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MAGNETIC RESONANCE

Preoperative prediction of deep myometrial invasion and tumor grade for stage I endometrioid adenocarcinoma: a simple method of measurement on DWI

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Abstract

Objectives To explore the utility of the tumor area ratio (TAR) for predicting deep myometrial invasion and tumor grade in stage I endometrioid adenocarcinoma (EEA).

Methods We retrospectively evaluated 86 patients with International Federation of Gynecology and Obstetrics (FIGO) stage I EEA. All patients underwent unenhanced contrast MRI and diffusion-weighted imaging (DWI) procedures. The volume and maximum area of the tumor and uterus were obtained, and the tumor volume ratio (TVR) and TAR were calculated. The Kruskal-Wallis test and Mann-Whitney *U* test were used to compare the differences in indexes (TVR and TAR) between the different tumor grades and between superficial and deep myometrial invasion.

Results The TVR and TAR values for deep myometrial invasion and high-grade EEA tumors were significantly higher than the values for superficial myometrial invasion and low-grade tumors (all $p = 0.000$). According to the receiver-operating characteristic (ROC) curve, the area under the curve (AUC) was significantly higher for TAR than for TVR for tumors with deep myometrial invasion (0.936 vs. 0.844, $p = 0.045$). However, no significant differences in the AUCs for TVR and TAR were observed between high- and low-grade tumors (0.865 vs. 0.863, $p = 0.956$). A TAR ≥ 34.6% predicted deep myometrial invasion in EEA with a sensitivity, specificity, and accuracy of 85.0%, 84.8%, and 86.0%, respectively. A TAR ≥ 38.9% predicted high-grade tumors with a sensitivity, specificity, and accuracy of 83.3%, 81.1%, and 82.6%, respectively.

Conclusion TAR is useful for predicting deep myometrial invasion and high-grade stage I EEA

Key Points

- *TAR is useful for predicting risk factors for EEA.*
- *TAR is easy to obtain and has high accuracy.*
- *TAR has excellent interobserver repeatability agreement (ICC range 95.1–99.6%).*

Keywords Endometrioid adenocarcinoma · Cell differentiation · Neoplasm staging · Diffusion · Magnetic resonance imaging

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Abbreviations

AUC	Area under the curve
CE-MRI	Contrast-enhanced MRI
CI	Confidence interval
DWI	Diffusion-weighted imaging
EC	Endometrial cancer
EEA	Endometrioid adenocarcinoma
FIGO	International Federation of Gynecology and Obstetrics
ICC	Interobserver correlation coefficient
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver-operating characteristic curve

TAR	Tumor area ratio
TV	Tumor volume
TVR	Tumor volume ratio

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries, and the incidence of EC is increasing rapidly in China [1]. The prognosis of EC depends on several factors, including the clinical stage, depth of myometrial invasion, histologic grade, cell type, lymphovascular invasion, and nodal status [2]. Preoperative risk stratification of EC contributes to the choice of surgical treatment plan (including whether to perform lymph node dissection) [2]. However, evidence is lacking on the survival benefit of lymphadenectomy in the International Federation of Gynecology and Obstetrics (FIGO) stage I EC [3] when high-risk factors (including high-grade tumor, deep myometrial invasion, and nonendometrioid histology [4]) are absent. Therefore, the preoperative prediction of the depth of myometrial invasion and tumor grade in FIGO stage I endometrioid adenocarcinoma (EEA) contributes to an improved prognosis for patients.

Currently, magnetic resonance imaging (MRI) is the main method for the preoperative assessment of the depth of myometrial invasion in EC [5]. Deep myometrial invasion is an independent prognostic factor and a high-risk factor for lymph node metastasis. However, in some cases, it is difficult to differentiate between superficial and deep myometrial invasion based on MRI. For example, in some postmenopausal patients or patients with a significantly enlarged uterine cavity, the junctional zone may appear unclear, leading to an over- or underestimation of tumor staging [6]. Additionally, when EC coexists with adenomyosis and/or uterine leiomyomas, it is challenging to obtain the correct staging of the tumor. The area of the uterine cornua is physiologically thinner than the normal myometrium, which further complicates staging [7]. Finally, MR images require subjective judgment by a physician for accurate staging of the tumor, which requires the physician to have long-term experience with EC diagnosis.

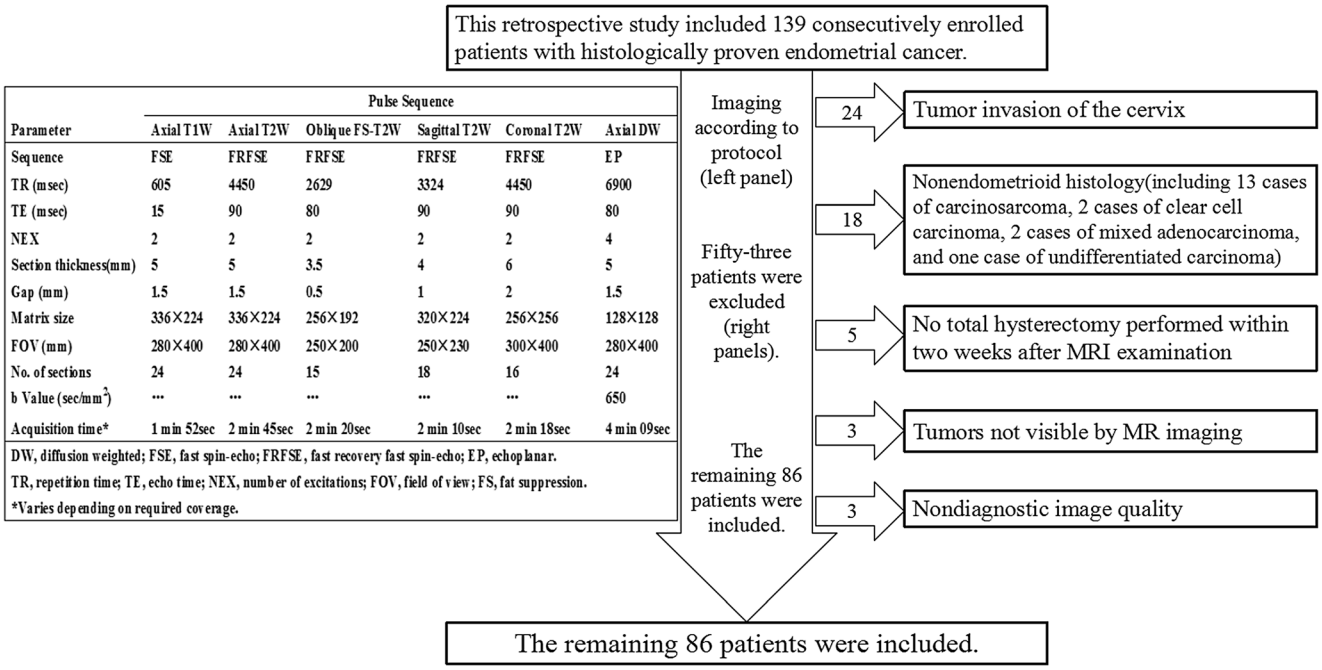
Diffusion-weighted imaging (DWI) detects water molecule diffusion in tissues in vivo and improves the detection rate of malignant tumors and aids the differentiation of benign from malignant lesions in EC [8, 9]. DWI has high sensitivity and specificity for detecting deep myometrial invasion [10–12]. However, there remains no consensus on the utility of the apparent diffusion coefficient (ADC) value for identifying the endometrial cancer grade [13–20]. The results of our previous study indicated that the mean ADC value was useful for identifying high- and low-grade EEA [2]. Moreover, other groups have reported an excellent correlation between tumor volume (TV) and tumor grade in EC [3]. Reported methods of TV measurement [3] are based on the sum of each pixel volume, which requires proprietary software for processing on a post-processing workstation. However, this software is not available in every hospital, including our own. With the goal of developing a simple method, the aim of this study was to preoperatively predict deep myometrial invasion and high-grade tumors in FIGO stage I EEA from transverse images using the area ratio of the tumor to the uterus. Our results demonstrate that the tumor area ratio (TAR) can be used to predict risk factors for EEA.

Materials and methods

Patients

Between September 2012 and July 2017, 139 patients with histologically proven EC underwent MR examinations before surgery. The mean age of the patients was 54.3 years (range, 24~74 years). The exclusion criteria were as follows: (1) EC of nonendometrioid histology; (2) tumor stage ≥ stage II EC according to the FIGO staging system; (3) no total hysterectomy performed within 2 weeks after the MRI examination; (4) preoperative treatment with chemoradiation; (5) tumors that were too small to be visible on MRI; (6) images with obvious motion artifacts; (7) contraindications for MRI examination. Fifty-three patients were excluded according to the exclusion criteria (Fig. 1). The remaining 86 patients were included (mean age = 53.5 years; range = 24~70 years). The study was approved by the local institutional ethics committee on human research of Shaanxi Provincial Tumor Hospital; the IRB number is 2012-018.

Surgical procedures were performed by two surgeons with > 20 years of experience in the field, and the clinical pathologic assessment was completed by a pathologist with more than 10 years of experience. According to the FIGO staging system, myoinvasion was stratified using binary classification (< 50% vs. ≥ 50%). The tumor grade of the EEA was first established (G1 = well differentiated; G2 = moderately differentiated; G3 = poorly differentiated). Then, the tumors were divided into two groups: high-grade (G3) and low-grade (G1 and G2). The cases were also divided into two groups based on the presence or absence of deep myometrial invasion. According to the mode of tumor growth, the cases of deep myometrial invasion were further divided into two groups: exophytic and diffuse. Of the EEAs, 21 cases also had uterine leiomyomas, 10 cases also had adenomyosis, and 7 cases had both leiomyomas and adenomyosis. These cases were distributed in the different categories. The details are summarized in Table 1.



Parameter	Pulse Sequence					
	Axial T1W	Axial T2W	Oblique FS-T2W	Sagittal T2W	Coronal T2W	Axial DW
Sequence	FSE	FRFSE	FRFSE	FRFSE	FRFSE	EP
TR (msec)	605	4450	2629	3324	4450	6900
TE (msec)	15	90	80	90	90	80
NEX	2	2	2	2	2	4
Section thickness(mm)	5	5	3.5	4	6	5
Gap (mm)	1.5	1.5	0.5	1	2	1.5
Matrix size	336×224	336×224	256×192	320×224	256×256	128×128
FOV (mm)	280×400	280×400	250×200	250×230	300×400	280×400
No. of sections	24	24	15	18	16	24
b Value (sec/mm^2)	···	···	···	···	···	650
Acquisition time*	1 min 52sec	2 min 45sec	2 min 20sec	2 min 10sec	2 min 18sec	4 min 09sec

DW, diffusion weighted; FSE, fast spin-echo; FRFSE, fast recovery fast spin-echo; EP, echoplanar.
TR, repetition time; TE, echo time; NEX, number of excitations; FOV, field of view; FS, fat suppression.
*Varies depending on required coverage.

Fig. 1 Inclusion of patients

MR protocol

All MRI examinations were performed using a 1.5-T system (EXCELART Vantage^{TM} powered by Atlas, Toshiba Medical Systems Corp., Tochigi, Japan) with an eight-channel phased-array coil. The details of the imaging protocol are presented in Fig. 1. Before scanning, 20 mg raceanisodamine hydrochloride injection (Hangzhou People's Livelihood Pharmaceutical Co., Hangzhou, Zhejiang Province, China) was administered intravenously to reduce artifacts from intestinal motility. Axial, sagittal, and coronal fast spin-echo T2-weighted (T2W) images and axial T1-weighted images of the pelvis were obtained (Fig. 1). Using a fat suppression (FS) sequence, abdominal fat showed a low signal on T2WI, thereby reducing motion artifacts caused by respiratory movement, which is conducive to displaying lesion boundaries. Therefore, axial oblique (perpendicular to the long axis of the uterus) FS-T2W images were obtained. Axial DWI of the pelvis was performed with a single shot spin-echo echo planar imaging sequence (Fig. 1). ADC maps were automatically reconstructed on a post-processing workstation.

MR image analysis and interpretation

Each patient was independently evaluated by two radiologists with more than 6 years of experience in diagnosing images of gynecologic tumors. In addition to the postoperative histopathologic findings of EEA, other data were treated with the corresponding information and methods blinded, including the location, pathologic stage, and histologic grade of the tumor and lymph node metastasis.

Table 1 The distribution of uterine leiomyomas and/or adenomyosis in endometrioid adenocarcinoma

Postoperative histologic finding	Patients (*n*)	Leiomyomas (*n*)	Adenomyosis (*n*)	Leiomyomas and adenomyosis (*n*)
Concomitant benign diseases	38	21	10	7
Myometrial invasion of EEA				
Superficial	29	15	8	6
Deep	9	6	2	1
Histologic grade of EEA				
Grade 1 (G1)	5	1	3	1
Grade 2 (G2)	28	16	6	6
Grade 3 (G3)	5	4	1	0

EEA endometrioid adenocarcinoma

On T2W images, the tumor contour was defined as areas of intermediate signal intensity that differed from the normal adjacent low-signal-intensity myometrium. On DW images, tumors exhibit significantly higher signal intensity than the surrounding background. Because the main end point of our preliminary study was the assessment of myometrial invasion, patients with cervical stromal invasion at surgery consistent with FIGO stage II disease were excluded.

The maximum tumor diameters were measured in three orthogonal planes: the transverse (x) and anteroposterior (y) diameters on oblique axial FS-T2W images and the craniocaudal (z) diameters on sagittal T2W images (Fig. 2a, b). The TV was then estimated using the following equation (assuming a spherical tumor shape): $TV = x \times y \times z/2$. The maximum uterine diameters were measured in the same three orthogonal planes, and the volume was estimated (Fig. 2c, d). The cervix was carefully excluded from the measurements. The uterus and cervix were delineated on the T2W images according to the low signal intensity of the outer layer of the cervix. Then, the tumor volume ratio (TVR) was obtained using the following equation: TVR = (volume of tumor/volume of uterus) × 100%.

Next, the area of the tumor was obtained. The radiologist selected the most representative slice, defined as the slice with the maximum tumor area, and successively manually outlined the whole visible component with a line on DWI (Fig. 2e). The area of the uterus, defined as the slice consistent with the tumor area, was determined by outlining the serosal surface of the uterus and successively manually outlining the whole visible component with a line on axial T2W images (Fig. 2f) because of this method's superior anatomical resolution. The TAR was obtained using the following equation: TAR = (area of tumor/area of uterus) × 100%.

Statistical analysis

Statistical analyses were performed with SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). The areas under

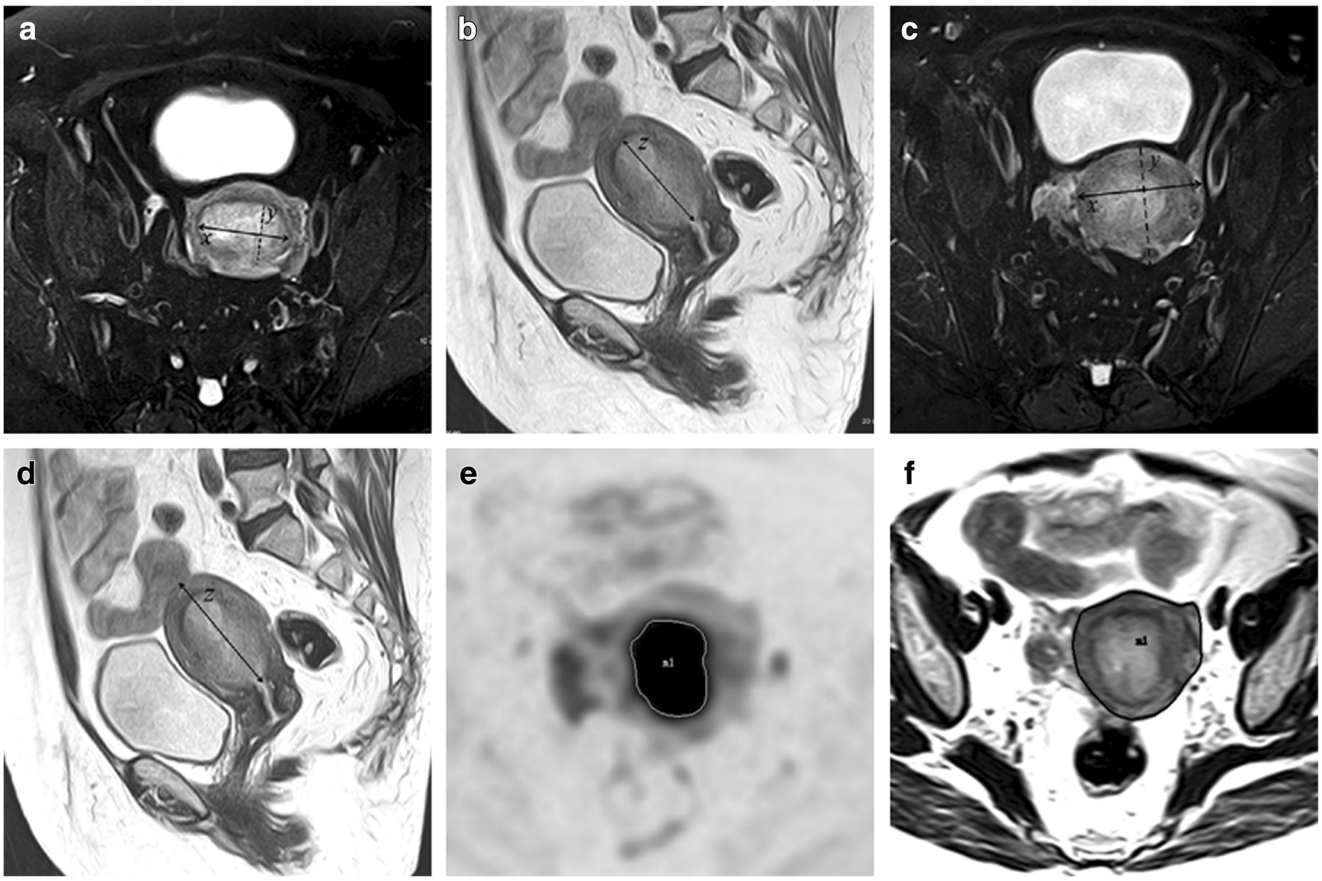


Fig. 2 A 68-year-old female with histopathologically proven grade 3 endometrioid adenocarcinoma (deep myometrial invasion). (**a**) Oblique axial fat suppression T2W image (FS-T2WI) showing a well-defined endometrial mass. The maximum tumor anteroposterior diameter (dotted line, *y*) and transverse diameter (arrowhead, *x*) were measured. (**b**, **d**) The maximum craniocaudal diameter (*z*) of the tumor and uterus were measured on sagittal T2WI. (**c**) Measurement of the uterine transverse diameter (arrowhead, *x*) with the bilateral uterine cornua on oblique axial FS-T2WI. Then, perpendicular to uterine transverse, uterine anteroposterior diameters (dotted line, *y*) were measured. The white solid line indicates the tumor border on the DW image (**e**, reverse image). The black solid line indicates the uterus border on the axial T2W image (**f**). The tumor and uterine areas were 1270.88 mm^2 and 2641.65 mm^2, respectively. The tumor area ratio was 48.1%

the receiver-operating characteristic (ROC) curves (AUCs) were compared with MedCalc version 11.4.2.0 (MedCalc, MedCalc Software bvba, Mariakerke, Belgium). The maximum diameter, areas of the tumor and the uterus, and TVR and TAR were indicated as $\bar{x} \pm s$. Due to differences in the incidence rates of tumor grades, there were large differences in the number of cases in each subgroup, resulting in a non-normal distribution of data. Therefore, nonparametric statistical calculations were performed. Moreover, the size of the tumors varied greatly, and uterine leiomyomas and adenomyosis greatly influenced the size of the uterus. Therefore, the median was used to indicate the TV and uterine volume. The interobserver correlation coefficient (ICC) was calculated for the interobserver agreement on the maximum diameters and the areas of the tumor and uterus. The TVR and TAR were compared among groups (G1, G2, and G3) using the Kruskal-Wallis test, and the Mann-Whitney *U* test was selected to compare G1 and G2, G1 and G3, and G2 and G3. The Mann-Whitney *U* test was also used to compare TVR and TAR between the groups with high- and low-grade tumors, superficial and deep myometrial invasion of EEA, and exophytic and diffuse cases of deep myometrial invasion. ROC curves were generated to evaluate the diagnostic accuracy with myometrial invasion and tumor grade as predictors using TVR and TAR. The AUC was calculated to compare the predictive power of the two methods of measurement. $p < 0.05$ indicated significant difference. To distinguish between superficial and deep myometrial invasion and between high- and low-grade tumors, the corresponding sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were determined at the optimal cutoff, which was determined by the Youden index.

Results

Histopathologic findings

All cases were confirmed by histopathology after surgery. The histologic grades of EEA are provided in Table 2.

Reader agreement

The two radiologists did not exhibit systematic disagreements in the measurement of the data, including the maximum

Table 2 The TVR and TAR values of stage I endometrioid adenocarcinoma in 86 consecutive patients

Postoperative histologic finding	Patients (*n*)	Median, cm^3		TVR, %, mean ± SD		*p*	TAR, %, mean ± SD		*p*
		Tumor volume	Uterus volume	TVR	95% CI		TAR	95% CI	
Histologic grade	86					0.000[a]			0.000[b]
Grade 1 (G1)	12	13.335	192.883	7.858±5.16	4.56~11.13		24.858±8.04	19.74~29.96	
Grade 2 (G2)	62	27.818	246.035	12.753±8.79	7.16~18.34		29.693 ±17.10	25.35~34.04	
Grade 3 (G3)	12	55.802	174.010	30.671 ±14.26	21.61~39.73		49.871 ±14.53	40.63~59.10	
Low grade (G1 and G2)	74	15.856	170.401	12.170 ±11.32	9.55~14.80	0.000[c]	28.910 ±16.04	25.19~32.63	0.000[d]
High grade (G3)	12	55.802	174.010	30.681 ±14.26	21.61~39.74		49.871 ±14.53	40.63~59.10	
Myometrial invasion						0.000[e]			0.000[f]
Superficial	66	14.989	191.827	10.342±8.61	8.23~12.46		24.882 ±10.29	22.35~27.41	
Deep	20	39.030	136.574	29.307 ±15.88	21.87~36.73		54.777 ±16.30	47.14~62.40	
Growth pattern (only including tumors of deep myometrial invasion)	20					0.007[g]			0.247[h]
Exophytic	10			20.35±12.80	11.19~29.52		49.10±19.29	35.29~62.90	
Diffuse	10			38.25±48.12	28.37~48.12		60.44±10.83	52.69~68.19	

TVR tumor volume ratio, *TAR* tumor area ratio, *CI* confidence interval

[a, b] *p* values from the Kruskal-Wallis test in different differentiation degrees of endometrioid adenocarcinoma

[c, d] *p* values from the Mann-Whitney *U* test between low- and high-grade endometrioid adenocarcinomas

[e, f] *p* values from the Mann-Whitney *U* test between superficial and deep myometrial invasion endometrioid adenocarcinomas

[g, h] *p* values from the Mann-Whitney *U* test between exophytic and diffuse endometrioid adenocarcinomas in deep myometrial invasion cases

diameters and areas of the tumors and uterus. The data are summarized in Table 3.

TVR, TAR, and deep myometrial invasion

Significant differences in TVR and TAR were observed between superficial (10.34% and 24.88%, n = 66) and deep myometrial invasion (29.30% and 54.77%, n = 20) of the tumors (p_{TVR} = 0.000, p_{TAR} = 0.000). Among cases of deep myometrial invasion, a significant difference between exophytic growth mode tumors (TVR and TAR: 20.35% and 49.10%, n = 10, Fig. 3) and diffuse tumors was observed only in TVR (TVR and TAR: 38.25% and 60.44%, n = 10, Fig. 4) (p_{TVR} = 0.007, p_{TAR} = 0.247, Table 2).

TVR, TAR, and tumor grade

As shown in Table 2, the TVR and TAR values differed significantly among the different tumor grades (p_{TVR} = 0.000, p_{TAR} = 0.000). However, no significant differences in TVR and TAR were observed between G1 and G2 tumors (p_{TVR} = 0.371, p_{TAR} = 0.500, Fig. 5). Furthermore, the differences in TVR and TAR between low-grade (12.17% and 28.91%, n = 74) and high-grade tumors (30.67% and 49.87%, n = 12) were significant (p_{TVR} = 0.000, p_{TAR} = 0.000, Table 2).

ROC curve analysis of TVR and TAR to distinguish between superficial and deep myometrial invasion and between low-grade and high-grade tumors

Since both TVR and TAR differed significantly between superficial and deep myometrial invasion and between low- and high-grade tumors, further ROC curve analysis was performed to assess the discriminating ability of these two tools (Fig. 6). For deep versus superficial myometrial invasion, the AUC was significantly higher for TAR than for TVR (0.936 vs. 0.844, Z = 1.998, p = 0.045, Fig. 6a), indicating that TAR was a better diagnostic tool than TVR for distinguishing deep from superficial myometrial invasion. However, for low- versus high-grade tumors, no significant differences in the AUCs for TAR and TVR were observed (0.863 vs. 0.865, Z = 0.054, p = 0.956, Fig. 6b), indicating that the two tools had the same efficacy in distinguishing low- and high-grade tumors.

The corresponding sensitivity, specificity, PPV, NPV, and accuracy at the optimal cutoff values of TAR to distinguish superficial and deep myometrial invasion and to distinguish low- and high-grade tumors are presented in Table 4.

Discussion

In this study, we evaluated TAR as a tool for predicting high-risk factors for FIGO stage I EEA. Our preliminary results showed that TAR is associated with deep myometrial invasion and high-grade EEA. Our research is not novel but is of clinical importance and interest.

TV can be used to evaluate deep myometrial invasion of EC and predict recurrence and survival [21]. Nougaret et al demonstrated that a TVR ≥ 25% predicted deep myometrial invasion with a sensitivity and specificity of 100% and 93%, respectively [17]. Moreover, Mainenti et al [21] proposed a special method for measuring TV, the diffusion volume (DV), defined as the sum of all voxels within a tumor with ADC values within a specific range. They found that the DV of low-risk EC (stage IA with G1 or G2) was significantly lower than that of medium- (stage IA with G3, stage IB with any G, or stage II) or high-risk EC (stage III or IV) [21]. However, a convenient method of measurement has been reported in the literature [22, 23], and our study referred to their method, as follows: TV = $x \times y \times z/2$. In addition to TV, the largest tumor

Table 3 Interobserver variability in the data measurements performed by two observers

Parameter	Read 1		Read 2		ICC
	Mean±SD, cm	95% CI	Mean±SD, cm	95% CI	
Maximum tumor anteroposterior diameter	3.285±1.358	2.993-3.576	3.161±1.426	2.855-3.467	0.951
Maximum tumor transverse diameter	1.885±1.014	1.667-2.102	1.907±0.954	1.702-2.112	0.962
Maximum tumor craniocaudal diameter	3.772±1.533	3.444-4.101	3.835±1.495	3.514-4.156	0.962
Maximum uterine anteroposterior diameter	6.046±1.558	5.712-6.381	6.046±1.602	5.703-6.390	0.975
Maximum uterine transverse diameter	5.090±1.621	4.742-5.437	5.147±1.618	4.800-5.494	0.987
Maximum uterine craniocaudal diameter	6.475±1.710	6.108-6.841	6.438±1.725	6.068-6.808	0.996
Area of tumor	837.107±593.700	709.817~964.397	817.966±557.038	698.537~937.395	0.983
Area of uterus	2784.344 ±1656.733	2429.140~3139.549	2812.523 ±1683.768	2451.522~3173.523	0.993

Anteroposterior and transverse diameters on oblique axial fat suppression T2W images and craniocaudal diameters on sagittal T2W images

CI confidence interval, *ICC* interobserver correlation coefficient

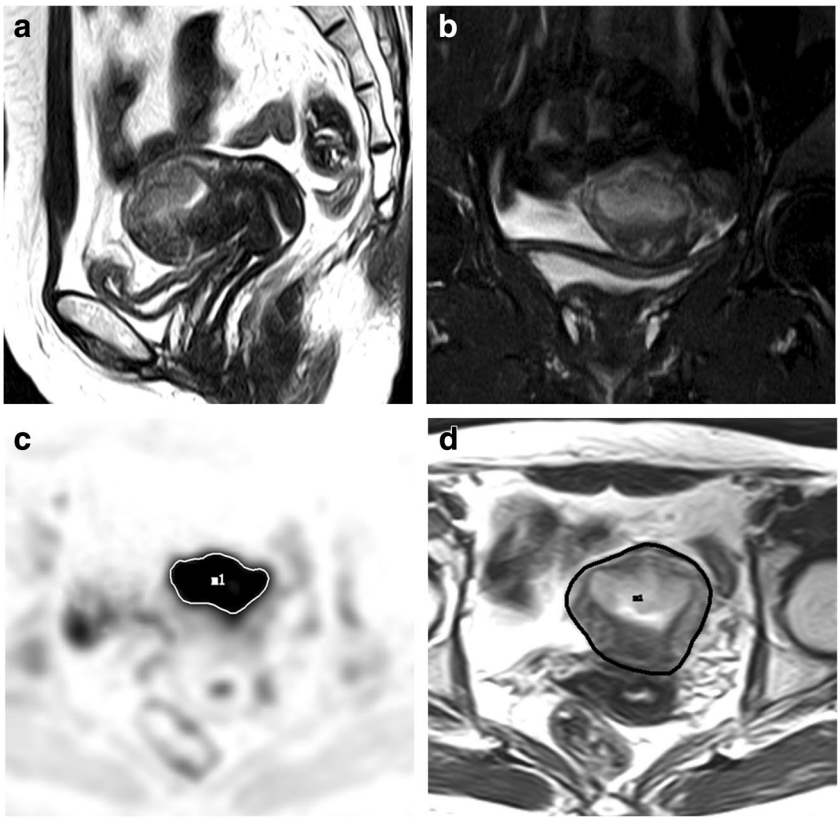


Fig. 3 A 56-year-old female with histopathologically proven grade 2 exophytic endometrioid adenocarcinoma (deep myometrial invasion). (**a**, **b**) The maximum tumor anteroposterior diameter, transverse diameter, and craniocaudal diameter were 1.98 cm, 4.23 cm, and 2.07 cm, respectively. The tumor volume ratio was 13.60%. The tumor (**c**) and uterine areas (**d**) were 847.5 mm^2 and 2010.2 mm^2, respectively. The tumor area ratio was 42.16%

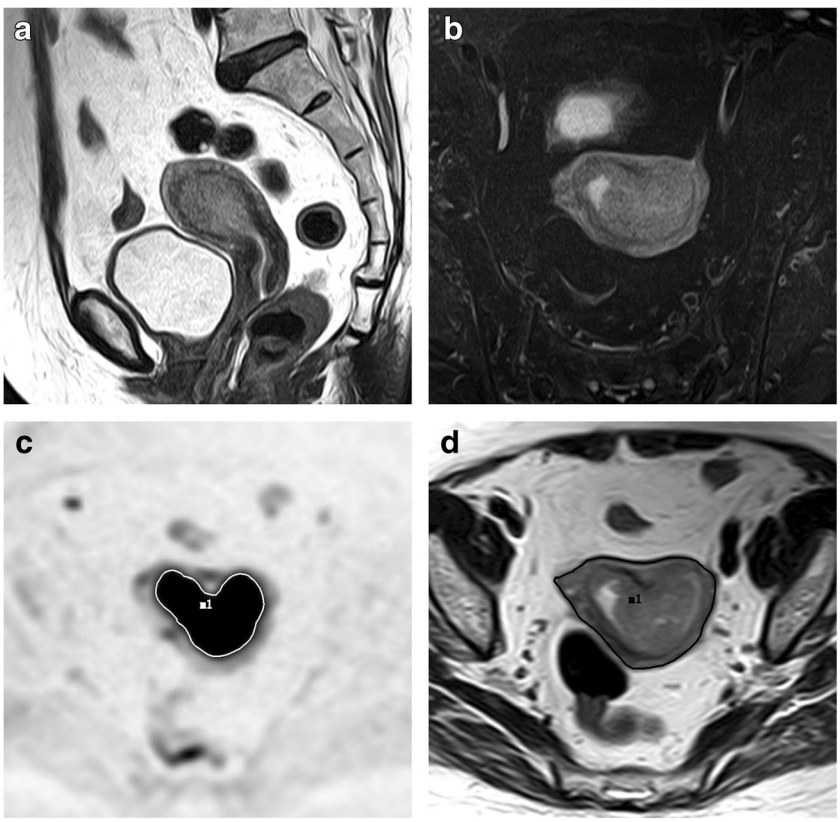


Fig. 4 A 66-year-old female with histopathologically proven grade 3 diffuse endometrioid adenocarcinoma (deep myometrial invasion). (**a**, **b**) The maximum tumor anteroposterior diameter, transverse diameter, and craniocaudal diameter were 3.73 cm, 5.62 cm, and 5.22 cm, respectively. The tumor volume ratio was 62.11%. The tumor (**c**) and uterine areas (**d**) were 1751.35 mm^2 and 2900.19 mm^2, respectively. The tumor area ratio was 60.39%

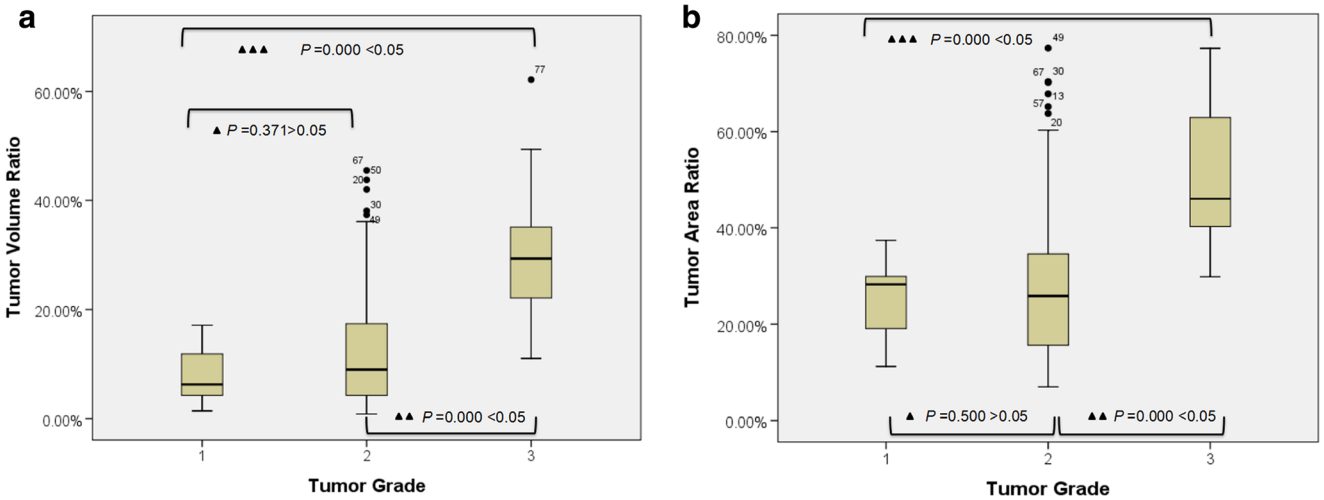


Fig. 5 The tumor volume ratio (**a**) and tumor area ratio (**b**) for different histologic grades of endometrioid adenocarcinoma according to the Mann-Whitney *U* test. "▲", "▲▲", and "▲▲▲" indicate *p* values for the comparisons of TVR and TAR of grade 1 (G1) and grade 2 (G2), G2 and grade 3 (G3), and G1 and G3 tumors, respectively

diameter has also been shown to be associated with deep myometrial invasion in EC [24].

In this study, we found that TAR provided useful and reliable information for predicting deep myometrial invasion of EEA. The greater the value of TAR was, the greater the probability of deep myometrial invasion. According to the ROC curve, the sensitivity, specificity, accuracy, PPV, and NPV were 85.0%, 84.8%, 86.0%, 65.4%, and 95.0%, respectively, for a cutoff TAR value of 34.6%. Moreover, according to our results, TAR was more valuable in predicting deep myometrial invasion than TVR. The AUC of TAR was greater than the AUC of TVR (0.936 vs. 0.844, $p = 0.045$). Some possible explanations for this finding are discussed. First, some cases of EC are complicated by uterine leiomyomas

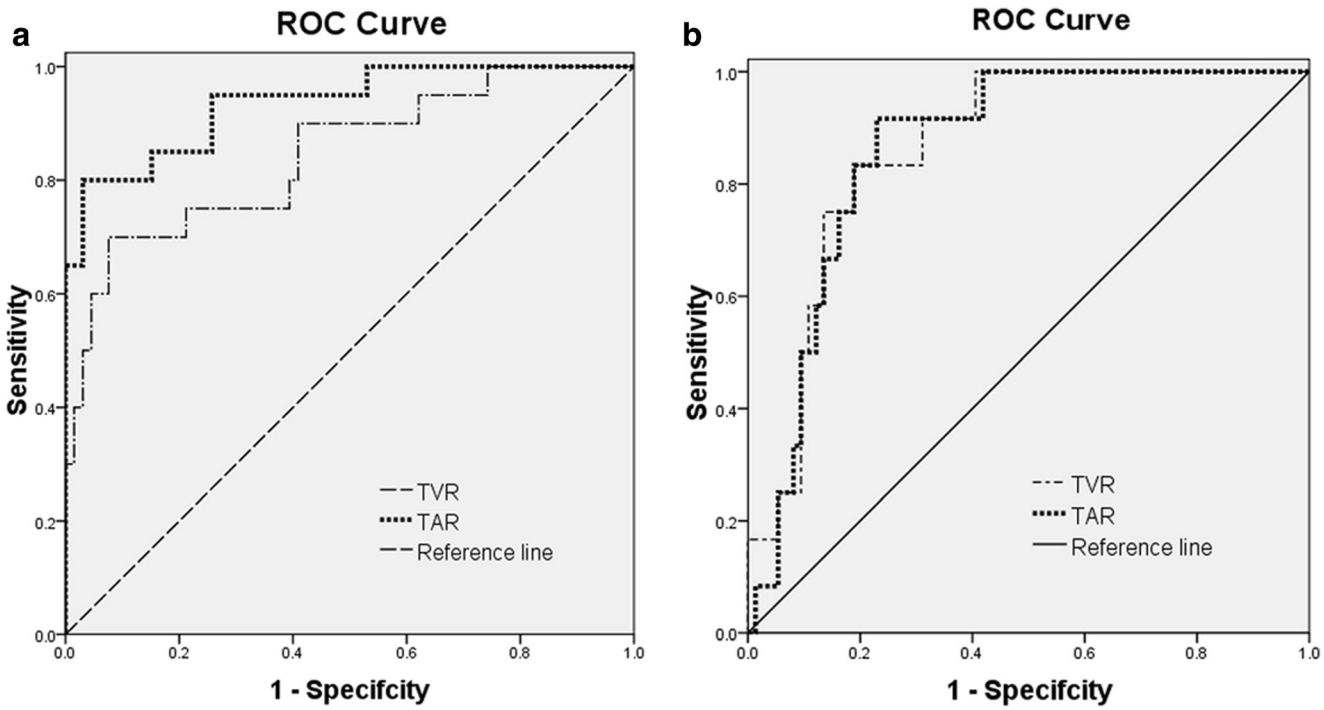


Fig. 6 The ROC curves of the TAR and TVR values used to distinguish deep myometrial from superficial myometrium invasion and to distinguish high- from low-grade endometrioid adenocarcinoma. (**a**) To distinguish deep myometrial from superficial myometrium invasion, the area under the curve (AUC) was 0.936 for TAR (95% CI, 0.873~0.999) and 0.844 for TVR (95% CI, 0.738~0.950) ($p = 0.045$). (**b**) To distinguish high- from low-grade endometrioid adenocarcinoma, the AUC was 0.863 for TAR (95% CI, 0.779~0.946) and 0.865 for TVR (95% CI, 0.779~0.951) ($p = 0.956$)

Table 4 Diagnostic performance of TAR in distinguishing superficial and deep myometrial invasion for differentiating low- from high-grade tumors

Model	Object	Cutoff , %	Sensitivity	Specificity	Accuracy	PPV	NPV
TAR	Depth myometrial invasion	34.6	85.0%	84.8%	86.0%	65.4%	95.0%
	Tumor grade	38.9	83.3%	81.1%	82.6%	83.3%	96.8%

TAR tumor area ratio, *PPV* positive predictive value, *NPV* negative predictive value

and/or adenomyosis, both of which lead to increased uterine volume. With increasing uterine volume, TVR decreases, and thus the ability of TVR to accurately predict deep myometrial invasion decreases. Although an increase in uterine volume may also lead to an increased uterine cross-sectional area in some cases, the effect of area measurement is far less than that of volume measurement. Moreover, EC has two growth patterns: exophytic and diffuse [25]. Exophytic EC mainly involves the myometrium, and the range of tumor growth along the long axis of the uterus may not be very large. Therefore, deep myometrial invasion occurs despite the fact that the TV is not too large. However, compared with TVR, TAR is less affected by the tumor growth pattern. We found that 50% (10/20) of cases of EEA with deep myometrial invasion were exophytic tumors. The TVR of the exophytic tumors was significantly lower than that of diffuse EEA (20.35% vs. 38.25%, p = 0.007). However, no significant difference in TAR was observed between exophytic and diffuse EEA (49.10% vs. 60.44%, p = 0.247). Therefore, TAR is a better prediction tool for deep myometrial invasion. Our measurement method is simpler than the previous volume measurement (based on the sum of all the voxels within a tumor), and the TAR results also achieved a higher diagnostic value. More importantly, the method is easy to use, and results can be obtained quickly. Thus, even a beginner can make accurate judgments. Therefore, we believe that TAR is more clinically useful.

Compared with low-grade EEA, high-grade tumors might have greater TAR values (28.91% vs. 49.87%, p = 0.000). TAR has not been reported as a useful prediction tool in the literature. However, studies have reported a similar correlation between TV and the tumor grade of EC. Nougaret et al [17] reported that the mean TV and TVR were significantly greater in patients with G3 tumors than in patients with G1 and G2 tumors. Using a threshold of 25%, a TVR ≥ 25% enabled the prediction of G3 tumors with a sensitivity of 83%, specificity of 65%, PPV of 55%, NPV of 92%, and accuracy of 70%. A study of the preoperative risk stratification of EC using ^{18}F-FDG PET/CT found that metabolic TV predicts high-grade EEA (p = 0.013) [26]. Our results agree with these findings. We observed that high-grade tumors might have a greater TVR than low-grade tumors (30.68% vs. 12.17%, p = 0.000). However, previous studies do not provide an explanation of why TV is a good predictor of tumor grade. We speculate that the lower the degree of tumor differentiation is, the higher the cell density and the faster the growth rate, leading to a greater tumor volume. In ROC curve analysis, no significant differences in the AUCs for TAR and TVR were observed (0.863 vs. 0.865, p = 0.956), indicating that the two models had the same efficacy in distinguishing low- and high-grade tumors. We found that the application of TAR to predict high-grade tumors yielded a sensitivity of 83.3%, specificity of 81.1%, accuracy of 82.6%, PPV of 83.3%, and NPV of 96.8% for a cutoff value of 38.9%.

This study differs from previous studies in the following two ways. (1) Only EEA was included because lymphadenectomy should be performed to determine the histologic subtypes of EC (mucinous carcinoma, serous carcinoma, clear cell carcinoma, mixed carcinoma, squamous cell carcinoma, and undifferentiated carcinoma), regardless of whether deep myometrial invasion is observed. (2) A simple measurement method was utilized to predict tumor histologic grade and deep myometrial invasion in EEA.

This study has several limitations. First, the study population was relatively small. Specifically, the number of G3 EEA cases was small. However, most EC is well to moderately differentiated and arises in a background of endometrial hyperplasia. Approximately 10% of EC features high-grade lesions [27]. Furthermore, some special types of EC (such as clear cell carcinoma, mixed adenocarcinoma, undifferentiated carcinoma, and carcinosarcomas) were excluded from this study. More cases are needed to increase the statistical power. Second, unenhanced contrast MRI and a DWI scan were performed in all patients in this group. Therefore the maximum diameter of the tumor was measured on T2WI. Consequently, the tumor boundary profile is not sufficiently accurate. However, according to previous studies [17], there was no significant difference in TV between axial oblique T2WI and CE-MRI. Moreover, omitting contrast agents improves the range of preoperative MR experiments and has greater economic benefits.

In conclusion, TAR was useful for predicting deep myometrial invasion and high-grade FIGO stage I EEA. By combining these two important pieces of information, most patients with FIGO stage I EEA can forgo lymphadenectomy to improve their prognosis.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Bin Yan, Department of Radiology, Shaanxi Provincial Tumor Hospital, Xi'an Jiaotong University, Xi'an Shaanxi, P.R China.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors (Wenjun Liu) has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in: Yan B et al Can the apparent diffusion coefficient differentiate the grade of endometrioid adenocarcinoma and the histological subtype of endometrial cancer? Acta Radiol, 2018, 59:363-370.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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