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Utility of the relative apparent diffusion coefficient for preoperative assessment of low risk endometrial carcinoma

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ABSTRACT

Objectives: Lymphadenectomy is not recommended for low risk stage I endometrial carcinoma (EC) patients. This study was to investigate the predictive value of apparent diffusion coefficient (ADC) values in predicting patients with low risk EC, and to identify an optimum ADC measurement for preoperative assessment.

Materials and methods: Eighty-one patients with stage I EC who underwent diffusion-weighted imaging (DWI) at 1.5T were included and divided into low group and intermediate-high risk group based on the ESMO-ESGO-ESTRO classification. Clinical indexes, conventional MRI parameters, minimum ADC values (minADC), mean ADC values (meanADC) and relative ADC values (rADC) were compared between those two groups. rADC was calculated using the equation ADC (cancer)/ADC (reference) with the obturator internus muscle as reference. The optimal ADC measurement and cut-off ADC value for low risk EC were calculated using the receiver operating characteristic (ROC) curve.

Results: The low risk group had significantly higher meanADC, minADC, and rADC values than did the intermediate-high risk group (1.095 vs. 0.902 × 10^{-3} mm^2/s, 0.755 vs. 0.657 × 10^{-3} mm^2/s, 0.754 vs. 0.603, respectively). In assessments of low risk EC patients, the area under the curve (AUC) values for meanADC, minADC, and rADC were 0.840 (95%CI, 0.749,0.931), 0.681 (95% CI: 0.561,0.800), and 0.876(95% CI: 0.798,0.954), respectively. The optimal cut-off rADC value for prediction was 0.669, the maximum Youden index, sensitivity, specificity, and accuracy values were 0.683, 81.8%, 86.5%, and 84.0%, respectively.

Conclusions: rADC is superior to minADC and meanADC for predicting patients with low risk EC, and could potentially aid to the surgical management of these patients in avoiding unnecessary lymphadenectomy.

1. Introduction

Endometrial carcinoma (EC) is the most common gynecological tumor in developed countries. As the disease is often symptomatic in early stages, 75% of cases are therefore diagnosed in stage I [1,2]. The five-year overall survival rate for stage I patients is reported to exceed 90% [3], but decreases substantially with metastatic disease or recurrence. The risk of lymph node metastasis in EC patients is correlated with key prognostic factors, including the depth of myometrial invasion and tumor grade. Accordingly, stage I EC patients are stratified as low, intermediate, and high risk based on these prognostic factors. In clinical management for stage I EC, the standard surgical treatment includes a total hysterectomy (TH), bilateral salpingo-oophorectomy (BSO), and lymphadenectomy [1]. However, the role and extent of lymphadenectomy in stage I EC remains controversial.

Several retrospective studies have demonstrated that patients with low risk EC have a low incidence of lymph node metastasis and show no survival advantage from lymphadenectomy [4–9]. By contrast, patients with intermediate and high-risk EC benefit greatly from systematic pelvic and para-aortic lymphadenectomy [10–12]. Moreover, lymphadenectomy can increase risk of leg lymphoedema and postoperative deep vein thrombosis [13,14]. There is growing consensus that routine lymphadenectomy can safely be omitted in low risk EC patients [4,15]. Thus, Accurate preoperative assessment of EC risk is essential for optimizing surgical therapy.

Magnetic resonance imaging (MRI) plays an established role in staging EC and in selection of optimal treatment [16]. Previous reports have suggested that diffusion-weighted imaging (DWI) combined with apparent diffusion coefficient (ADC) is useful for assessing the depth of MI and for pathological grading as well as for monitoring prognosis [17–21]. With regard to other pelvic diseases, ADC value is reported to be a promising tool for detecting tumor recurrence and estimating aggressiveness [22,23]. Therefore, the quantitative ADC value may be of value for the estimation of EC risk stratification before surgery.

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The present study aimed to explore the predictive power of ADC values for predicting low risk stage I EC and to identify an optimum ADC measurement for aiding adapted selection for surgical treatment.

2. Materials and methods

2.1. Study population

This retrospective study was approved by Institutional Review Board and the requirement for informed consent was waived. From July 2011 to June 2015, data were retrospectively collected from stage I EC patients at our hospital who underwent TH plus BSO. The inclusion criterion was as follows: 1) patients with EC verified by preoperative endometrial biopsy and surgery; 2) Each patient underwent complete preoperative MRI with DWI before surgery. Patients who were pregnant or patients with histories of preoperative chemotherapy or radiotherapy were excluded from the study. The risk groups of stage I EC were defined as follows: low risk was classified as stage IA, grade 1 or 2 endometrioid carcinoma; intermediate risk was classified as stage IB, grade 1 or 2 endometrioid carcinoma, and stage IA, grade 3 endometrioid carcinoma; and high risk was classified as stage IB, grade 3 endometrioid carcinoma, and stage I nonendometrioid carcinoma.

2.2. MRI technique

All MR images were obtained on a 1.5-T scanner (Signa HDxt; GE Healthcare, Milwaukee, WI) with an eight-channel phased-array coil. Axial T1-weighted (T1W) spin-echo images and axial and sagittal T2-weighted (T2W) fast spin-echo images with or without fat suppression were obtained. Axial DWI was performed using spin-echo type and single-shot echo planar imaging (b-values = 0 and 600 s/mm^2) with the following parameters: repetition time (TR)/echo time (TE) = 4400/minimum ms; field of view (FOV) = 36 × 36 cm^2; slice thickness = 5.0 mm; gap = 2.0 mm.

2.3. MR analysis

EC lesions showed isointensity on T1W images and mildly hyperintensity on T2W images relative to normal myometrium. In DWI, the tumors exhibited higher signal intensity relative to the surrounding normal tissue. The meanADC and minADC values of the tumors were measured from the ADC maps using ADC software (AW 4.6 Workstation, GEMS) by one radiologist. For each patient, a region of interest (ROI) was manually drawn in the largest tumor slice. ROI was placed on the solid component of the tumor as large as possible, avoiding any necrotic, cystic, or hemorrhagic portion. All values were calculated as an average of three repeated measurements for each patient. To reduce the influence of the ROI method and individual differences, we used the obturator internus as an internal reference for the relative ADC. Relative ADC (rADC) was calculated as tumor ADC/reference ADC. A ROI was placed in the maximum obturator internus cross-section to obtain the reference ADC value. Two radiologists (*.Y. and *.Z., with 3 and 11 years of experience in gynecologic imaging, respectively) independently reviewed and measured the MR images while blinded to the original clinical and histologic information.

2.4. Statistical analyses

Statistical analysis was performed with SPSS statistical software (version 21.0). Continuous variables are presented as arithmetic means and standard deviations(SD). The Shapiro-Wilk test was used to test the normality of the data distributions. *F* tests were used to test the variance homogeneity of the data. If data were normally distributed with equal variance, Student's *t*-test was used to compare ADC values between low risk and intermediate-high risk EC; otherwise, the Mann–Whitney *U* test was used. A value of $p < 0.05$ was considered statistically significant.

Table 1
Clinical and conventional MRI parameters for patients with stage I EC.

Variables	Low risk (n = 44)	Intermediate-high risk (n = 37)	*P*
Age	52.9 ± 8.1	56.6 ± 9.1	0.054
Postmenopausal	24	25	0.232
Clinical manifestation			
Abnormal vaginal bleeding	38	29	0.344
Menstrual changes	4	8	0.130
Abdominal pain	2	0	0.498
Myometrial invasion			0.000
< 50%	44	13	
≥50%	0	24	
Histologic grade(endometrial adenocarcinoma)			
Grade 1	12	2	0.016
Grade 2	32	13	0.001
Grade 3	0	22	0.000
Lymphvascular space involvement			0.043
Yes	1	6	
No	43	31	
Solid components on T2WI			
Slight hyporintensity	0	0	–
Isointensity	4	3	1.000
Slight hyperintensity	40	34	1.000
Solid components on T1WI			
Slight hyporintensity	10	5	0.288
Isointensity	34	32	0.288
Slight hyperintensity	0	0	–
DWI			0.404
Hyperintensity	42	33	
Markedly hyperintensity	2	4	

For the ROC analysis, the area under the (AUC) was calculated to compare the differential diagnostic capacity of three types of ADC values (meanADC, minADC, rADC) between low-risk group and intermediate-high risk group. The optimal ADC cut-off value was determined using the maximum Youden index (YI = Sensitivity + Specificity-1). The sensitivity, specificity, and accuracy of the optimal ADC cut-off value were calculated, and are presented with 95% CI. The interobserver agreements for measuring minADC, meanADC and rADC were assessed using the intraclass correlation coefficient (ICC) with 95%CI.

3. Results

3.1. Clinical and conventional MRI parameters

A total of 81 patients with stage I EC were included in our study. Of 81 patients, 44 (54.3%) were classified as low risk, 37 (45.7%) were intermediate-high risk. The clinical and conventional MRI parameters are summarized in Table 1. There were no significant statistically differences in age, postmenopausal state, clinical manifestations or conventional MRI appearance.

3.2. Comparison of meanADC, minADC, and rADC for stage I EC

For the lesions of 81 stage I EC patients, meanADC、minADC, and rADC values were $(1.007 \pm 0.171) \times 10^{-3}$ mm^2/s, $(0.710 \pm 0.161) \times 10^{-3}$ mm^2/s, and 0.685 ± 0.118, respectively. There were statistically significant differences between the low risk group and intermediate-high risk group in terms of meanADC, minADC, and rADC ($P < 0.05$ for all; Table 2, Figs. 1–3). The interobserver agreements in measurements of minADC, meanADC and rADC values were excellent between two readers, with ICC values were 0.933 (95%CI, 0.895, 0.957), 0.959 (95%CI, 0.936.0.974) and 0.956 (95%CI, 0.932,0.972), respectively.

Table 2
Comparison of meanADC, minADC and rADC for patients with stage I EC.

	Low risk (mean ± SD)	Intermediate-high risk (mean ± SD)	*P*
meanADC	1.095 ± 0.150	0.902 ± 0.131	0.000
minADC	0.755 ± 0.155	0.657 ± 0.154	0.006
rADC	0.754 ± 0.100	0.603 ± 0.079	0.000

meanADC, the mean apparent diffusion coefficient; minADC, the minimum apparent diffusion coefficient; rADC, the relative apparent diffusion coefficient. Mean ± SD, arithmetic mean and standard deviation; *P*, comparing ADC values between low risk and intermediate-high risk by Student's *t*-test, Mann-Whitney U test.

3.3. Diagnostic performance of meanADC, minADC, and rADC for stage I EC

According to the ROC curve analysis (Fig. 4), the AUC for meanADC and rADC were significantly larger than the values for minADC for differentiation between the low risk group and intermediate-high risk group ($P < 0.05$), indicating that meanADC and rADC are effective measurements for predicting low risk EC. The optimal cut-off value of rADC for predicting low risk EC was 0.669 with a 0.683 maximum YI, 81.8% sensitivity, 86.5% specificity, and 84.0% accuracy. The optimal cut-off value of meanADC was 0.963 with a 0.625 maximum YI, sensitivity 84.1%, 78.4% specificity, and 82.7% accuracy (Table 3).

4. Discussion

Although overall prognosis is favorable for stage I EC, the five-year survival rate varies from 20%–91% [3,24]. In our research, clinical and conventional MRI parameters could not differentiate low risk EC from intermediate-high risk EC. However, our results suggested that ADC values were significantly associated with risk classification, and may further contribute to tailor treatment strategies in patients with stage I EC.

In this study, all three ADC values were significantly higher in the low risk group than they were in the intermediate-high risk group. Previous research has investigated the correlation between ADC values and prognostic factors of EC, such as depth of MI and tumor grade [17,20,21,25,26]. However, few studies have explored the relationship between risk classification and ADC values. As a functional imaging technique based on water molecule diffusion, DWI can yield information about the nuclear-to-cytoplasmic ratio, cellular density, and integrity of the cellular membrane [17,27,28]. It can also assess tumor microstructure derived from a quantitative parameter, namely the ADC value [29]. In stage I EC, the decreased ADC value reflects the magnitude of diffusion of water molecules, which correlates positively with cell density and aggressiveness of tumor.

Our results showed that the AUC for meanADC and rADC were higher than were those for minADC. Moreover, the optimal threshold of rADC achieved a maximum YI, suggesting that rADC offered the best diagnostic value for identification of low risk stage I EC patients. Possible reasons for this were as follows: Firstly, ROI shape and position influenced the minADC measurements. Previous studies [30,31] have suggested that round ROI is a simple and effective method for acquiring minADC values, and that a large ROI size can reduce intra- and inter-observer variability in ADC measurements. The minADC value reflected the region with the highest celluarity of each tumor [32]. Although effort was made to avoid inclusion by manual placement, the ROI inevitably contained microscopic cystic or necrotic areas. Secondly, meanADC values varied due to individual differences and/or technical factors. Consequently we calculated the rADC values and all patients were scanned on GE 1.5-T instruments. Regarding the choice of b values, too high b values (e.g., $b > 1000\ mm^2/s$) were less optimal for ADC calculation due to poorer SNR [33], and too low b values (e.g., $b \leq 500\ mm^2/s$) caused the perfusion-induced ADC overestimation increased substantially. Accordingly, we used a moderate high b value to both minimize the noise causes underestimation of ADC and benefit the quantitative assessments of ADC values. Moreover, Koc et al. [34] demonstrated that appropriate b values for differentiation between benign and malignant gynecological lesions were between $600\ mm^2/s$ and $800\ mm^2/s$. ADC values with $b = 0$ and $= 600\ mm^2/s$ reached the best diagnostic efficiency. No significant difference was observed among ADCs with b values of $600\ mm^2/s$, $800\ mm^2/s$ and $1000\ mm^2/s$. In our results, rADC yielded the best diagnostic performance among three ADC measurements. A prior study by Itatani et al. [23] compared the efficacy of ADC and normalized ADC (nADC) for differentiating between prostate cancer with low risk and intermediate-high risk, and concluded that nADC was a valuable noninvasive technique for estimating aggressiveness. Similarly, Kuwahara et al. [21] in their study applied urine as reference to calculate the nADC values. Multivariate analysis showed that nADC was independently associated with shorter recurrence free survival (RFS) and might improve existing risk stratification. In our study, we uniquely applied the obturator internus as an internal reference. On the one hand, urine concentration varies with different people and water intake, which will affect the veracity of measure results. On the other hand, the obturator internus has a clear, stable structure on DW images. Karakas et al. [35] in their study used uterine myometrium as a reference and found that different menstrual cycles may result in histological changes to normal myometrium. This could result in the three distinct layers of a normal uterus, especially the myometrium, being confused in cases complicated with uterine leiomyomas and/or adenomyosis. Measurement of rADC may therefore be reliable for reducing variability in ADC values for the estimation of low risk EC.

There were several limitations of this study. First, as our study cohort was relatively small, more cases are needed to increase the statistical power. Secondly, our study was a single-institution research.

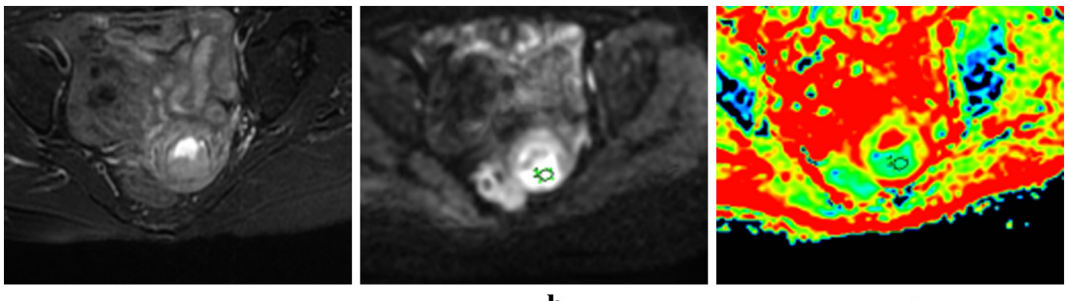

Fig. 1. A 60-year-old woman with low risk endometrial carcinoma (stage IA, grade 2). (A) Axial T2W imaging showed a mild-hyperintensity lesion within uterine cavity. (B) On DW imaging, the lesion showed hyperintensity. (C) On ADC map, the meanADC, minADC and rADC were $1.047 \times 10^{-3}\ mm^2/s$, $0.833 \times 10^{-3}\ mm^2/s$ and 0.701.

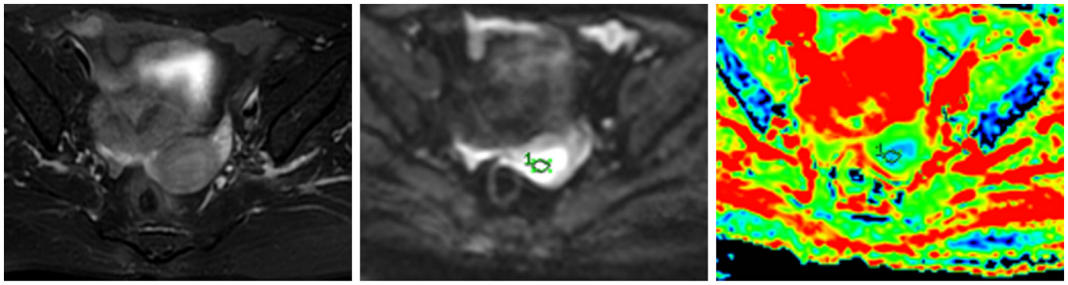

Fig. 2. A 76-year-old woman with intermediate risk endometrial carcinoma (stage IA, grade 3). (A) Axial T2W imaging showed a mild-hyperintensity lesion within uterine cavity. (B) On DW imaging, the lesion showed hyperintensity. (C) On ADC map, the meanADC、minADC and rADC were $0.765 \times 10^{-3}\,mm^2/s$, $0.578 \times 10^{-3}\,mm^2/s$ and 0.512.

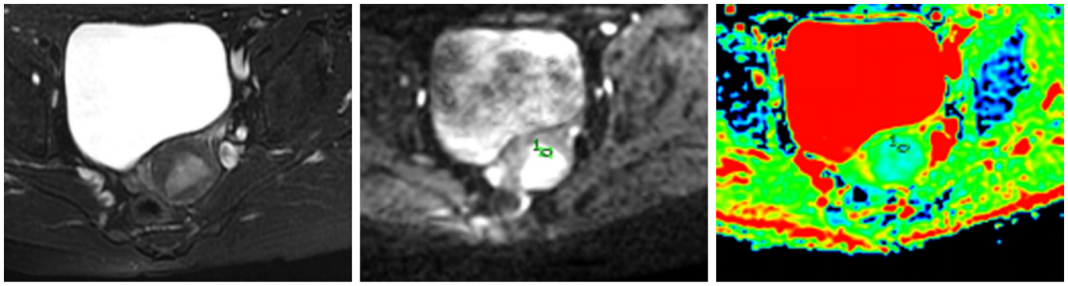

Fig. 3. A 56-year-old woman with high risk endometrial carcinoma (stage IB, grade 3). (A) Axial T2W imaging showed a moderate-hyperintensity lesion with deep myometrial invasion. (B) On DW imaging, the lesion showed hyperintensity. (C) On ADC map, the meanADC, minADC and rADC were $0.985 \times 10^{-3}\,mm^2/s$, $0.709 \times 10^{-3}\,mm^2/s$ and 0.666.

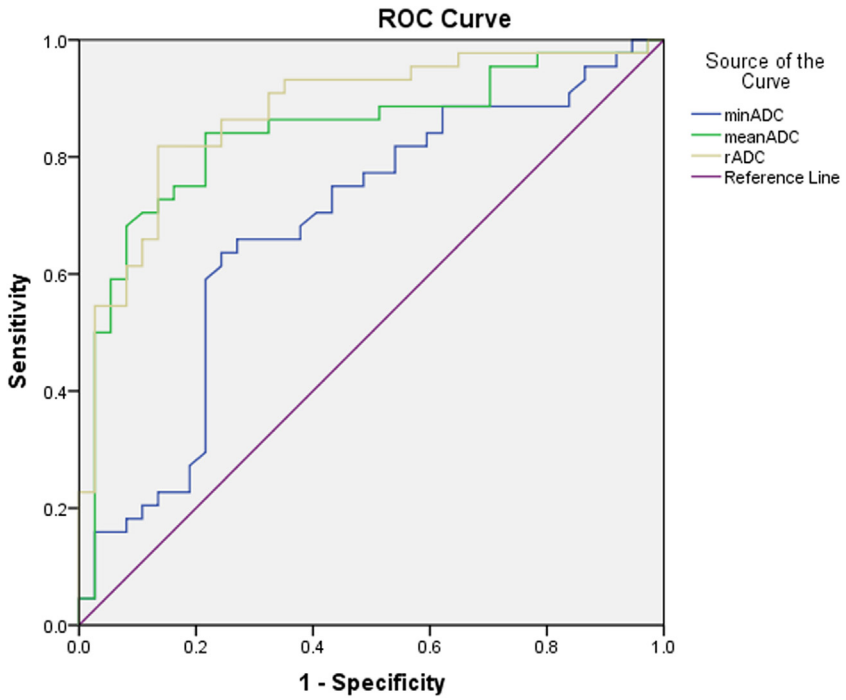

Fig. 4. The ROC curves of the meanADC, minADC and rADC values used to distinguish low risk EC from intermediate-high risk EC.

Thus, further study are needed to validate the fesibility of rADC in other instruments and centers.

5. Conclusion

In summary, as a noninvasive technique, rADC was superior to meanADC and minADC in the preoperative assessment of stage I EC at our institution. This measure, if proven to be valid, and in addition to standard preoperative assessment could potentially be used to improve surgical management and stratify low risk EC patients from undergoing unnecessary lymphadenectomy.

Table 3
The comparison of diagnostic performance of meanADC, minADC and rADC for low risk stage I EC.

	AUC (95%CI)	Maximum YI	Cut-off value	Sensitivity (%)	Specificity (%)	Accuracy (%)	*P*
meanADC	0.840 (0.749,0.931)	0.625	0.963	84.1	78.4	82.7	0.000
minADC	0.681 (0.561,0.800)	0.375	0.717	59.1	78.4	67.9	0.005
rADC	0.876 (0.798,0.954)	0.683	0.669	81.8	86.5	84.0	0.000

AUC, the area under the curve; 95%CI: 95% confidence interval.

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No.

Conflict of interest

The authors report no conflicts of interest.

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