence is a fast, simple, non-invasive method that has a significant contribution to the diagnostic capability of MRI in the distinction between benign and malignant pelvic lymph nodes.

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Received on July 26, 2019
Revised on October 12, 2020
Accepted on October 13, 2020
Online First October, 2020