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Detection of Lymph Node Metastasis in endometrial Cancer by Conventional techniques Magnetic Resonance Imaging at 3T.

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Abstract:
Purpose: *To evaluate conventional techniques Magnetic Resonance Imaging for detection of pelvic lymph node metastasis in patients with cervical and uterine cancers.*
Materials and Methods: *In this retrospective study, 30 patients with proved endometrial cancer were studied in MRI ward of the imaging center of Imam Khomeini Hospital in Tehran. The subjects, selected by purposeful sampling method, underwent the pelvis imaging before the surgery. T1W and T2W, T1-W sequence with contrast enhancement, and adoption of the results correlation with pathological result*
Results: *45 lymph nodes among 30 patients were assessed. Mean age of patients was 54.9±10.1 years, 16 lymph nodes were malignant in pathology result. Sensitivity, specificity, positive and negative predictive value and accuracy were respectively for the; morphology (94, 83, 76, 96 and 87%) T1W (88, 83, 75, 92, and 85%) T2W (82, 77,*
66, 88 and 79%), Short axis size at cutoff point ≥10 mm was respectively (76, 87, 76, 87 and 38%). As for the contrast enhancement the AUC was Difference of signal intensity after contrast 0.68 and Percentage of Signal intensity difference after contrast 54 (P-Values=0.037and 0.69 respectively).
Conclusion: *The combination of size, morphology, T1W and T2W was useful in detecting pelvic lymph node metastasis in patients with endometrial cancer.*
Key Words: *endometrial cancer; conventional techniques; lymph node metastasis; magnetic resonance imaging; 3T.*

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I. Introduction:

Endometrial cancer is the sixth most common malignant disorder in female all over the world (1). Incidence of endometrial cancer with age is just above the level of obesity fashion. 75% of cases occur in postmenopausal women with an average age of 70 year (2). The incidence differs between continents, and is presently ten times higher in Europe and North-America, than in less developed regions of the world. Endometrial cancer is the second most common gynecologic malignancy (cervical cancer being by far the most common), but the specific mortality rate is higher. 80-90% of endometrial cancers are adenocarcinomas arising from endometrial cells, of which the endometrioid carcinoma is the most common subtype. In international studies, the 5- year survival for all stages taken together, is reportedly around 80% (3). CT and MRI are widely used to assess metastatic LNs of patients with endometrial cancer; However, the sensitivity of these imaging techniques for the detection of LN metastasis in uterine cervical cancer is between only 30% for CT scan, and 73% for MRI, while the specificity is between 44% for CT scan, and 93% for MRI (4, 5). The Fluorine-18 fludeoxyglucose positron emission Tomography/CT is considered to be a useful technique in the detection of LN metastasis for tumor with high sensitivity and specificity, especially as it could provide diagnostic information of the entire body, but so far it has not been widely used for clinical application owing to high cost (6). Therefore MRI means the most accurate and important among other means of medical Imaging modality.

Where MRI uses different techniques like (T2-weighted, T1- weighted, with fat suppression, dynamic contrastenhanced). It is thought that the lymph node prepares for metastatic cell implantation by reorganizing lymphatic and vascular structures and, as a consequence, new blood vessels develop within and around lymph nodes (7). The T1-weighted turbo spin-echo (TSE) and T2-weighted fast or turbo spin-echo sequences are used for anatomic localization; the T1-weighted sequence in particular is necessary for identification of a fatty hilum. Such identification is critical for correct interpretation of the postcontrast images (8). It should be noted The current International Federation of Gynecology and Obstetrics (FIGO) staging system does not include modern imaging modalities (9). Therefore, in this study we prove that the adoption of MRI for the detection of metastases to LNs and distinguish them would be potentially important means may substitute for biopsy and pathology.

II. Materials and methods:

This study is retrospective; the patients with proved endometrial cancer were studied in MRI ward of the imaging center of Imam Khomeini Hospital in Tehran. The subjects, selected by purposeful sampling method, underwent the pelvis imaging before the surgery. We enrolled all of patients with proved diagnosis of endometrial cancer in a 5 year from (March 2014-April 2016) time period. The number of samples is

30 involved patients endometrial cancer. Inclusion criteria for the study; histologically confirmed endometrial cancer in patients. None of the patients had Radiotherapy or chemotherapy for uterine endometrial cancer prior to their MR examination. The pathological examination reports were visualized as the location of the dissection lymph nodes available to each patient. Patients were excluded: Who were suffering from kidney problems. Who had Ferromagnetic surgical clips or staples. Pregnancy (risk vs. benefit ratio to be assessed) or any they had metal pelvic/hip prostheses. The MR imaging protocol consisted of following sequences.

1-T1-weighted turbo spin-echo images: sag, axial, coronal, with and without fat sat, small and large FOV. 2-T2 -weighted turbo spin-echo images: sag, axial, coronal, with and without fat sat, small and large FOV. 3-Contrast-enhanced fat-suppressed T1-weighted turbo spin-echo images: sag, axial, coronal, with fat sat, dynamic technique in phases including (30, 90, 180) sag, and axial (4 Minute).

III. Data analysis method:

Statistical analysis will be done using SPSS software, descriptive statistics [such as frequency, mean and standard deviation will be calculated for all variables. Comparison of nominal and categorical variables will be done by chi square test. Comparison of continuous data between two groups will be done by t-test or Mann Whitney test. For calculating the diagnostic test indices, cross tables will be used for this purpose. For assessment of diagnostic efficacy of continuous variables, ROC analysis will be used and appropriate cut off points will be selected from the curve to calculate the diagnostic indices.]

IV. Result:

Totally 48 lymph nodes among 30 patients were assessed. Mean age of patients was 54.9±10.1 years [range=30-78]. Totally 16 lymph nodes were malignant in pathology [35.5%]. The frequency of different categorical variables including morphology, T1, T2 has been compared between benign and malignant lymph nodes. As we can see, all comparisons were statistically significant between two groups. Comparison of malignancy in different subgroups of patients classified based on morphology, T1W, T2 W. As in (Table 1)

Table 1 frequency of different categorical variables

variables	state of the variable	Malignancy Percentage	Odds Ratio [95% CI]	P-Value
Morphology	round	80 [16/20]	84.2	<0.001
	oval	4 [1/25]	[8.9-778]	
T1	fatty hilum preserved	7.6 [2/26]	40	<0.001
	loss of fatty hilum	78 [15/19]	[6.7-226.4]	
T2	homogeneous	12 [3/25]	17	<0.001
	inhomogeneous	70 [14/20]	[3.6-72]	

All continuous variables, ROC (receiver operating characteristic) curves and their AUC (area under the curve) , [95% CI of AUC] and P-value respectively were for Long axis size: 0.77 and 0.60-0.94 and 0.003, Short axis size: 0.88, 0.78-0.98 and <0.001 As for CE-MRI We measured the signal intensity by drawing a region of interest (ROI) over mid the LN of the variance for each lymph node (metastasis and non-metastatic) and measured the difference between the two groups after and before contrast enhancement, result AUC , [95% CI of AUC] and P-value respectively were for non- enhanced 0.68, 0.52-0.85, 0.037, Dynamic Enhanced:

0.54, 0.36-0.71 and 0.69, Difference of Signal intensity after contrast: 0.68, 0.52-0.85 and 0.037, Percentage of Signal intensity difference after contrast: 0.54, 0.36-0.71 and 0.69.
The diagnostic indices of different categorical variables have been mentioned in below table: (Table 3) diagnostic indices of Morphology (round vs. oval), T1- WI (lose of fatty hilum vs. presence of fatty hilum), T2 (inhomogeneous vs. homogenous)

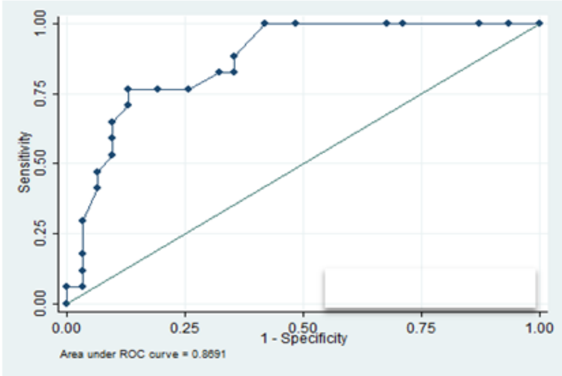
Table 2 diagnostic indices

Index	Symbol	Estimate	Lower 95% CI	Upper 95% CI
Morphology (round vs. oval)				
Sensitivity	SE	0.9412	0.7131	0.9985
Specificity	SP	0.8387	0.6627	0.9455
Efficiency (Correct classification rate)	EFF	0.8750	0.7475	0.9527
Predictive value of positive test	PVP	0.7619	0.5283	0.9178
T1-WI (lose of fatty hilum vs. presence of fatty hilum)				
Sensitivity	SE	0.8824	0.6356	0.9854
Specificity	SP	0.8387	0.6627	0.9455
Efficiency (Correct classification rate)	EFF	0.8542	0.7224	0.9393
Predictive value of positive test	PVP	0.7500	0.5090	0.9134
Predictive value of negative test	PVN	0.9286	0.7650	0.9912
Predictive value of negative test	PVN	0.9286	0.7650	0.9912
T2 (inhomogeneous vs. homogenous)				
Sensitivity	SE	0.8235	0.5657	0.9620
Specificity	SP	0.7742	0.5890	0.9041
Efficiency (Correct classification rate)	EFF	0.7917	0.6501	0.8953
Predictive value of positive test	PVP	0.6667	0.4303	0.8541
Predictive value of negative test	PVN	0.8889	0.7084	0.9765

Based on the ROC curves and their AUCs, their cut off points were selected. Then we calculated indices of these variables and cutoff points see (Table 4) AUCs cutoff points' size and Graph(1) Short axis.

Table 3 AUCs cutoff points' size

Variable	Cutoff	Sen. [95% CI]	Spec. [95% CI]	PPV [95% CI]	NPV [95% CI]	PLR [95% CI]	NLR [95% CI]	Efficacy [95% CI]
				Short axis	≥6 mm	1	0.68	0.67
						1	2.4	------
						0.73		
					≥10 mm	0.76	0.87	0.76
						0.87	5.9	3.7
						0.83		



V. Discussion

The differentiation between lymph node metastasis and non-metastasis lymph nodes is essential for staging, therapy planning and follow-up of a primary carcinoma(10), wherefore noninvasive technique that accurately detects lymph node metastasis would be of great advantage to patients with endometrial cancer, whereas surgical lymph node evaluation which is considered the gold standard for the diagnosis of lymph node metastasis, will increase the time and cost of diagnosis and with an increased risk of immediate and delayed complications to the patient (11, 12), and conventional MR techniques are commonly used in the evaluation of pelvic nodes in patients with gynecologic malignancy (13). The size criterion for pelvic lymph node metastasis varies between 1.0 and 2.0 cm in diameter (14-18) but recently defining as metastatic those nodes with short-axis diameter >10 mm or >8 mm (10, 19). Commonly used as the cut-off for benign and malignant lesions revealed a relevantly low sensitivity (25–62 %) (6, 20). The study Yun B. Chen etc. 1118 lymph node from patients with cervical Cancer total dissected and histopathologically evaluated pelvic lymph nodes, 153 enlarged nodes with short-axis diameter larger than 5 mm, sensitivity and specificity for distinguishing malignant from hyperplastic nodes using size (short axis diameter is 0.85, 59.1%) (21). In our study we had 45 LNs, Long axis size for Minimum 5 mm, Maximum 64 mm, mean 16 mm, and Short axis size for Minimum 3 mm, Maximum 30 mm, mean 9.5 mm, Depending on the pathological results we had 29 non-metastatic LNs and 16 metastatic LNs, borderline significant difference between metastatic and non- metastatic LNs for Long axis size, for non- metastatic and metastatic LNs Mean ±SD: 13± 5.1, 21± 13 mm with P-Value 0.003. And for Short axis size non- metastatic and metastatic LNs Mean ±SD: 6.9± 4.9, 14.2± 6.9 mm with P-Value <0.001, In addition to the statistical values of ROC (receiver operating characteristic) curves and their AUC (area under the curve) were calculated Long axis size AUC: 0.77, P- Value: 0.003, and for Short axis size AUC: 0.88, P-Value: <0.001. Where the values and statistical results show that the short axis size is more accurate to be adopted to measure the lymph nodes this is in line with previous studies of lymph nodes in the pelvic region (4, 11, 20-24). Thereafter based on the ROC curves and their AUCs, a total of cut of points were selected for the short axis size and statistical criteria whereas at the cut of points ≥6 mm the most sensitivity 100% and cut of points ≥10 mm specificity 87%, see table 4. Although the size standard is important and help us to adopt it in the differentiation between metastatic and non-metastatic lymph nodes. Morphology (shape) as diagnostic criteria would improve the ability of MRI to discriminate between benign and metastatic lymph nodes, (25-27) several studies has confirmed normal lymph nodes typically have an oval shape. Even when Pelvic area lymph nodes are enlarged because of a benign inflammatory process, they usually retain this shape, whereas malignant lymph nodes change their shape to rounded The predisposition of benign nodes to be oval and malignant nodes to round have also been informed by Studies (28-31). In study of Kuna et al. confirmed 66% of metastases followed this pattern, whereas 88.2% of benign lymph nodes retained an oval shape (32). In Chen, et al.2011 study; sensitivity for distinguishing malignant from hyperplastic nodes using shape (short-to- long axis ratio is 0.77, 56.1%) (33) . It is worth mentioning, there are many studies that confirm that the criteria of morphology is inaccurate and unreliable to differentiate benign nodes from those containing metastases (5, 6, 10, 24, 34). In our study we had LNs 25 is oval, 20 is round, where the largest percentage was oval shape 62.5%, Sensitivity and specificity for distinguishing malignant from hyperplastic nodes 94%, 83 %, PPV (Predictive value of positive test) 76%, PVN 96%, EFF 87.5%, see Table 2. Normal pelvic lymph nodes may appear homogenous or have a central fatty hilum. They are best detected on T1-weighted images, where they appear of homogenous low or intermediate signal contrasting well with the surrounding high signal fat, or have a high signal hilum consistent with intra- nodal fat, surrounded by an intermediate signal rim giving a characteristic target appearance (35). A normal lymph node has a fatty hilum and is an oblong kidney- bean–shaped structure. It ordinarily has a smooth outline except for small vessels at the hilum of the node (36).There are several previous studies Such as; Arslan, et al. 2016 Confirmed found significant correlation between no fatty hilum and metastatic lymph nodes. Where fatty hilum was seen in 40 % of metastatic nodes (n = 6), it was seen in all (n = 20) reactive nodes. This difference was statistically significant (p = 0.001; p < 0.01), the sensitivity specificity and accuracy was 60 %. 100 and 82.86 %, respectively, the positive predictive value was 100 % and negative predictive value was 76.92 % (37). Our study also proved correlation between no fatty hilum and metastatic lymph nodes, where statistical results showed, 26 LNs fatty hilum preserved, 19 LNs loss of fatty hilum. Frequency of different categorical variables T1 have been compared between benign and malignant lymph nodes percentage of lymph nodes was metastatic 78% is loss of fatty hilum (Table 1) And the sensitivity specificity and a Efficiency (Correct classification rate) was 88%, 83 and 85%, the Predictive value of positive test 75% and Predictive value of negative test 92%, (P-Value <0.001), see (Table 2). MR diagnostic criteria based on the T2 protocol, such as the short axis and short to long axis ratio were also considered and appearance of homogeneity for the T2WI signal used to differentiate between metastasis from non- metastasis LNs where homogeneous signal intensity was considered as normal, Heterogeneous signal intensity was considered as indicative of metastatic lymph nodes (38). In a previous study Dooms, et al. in 1985 the signal differences between positive and negative nodes on T2- weighted images are not significant (39). In our study in T2 -WI ; 25 homogeneous LNs , 20 inhomogeneous LNs, the frequency of different categorical variable T2 have been compared between benign and malignant lymph nodes; Inhomogeneous 70%, homogeneous 12% as in Table 1, the sensitivity specificity and a Efficiency were 82%, 77% and 79%. Predictive value of positive test (PPV) 66% and Predictive value of negative test (PVN) 88%. as in Table 2.The inside structure of a lymph node was considered as homogeneity, slight heterogeneity, or main (more than or equal to half of lymph node) heterogeneity. We have identified all the lymph nodes regardless of the size where the MRI 3T helped us to be more precise. Some studies have used this standard (homogeneity) only in largest lymph node which used MRI 1.5T as a study Matsuoka H**,** et al. of Lymph Node Metastasis in Patients with Rectal Carcinoma (40).

As for the T1 CE-MRI (T1 weighted image contrast enhancement) it was observed that the lymph nodes metastatic enhanced with contrast and at the same time observed the reactive lymph nodes enhanced of the contrast also therefore, we calculated the mean of signal intensity in case of enhancement and non-enhancement

Table 4 differentiation values for CE-MRI to measure the amount of enhancement and know-how amount of enhancement between the metastatic and non- metastatic lymph nodes, the results were after calculated the difference of signal intensity between nonenhanced and enhanced images. As in table 4

Table 4 differentiation values for CE-MRI

	pathology	N	Mean	Std. Deviation	P-Value
non-enhanced signal intensity	Nonmetastasis	29	303.5	166.5	
	Metastasis	16	442.9	170	0.009
Enhanced signal intensity	Nonmetastasis	29			0.58
	Metastasis	16			
Difference of Signal intensity after contrast	Nonmetastasis	30	389.6	222.6	0.18
	Metastasis	17	284.6	295.5	
Percentage of Signal intensity difference after contrast	Nonmetastasis	30	323.2	534.5	0.037
	Metastasis	17	83.1	92.4	

We calculated the AUC of ROC curve; the AUC was Difference of Signal intensity after contrast 0.68

and Percentage of Signal intensity difference after contrast 54 (P-Values=0.037and 0.69 respectively). This means CE-MRI is useless in differentiating between metastatic and non-metastatic lymph nodes this is consistent with several studies such as Bahri, et al. , Kvistad, et al. they confirmed the dynamic contrast enhancement MRI has been proven to be low in sensitivity for detecting axillary lymph node metastases also (26, 41) and Chuanming, et al. Showed inaccurate dynamic contrast-enhanced MRI (sensitivity, 25%; specificity, 98%) (42). While there are studies reported the difference such as Klerkx, et al. Which confirmed the total accuracy of gadolinium- enhanced magnetic resonance imaging for the detection of nodal metastases is moderate. Combining contrast enhancement in the malignancy criteria considerably improves the accuracy of this diagnostic test (12).

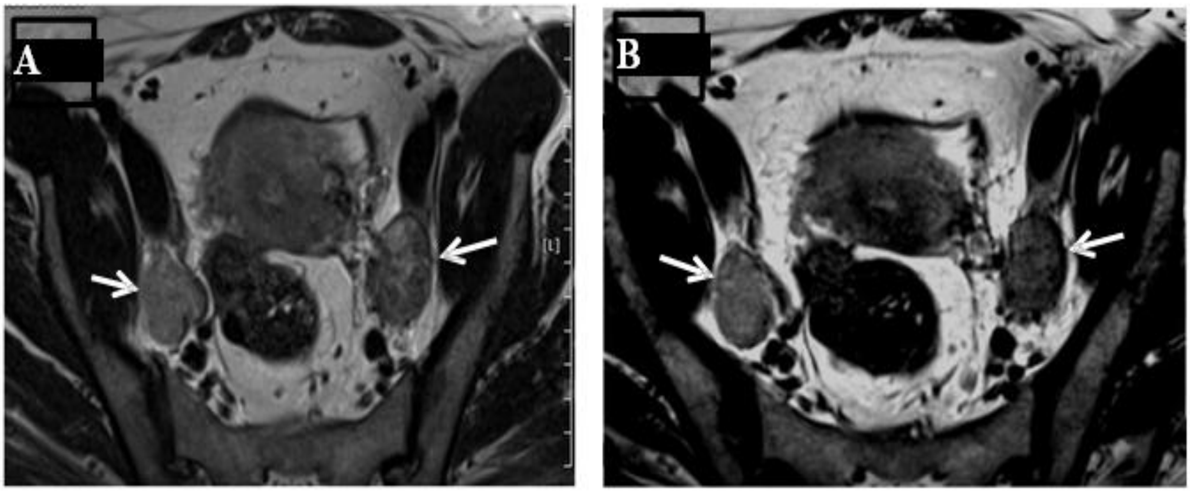


Figure 1 MRI endometrial cancer with lymph nodes metastases

A-B: MR images of a 47-year-old woman with endometrial cancer. At post-operative histopathological analysis, lymphadenopathies (metastatic) nodes were found in the left and right internal iliac region. A: Oblique axial T2-weighted image (TE: 101 ms; TR5000 ms) shows two enlarged metastatic lymph nodes size (30×27mm and 27×17 mm) in the right and left internal iliac region which appear non-homogeneous and round shape. B: axial T1-weighted image (TE: 13 ms; TR: 999 ms) shows lose of fatty hilum.

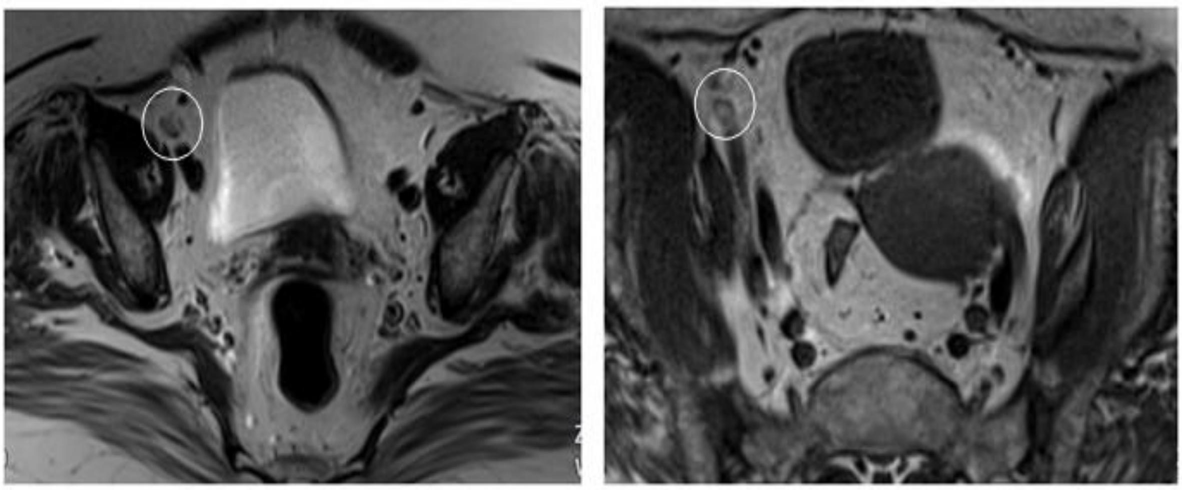


Figure 2 MRI endometrial cancer with reactive lymph node

A-B: MR images of a 78-year-old woman with endometrial cancer. At post-operative histopathological analysis, no metastatic nodes were found in any of the dissected nodal regions A: Oblique axial T2-weighted image (TE: 96 ms; TR4200 ms) shows an enlarged reactive lymph node size 15.5×8 mm in the right external iliac region which appear homogeneous and oval shape. B: axial T1-weighted image (TE: 10 ms; TR: 851 ms) shows preserved fatty hilum.

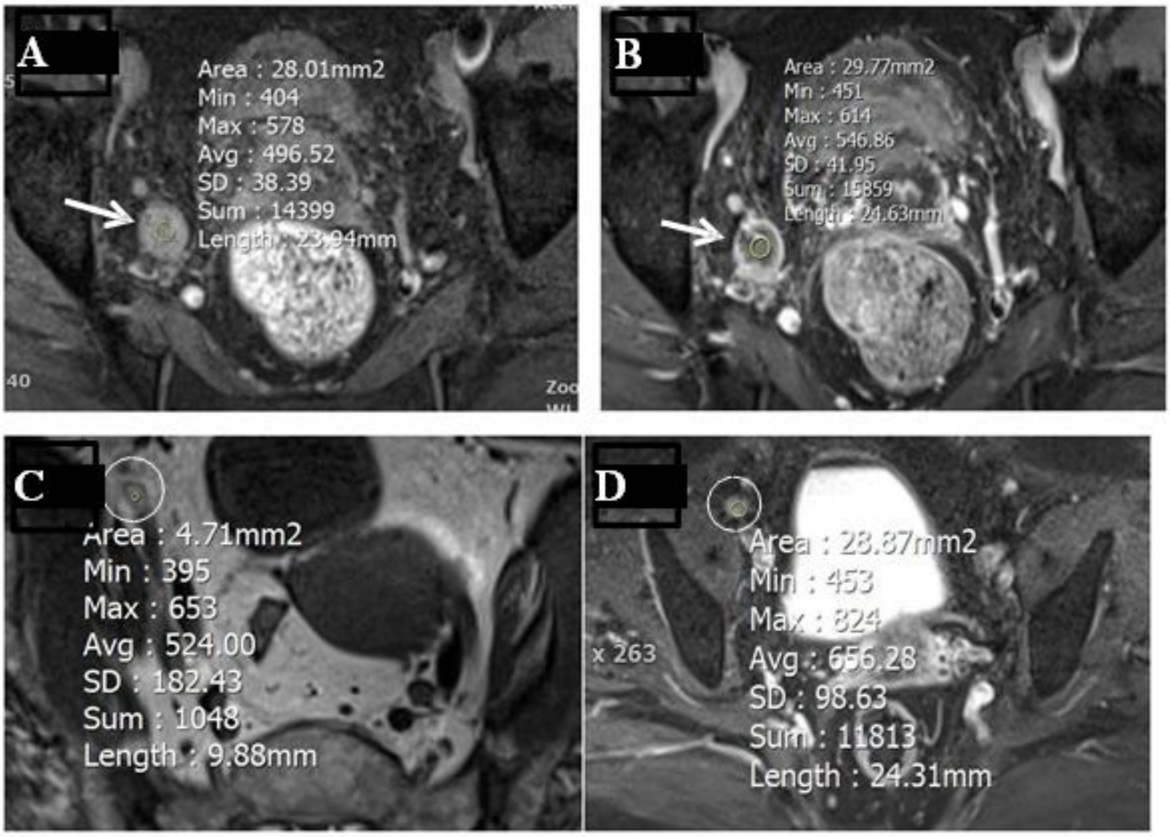


Figure8 MR T1-weighted images with and without contrast

A-B: MR images of a 56-year-old woman with endometrial cancer. At post-operative histopathological analysis, metastatic node was found in the right internal iliac region. A: axial fat-saturated spin-echo T1-weighted image (TE: 12 ms; TR: 975 ms) shows signal intensity Pre contrast injection the average of signal appear less than after contrast image. B: axial gadolinium- enhanced fat-saturated spin-echo T1-weighted image (TE: 13 ms; TR: 900 ms) shows signal intensity post contrast injection the average of signal appear more than before contrast image. C.D: MR images of a 78-year-old woman with endometrial cancer. At post-operative histopathological analysis, no metastatic nodes were found in any of the dissected nodal region.

C: axial spin-echo T1-weighted image (TE: 10 ms; TR: 851 ms) shows signal intensity Pre contrast injection the average of signal appear less than after contrast image. D: axial gadolinium-enhanced fat-saturated spin-echo T1-weighted image (TE: 11 ms; TR: 670 ms) shows signal intensity post contrast injection the average of signal appear more than before contrast image. Comparing the signal intensity Pre and post contrast injection and counting the difference statistically to show Difference of Signal intensity after contrast and Percentage of Signal intensity difference after contrast.

VI. Conclusions

MRI useful means for differentiation between metastatic and benign LNs in patients with endometrial cancer, Several Standard criteria are size, Morphology, T1WI and T2WI have sensitivity, specificity and different accuracy percentages. By combining all these techniques to complement each other, to be a promising noninvasive modality for evaluating lymph nodes in patients with endometrial cancer and can provide supplementary information to determine therapeutic strategies.

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