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Three-dimensional power Doppler angiography in endometrial cancer: correlation with tumor characteristics

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KEYWORDS: endometrial cancer; histological characteristics; power Doppler; three-dimensional ultrasound

ABSTRACT

Objective *To assess the correlation between intratumoral vascularization using three-dimensional power Doppler angiography (3D-PDA) and several histological tumor characteristics in a series of patients with endometrial carcinoma.*

Methods *Ninety-nine women (mean age, 61.7 (range, 31–84) years) diagnosed as having endometrial cancer were assessed by transvaginal 3D-PDA before surgical staging. Endometrial volume (EV) and 3D-PDA vascular indices (vascularization index (VI), flow index (FI) and vascularization flow index (VFI)) were calculated using the Virtual Organ Computer-aided AnaLysis (VOCAL™) method. All patients were surgically staged. Individual tumor features such as histological type, tumor grade, myometrial infiltration depth, lymph-vascular space involvement, cervical involvement, lymph node metastases and tumor stage were considered for analysis. Multivariate logistic regression (MLR) analysis was used to determine which 3D-PDA parameters were independently associated with each histological characteristic.*

Results *MLR analysis showed that only EV and VI were independently associated with myometrial infiltration (EV: odds ratio (OR), 1.119 (95% CI, 1.025–1.221),* P = *0.012; VI: OR, 1.127 (95% CI, 1.063–1.195),* P = *0.001) and tumor stage (EV: OR, 1.103 (95% CI, 1.012–1.202),* P = *0.025; VI: OR, 1.120 (95% CI, 1.057–1.187),* P = *0.001), only VI was independently associated with tumor grade (OR, 1.056 (95% CI, 1.023–1.091),* P = *0.001) and only EV was independently associated with lymph node metastases (OR, 1.086 (95% CI, 1.017–1.161),* P = *0.001).*

Conclusion *3D-PDA analysis of tumor vascularization in endometrial cancer correlates with some prognostic histological characteristics.*

INTRODUCTION

Angiogenesis plays a crucial role in tumor growth and mestastasis[1]. Specifically, it has been shown to be an important event in the development of endometrial cancer[2]. Two-dimensional (2D) Doppler ultrasound allows *in-vivo* assessment of tumor vascularization[3], which in turns reflects tumor angiogenesis[4]. This technique has been applied for assessing angiogenesis in endometrial cancer and its correlation with tumor features, but with conflicting results[5–11].

Three-dimensional (3D) ultrasonography and power Doppler angiography (PDA) has been introduced as a new sonographic diagnostic tool. This technology allows acquisition of an endometrial volume and evaluation of the vascularity of the entire endometrium using 3D power Doppler mapping. Using Virtual Organ Computer-aided AnaLysis (VOCAL™) software, three vascularity indices can be calculated automatically: the vascularization index (VI), the flow index (FI) and the vascularization flow index (VFI)[12]. This technique has been shown to have high reproducibility for assessing endometrial volume and 3D power Doppler indices in cases of endometrial cancer[13].

The aim of this study was to assess the correlation of intratumoral vascularization using 3D-PDA with several individual tumor characteristics in a series of patients with endometrial carcinoma.

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METHODS

Patients

Institutional review board approval was obtained before starting the study and all women gave verbal informed consent. From January 2004 to December 2008, 118 consecutive women diagnosed as having endometrial cancer were recruited for this prospective observational study. Patients were collected at two centers: Clinica Universitaria de Navarra, Pamplona, Spain ($n = 102$ (86%)) and Ruber International Hospital, Madrid, Spain ($n = 16$ (14%)). All patients had histologically proven endometrial cancer following office microcurettage or hysteroscopic biopsy and were scheduled for surgical staging.

We excluded 19 women from the study for the following reasons: surgery not performed ($n = 4$), final histological diagnosis other than epithelial endometrial cancer ($n = 6$), incomplete pathological report ($n = 4$), or 3D volume not adequate ($n = 5$), either because the endometrium was not included completely within the volume ($n = 2$) or there was an intrauterine fluid collection that disturbed endometrial volume assessment ($n = 3$).

Ultrasound examination

All sonographic examinations were performed within 1 week prior to surgery, with patients in the lithotomy position and their bladder empty, using a Voluson 730 Expert (GE Healthcare, Milwaukee, WI, USA) machine equipped with a multi-frequency endovaginal probe (3–9 MHz). Three operators (J.L.A., L.M. and R.G.) with 7, 7 and 3 years' experience in 3D ultrasound, respectively, performed all examinations according to a predetermined strict scanning protocol[13]. A 2D ultrasound exploration of the uterus and adnexa was carried out initially. Endometrial thickness was measured in the sagittal plane, including both layers, at the level of maximal thickness. After B-mode evaluation, the 2D power-Doppler gate was activated to assess vascularization of the myometrium and endometrium. Power Doppler settings were set to achieve maximum sensitivity to detect low velocity flow without noise (frequency, 5 MHz; power Doppler gain, 0.8; dynamic range, 20–40 dB; edge, 1; persistence, 2; color map, 5; gate, 2; filter, L1; pulse repetition frequency, 0.6 kHz). The 3D volume was then activated to obtain a 3D box from the uterus. Using a sweeping angle of 90°, the acquisition box of the 3D volume was placed over the power Doppler window. Asking the patient to remain as still as possible, volume acquisition was performed during a 15–20-s time interval. Volume acquisition was repeated if there were flash-type artifacts due to respiratory or intestinal movements. In four (4%) cases no color signal was detected within the endometrium, but these cases were not excluded from analysis.

Stored volume analysis

Two examiners (J.L.A. and L.M.) performed all volume analyses. Examiners knew patients had cancer but they were blinded to definitive histological results. Using the VOCAL program (4DView software, GE Healthcare), the endometrial area was outlined manually in the coronal plane. Using a rotational technique with a 9° step, 20 endometrial slices were obtained outlining the endometrium at the myometrial–endometrial junction from the fundus to the internal cervical os. In those cases in which cervical involvement was suspected on ultrasound, we included this also in the 3D-volume assessment (Figure 1). The 3D power Doppler indices (VI, FI and VFI) were calculated automatically by the VOCAL software (Figure 2). VI, expressed as percentage, measures the number of color voxels in the studied volume, representing the blood vessels within the tissue. FI, expressed as a number ranging from 0 to 100, is the average color value of all color voxels, representing the average color intensity. VFI, also expressed as a number ranging from 0 to 100, represents the mathematical relationship between VI and FI.

Surgical staging

All patients underwent surgical staging. In most cases this included total abdominal hysterectomy with bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection or sampling, pelvic and abdominal cytological washings and infracolic omentectomy. Para-aortic sampling and infracolic omentectomy were not performed in well-differentiated endometrioid adenocarcinomas with $\leq 50\%$ myometrial infiltration at intraoperative frozen section assessment.

In all cases, pathological data such as histological type, tumor grade, myometrial infiltration depth, lymph-vascular space involvement (LVSI), cervical involvement and lymph node metastases were obtained. Tumor histological grade was determined according to the three-grade system, in which Grade 1 (G1) had gland formation in $> 95\%$ of the tumor area, Grade 2 (G2) had a solid growth pattern in 5–50% of the tumor and Grade 3 (G3) had a solid pattern in $> 50\%$ of the tumor. Tumors were staged according to FIGO criteria[14].

For analytical purposes the following histological characteristics were dichotomized: histological type: endometrioid vs. other (including adenoachantoma, adenosquamous, clear-cell, serous-papillary); histological grade: G1–G2 vs. G3; myometrial infiltration: none or $< 50\%$ vs. $\geq 50\%$; tumor stage: Ia–Ib vs. $\geq$ Ic.

Statistical analysis

Kolmogorov–Smirnov's test was used to evaluate normal distribution of continuous data. All results are presented as mean and SD values or as median and interquartile range according to the distribution of data. Categorical results are presented as numbers of

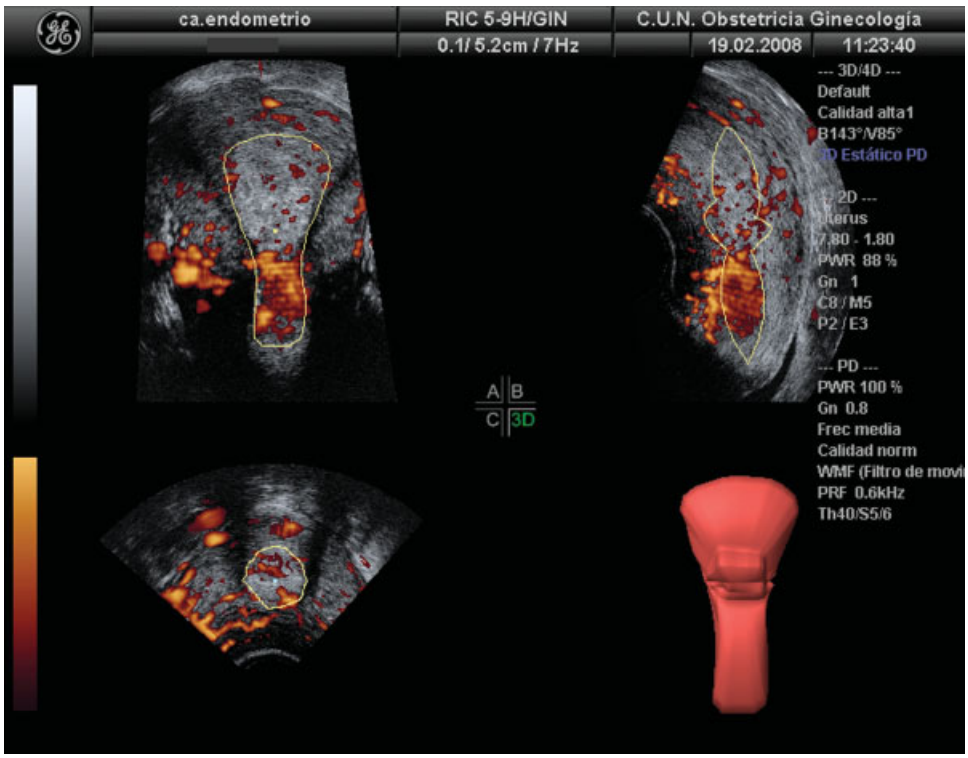

Figure 1 Three-dimensional endometrial volume estimation in a case of endometrial cancer. The tumor arises from the isthmus and extends to the cervix. Vascular Doppler signals are seen mainly at the level of the isthmus and the cervical channel is seen to be enlarged.

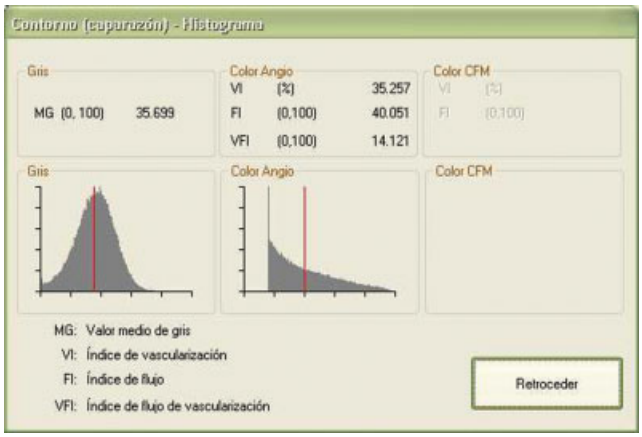

Figure 2 Three-dimensional power Doppler indices calculated from the volume obtained in Figure 1: mean gray value (MG), vascularization index (VI), flow index (FI) and vascularization flow index (VFI).

cases and percentages. For univariate analysis, continuous variables were compared using one-way analysis of variance or the Mann–Whitney *U*-test, depending on the distribution of raw data. Categorical variables were compared using the chi-square test. Pearson's correlation coefficient was used to assess the correlation between endometrial thickness and endometrial volume. Those variables found to be statistically significant during univariate analysis then underwent multivariate step forward logistic regression (MLR) analysis to determine which were associated independently with each histological characteristic. Receiver–operating characteristics (ROC) curves were then plotted for those variables found to be independently related to each tumor feature in order to determine the best cut-off. Sensitivity, specificity, positive likelihood ratios (LR+) and negative likelihood ratios (LR−) were calculated.

A significance level of $P < 0.05$ was used in all tests. All statistical procedures were carried out using SPSS version 15 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Ninety-nine women were included in the final analysis. Their mean age was 61.7 (range, 31–84) years. Eighty-two (82.8%) were postmenopausal and seventeen (17.2%) were premenopausal.

Tumor histological characteristics are shown in Table 1. Lymph node sampling was not performed in 29 patients with well-differentiated endometrioid adenocarcinomas and < 50% myometrial infiltration on frozen section analysis, due to the very low risk of node involvement. These were considered as negative for analysis.

Myometrial infiltration was related to histological grade (deep myometrial infiltration was found in 81% of G3 tumors vs. 27% of G1–G2 tumors, $P < 0.001$). Lymph node metastases was related to myometrial infiltration (lymph node metastases were found in 31.5% of deeply infiltrating tumors vs. 6.5% of superficially infiltrating tumors, $P < 0.001$).

Table 1 Histological characteristics of endometrial cancer ($n = 99$)

Characteristic	n	%
Histological type		
Endometrioid	83	83.9
Adenosquamous	11	11.1
Serous-papillary	4	4.0
Clear-cell	1	1.0
Histological grade		
Well differentiated (G1)	45	45.5
Moderately differentiated (G2)	33	33.3
Poorly differentiated (G3)	21	21.2
Myometrial infiltration		
None*	13	13.1
$< 50\%$	48	48.5
$\geq 50\%$	38	38.4
Cervical involvement		
No	84	84.8
Yes	15	15.2
LVSI		
No	87	87.8
Yes	12	12.2
Lymph node metastases*		
No	83	83.8
Yes	16	16.2
Tumor stage		
Ia	13	13.1
Ib	42	42.4
Ic	13	13.1
II	11	11.1
III	15	15.1
IV	5	5.1

*Definitive gold standard not available in 29 patients. LVSI, lymph-vascular space involvement.

The mean endometrial thickness was 14.1 (SD, 7.6; range, 1.0–39.8) mm. There were no statistically significant differences regarding endometrial thickness according to tumor type, tumor grade, cervical involvement, lymph node metastases or LVSI. However, tumors with deep myometrial infiltration and advanced stage had a significantly thicker endometrium (Table 2). Endometrial thickness was significantly correlated with endometrial volume ($r = 0.719$, $P < 0.001$), so only endometrial volume, and not endometrial thickness, was entered in the MRL analysis. There was one case of endometrial cancer with an ET of 1.0 mm. This was a 56-year-old postmenopausal woman who was not taking any kind of treatment and who presented with uterine bleeding. The endometrium was quite thin on B-mode ultrasound but on power Doppler examination we noticed a significant amount of blood flow in a focal area at the level of the myometrial–endometrial interface as well as in the endometrium. For this reason we performed endometrial biopsy and cancer was detected. After hysterectomy, pathological analysis revealed a well-differentiated endometrioid carcinoma ($1.6 \times 0.6 \times 0.3$ cm) infiltrating the myometrium superficially.

There was no statistical difference for endometrial volume according to tumor histological type (Table 2). However, endometrial volume was significantly higher in poorly differentiated tumors and deeply invasive tumors, as well as in cases of cervical involvement, lymph node metastases, positive LVSI and tumor stage $\geq$ Ic (Table 2).

Table 2 Endometrial volume (EV) and thickness (ET) according to different dichotomized histological characteristics of endometrial cancers ($n = 99$)

	EV		*ET*	
Characteristic	*EV (mL)*	P	*ET (mm)*	P
Histological type		0.191*		0.270*
Endometrioid	4.682 ± 6.6		13.8 ± 7.5	
Non-endometrioid	7.901 ± 12.4		16.1 ± 8.0	
Histological grade		0.003†		0.181†
Moderately–well differentiated (G1–G2)	4.576 (6.1)		12.6 (8.2)	
Poorly differentiated (G3)	8.381 (10.5)		13.0 (10.0)	
Myometrial infiltration		0.001†		0.001†
$< 50\%$	4.297 (4.5)		11.0 (6.0)	
$\geq 50\%$	8.862 (10.1)		17.3 (10.9)	
Cervical involvement		0.035*		0.085*
No	4.632 ± 5.9		13.6 ± 7.7	
Yes	9.020 ± 9.3		17.2 ± 7.4	
LVSI		0.026†		0.223†
No	4.302 (5.7)		12.0 (6.5)	
Yes	8.542 (9.9)		12.5 (20.5)	
Lymph node metastases‡		0.019*		0.106*
No	4.622 ± 6.2		13.6 ± 7.2	
Yes	8.252 ± 13.1		16.9 ± 8.9	
Tumor stage		0.001†		0.001†
Ia–Ib	3.338 (4.1)		10.0 (6.0)	
$\geq$ Ic	8.541 (9.4)		17.0 (9.5)	

Data are expressed as mean $\pm$ SD or median (interquartile range). *ANOVA one-way test. †Mann–Whitney *U*-test. ‡Definitive gold standard not available in 29 patients. LVSI, lymph-vascular space involvement.

Table 3 Three-dimensional power Doppler angiography indices according to different dichotomized histological characteristics of endometrial cancers ($n = 99$)

	VI		*FI*		*VFI*	
	VI (%)	P*	*FI*	P*	*VFI*	P*
Histological type		0.190		0.171		0.658
Endometrioid	8.271 (16.0)		30.200 (11.4)		2.335 (4.8)	
Non-endometrioid	16.248 (31.4)		32.164 (12.4)		4.799 (11.5)	
Histological grade		0.001		0.028		0.001
Moderately–well differentiated (G1–G2)	7.311 (13.8)		29.211 (11.4)		2.042 (4.3)	
Poorly differentiated (G3)	22.000 (28.6)		33.167 (5.2)		6.101 (8.4)	
Myometrial infiltration		0.001		0.001		0.001
< 50%	3.110 (10.9)		26.510 (9.7)		0.813 (3.0)	
≥ 50%	23.915 (26.1)		34.731 (6.4)		7.372 (10.3)	
Cervical involvement		0.003		0.008		0.002
No	7.585 (16.6)		29.910 (11.9)		2.193 (4.9)	
Yes	17.612 (35.3)		33.617 (10.1)		6.101 (11.1)	
LVSI		0.046		0.008		0.041
No	7.307 (16.3)		29.100 (11.9)		1.574 (4.4)	
Yes	16.306 (32.1)		36.422 (5.1)		6.221 (11.4)	
Lymph node metastases†		0.023		0.071		0.039
No	7.315 (16.1)		30.157 (12.8)		2.077 (5.2)	
Yes	14.550 (14.5)		33.614 (6.9)		4.369 (4.0)	
Tumor stage		0.001		0.001		0.001
Ia–Ib	3.052 (9.5)		26.427 (10.2)		0.765 (2.3)	
≥ Ic	18.641 (25.3)		33.614 (6.7)		5.715 (9.7)	

Data are expressed as median (interquartile range). *Mann–Whitney *U*-test. †Definitive gold standard not available in 29 patients. FI, flow index; LVSI, lymph-vascular space involvement; VFI, vascularization flow index; VI, vascularization index.

Regarding 3D-PDA analysis, as expected, in those four cases without blood flow detected, the VI, FI and VFI values were 0. However, these cases were included in the final analysis. Their histological types included two endometrioid adenocarcinomas, one serous-papillary adenocarcinoma and one adenosquamous carcinoma. As with endometrial volume, there were no statistical differences for VI, FI and VFI according to tumor histological type (Table 3), while all three were significantly higher in poorly differentiated tumors and deeply invasive tumors, as well as in cases of cervical involvement, lymph node metastases, positive LVSI and tumor stage ≥ Ic, except in the case of FI according to lymph node metastases (Table 3).

MLR analysis revealed that only endometrial volume and VI were independently associated with myometrial infiltration and tumor stage (Table 4), only VI was independently associated with tumor grade and only endometrial volume was associated with lymph node metastases. Neither endometrial volume nor 3D-PDA indices was independently associated with cervical involvement or LVSI.

ROC curves showed that the best cut-off for predicting deep myometrial infiltration was 2.328 cm^3 for endometrial volume (sensitivity, 92%; specificity, 38%; LR+, 1.5 (95% CI, 1.2–1.8); LR−, 0.2 (95% CI, 0.1–0.7)) and 6.950% for VI (sensitivity, 92%; specificity, 62%; LR+, 2.5 (95% CI, 1.7–3.6); LR−, 0.1 (95% CI, 0.04–0.4)). The best cut-off for predicting tumor stage ≥ Ic was 3.960 cm^3 for endometrial volume (sensitivity, 89%; specificity, 60%; LR+, 2.2 (95% CI, 1.6–3.1); LR−, 0.2 (95% CI, 0.1–0.4)) and 7.343% for VI (sensitivity, 86%; specificity, 69%; LR+, 2.8 (95% CI, 1.8–4.2); LR−, 0.2 (95% CI, 0.1–0.4)). The best cut-off for endometrial volume for predicting lymph node metastases was 4.632 cm^3 (sensitivity, 81%; specificity, 51%; LR+, 1.6 (95% CI, 1.2–2.3); LR−, 0.4 (95% CI, 0.1–0.9)). The best cut-off for VI for predicting poor differentiated histological grade was 9.821% (sensitivity, 81%; specificity, 60%; LR+, 2.0 (95% CI, 1.4–2.9); LR−, 0.3 (95% CI 0.1–0.8)).

Table 4 Multivariate logistic regression analysis for histological characteristics of endometrial cancers ($n = 99$)

	Coefficient	*Odds ratio (95% CI)*	P
Myometrial infiltration			
Endometrial volume	0.112	1.119 (1.025–1.221)	0.012
VI	0.119	1.127 (1.063–1.195)	0.001
Tumor stage			
Endometrial volume	0.098	1.103 (1.012–1.202)	0.025
VI	0.114	1.120 (1.057–1.187)	0.001
Lymph node metastases			
Endometrial volume	0.083	1.086 (1.017–1.161)	0.001
Tumor grade			
VI	0.055	1.056 (1.023–1.091)	0.001

VI, vascularization index.

DISCUSSION

Our results showed that endometrial volume and 3D vascular indices correlated with most individual

tumor histological characteristics. Interestingly, both endometrial volume and VI were related independently to myometrial infiltration depth and tumor stage, whereas only VI was related to tumor grade and only endometrial volume was related with lymph node metastases. These results make sense if we consider current knowledge derived from histological data. The risk of deep myometrial infiltration is known to increase with tumor size[15] and angiogenesis is higher in poorly differentiated tumors[16,17]. Myometrial infiltration and tumor grade are the two most important histological factors associated with lymph node metastases[18]. Furthermore, angiogenesis itself has been shown to be an independent prognostic indicator in endometrial carcinoma[19–21].

It has been shown that the use of color Doppler ultrasound allows the preoperative *in-vivo* assessment of tumor angiogenesis[4]. It seems logical, therefore, to suppose that tumor blood flow could be correlated with individual tumor histological features. Yet, several papers assessing the correlation between pulsed Doppler velocimetric indices and tumor characteristics in endometrial cancer have produced conflicting results. Some authors did not observe any relation between intratumoral Doppler and tumoral stage, histological grade, myometrial infiltration and metastases in the lymphatic nodes[5,6,8], while others found that intratumoral pulsed Doppler correlates with tumor grade and can predict tumoral dissemination both at a regional level (myometrium and cervix) and at a distance (lymph nodes)[7,9–11]. These conflicting results could be explained by the low reproducibility of pulsed Doppler measurements and the overlapping observed for velocimetric indices[11,22].

3D power Doppler seems capable of overcoming at least one of these limitations: reproducibility of the technique. Several papers have shown high interobserver reproducibility for endometrial volume calculations and 3D vascular index estimation[12,23]. Specifically, we have demonstrated this in cases of tumoral endometria[13]. To date, however, very few studies have evaluated the role of 3D power Doppler in the assessment of endometrial pathology. Odeh *et al.*[24] and Mercé *et al.*[25] showed that endometrial cancer exhibits a higher vascularization as assessed by 3D-PDA than does endometrial hyperplasia, and this was recently confirmed by our group[26], but, to our knowledge, no study has analyzed the correlation of tumor vascularity as assessed by 3D-PDA and individual endometrial tumor characteristics.

De Smet *et al.*[27] analyzed the correlation between endometrial volume and myometrial infiltration in a series of 97 women with endometrial cancer. Using MLR analysis they found that the predicted probability of deep myometrial infiltration increased when the endometrial thickness increased, while this probability decreased when endometrial volume increased. The authors themselves remarked that this was an unexpected finding but could be explained by non-linear effects. However, they calculated endometrial volume according to the formula for a prolate ellipsoid, while we used a 3D rotational method. For this reason our results might not be comparable.

Although our findings are interesting, the application of these results in clinical practice may be limited as we observed some overlapping of 3D-PDA values, which could make it difficult to establish a clinically useful cut-off. In fact, the overall diagnostic performance for predicting myometrial infiltration, tumor grade, lymph node metastases and tumor stage was only moderate with the best cut-offs we determined.

In conclusion, although our series was relatively small, our data indicate that 3D-PDA analysis of tumor vascularization in endometrial cancer correlates with some prognostic histological characteristics. Further studies in larger series are needed to confirm or refute these preliminary data.

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