

Tumoral volume measured preoperatively by magnetic resonance imaging is related to survival in endometrial cancer

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Background. The aim of the study was to determine if the endometrial tumor volume (TV) measured by magnetic resonance imaging (MRI-TV) is associated with survival in endometrial cancer and lymph nodes metastases (LN+).

Patients and methods. We evaluated the MRI imaging and records of 341 women with endometrial cancer and preoperative MRI from 2008 to 2018. The MRI-TV was calculated using the ellipsoid formula measuring three perpendicular tumor diameters. Tumor myometrial invasion was also analyzed.

Results. Higher MRI-TV was associated with age ≥ 65 y, non-endometrioid tumors, grade-3, deep-myometrial invasion, LN+ and advanced FIGO stage. There were 37 patients with LN+ (8.8%). Non-endometrioid tumors, deep-myometrial invasion, grade-3 and MRI-TV ≥ 10 cm³ were the factors associated with LN+. Using a receiver operating characteristic [ROC] curve, the MRI-TV cut-off for survival was 10 cm³ (area under curve [AUC] = 0.70; 95% CI: 0.61–0.73). 5 years disease-free (DFS) and overall survival (OS) was significantly lower in MRI-TV ≥ 10 cm³ (69.3% vs. 84.5%, and 75.4% vs. 96.1%, respectively). MRI-TV was considered an independent factor of DFS (HR: 2.20, 95% CI: 1.09–4.45, $p = 0.029$) and OS (HR: 3.88, 95% CI: 1.34–11.24, $p = 0.012$) in multivariate analysis.

Conclusions. MRI-TV was associated with LN+, and MRI-TV ≥ 10 cm³ was an independent prognostic factor of lower DFS and OS. The MRI-TV can be auxiliary information to plan the surgery strategy and predict the adjuvant treatment in women with endometrial cancer.

Key words: tumoral volume; magnetic resonance image; endometrial cancer; recurrence; survival

Introduction

Endometrial cancer (EC) is the most common malignant tumor of the female reproductive tract in developed countries. Its prevalence has increased worldwide in the last years.^{1,2,3} In Spain, EC is the third most common cancer in women and the most common tumor of the female genital tract.⁴

Patient prognosis depends on different factors, including stage, depth of myometrial invasion

(DMI), lymphovascular space invasion, grade, and nodal status. Besides molecular alterations, DMI is one of the most important morphologic prognostic factors, correlating with tumor grade, presence of lymph node (LN) metastases and survival.^{5,6} Preoperatively, magnetic resonance imaging (MRI) can accurately assess the DMI⁴, whereas histologic type and grade only can be determined with endometrial tumor sampling.

Standard surgical therapy for localized EC includes hysterectomy with bilateral salpingo-oophorectomy (HT & BSO); however, the criteria for selecting patients for lymphadenectomy (LND) are still controversial.^{7,8} During the last two decades many authors have attempted to identify prognostic factors for stratifying women with EC into risk categories, in order to tailor the surgical and adjuvant treatment on the basis of estimated risk of tumor dissemination and recurrence.⁷ Different investigators have defined low-risk groups consistent with disease confined to the uterine corpus, histologic grade 1 or 2, endometrioid histologic subtype, less than 50% DMI and tumor diameter of 2 cm or less to avoid LND.^{7,9,10} The LN evaluation is recommended in intermediate and high-risk EC.⁸ However, recent matched-pair studies have observed a lack of survival benefit of the systematic LND in those types of EC.^{11,12}

Although tumor size is a factor that determines the stage of disease in many types of cancer (head and neck, breast, lung, renal, uterine cervix, vulva, uterine sarcoma, melanoma and soft tissue sarcoma), it is not involved in defining the stage of EC.¹³ Different authors have been trying to demonstrate the relationship between tumor diameter in resected uterine specimens and prognosis in EC.^{9,10} Naturally, postoperative assessment is not suitable for taking decisions of the better surgical approach and for selecting patients for neoadjuvant therapies. Therefore, preoperative assessment impacts the planning for surgery.¹⁴ Hence, some recent Japanese studies measured preoperatively tumor volumes by MRI, concluding that it is effective for predicting LN metastases and planning the LND.^{15,16} However, there is no good evidence about the role of tumor volume (TV) measured by MRI in the patient's prognosis.

The aim of this study was to determine if the tumor volume measured in the preoperative MRI study (MRI-TV) has a relationship with disease-free survival (DFS) as a primary objective and with overall survival (OS) and LN involvement as secondary goals.

Patients and methods

A historical cohort of women diagnosed of EC between 2008 and 2018 was analyzed in Hospital Clinico San Carlos in Madrid, Spain. We included all women diagnosed of EC who underwent a presurgical MRI. All the patients had undergone HT & BSO. Pelvic or pelvic and para-aortic LND

were always performed by the same oncological team. Women diagnosed with uterine sarcomas or concomitant neoplasm, those who had been treated with primary chemo and/or radiotherapy or had been operated without presurgical MRI were excluded. The study was approved by the local Institutional Review Boards (No. 16/443-E). All patients were managed according to the guidelines approved by the Spanish Society of Gynecology and Obstetrics and all of them signed a specific consent form.¹⁷

All MRI studies were performed in 1.5T magnets (Signa Excite and Signa HDx, General Electric Medical Systems) using a standard protocol. High-resolution T2 weighted images were acquired in three perpendicular planes and then contrast enhanced T1 fat suppressed series were acquired in two or three different planes. Diffusion weighted sequences ($b \geq 800$ s/mm²) were acquired in most, but not in all the cases. All MR images were analyzed in the Radiology Service of the center by expert radiologists. The maximum tumor diameters were measured in three perpendicular axes, on the images that showed better the tumor-to-myometrium contrast (usually on the gadolinium enhanced series, having the T2 and diffusion images as references). The tumoral volume was calculated using the ellipsoid volume formula ($\text{length} \times \text{height} \times \text{width} \times [\pi/6]$).

In addition, DMI was assessed following the standardized criteria using unenhanced T2 and gadolinium enhanced T1 series. DMI was defined as the distance between the myometrial interface and the deeper invasion point. Deep myometrial invasion was considered when the tumor affected 50% or more of the myometrial thickness.

In 237 cases in which it was the retrieved ultrasound reports, there was information about the DMI that was recorded and included. DMI was assessed during a real-time two-dimensional examination, and deep myometrial invasion was measured as the distance between endometrium-myometrium junction and maximum tumor depth.

In our center, intraoperative frozen section evaluation (FSE) of DMI is routinely performed. This information was available and recorded in 189 cases. Two pathologists with wide experience in gynecological cancers where the ones that performed the intraoperative assessment of myometrial invasion and histological grade in all of the samples.

Continuous variables were described as median and interquartile range [p25-p75] and were compared using the T-test in normal distributions or the Mann-Whitney test in non-parametrical dis-

tributions. Discrete variables were represented with absolute frequencies and percentages, and they were compared by the Chi-squared test or the Fisher's exact test in case of small cell comparisons. The McNemar test was used to assess the differences among the techniques evaluating the deep myometrial invasion. Receiver operating characteristic (ROC) curve was calculated to analyze the relation between the tumoral volume measured by MRI and the recurrence in order to identify the tumoral volume cut-off predicting the relapse. For survival analysis, Cox's method was used in order to assess which factors were directly associated with survival. Multivariate modeling using Cox's proportional hazard models, including the significant variables in univariate analysis, was performed to obtain a subset of independent predictors of DFS and OS. Hazard ratio (HR) with a 95% confidence interval (CI) was calculated. The Kaplan-Meier method was used to estimate the survival distribution depending on the tumoral volume using the cut-off chosen. The Log-Rank (Mantel-Cox) test was used to calculate the statistical signification between the groups in relation to disease recurrence and death. All statistical tests were 2-sided and statistical significance was defined as a *p*-value lower than 0.05. All computations were performed using IBM SPSS Statistic version 22.0 for Windows.

Results

The series baseline is shown in the Table 1. The highest accuracy for detecting DMI was the intra-operative FSE (sensitivity 94%, 95% CI: 88–100%) The MRI had sensitivity of 75%, 95% CI: 66–84% and transvaginal ultrasound 58%, 95% CI: 47–69%, respectively. FSE was significantly more sensitive in detecting deep myometrial invasion than MRI (*p* = 0.049).

The median of MRI-TV was 8.2 cm³ (interquartile range [IQR]: 1.9–20.4). We found that higher MRI-TV was associated with advanced age, the highest histological grade 3, deep myometrial invasion, advanced International Federation of Gynecology and Obstetrics (FIGO) stage, LN involvement, disease recurrence and death (Table 2).

In order to identify a MRI-TV cut-off that could be considered a risk factor in EC, we performed a ROC curve. The more efficient cut-off in detection of tumor recurrence was a TV = 10 cm³, showing a 72.5% sensitivity and 59.8% specificity detecting the tumor recurrence (area under curve [AUC] = 0.70; 95% CI: 0.61–0.73).

TABLE 1. Baseline patient's characteristics

Variable	N=341
Age (years)	65.7 [58.0–74.0]
< 65y	186 (54.5%)
≥ 65y	155 (45.5%)
BMI (kg/m²)	29.3 [24.8–33.0]
< 30	200 (58.7%)
≥ 30	141 (41.3%)
Histologic subtype	
Endometrioid	278 (81.5%)
Mucinous	5 (1.5%)
Squamous	6 (1.8%)
Serous Papillary	23 (6.7%)
Clear cells	13 (3.8%)
Mixed mesodermal tumors	12 (3.5%)
Undifferentiated	1 (0.3%)
Histological Grade	
G1	159 (46.6%)
G2	86 (25.2%)
G3	96 (28.25%)
Myometrial invasion	
< 50%	207 (60.7%)
≥ 50%	134 (39.3%)
FIGO stage	
I	270 (79.2%)
II	15 (4.4%)
III	45 (13.2%)
IV	11 (3.2%)
Surgical treatment	
HT & BSO alone	96 (37.4%)
With pelvic lymphadenectomy	74 (28.8%)
With pelvic & paraaortic lymphadenectomy	87 (33.9%)
Lymph nodes status (N = 216)	
Negatives	179 (82.9%)
Positives	37 (17.1%)
Adjuvant treatment	
None	150 (44.0%)
Irradiation	146 (42.8%)
Chemotherapy	9 (2.6%)
Irradiation and Chemotherapy	36 (10.6%)
Follow-up (months)	30.5 (18.5–46.2)
Recurrence	51 (15.0%)
Decrease	29 (8.5%)

Data are given as median and [interquartile range, p25-p75] or number (percentage).

BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics; HT & BSO = hysterectomy with bilateral salpingo-oophorectomy

Analyzing only the 216 cases in which LND was performed, we found that the LN involvement was associated with the histological subtype, grade 3 and DMI. MRI-TV ≥ 10 cm³ was significantly associated with LN metastases (Table 3).

After a median follow-up of 30.5 months (IQR 18.5–46.2), 51 (15.0%) women presented a relapse and 29 (8.5%) deceased. Among the relapsed patients, 8 were alive and free of disease, 22 were alive with disease, and 21 died. Among the deceased patients, 21 women had disease-related death, and 8 died due to other causes.

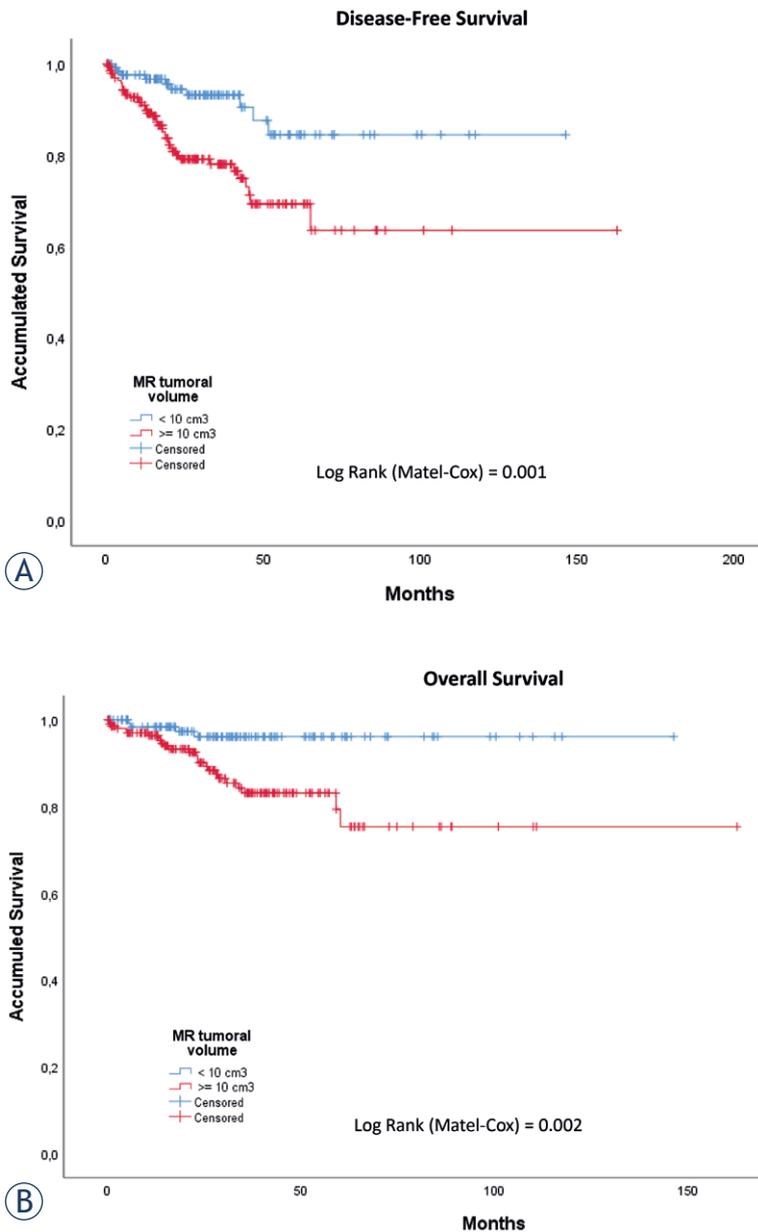


FIGURE 1. Kaplan Meier curves representing the survival in relation of tumoral volume measured by magnetic resonance. **(A)** Disease-free survival; **(B)** Overall Survival.

Survival analysis showed a 5-year DFS of 69.3% in tumors $\geq 10 \text{ cm}^3$, which was significantly lower than in tumors of $< 10 \text{ cm}^3$ (84.5%, Log Rank test: 0.001) (Figure 1A). In relation to OS, 5-year OS survival was lower in tumors $\geq 10 \text{ cm}^3$ in comparison with tumors $< 10 \text{ cm}^3$ (75.4% vs. 96.1%, Log Rank test: 0.002) (Figure 1B). Cox's univariate analysis identified the age ($p < 0.001$), MRI-TV ($p = 0.001$), non-endometrioid tumors ($p = 0.006$), grade-3 ($p < 0.001$), myometrial invasion ($p = 0.009$) and advanced stage ($p < 0.001$) as predicting factors of

TABLE 2. Relation between tumor volume measured by magnetic resonance and pathological factors in 341 endometrial cancer

Variables	MR tumor volume cm^3	p value*
Tumoral volume	8.2 (1.9–20.4)	-
Age (years)		
< 65	5.4 (1.5–15.4)	0.001
≥ 65	11.0 (2.8–30.0)	
BMI (kg/m²)		
< 30	9.1 (2.3–22.3)	0.525
≥ 30	7.5 (1.6–23.6)	
Histologic subtype		
Endometrioid	7.9 (1.8–20.4)	0.859
Non endometrioid	12.4 (3.3–40.1)	
Histological Grade		
G1–G2	6.7 (1.3–17.2)	< 0.001
G3	13.8 (4.6–41.0)	
Myometrial invasion		
< 50%	4.6 (1.2–15.4)	< 0.001
$\geq 50\%$	14.1 (5.7–35.1)	
FIGO stage		
I–II	7.6 (1.5–19.6)	< 0.001
III–IV	15.6 (6.5–44.7)	
Lymph node status (N = 216)		
Negatives	9.3 (3.3–20.9)	0.008
Positives	15.6 (6.3–40.7)	
Recurrence		
No	7.6 (1.7–17.4)	< 0.001
Yes	22.4 (5.6–49.2)	
Overall Survival		
Alive	8.0 (1.8–18.6)	< 0.001
Death	30.5 (9.6–56.4)	

Data are given as median (p25–p75).

* = Mann-Whitney U independent sample test; BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics

recurrence (Table 4). MRI-TV ($p = 0.029$), grade 3 ($p < 0.001$) and advanced stage (III–IV) ($p = 0.047$) were the independent factors of recurrence in the multivariate analysis (Table 5). In relation with OS, the age ($p < 0.001$), MRI-TV ($p = 0.005$), grade-3 ($p = 0.001$) and advanced stage ($p = 0.001$) were the predictor factors of mortality (Table 4). In multivariate analysis, MRI-TV ($p = 0.012$) and grade-3 ($p = 0.011$) were the independent factors of OS.

Discussion

In woman with EC, the preoperative MRI-TV correlates with the LN involvement and is an independent prognostic factor for DFS and OS in this series. A cut-off of 10 cm^3 determines properly the cases that might present with positive LN and should undergo LND. It also adds information about poor prognosis and the need for adjuvant treatment. The relation between relapse and MRI-

TV in EC has been described by other studies. A Japanese study in 667 women with EC and using a volume index defined as the product of the maximum diameter in the 3 planes (longitudinal, anteroposterior and horizontal), found a MRI-TV $\geq 36 \text{ cm}^3$ as an independent prognostic factor of OS (HR 2.0; 95% CI:1.3–3.1).¹⁸ This study used as cut-off a fixed value of MRI-TV based on other study from the same group¹⁶, and considered the volume of the endometrial cavity as a single measure of three measures. In our study, the endometrial cavity was considered as ellipsoid, more like the real shape of the endometrial tumor. However, both studies have similar outcomes, suggesting the MRI-TV is an independent prognostic factor to take in consideration in the preoperative assessment of women diagnosed of EC. In addition, the MRI-TV in the Japanese study was significantly associated with LN involvement, especially when TV was $\geq 125 \text{ cm}^3$. Similar finding was also found in our study when we analyzed the MRI-TV both as continuous variable and as qualitative using 10 cm^3 as cut-off value. The differences in the cut-off may be because of the different method to measure the endometrial cavity. A Japan-Korea cooperative study with the same methodology, found similar results in 327 cases, showing a MRI-TV $> 36 \text{ cm}^3$ as an independent prognostic factor of LN metastases.¹⁹ Other studies analyzing the preoperative metabolic volume by PET/CT and MRI found the tumor volume as an independent prognostic factor for DFS and it was significantly associated with recurrence in patients with endometrioid EC.²⁰

MRI has been considered as the best technique to diagnose deep myometrial invasion. However, in our series, the best option was FSE. A recent study found a higher performance using fusion of T2-weighted magnetic with diffusion-weighted MR images, with a sensitivity of 92.3% and specificity of 95.5% for deep myometrial invasion detection.²¹ In relation to ultrasound, we obtained a poor result in order to detect the deep myometrial invasion. A recent study analyzing 210 women with proven EC found that both subjective assessment and objective ratios were significant predictors of the myometrial invasion, but subjective assessment was confirmed as the most reliable method to assess myometrial invasion (sensitivity 79% and specificity 73%).²² A meta-analysis of 35 studies with 6387 women diagnosed of EC found that FSE had a significantly better diagnostic performance than intraoperative gross evaluation (sensitivity 84% vs. 71%) for the intraoperative diagnosis of deep myometrial invasion.

TABLE 3. Predictor factors of lymph node metastases in 216 cases of endometrial cancer with known lymph node status

Variables	No lymph node metastases N = 179	Lymph node metastases N = 37	p value
Age (years)			
< 65	78 (43.6%)	12 (32.4%)	0.211
≥ 65	101 (56.4%)	25 (67.6%)	
Histologic subtype			
Endometrioid	147 (82.1%)	23 (62.2%)	0.007
Non endometrioid	32 (17.9%)	14 (37.8%)	
Histological Grade			
G1–G2	118 (56.9%)	13 (35.1%)	< 0.001
G3	61 (43.1%)	24 (64.9%)	
Myometrial invasion			
< 50%	90 (50.3%)	8 (21.6%)	0.001
$\geq 50\%$	89 (49.7%)	29 (78.4%)	
Maximum tumor size			
< 2 cm	43 (24.0%)	6 (16.2%)	0.390
$\geq 2 \text{ cm}$	136 (76.0%)	31 (83.8%)	
MR tumor volume			
< 10 cm^3	61 (34.1%)	5 (13.5%)	0.013
$\geq 10 \text{ cm}^3$	118 (65.9%)	32 (86.5%)	

TABLE 4. Analysis of disease-free and overall survival using Cox regression model

Variables	Disease-free	p value	overall	p value
Age (continue, years)	1.06 (1.03–1.09)	< 0.001	1.09 (1.05–1.13)	< 0.001
MRI tumor volume				
< 10 cm^3	1		1	
$\geq 10 \text{ cm}^3$	2.99 (1.50–5.99)	0.001	4.50 (1.56–12.93)	0.005
Histologic subtype				
Endometrioid	1		1	
Non endometrioid	2.55 (1.30–5.01)	0.006	2.40 (0.97–5.95)	0.052
Histological Grade				
G1–G2	1		1	
G3	4.02 (2.31–6.98)	< 0.001	3.55 (1.71–7.37)	0.001
Myometrial invasion				
< 50%	1		1	
$\geq 50\%$	2.10 (1.20–3.64)	0.009	1.89 (0.91–3.93)	0.088
FIGO stage				
I–II	1		1	
III–IV	6.70 (3.83–11.72)	< 0.001	3.94 (1.79–8.68)	0.001

Data are given in Hazard Ratio (95% confidence interval).

FIGO = International Federation of Gynecology and Obstetrics; MRI = magnetic resonance image

The tumoral size has been associated with several classic prognostic factors and it has been considered as a prognostic factor in many human tumors, including gynecological tumors such as cervix, vulva and breast, but not in ovarian and EC.¹³ The Mayo clinic criteria in EC⁹, suggested the tumoral size $> 2 \text{ cm}$ as high risk of LN metastases. In our series, the MRI-TV was associated with the classical prognostic factors in the EC. This finding was also found by other authors.^{18,19} High-risk clinico-

TABLE 5. Multivariate analysis of disease-free and overall survival using Cox regression model with the classic histological prognostic factors

Variables	Disease-free survival	p value	Overall survival	p value
MRI tumor volume				
< 10 cm ³	1		1	
≥ 10 cm ³	2.20 (1.09–4.45)	0.029	3.88 (1.34–11.24)	0.012
Histologic subtype				
Endometrioid	1		1	
Non endometrioid	1.06 (0.50–2.24)	0.873	1.16 (0.43–3.16)	0.766
Histological Grade				
G1–G2	1		1	
G3	3.60 (1.95–6.66)	< 0.001	3.07 (1.47–6.41)	0.003
Myometrial invasion				
< 50%	1		1	
≥ 50%	1.77 (1.01–4.46)	0.047	1.51 (0.72–3.17)	0.279

Data are given in Hazard Ratio (95% confidence interval).

MRI = magnetic resonance image

pathological features (such as deep myometrial invasion, histological grade and non-endometrioid subtypes), LN involvement and advanced FIGO stages were increased with higher MRI-TV, suggesting a positive correlation between it and the adverse outcomes.

Sentinel node biopsy is a good way to have LN status information and to avoid the complete LND.²³ However, this procedure is not free of complications and a preoperative information predicting the LN involvement could help in the process of making the decision of whether or not to perform the LN assessment. Based on our results, we suggest performing a LN assessment in EC with large TV. Nevertheless, we cannot set the best TV cut-off from which assess the LN status.

In our study, the TV was measured by different radiologist, and even though we used the same criteria, it could be a limitation because of the inter-observer variability that can alter the endometrial measures. On the other hand, the type of adjuvant treatment and the type of surgery could differ between the cases and this could have influenced the patients' survival. The main strength of this study, with respect to others that also analyzed the TV, is the use of an ellipsoid to measure the TV, because is the shape more similar to endometrial cavity, and the result of the product of three single measures results on a cubic shape.

Conclusions

In conclusion, the TV measured by MRI is a predictor of high-risk pathological factors, and it is positively associated with LN involvement. The

TV higher than 10 cm³ is related with poor prognosis in univariate and multivariate analysis. The preoperative measure of TV by MRI can therefore be a good tool to determine the best surgery strategy in EC.

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