Sonographic, demographic characteristics, and the Proactive Molecular Risk Classifier for Endometrial cancer (ProMisE) in the prediction of tumor recurrence or progression

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Short title: Prognosis in endometrial cancer - ProMisE and TVS

Keywords: Endometrial Neoplasm, Ultrasonography, Diagnostics Molecular, Risk Assessment, Neoplasm Assessment

What are the novel findings of this work?
A combination of demographic, sonographic and ProMisE prognostic factors had higher ability to predict recurrence or progression than the ESMO classification. Ultrasound tumor size < 2 cm and non-p53 abn status can identify a large group (~50%) at very low risk of recurrence or progression.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.23573

What are the clinical implications of this work?

Ultrasound assessment has an independent prognostic role beyond the ESMO classification, as ultrasound tumor size and p53 status can identify a large group with an excellent prognosis, where sentinel node biopsy or adjuvant treatment may be not be considered necessary. Our findings support the use of ProMisE in preoperative risk stratification.

Abstract

Objectives:
To identify and assess demographic, sonographic and Proactive Molecular Risk Classifier for Endometrial cancer (ProMisE) prognostic factors for recurrence or progression in endometrial cancer (EC).

Methods:
We prospectively included 339 women with EC, undergoing expert transvaginal ultrasound before surgery. Tumors were classified according to FIGO, and ProMisE (MMR-D, POLE EDM, p53wt and p53abn). ProMisE subtypes were compared regarding demographic, sonographic characteristics, recurrence or progression, and survival. Cox regression was used to identify prognostic factors associated with recurrence or progression, with univariable models to study crude associations and multivariable models to study adjusted associations. Logistic regression and ROC curves analysis was used to assess the predictive ability of the prognostic factors, regarding recurrence or progression within three years, and to compared their predictive ability to that of the European Society for Medical Oncology (ESMO) classification. In separate sub analysis, tumors were stratified by p53 status (present/absent) and ultrasound tumor size (< 2 cm/≥ 2 cm).

Results:
Median follow-up time was 58 (IQR, 48—71, range 0—102) months. Recurrence/progression occurred in 51/339 (15%), in MMR-D 14%, POLE EDM 8%, p53wt 9%, and p53abn 46%. The multivariable 'ProMisE model' (ProMisE subtype, age, waist circumference, ultrasound tumor extension and ultrasound tumor size) (AUC 0.89, 95% CI 0.85—0.93) predicted recurrence/progression with comparable ability to the multivariable 'histotype and grade model' (histotype and grade, age, waist circumference, ultrasound tumor extension and ultrasound tumor size) (AUC 0.88, 95% CI 0.83—0.92) and with higher ability than both the preoperative (AUC 0.74, 95% CI 0.67—0.82), p <0.01), and postoperative (AUC 0.79, 95% CI 0.72—0.86), p <0.01) ESMO classification. The 48% with the combination of non-p53abn subtype and tumor size <2cm had a very low risk (1.8%) of recurrence/progression.

Conclusion
A combination of demographic, sonographic and ProMisE prognostic factors had higher ability to predict recurrence or progression than the ESMO classification, supporting their use in preoperative risk stratification. The p53 status combined with ultrasound tumor size has the potential to preoperatively identify a large group of women with a very low risk of recurrence or progression.

INTRODUCTION

Transvaginal ultrasound can be used together with histotype and grade from endometrial biopsy to preoperatively predict the risk of lymph node metastases according to the European Society for Medical Oncology (ESMO) classification[1]. While preoperative ESMO classification (depth of myometrial invasion, histotype, grade) guides decision making for lymphadenectomy, postoperative ESMO classification (surgical stage, grade, histotype, lymphovascular space invasion (LVSI)), guides adjuvant therapy use, based on the risk of recurrence according to variables from the surgical specimen.

Ultrasound is already an established modality in preoperative risk assessment[1], while the ability of ultrasound to predict recurrence or progression before surgery has not been studied. Moreover, the value of biometric variables to predict adverse prognosis needs to be further explored.

Tumor histotype and grade are important in both pre- and postoperative ESMO classification, but have limited reproducibility, particularly in high-grade tumors[2-5]. Moreover, agreement of grade between endometrial biopsy and the hysterectomy specimen is only moderate[6]. These limitations hinder a reproducible categorization of endometrial cancer and limit the value of histotype and grade as risk predictors.

The Cancer Genome Atlas (TCGA) Research Network developed a genomic classification of endometrial cancer with four prognostic subgroups: polymerase-ε (POLE) ultramutated, microsatellite instability (MSI) hypermutated, copy-number low (CN low) and copy number high (CN high)[7], however requiring costly and complex methodologies. The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) was developed and validated as a clinically applicable surrogate molecular classifier[8-11], rendering the corresponding prognostic subgroups: polymerase-ε exonuclease domain mutations (POLE EDM), mismatch repair proteins deficiency (MMR-D), protein 53 wild type (p53 wt) and protein 53 abnormal (p53 abn). A molecular classification system is more robust and objective than histotype and grade, as it is based on the presence or absence of a protein or mutation. It allows classification of all endometrial cancers already in the preoperative setting, where several prognostic factors, such as surgical stage and LVSI, are not available. Moreover, in contrast to histotype and grade, ProMisE is highly concordant on diagnostic endometrial biopsy and hysterectomy specimen[11, 12].

The objective of this study was to preoperatively identify and assess demographic, sonographic and ProMisE prognostic factors for recurrence or progression in women with endometrial cancer.

METHODS

The study cohort consisted of women with endometrial cancer from the Stockholm center of the prospective IETA (International Endometrial Tumor Analysis) 4 study[13]. Inclusion lasted between January 1st 2011 and December 31st 2015, with end of follow up on August 31st 2019. Inclusion criterion was histologically confirmed endometrial cancer in the preoperative biopsy and/or the hysterectomy specimen. Only epithelial malignant tumors (endometrial carcinomas: endometrioid-, mucinous-, serous-, clear cell-, mixed cell-, and undifferentiated carcinoma) and mixed epithelial and mesenchymal malignant tumors (carcinosarcomas) were included. Exclusion criteria were hysterectomy; not performed, carried out at another hospital or performed more than 120 days after the ultrasound examination, final diagnosis other than endometrial cancer, incomplete ultrasound data, duplicate entries, error in the identification key and insufficient material for the construction of a tissue microarray and isolation of genomic DNA from formalin-fixed paraffin-embedded tumor tissue.

All women had been subject to preoperative ultrasound examination by one and the same ultrasound expert, before surgery with hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy. Ultrasound tumor size (anteroposterior (AP) tumor diameter), extension and morphology were assessed according to the IETA examination technique and terminology[14]. Tumor AP diameter was measured in the sagittal plane. Color/power Doppler examinations were carried out at pulse repetition frequency of 0.3 to 0.9 kHz. Pathologists classified all cases according to the FIGO 2009 staging system[15] and grade according to the standard FIGO grading system[16]. Detailed medical and reproductive history, using a standardized questionnaire, and biometric data (height, weight and waist circumference, measured by the physician/nurse on the day of ultrasound examination) were included in the study protocol. All demographic and sonographic variables were entered into an internet-based data capture software (Clinical Data Miner (https://cdm.esat.kuleuven.be)[17]) on the day of ultrasound examination. Histological outcome and stage was entered into the database after surgery. Data on recurrence, progression, and survival was obtained through review of the patient´s digital medical records.

The ProMisE subtypes (MMR-D, POLE EDM, p53 wt and p 53 abn) were analyzed retrospectively on biobanked tumor tissue. Two pathologists, blinded for patient characteristics and outcomes, reviewed all immunohistochemistry stains independently and resolved any interpretative discrepancies at a multiheaded microscope, by consensus. As p53 immunohistochemistry staining was performed as clinical routine in all endometrial cancer cases, it was obtained from full tumor sections. To assess p53 the immunohistochemistry was assigned into three groups: 0 = completely absent, 1 = 1 — 80% of the tumor nuclei showed heterogeneous staining, 2 = > 80% of tumor nuclei showed strong positive staining. Group 1 was considered as p53 wt and groups 0 and 2 as p53 abn. Mismatch repair (MMR) status was analyzed by immunohistochemistry on tissue microarrays from formalin-fixed paraffin-embedded tumor tissue. The microsatellite-stability proteins (MSH2, MSH6, PMS2, MLH1) were interpreted in the following way: the tumor was considered aberrant if tumor cells showed complete absence of nuclear staining of ≥ 1 of the microsatellite-stability proteins, and intact if tumor cells showed nuclear positivity.

Mismatch repair proteins were considered absent (MMR-D) if ≥ 1 of four microsatellite-stability proteins were missing, or intact if all four microsatellite-stability proteins were present. POLE was analyzed from genomic DNA, which was isolated from two 1 mm core punches of formalin-fixed paraffin embedded tissue. Mutations of the POLE gene (NM.006231) exons 9 to 14 were analyzed by Sanger sequencing. The following POLE mutations were considered pathogenic: P286R, V411L, S297F, A456P or S459F. These are the five most common pathogenic variants described and have the strongest data linking them to the ultramutated phenotypes[8, 18-20]. ProMisE classification of the tumors was performed according to the pragmatic model by Talhouk et al[10]. Tumors with deficient mismatch repair proteins were classified as "MMR-D". Of the remaining cases, tumors with polymerase-ε exonuclease domain mutations were classified as "POLE EDM". Of the remaining cases, tumors with p53 wild type were classified as "p53 wt". The rest of the tumors with p53 null/missense mutations were classified as "p53 abn".

Endometrial biopsies, through simple biopsy, dilatation and curettage or hysteroscopic resection, were performed before study inclusion and analyzed in various pathology departments in Stockholm, whereas the hysterectomy specimens were analyzed in the same department at the university hospital where surgery took place. For practical reasons (i.e. access to tissue blocks), ProMisE was analyzed on tumor tissue from the hysterectomy specimen.

Preoperative ESMO classification[1] was based on variables from endometrial biopsy and transvaginal ultrasound, with the following risk group definition; low risk: grade 1—2 endometrioid cancer without deep myometrial invasion; intermediate risk: deep myometrial invasion or grade 3 endometrioid cancer without deep myometrial invasion; high-risk: grade 3 endometrioid cancer with deep myometrial invasion or non-endometrioid cancer. Cases with cervical stromal invasion and extrauterine spread were added to the high-risk group. Postoperative ESMO classification[1] was based on variables from the surgical specimen (histotype, grade, surgical stage and presence of LVSI) using the established risk groups (Low, Intermediate, Intermediate-High, High, Advanced, Metastatic). Due to the low number of women, the advanced and metastatic risk groups were combined.

Recurrence was defined as recurrent tumor in a woman who had been tumor free, either directly after surgery or at the end of primary treatment. Date of recurrence was defined as date of biopsy confirmed recurrence in all cases but three, where confirmative biopsy was not performed initially or not performed at all. In these cases recurrence date was defined as the date of recurrence according to computer tomography or clinical examination. Progression was defined as tumor progression in a woman who had remaining tumor at the end of primary treatment. Date of progression was defined as the date of progression according to computer tomography. Overall survival was defined as time from surgery until death of any cause, loss of follow up or end of follow up, whichever occurred first. Disease-free survival time was defined as time from surgery to detection of recurrence, loss of follow up, death of any cause or end of follow up, whichever occurred first.

The study was approved by local Ethics committee (LU 2016/362). The biobanking of tissue was granted from the regional biobank review board (2018-00479). All women gave written consent for use of their biobanked tissue for research purposes.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (Armonk, NY, IBM Corporation), STATA/IC 12.1 and R version 3.6.1. The Fisher's exact test was used for categorical variables, the Mann-Whitney U test for continuous variables comparing two groups and the Kruskal-Wallis test for continuous variables comparing more than two groups. Categorizations for age[13], BMI[21], waist circumference[22] and ultrasound tumor size[23] were chosen from previous publications.

We compared demographic, sonographic characteristics, recurrence/progression, and survival between the ProMisE subtypes, with focus on the p53 abn subtype, as it is known to be associated with adverse outcome[8-10, 12, 20]. Tumors were stratified by p53 status (present/absent) and ultrasound tumor size (< 2 cm/≥ 2 cm), clinically easily obtained prognostic factors known to be associated with adverse outcome[23, 24], and compared regarding risk of recurrence or progression.

Survival analysis was performed using Kaplan Meier curves, with pairwise comparison of ProMisE subtypes using the log rank test. Cox regression was used to identify variables associated with recurrence or progression. Univariable models were used to study crude associations and multivariable models to study adjusted associations. All variables associated with recurrence or progression in univariable models were analyzed in multivariable models. The variables histotype/grade and ProMisE were strongly associated in multivariable analysis. Hence, they were analyzed in separate, otherwise identical, multivariable models, the 'Histotype and grade model' (histotype and grade, age, waist circumference, ultrasound tumor extension and ultrasound tumor size) and the 'ProMisE model' (ProMisE, age, waist circumference, ultrasound tumor extension and ultrasound tumor size). The ProMisE model was also adjusted for the ESMO postoperative classification, to determine if the variables had an independent association beyond the ESMO classification. All women were followed until recurrence or progression (event), or censured due to death, loss of follow up or end of follow up, whichever occurred first.

To study if prognostic factors associated with progression or recurrence in multivariable Cox regression analysis also had predictive value, the Histotype and grade model, the ProMisE model and the ESMO classification were analyzed using logistic regression with a fixed time (recurrence or progression within three years (yes/no), as all women had a follow-up of at least 42 months). The ability to predict recurrence or regression was assessed as area under the receiver operating characteristic curves (AUC). The statistical significance of a difference in AUC was determined using pairwise comparison through DeLong test. These analyses were performed to assess the ability of the preoperative prognostic factors to predict recurrence or progression, and to compare their predictive ability to that of the ESMO classification. All tests were 2-sided, p values < 0.05 was considered statistically significant.

RESULTS

Eligible for inclusion were 409 women from the Stockholm center of the prospective IETA 4 database, with the addition of another two women, examined at the Stockholm center according to the same protocol (n = 411). Seventy-two women were excluded from the study cohort because of: surgery performed in another hospital (n = 6), too little or no remaining tumor in hysterectomy specimen (n = 38), incorrect personal security number (n = 2), incomplete ProMisE analysis (n = 8), duplicate case (n = 1) and ProMisE analysis not performed (n = 17), leaving a study cohort of 339 women. Lymphadenectomy was performed in 91 women (27%), of which 21 (23%) had lymph node metastases. Median follow-up time from surgery was 58 months (IQR 48—71, range 0—102). Two women died within one month after surgery, one due to postoperative complications after 30 days and one of unknown cause in her home, after three days. Three women moved to another county and were thus lost to follow up after 29, 30 and 40 months, respectively. Demographic, sonographic and histopathological characteristics are presented in Table 1, together with a comparison of the women with (15%) and without (85%) recurrence or progression. Women with recurrence or progression were significantly older, had a larger waist circumference, tumors were more often non-endometrioid, ProMisE p53 abn and of higher stage and on ultrasound tumors were larger, with higher color score and more advance tumor extension. Recurrence or progression was detected because of symptoms in half of the women, and was detected at routine follow up in the other half. The vast majority (88%, n = 38/43) of recurrences occurred within three years, and all progressions (100%, n = 8/8) within 2 years.

The clinical and sonographic characteristics of the ProMisE subtypes are presented in Table 2. Compared with the other subtypes, p53 abn was associated with older age, larger tumors on preoperative ultrasound, non-endometrioid cancer, higher stage, more advanced postoperative ESMO risk group, death from disease and lower 5-year disease free- and overall survival. The Kaplan-Meier plot on recurrence or progression for the ProMisE subtypes, presented in Figure 1, shows that women with p53 abn had a higher probability of recurrence or progression.

All preoperative variables but BMI were associated with recurrence or progression in univariable analysis (Table 3). Among the ProMisE subtypes, only p53 abn was associated with recurrence or progression. Multivariable analysis, containing all preoperative variables associated with recurrence or progression in univariable analysis, revealed that only age, waist circumference, ProMisE, ultrasound tumor extension and ultrasound AP tumor diameter remained associated with recurrence or progression (Table 4).

Tumor size according to ultrasound remained associated with recurrence or progression in all versions of multivariable analysis (Table 4). In women with defined tumor on ultrasound (n = 317), tumor AP diameter ≥ 2 cm, as compared to < 2 cm, was associated with deep myometrial invasion (56% (76/137) vs. 16% (29/180) , p < 0.01), lymph node metastases, among those undergoing lymphadenectomy (n=84) (30% (17/57) vs. 7% (2/27), p = 0.03), worse survival (5-year overall survival 78% vs. 93%, p < 0.01) and a higher risk of recurrence or progression, also among women (n = 154) with preoperative ESMO low risk (15% (4/27) vs. 3% (4/127), p = 0.03).

When stratifying women by tumor size (AP diameter < 2 cm vs. ≥ 2 cm) and p53 abn status (p53 abn vs. non-p53 abn), we found that women with the combination of AP diameter < 2cm and non-p53 abn status, constituting half of the study population (48%, 164/339), were at very low risk of recurrence or progression (1.8% (3/164)), 95% CI 0.4%—3.2%) (Figure 2).

The prognostic factors associated with recurrence or progression within three years are presented in Table 5. These multivariable models constitute the basis for the ROC curves analysis, comparing the ability to predict recurrence or progression by the ProMisE model, the Histotype and grade model, preoperative ESMO classification (ESMO pre) and postoperative ESMO classification (ESMO post) (Figure 3). The ProMisE model (AUC: 0.89, 95% CI 0.85—0.93) predicted recurrence or progression with comparable ability as the Histotype and grade model (0.88, 95% CI 0.83—0.92), $p = 0.22$) and with higher ability than both the preoperative (AUC 0.74, 95% CI 0.67—0.82, $p < 0.01$) and postoperative (AUC 0.79, 95% CI 0.72— 0.86, $p < 0.01$) ESMO classification (Figure 3). The use of the ProMisE model was superior to the ProMisE classification alone (AUC 0.70, 95% CI 0.61—0.79).

DISCUSSION

We verified p53 abn as an adverse prognostic factor, as it was associated with larger tumors on ultrasound, non-endometrioid cancer, higher stage, increased risk of recurrence or progression and worse survival, compared to the other ProMisE subtypes. The combination of non-p53 abn status and ultrasound tumor AP diameter < 2 cm showed the potential to identify a large group of women (48%) at very low risk (1.8%) of recurrence or progression. The ProMisE model, including ProMisE, demographic (age, waist circumference) and sonographic (tumor size and extension) prognostic factors, predicted risk of recurrence or progression with higher ability than both the current pre- and postoperative ESMO classification, already before surgery, supporting the use of these prognostic factors in preoperative risk stratification.

Strengths of this study are the prospective study cohort, which represents a general population and not a high-risk sample and was gathered during a recent and limited period of time, and the comprehensive prospective cohort database, containing detailed clinical information, where all data was locked after being saved. Near half of the study population had a follow up of 5 years or longer and all have high quality ultrasound data.

It is a shortcoming that analysis of ProMisE was performed on the hysterectomy specimen and not on the preoperative endometrial biopsy. However, high concordance of ProMisE between preoperative biopsy and hysterectomy has been proven[11, 12] and it has been concluded that the results of molecular markers, such as p53, on hysterectomy specimen safely can be translated towards the preoperative endometrial biopsy[25]. Also, the fact that the prognostic factors were identified from the same dataset that was used to compare their predictive ability to that of the ESMO classification, may have favored the ProMisE and histotype and grade models. The prognostic factors found in our study could serve as a foundation for future studies aiming to create preoperative risk prediction models for recurrence or progression, based on a larger cohort, with ProMisE analysis on preoperative biopsy, variable choice based on a priori knowledge and external validation.

Previous studies have found that tumor size on hysterectomy specimen[23, 24, 26], ultrasound[13] and MRI[27] are predictive of lymph node metastases[23, 24, 26, 27], survival[23, 24] and high-risk disease[13]. In accordance, we found that tumors with an AP tumor diameter ≥ 2 cm were associated with more advanced tumor extension on ultrasound, a higher degree of lymph node metastases and worse survival outcomes, supporting the potential for tumor size to predict adverse outcome already before surgery. In addition, we found tumor size according to preoperative ultrasound predictive of recurrence or progression, also within preoperative ESMO low-risk cases.

An increased BMI, consistent with overweight or obesity, is associated with an increased risk of endometrial cancer development[28] and obesity at diagnosis has been associated with worse survival, though evidence have been insufficient to establish an increased risk of recurrence[29]. Changes in insulin resistance, systemic inflammation, alterations in hormone levels and in growth factors are factors implicated to promote cancer development and progression in overweight or obesity[30]. In spite of this, we found no association between BMI and tumor recurrence or progression (Table 3). However, a waist circumference of ≥ 88 cm proved an independent predictor, with at

least a doubled risk (Table 4 and Table 5). The discrepancy might be explained by the fact that BMI constitutes a poor proxy for adiposity, as it does not describe the adipose tissue distribution or distinguish adipose tissue from muscle mass[30]. Postmenopausal women with endometrial cancer exhibit higher levels of estradiol from subcutaneous fat than from visceral fat, indicating that subcutaneous fat might be relevant for endometrial cancer carcinogenesis[31] and women with increasing visceral fat percentage have a significantly reduced disease-specific survival, independent of BMI[32]. This indicates that the location of the body fat is prognostic, and it can be stipulated that our divergent findings on BMI and waist circumference indicate that abdominal adiposity is a worse prognostic factor than general adiposity. To the best of out knowledge, this is the first time that waist circumference is reported an independent predictor of recurrence or progression in endometrial cancer.

The ProMisE classification was validated in a population-based cohort of 452 women[11], similar to our cohort. They presented a comparable ProMisE subtype distribution to ours, and also identified p53 abn as an adverse prognostic factor. The ProMisE classification has several implications, showing a higher concordance between endometrial biopsy and hysterectomy specimen compared to histotype and grade[11, 12], differentiating high grade tumors with excellent (POLE EDM) from poor (p53 abn) prognosis[8-10], evaluating tumors in the grey zone between endometrioid and serous histotype and identifying women with MMR-D, who may have Lynch syndrome and should be referred for genetic counseling and testing.

In the sentinel node era, the clinical importance of preoperative ultrasound has been questioned, at least if sentinel node biopsy is offered to all women. This study indicates, however, that ultrasound variables have an independent prognostic role beyond the ESMO classification and that the combination of ultrasound and p53 status, often obtained in routine histopathology assessment, can identify a large group of women (48%) at very low risk of recurrence or progression (1.8%) where not even sentinel node biopsy, nor adjuvant treatment, may be considered necessary. Moreover, a combination of demographic, sonographic and ProMisE prognostic factors predicted recurrence with higher ability than the ESMO classification, supporting their use in preoperative risk stratification.

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Figure Legends

Figure 1. Kaplan-Meier plot on probability of survival for the ProMisE subtypes.

Figure 2. Risk of recurrence or progression stratified by ultrasound tumor size and p53 abnormal status.

Figure 3. ROC curves comparing the ability to predict recurrence or progression within three years by the ProMisE model (ProMisE, age, waist circumference, ultrasound tumor extension and ultrasound tumor size), the Histotype and grade model (histotype and grade, age, waist circumference, ultrasound tumor extension and ultrasound tumor size), preoperative ESMO classification (ESMO pre) and postoperative ESMO classification (ESMO post)

Table 1. Demographic, sonographic, and surgical characteristics and survival data (n=339)

	All *n* = 339	No recurrence or progression *n* = 288	Recurrence or progression *n* = 51	*p**
Demographic characteristics				
Age (years)	67 (60 — 72)	66 (59 — 72)	70 (66— 75)	<0.01
Body Mass Index (kg/m^2)	27.3 (23.5 — 33.0)	27.0 (23.3 — 33.0)	29.1 (24.6 — 33.1)	0.17
Waist circumference (cm)	95 (85— 110)	93 (84— 110)	105 (89 — 115)	0.02
Hypertension	170 (50.1)	138 (47.9)	32 (62.7)	0.07
Nulliparity	80 (23.6)	69 (24.0)	11 (21.6)	0.86
Postmenopausal status	310 (91.4)	260 (90.3)	50 (98.0)	0.10
Use of HRT or local estrogens	82 (24.2)	69 (24.0)	13 (25.5)	0.86
Sonographic characteristics				
Tumor extension				
MI < 50%, no CSI	221 (65.2)	205 (71.2)	16 (31.4)	<0.01
MI ≥ 50%, no CSI	69 (20.4)	53 (18.4)	16 (31.4)	
CSI present ± MI ≥ 50 %	33 (9.7)	23 (8.0)	10 (19.6)	
Extrauterine spread	16 (4.7)	7 (2.4)	9 (17.6)	
AP tumor diameter ≥2 cm†	137 (43.2)	97 (36.1)	40 (83.3)	<0.01
Color Doppler score 3 to 4‡	214 (64.5)	175 (62.1)	39 (78.0)	0.04
Surgical characteristics				
Histotype				
Endometrioid	290 (85.5)	259 (89.9)	31 (60.8)	<0.01
Non-endometrioid	49 (14.5)	29 (10.1)	20 (39.2)	
Grade				
Grade 1	141 (41.6)	132 (45.8)	9 (17.6)	0.03
Grade 2	103 (30.4)	90 (31.3)	13 (25.5)	
Grade 3	46 (13.6)	37 (12.8)	9 (17.6)	
Stage				
IA	205 (60.5)	195 (67.7)	10 (19.6)	<0.01
IB	72 (21.2)	55 (19.1)	17 (33.3)	
II	28 (8.3)	23 (8.0)	5 (9.8)	
III	24 (7.1)	15 (5.2)	9 (17.6)	
IV	10 (2.9)	0 (0)	10 (19.6)	
ProMisE				
MMR-D	118 (34.8)	102 (35.4)	16 (31.4)	<0.01
POLE EDM	26 (7.7)	24 (8.3)	2 (3.9)	
p53 wt	151 (44.5)	138 (47.9)	13 (25.5)	
p53 abn	44 (13.0)	24 (8.3)	20 (39.2)	
Adjuvant therapy	113 (33.3)	81 (28.1)	32 (62.7)	<0.01
Survival data				
Death from disease	32 (9.4)	0 (0)	32 (62.7)	<0.01
Death from other/unknown cause	16 (4.7)	16 (5.6)	0 (0)	

5-year overall survival[§] (%)	87	96	38	<0.01

Results are presented as median (IQR) or n (%)
* Comparison of women with and without recurrence or progression.
Mann-Whitney U test was used for continuous variables, Fisher´s exact test for categorical variables and log-rank test for Kaplan-Meier plots
† In the 317 women with defined tumor on ultrasound
‡ In the 332 women with visible endometrium on ultrasound
§ Estimation from Kaplan-Meier curves
AP: anteroposterior; CSI: cervical stromal invasion; HRT: hormone replacement therapy; MI: myometrial invasion; MMR-D: mismatch repair proteins deficiency; p53 abn: protein 53 abnormal; P 53 wt: protein 53 wild type; POLE EDM: polymerase-varepsilon exonuclease domain mutations; ProMisE: Proactive Molecular Risk Classifier for Endometrial Cancer

Table 2. Demographic, sonographic, surgical characteristics and survival data in different Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) groups (n=339)

	MMR-D *n* = 118 *n* (%)	POLE EDM *n* = 26 *n* (%)	p53 wt *n* = 151 *n* (%)	p 53 abn *n* = 44 *n* (%)	*p*	*p**
Demographic characteristics						
Age (years)	68 (61 — 72)	62 (52 — 65)	67 (60 — 71)	70 (64 — 75)	< 0.01	0.04
Body Mass Index (kg/m2)	27.3 (24.0 — 33.0)	25.1 (22.0 — 31.9)	27.5 (23.6 — 35.0)	26.5 (23.2 — 26.5)	0.24	0.47
Waist circumference (cm)	95 (85 — 110)	87 (83 — 103)	97 (84 — 115)	95 (86 — 107)	0.33	0.76
Sonographic characteristics						
Cases with visible endometrium	*n* = 118 (100)	*n* = 26 (100)	*n* = 146 (96.7)	*n* = 42 (95.5)		
Endometrial-myometrial junction						
Regular	23 (19.5)	2 (7.7)	35 (24.0)	5 (11.9)	0.14	0.22
Irregular/interrupted/ undefined	95 (80.5)	24 (92.3)	111 (76.0)	37 (88.1)		
Endometrial morphology						
Uniform	66 (55.9)	13 (50.0)	107 (73.3)	24 (57.1)	< 0.01	0.40
Non-uniform	52 (44.1)	13 (50.0)	39 (26.7)	18 (42.9)		
Color score						
1—2 (no to minimal flow)	34 (28.8)	10 (38.5)	65 (44.5)	9 (21.4)	0.01	0.06
3—4 (moderate to abundant flow)	84 (71.2)	16 (61.5)	81 (55.5)	33 (78.6)		
Vascular pattern						
multiple vessels with multifocal origin	50 (42.4)	10 (38.5)	63 (43.2)	20 (47.6)	0.96	0.62
others	68 (57.6)	16 (61.5)	83 (56.8)	22 (52.4)		
Cases with tumor defined on ultrasound	*n* = 114 (96.6)	*n* = 26 (100)	*n* = 138 (91.4)	*n* = 39 (88.6)		
Tumor AP diameter, mm	20.0 (13.0 — 27.0)	13.5 (9.0 — 24.0)	14.0 (9.8 — 25.0)	26.0 (14.0— 36.0)	< 0.01	< 0.01
Surgical characteristics	*n* = 118 (100)	*n* = 26 (100)	*n* = 151 (100)	*n* = 44 (100)		
Histotype						
Endometrioid	105 (89.0)	26 (100)	149 (98.7)	10 (22.7)	< 0.01	< 0.01
Non-endometrioid	13 (11.0)	0 (0)	2 (1.3)	34 (77.3)		
Grade						
Grade 1	36 (30.5)	11 (42.3)	93 (61.6)	1 (2.2)	< 0.01	< 0.01
Grade 2	51 (43.2)	5 (19.2)	45 (29.8)	2 (4.5)		
Grade 3	18 (15.3)	10 (38.5)	11 (7.3)	7 (15.9)		
Stage						
I	97 (82.2)	88.5 (23)	131 (86.8)	26 (59.1)	< 0.01	< 0.01
II—IV	21 (17.8)	3 (11.5)	20 (13.2)	18 (40.9)		
ESMO post[†]						
Low	54 (45.8)	11 (42.3)	89 (58.9)	3 (6.8)	< 0.01	<0.01
Intermediate	10 (8.5)	1 (3.8)	26 (17.2)	0 (0)		
High Intermediate	17 (14.4)	7 (26.9)	15 (9.9)	2 (4.5)		
High	35 (29.7)	7 (26.9)	17 (11.3)	33 (75.0)		
Advanced/Metastatic	2 (1.7)	0 (0)	4 (2.6)	6 (13.6)		
Survival data						
Recurrence or progression	16 (13.6)	2 (7.7)	13 (8.6)	20 (45.5)	< 0.01	<0.01
Death from disease	7 (5.9)	1 (3.8)	7 (4.6)	17 (38.6)	< 0.01	<0.01
5-years disease free survival[‡] (%)	83	96	87	51	< 0.01	<0.01
5-years overall survival[‡] (%)	90	96	91	58	< 0.01	<0.01

Results are presented as median (IQR) or *n* (%)
* Comparison of p53 abn vs. others.
Mann-Whitney U test was used for continuous variables comparing two groups, Kruskal-Wallis test for continuous variables comparing
four groups, Fisher´s exact test for categorical variables and log-rank test for Kaplan-Meier plots.
† Postoperative ESMO classification[1], ‡ estimation from Kaplan-Meier plots
AP: anteroposterior; ESMO: European Society for Medical Oncology

Table 3. Univariable Cox regression analysis; association of preoperative variables to tumor recurrence or progression (n = 339)

	n	recurrence or progression *n* (%)	HR	95 % CI	*p**
Demographic variables					
Age (years)					< 0.01
< 65	131	8 (6.1)	Ref		
≥ 65	208	43 (20.7)	3.7	1.7 — 7.8	
Body Mass Index (kg/m^2)					0.1
<25	117	13 (11.1)	Ref		
≥25	222	38 (17.1)	1.6	0.8 — 3.0	
Waist circumference (cm)					0.03
< 88	120	11 (9.2)	Ref		
≥ 88	219	40 (18.3)	2.1	1.1 — 4.0	
Histopathological variables					< 0.01
Histotype and grade					
Endometrioid grade 1—2	229	21 (9.2)	Ref		
Endometrioid grade 3	32	8 (25.0)	3.0	1.3 — 6.7	
Non-endometrioid	48	20 (41.7)	5.3	2.9 — 9.8	
Other†	30	2 (6.7)	0.7	0.2 — 3.1	
ProMisE‡					< 0.01
p53 wt	151	13 (8.6)	Ref		
MMR-D	118	16 (13.6)	1.6	0.8 — 3.4	
POLE EDM	26	2 (7.7)	0.9	0.2 — 3.8	
p 53 abn	44	20 (45.5)	6.5	3.2 — 13.2	
Sonographic variables					
Tumor extension					< 0.01
MI < 50%, no CSI	221	16 (7.2)	Ref		
MI ≥ 50%, no CSI	69	16 (23.2)	3.4	1.7 — 6.9	
CSI present ± MI ≥ 50 %	33	10 (30.3)	4.9	2.2 — 10.7	
Extrauterine spread	16	9 (56.3)	11.4	5.0 — 25.8	
Tumor AP diameter (cm)					< 0.01
<2	180	8 (4.4)	Ref		
≥ 2	137	40 (29.2)	7.8	3.7 — 16.8	
tumor not defined	22	3 (13.6)	3.4	0.9 — 12.7	
Endometrial-myometrial junction§					0.01
Regular	65	3 (4.6)	Ref		
Irregular/interrupted/undefined	267	47 (17.6)	4.3	1.3 — 13.8	
Endometrial morphology§					0.03
Uniform	210	25 (11.9)	Ref		
Non-uniform	122	25 (20.5)	1.8	1.05 — 3.2	
Color score§					0.04
1—2	118	11 (9.3)	Ref		
3—4	214	39 (18.2)	2.1	1.1 — 4.0	
Vascular pattern§					< 0.01
Other	189	18 (9.5)	Ref		
Multiple multifocal	143	32 (22.4)	2.5	1.4 — 4.5	
ESMO pre¶					< 0.01
Low	164	8 (4.9)	Ref		
Intermediate	49	10 (20.4)	4.4	1.7 — 11.1	
High	96	31 (32.3)	7.6	3.5 — 16.6	
Other†	30	2 (6.7)	1.4	0.3 — 6.5	

*Test of variable including all categories
† Endometrioid cancer not graded (n = 5), suspicion of endometrial cancer (n = 24), no biopsy (n = 1)
‡ Analyzed on hysterectomy specimen
§ In the 332 cases with visible endometrium on ultrasound
¶ Preoperative ESMO classification[1]
AP: anteroposterior; CI: confidence interval; CSI: cervical stromal invasion; ESMO: European Society for Medical Oncology; MI: myometrial invasion

Table 4. Multivariable Cox regression analysis; associations of preoperative variables on tumor recurrence or progression (n=339)

	all variables significant in univariable analysis			Histotype and grade model			ProMisE model			ProMisE model adjusted for ESMO post†		
	HR	95 % CI	p^*	HR	95 % CI	p^*	HR	95 % CI	p^*	HR	95 % CI	p^*
Demographic variables												
Age (years)			< 0.01			< 0.01			< 0.01			< 0.01
< 65	Ref			Ref			Ref			Ref		
≥ 65	4.0	1.7—9.5		4.4	2.0—9.8		3.8	1.7—8.4		4.1	1.7—9.5	
Waist circumference (cm)			0.01			0.01			0.02			0.01
< 88	Ref			Ref			Ref			Ref		
≥ 88	2.6	1.2—5.6		2.5	1.2—5.1		2.5	1.2—5.1		2.6	1.2—5.5	
Histopathological variables												
Histotype and grade			0.40			< 0.01						
Endometrioid grade 1—2	Ref			Ref			—		—	—		—
Endometrioid grade 3	2.0	0.8—5.0		2.6	1.1—6.0		—	—		—	—	
Non-endometrioid	1.9	0.7—4.8		4.4	2.3—8.2		—	—		—	—	
Other‡	0.8	0.2—3.5		0.8	0.2—3.4		—	—		—	—	
ProMisE§			0.04						< 0.01			0.02
p53 wt	Ref			—		—	Ref			Ref		
MMR-D	1.1	0.5—2.4		—	—		1.1	0.5—2.4		1.5	0.7—3.4	
POLE EDM	1.0	0.2—5.1		—	—		1.3	0.3—6.3		1.9	0.4—9.6	
p53 abn	3.9	1.3—11.1		—	—		5.7	2.8—11.7		4.6	1.7—12.5	
Ultrasound variables												
Tumor extension			< 0.01			< 0.01			< 0.01			0.01
MI < 50%, no CSI	Ref			Ref			Ref			Ref		
MI ≥ 50%, no CSI	1.4	0.5—3.5		1.4	0.6—3.0		1.6	0.7—3.5		1.2	0.5—2.9	
CSI present ± MI ≥ 50 %	1.8	0.6—5.5		2.2	0.9—5.3		2.2	0.9—5.4		2.0	0.7—5.5	
Extrauterine spread	9.7	3.0—30.7		7.4	2.8—19.7		11.5	4.2—31.0		6.5	1.8—23.4	
Tumor anteroposterior diameter (cm)			< 0.01			< 0.01			0.01			0.01
<2	Ref			Ref			Ref			Ref		
≥ 2	4.7	1.8—12.4		3.9	1.6—9.7		3.8	1.6—9.4		4.3	1.6—11.3	
Tumor not defined	5.3	1.02—27.2		4.2	1.1—16.7		3.8	0.96—15.3		4.1	1.01—16.8	
Endometrial-myometrial junction¶			0.30			—			—			—
Regular	Ref			—	—		—	—		—	—	
Irregular/interrupted/undefined	2.0	0.6—7.4		—	—		—	—		—	—	
Endometrial morphology¶			0.30			—			—			—
Uniform	Ref			—	—		—	—		—	—	
Non-uniform	1.3	0.7—2.4		—	—		—	—		—	—	
Color score¶			0.07			—			—			—
1—2	Ref			—	—		—	—		—	—	
3—4	0.4	0.2—1.1		—	—		—	—		—	—	
Vascular pattern¶			0.60			—			—			—
Other	Ref			—	—		—	—		—	—	
Multiple multifocal	1.2	0.5—3.0		—	—		—	—		—	—	

* Test of variable including all categories

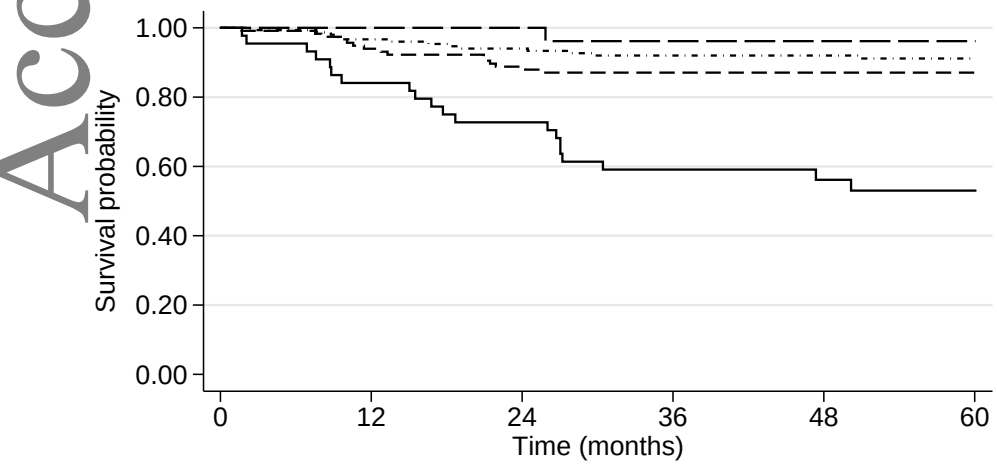
† Postoperative ESMO classification[1]
‡ Endometrioid cancer not graded (n = 5), suspicion of endometrial cancer (n = 24), no biopsy (n = 1)
§ Analyzed on hysterectomy specimen
¶ In the 332 cases with visible endometrium on ultrasound
CI: confidence interval; CSI: cervical stromal invasion; ESMO: European Society for Medical Oncology; MI: myometrial invasion

Table 5. Multivariable logistic regression analysis; associations of preoperative variables on tumor recurrence or progression within 36 months (n = 339)

		Recurrence or progression	All			Histotype and grade model			ProMisE model		
	n	n (%)	OR	95% CI	p^*	OR	95% CI	p^*	OR	95% CI	p^*
Demographic variables											
Age (years)					< 0.01			< 0.01			< 0.01
< 65	131	7 (5.3)	Ref			Ref			Ref		
≥ 65	208	39 (18.8)	5.9	2.0—17.2		6.7	2.3—19.4		5.7	2.0—16.3	
Waist circumference (cm)					< 0.01			0.03			< 0.01
< 88	120	8 (6.7)	Ref			Ref			Ref		
≥ 88	219	38 (17.4)	4.0	1.5—11.1		4.3	1.6—11.2		3.9	1.4—10.6	
Histopathological variables					0.50			< 0.01			—
Endometrioid grade 1—2	229	19 (8.3)	Ref			Ref			—	—	
Endometrioid grade 3	32	8 (25.0)	1.9	0.6—6.2		3.0	1.03—9.0		—	—	
Non-endometrioid	48	17 (35.4)	2.0	0.5—7.8		5.7	2.3—14.3		—	—	
Other†	30	2 (6.7)	0.6	0.1—3.3		0.7	0.1—3.5		—	—	
ProMisE‡					0.10			—			< 0.01
p53 wt	151	12 (7.9)	Ref			—	—		Ref		
MMR-D	118	15 (12.7)	1.3	0.5—3.5		—	—		1.5	0.6—3.9	
POLE EDM	26	1 (3.8)	0.7	0.07—7.7		—	—		1.0	0.1—10.3	
p53 abn	44	18 (40.9)	5.0	1.2—20.9		—	—		9.1	3.3—25.5	
Ultrasound variables											
Tumor extension					< 0.01			0.02			< 0.01
MI < 50%, no CSI	221	14 (6.3)	Ref			Ref			Ref		
MI ≥ 50%, no CSI	69	14 (20.3)	1.6	0.6—4.4		1.4	0.5—3.9		1.7	0.6—4.8	
CSI present ± MI ≥ 50%	33	10 (30.3)	3.0	0.9—10.2		2.7	0.8—9.0		3.2	0.9—10.5	
Extrauterine spread	16	8 (50.0)	13.5	2.9—63.4		10.0	2.2—45.3		16.2	3.5—74.8	
Tumor AP diameter (cm)					< 0.01			< 0.01			< 0.01
<2	180	6 (3.3)	Ref			Ref			Ref		
≥ 2	137	37 (27.0)	5.8	1.9—17.8		5.7	1.9—17.3		5.7	1.8—17.4	
Tumor not defined	22	3 (13.6)	5.9	1.1—31.9		6.2	1.2—31.7		5.8	1.1—30.8	

ESMO pre[§]					< 0.01
Low	16 4	7 (4.3)	Ref		
Intermediate	49	9 (18.4)	5.0	1.8—14.4	
High	96	28 (29.2)	9.2	3.8—22.2	
Other[†]	30	2 (6.7)	1.6	0.3—8.1	
ESMO post[¶]					0.03
Low	15 7	5 (3.2)	Ref		
Intermediate	37	5 (13.5)	4.8	1.3—17.4	
High Intermediate	41	5 (12.2)	4.2	1.2—15.4	
High	92	19 (20.7)	7.9	2.8—22.0	
Advanced/Metastatic	12	12 (100.0)	NA		

* Test of variable including all categories
† Endometrioid cancer not graded (n = 5), suspicion of endometrial cancer (n = 24), no biopsy (n = 1)
‡ Analyzed on hysterectomy specimen
§ Preoperative ESMO classification[1]
¶ Postoperative ESMO classification[1]
AP: anteroposterior; CI: confidence interval; CSI: cervical stromal invasion; ESMO: European Society for Medical Oncology; MI: myometrial invasion; NA: odds ratio estimate not available due to recurrence or progression in all women



Number at risk

MMR−D	118	109	103	100	88	60
POLE EDM	26	26	26	25	21	13
p53 wt	151	145	141	136	121	62
p53 abn	44	37	32	26	19	11