Creation of a scoring system to determine endometrial cancer risk using the International Endometrial Tumor Analysis (IETA) features*

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ABSTRACT

General Objective: To determine endometrial cancer risk among patients with abnormal uterine bleeding based on the International Endometrial Tumor Analysis (IETA) features.

Specific Objectives: 1. To described the profile of patients with AUB suspected of having endometrial pathology; 2. To describe sonologic features of patients with AUB suspected of endometrial cancer using IETA features; and 3. To determine the association of a scoring system and endometrial cancer risk.

Methods: We prospectively studied 542 participants who came in the CWCU of CSMC with a diagnosis of AUB from July 1, 2016 to December 31, 2016. We excluded patients with endometrial thickness of less than 4 mm on gray-scale sonography, those with technical difficulties in assessing the endometrium such as in cases of very large myomas, absence of histopathological diagnosis, and those whose sampling was done as an office procedure. A total of 98 participants were included, 89 (90.8%) had benign pathologies and 9 (9.2%) were malignant. Patient characteristics including, age, gravidity, BMI, medical history, and endometrial assessment using IETA were tabulated with each characteristic given a score of 0-3 depending on the degree of risk factor. Percentages, Pearson Chi-square Test with corresponding P-value and ROC curve analysis were performed.

Results: The best predictors for endometrial cancer were age more than 50 years, nulligravid, BMI of more than 25, and presence of hypertension and diabetes mellitus. Sonographic features based on IETA showed an endometrial thickness of more than 20 mm, irregular endometrial-myometrial junction, heterogenous endometrium, presence of multiple and large vessels on doppler analysis, contributed to endometrial cancer risk. These variables were used to create a scoring system with an area under the curve of 0.974 giving the best cut-off value of more than or equal to 9, with 100% sensitivity and 89% specificity.

Conclusion: Among patients with abnormal uterine bleeding and endometrial thickness of more than 4mm, we can predict the risk for endometrial cancer and aid the clinician in decision making on who may be managed conservatively or aggressively based on the value obtained from the scoring system. The study, however, needs to be validated prior to use in clinical practice.

Keywords: AUB, endometrial pathology, colon stone, IETA

RESEARCH QUESTION

Among patients with abnormal uterine bleeding, what is the risk of having endometrial cancer based on the International Endometrial Tumor Analysis (IETA) features?

INTRODUCTION

Endometrial cancer is the third most common genital tract malignancy in the Philippines, next to cervical and ovarian cancer.[1] The most common presenting symptom is abnormal uterine bleeding, either in the perimenopausal and postmenopausal state or in the reproductive age group who have heavy menstrual bleeding. Ninety percent occur in women more than 50 years of age and less than 5% in women less than 40.

Defined risks for endometrial carcinoma include obesity, unopposed estrogen, chronic anovulation, nulliparity, polycystic ovarian syndrome, early menarche and late menopause, feminizing ovarian tumors, use of the drug Tamoxifen, other related medical diseases namely diabetes mellitus and hypertension, a personal or family history of breast or colon cancer, and a previous endometrial biopsy result of atypical hyperplasia. [1]

Transvaginal sonography is the first line of investigation to reliably discriminate between women who are at low or high risk of endometrial cancer. Findings of endometrial thickness 4 mm or less decreases the likelihood of endometrial cancer both in users and non-users of hormone replacement therapy and a

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finding of endometrial thickness ≥ 4-5 mm may indicate malignancy.[2,3,4,5] Patients assessed to have thickened endometrium may undergo diagnostic sampling, hysteroscopy, curettage or hysterectomy for a definitive diagnosis. However, 80-90% of these examinations will not reveal a cancer in a population considered at risk of malignancy.[6] The goal then is to minimize invasive procedures in patients identified as high risk based solely on the above mentioned risk factors.

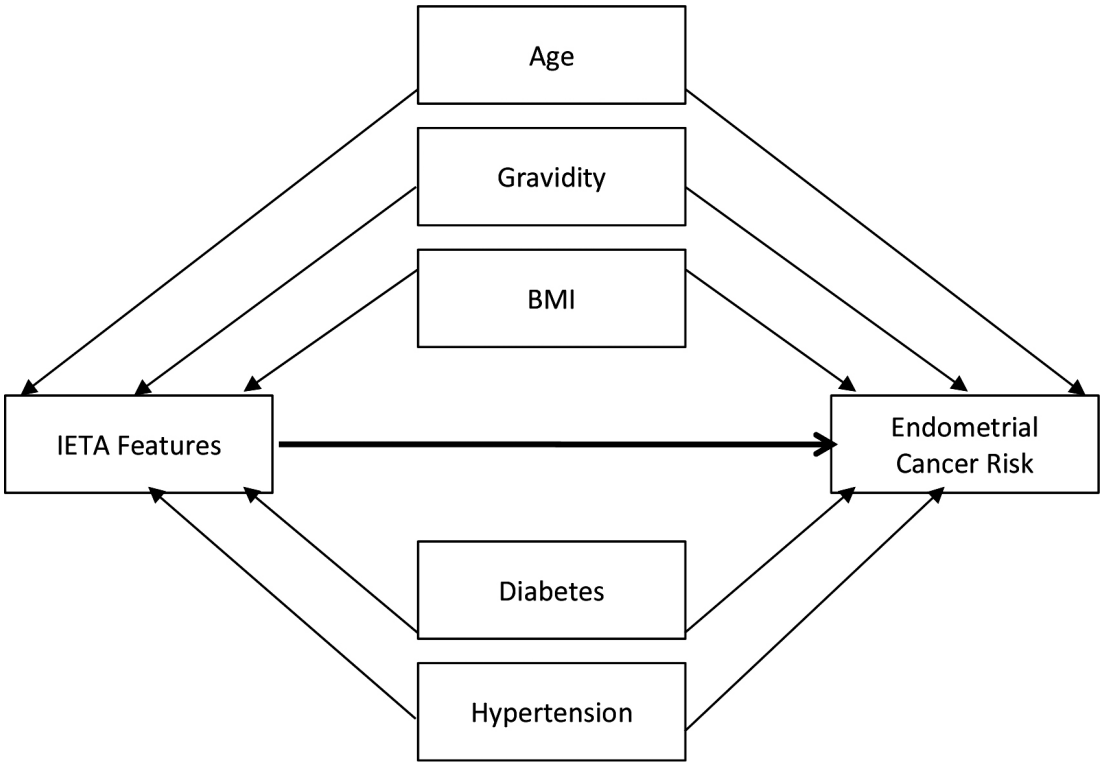
The International Endometrial Tumor Analysis (IETA) group was formed in Chicago at the World Congress of Ultrasound in Obstetrics and Gynecology in 2008 with the aim of agreeing on terms and definitions to describe ultrasound findings in the uterine cavity.[2] The group formed a consensus statement on terms, definitions and measurements to describe the sonographic features of the endometrium and uterine cavity at gray-scale sonography, color flow imaging and sonohysterography. On the basis of these descriptions, several studies came up equating the sonographic findings based on the IETA features and the risk for endometrial cancer. IETA features linked to endometrial cancer risks include endometrial thickness, internal endometrial echo structure, characteristic of the subendometrial halo, determination of interruption of texture and endomyometrial border, and Power Doppler analysis of vessels. Additonal parameters defined by IETA include presence of localized lesions to diagnose presence of a polyp, myoma or a possible carcinomatous pathology.

A study done by Dueholm and others in 2013,[7] involving 174 postmenopausal patients with endometrial thickness of ≥ 5 mm showed a correlation between interrupted myometrial junction, irregular surface, and doppler flow score, and the prediction of endometrial cancer. A similar study done by Opolskiene and others in 2007,[8] which involved 120 symptomatic women, showed that the best ultrasound variables to predict malignancy were heterogenous endometrial echogenicity, endometrial thickness, and irregular branching of endometrial blood vessels. However, the later study need to be tested prospectively prior to use in clinical practice.

Endometrial cancer risk is associated with body mass index, nulliparity and postmenopausal women, but results may vary across racial/ethnic groups. In 5 multiethnic prospective cohort study regarding the effect of body size and lifestyle factors. The study concluded that adult obesity and increase in adiposity, in general, are risk factors for endometrial cancer.[9] Similarly, diabetes, hypertension and Tamoxifen therapy were among the parameters which improved the appropriateness of model prediction for endometrial cancer risk, in postmenopausal women with thickened endometrium.[6]

Development of an ultrasound algorithm in correlation with patient characteristics for the identification of endometrial cancer will aid the clinician in selection of high-risk patients who will undergo more invasive diagnostic procedures. On the other hand, patients with lower risk may undergo individualized management and endometrial sampling may not be warranted.

Conceptual Framework



Relevance of the Study

To Research

Based on clinical and ultrasonographic parameters, several models have been proposed for the diagnosis of patients with endometrial pathology. A creation of a scoring system for the endometrium contributes as a baseline for future studies that would hopefully lead to standardization of endometrium assessment.

To Clinical Practice

A scoring system is a simple way for the clinician to interpret patients with abnormal uterine bleeding as their chief complaint. This will be an aid to lessen surgical intervention to diagnose endometrial pathology. Treatment options would be less invasive for patients at lower risk, and more aggressive to patients at higher risk for malignancy.

OBJECTIVES

General Objective:

To determine endometrial cancer risk among patients with abnormal uterine bleeding based on the International Endometrial Tumor Analysis (IETA) features.

Specific Objectives:

1. To describe the profile of patients with abnormal uterine bleeding suspected of having endometrial pathology
2. To describe sonologic features of patients with abnormal uterine bleeding suspected of endometrial cancer using the IETA features
3. To determine the association of a scoring system and endometrial cancer risk.

Study Design

A cross sectional prospective study was conducted on patients who came in with abnormal uterine bleeding at the Comprehensive Women's Care Unit of Cardinal Santos Medical Center from July 2015 to December 2015.

Inclusion Criteria

All women from reproductive age until postmenopausal age with a clinical diagnosis of abnormal uterine bleeding, who came in for ultrasound at the Comprehensive Women's Care Unit of Cardinal Santos Medical Center from July to December 1, 2015.

Exclusion Criteria

The following patients are exluded in the study:

1. Those with endometrial thickness of less than 4 mm on gray-scale sonography
2. Technical difficulties in assessing the endometrium such as in cases of very large myomas where morphology and vascularity features cannot be classified
3. Absence of histopathological diagnosis wherein patients could have been medically managed or biopsy done in another institution, and
4. When endometrial sampling was done as an office procedure.

Sampling Scheme

With reference to the census of abnormal uterine bleeding who have a histopathologic diagnosis, in Cardinal Santos Medical Center for the period of January to December 2014, and using the frequency of 50% and confidence interval of 5%, sample size computed using epi info 7.0 is 97 subjects.

All patients who came in at the Comprehensive Women's Care Unit for gynecologic ultrasound evaluation who fits in the inclusion criteria were approached and oriented by an assigned nurse. Details of the study were explained and a written informed consent was completed.

Definition of Procedures and Measurement of Outcomes

Gray scale sonography – conventional 2-D ultrasonography that displays small differences in an acoustical impedance as if they were different shades of gray.

Doppler sonography – use of Power Doppler sonography where blood flow through blood vessels is sonologically identified using a 3D/4D capable machine.

IETA system – International Endometrial Tumor Analysis system describes the endometrium qualitatively based on established criteria.

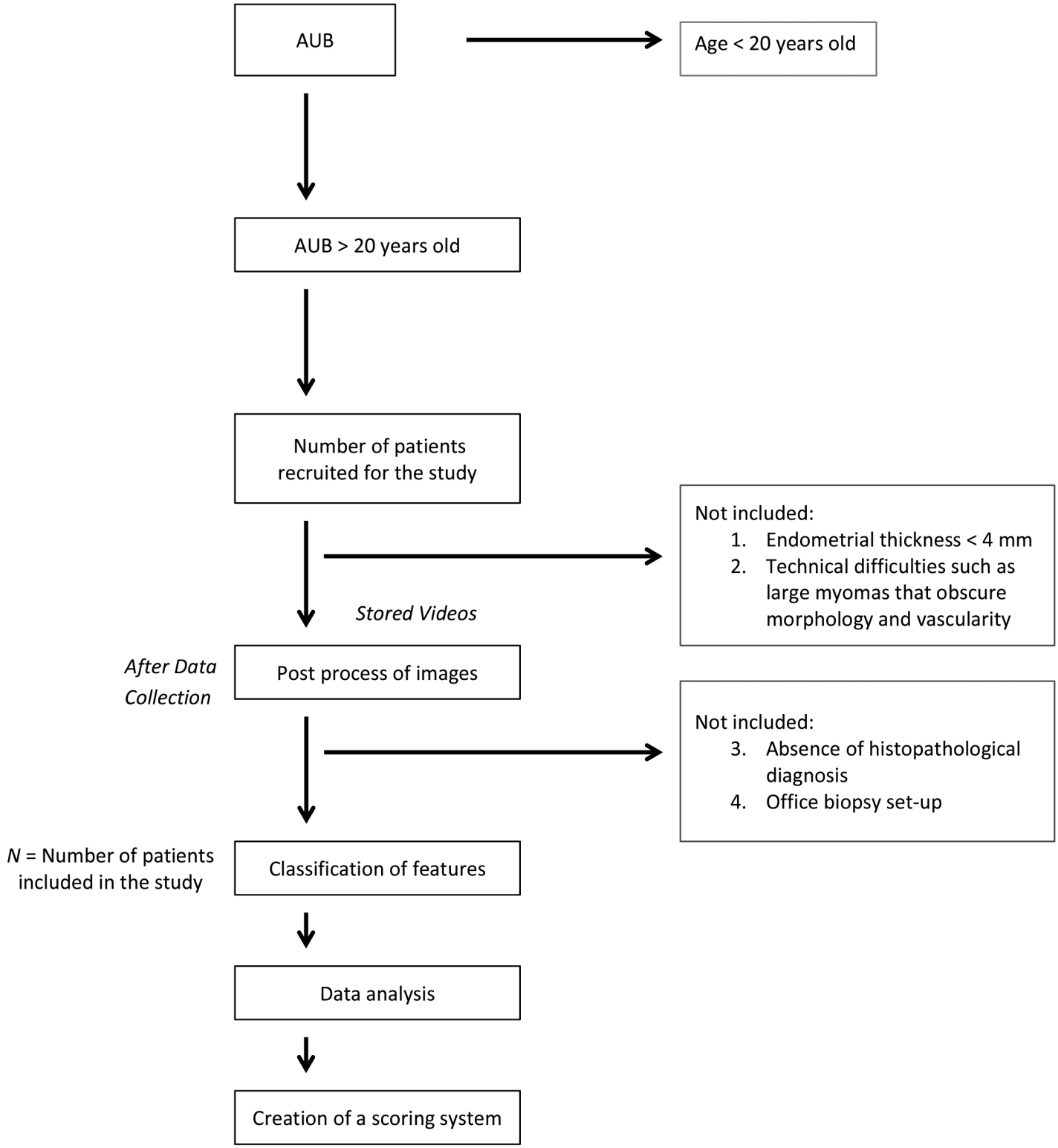
Histopathologic diagnosis – biospsy results of patients who underwent endometrial sampling through hysterscopy, curettage or hysterectomy.

Reproductive age – women among the 20 to 30 year age group.

Postmenopausal women – cessation of menstruation for more than 12 months without any medical or surgical intervention to induce amenorrhea.

Body mass index – weight in kilogram over height in m2. Abnormal uterine bleeding (AUB) - any significant deviation from normal frequency, regularity, heaviness (volume or amount) and duration of menstrual bleeding. It is used to describe all abnormal menstrual signs and symptoms arising from the uterine corpus.

Algoritm of Procedure



PATIENTS AND METHODS

Our study group comprised of women with a diagnosis of abnormal uterine bleeding who came in at the Comprehensive Women's Care Unit of Cardinal Santos Medical Center starting July 1, 2015 to December 31, 2015. All participants were referred for a transvaginal or transrectal ultrasound and underwent the procedure according to the unit's protocol. Research Ethics Review Committee of the said institution approved the study and all women gave written consent. The total number of patients referred during the study period was 542. We excluded patients with endometrial thickness of less than 4 mm, patients with endometrium that was difficult to assess, and those who were managed medically or biopsy done in another institution or if the biopsy was done only as an office procedure. There were a total of 98 participants included in this prospective study.

Patients' data were obtained including age and gravidity. History taking of these patients was standard to all those undergoing routine gynecologic sonography. Although this is a prospective study, patient's height, weight and medical history was retrospectively obtained from data gathered during hospital admission.

Gray-scale sonography and color doppler evaluation were done using the Voluson E6 GE Healthcare ultrasound machine equipped with a 7.5 to 9 MHz transvaginal and transrectal probes. The procedure was processed by one fellow in training together with one experienced certified OB sonologist given careful visual evaluation of the endometrium based on the IETA system. Initial conventional gray-scale ultrasound examination of the uterus was performed followed by color doppler ultrasound examination. The images were saved in SonoView in a separate file with a specified identity number. These were re-evaluated using a personal computer by fellow and the OB sonologist.

Six months after data collection, endometrial morphology and vascularity were assessed. Endometrial thickness was measured in a sagittal plane as the sum of the thickest part of the anterior and posterior endometrium, and classified into one of four categories: 5-10, 10-15, 15-20 and > 20 mm. Parameters as defined by the IETA features include:

- presence of bright edge (yes,no);
- presence of midline echo (yes, no);
- regularity of the endometrial-myometrial junction (regular, irregular);
- internal endometrial structure (hypochogenic, hyperechogenic, mix); and
- homogeneity of endometrial echogenicity (homogenous, heterogenous).

Doppler analysis include visual evaluation of the following parameters:

- number of blood vessels crossing the myometrial-endometrial junction (none, one, multiple);
- size of blood vessels (one, small, large);
- regularity of vessel branching (regular, irregular); and
- presence of area(s) of densely packed blood vessels (yes, no).

A standardized coding sheet was used to plot all findings for each parameter (patient characteristics and sonologic data obtained) to avoid missing values.

Individual histopathological diagnosis for those who underwent dilatation and curettage, hysteroscopy guided biopsy, or hysterectomy were obtained from the Laboratory Section of Cardinal Santos Medical Center. These results were used as reference standards.

In our study, we chose the gray-scale sonographic and doppler features of the endometrium based on the IETA that are best fitted to predict the pathological outcome of benignity or malignancy and combined these features with the patients' characteristics to create a scoring system.

Tables and figures were used to present the data. Open Epi Version 3, online statistical software was used to generate the statistics. Variables were expressed as percentages and Pearson Chi-square test used to compute for the p-value. A P-value of <0.05 was considered statistically significant. Receiver operative characteristic (ROC) curve analysis was used to determine the optimal cut-off in association with endometrial cancer risk. Area under the curve (AUC), sensitivity and specificity were calculated using Med Calc Version 16.2.1 online statistical software.

RESULTS

A total of 98 patients were included in the study. Table 1 shows the patients' demographic data. Three patients (3.1%) were less than 30 years of age, 21 (21.4%) were from the 30 to 40 year age group, 49 (50%) from the 41-50 age group and the remaining 25 (25.5%) were more than 50 years of age. Seventeen patients (17.3%) were nulligravid and 7 (7.1%) were multigravid, and the remaining 74 patients (75.5%) had 1 to 4 pregnancies. Among the subjects, majority had normal BMI but a significant percentage were either overweight (22.4%) or obese (9.2%). Twenty patients (20.4%) were hypertensive and 10 (10.2%) had diabetes mellitus.

Overall, 89 patients (90.8%) confirmed to have benign pathologies, and 9 patients (9.2%) had malignant pathologies based on the histopathological

Table 1. Patient characteristics and diagnostic performance of most common clinical parameters for predition of endometrial cancer

Parameter		N	(%)	Endometrial Pathology		P value
				Benign N(%)	Malignant N(%)	
Age (years)	<30	3	3.1	3 (100)	0	0.031
	30-40	21	21.4	20 (95.2)	1 (4.8)	
	41-50	49	50	47 (95.9)	2 (4.1)	
	>50	25	25.5	19 (76.0)	6 (24.0)	
Gravidity	G0	17	17.3	13 (76.5)	4 (23.5)	0.058
	G1-G4	74	75.5	70 (94.6)	4 (5.4)	
	≥ G5	7	7.1	6 (85.7)	1 (14.3)	
BMI	Normal	67	68.4	67 (100)	0	0.0001
	Overweight	22	22.4	16 (72.7)	6 (27.3)	
	Obese	9	9.2	6 (90.8)	3 (9.2)	
History of hypertension	Positive	20	20.4	14 (70)	6 (30)	0.0001
	Negative	78	79.6	75 (96.2)	3 (3.8)	
History of diabetes	Positive	10	10.2	83 (60)	5 (40)	0.0001
	Negative	88	89.9	6 (94.3)	4 (5.7)	

Table 2. Histopathological diagnosis

Finding	N (%)
Proliferative or atrophy	3 (3.1)
Submucous myoma	1 (1)
Endometrial Polyps	79 (80.6)
Simple hyperplasia, without atypia	1 (1)
Complex hyperplasia without atypia predominantly Simple hyperplasia	1 (1)
Endometrial polyp with simple hyperplasia without atypia	4 (4.1)
Endometrial cancer	9 (9.2)

diagnosis (Table 2). The combined percentage and computed p-value presented the following demographic parameters as significant predictors of malignancy: age more than 50, nulligravid, body mass index of more than 25, and presence of hypertension and/or diabetes mellitus.

Gray-scale ultrasound features differed significantly between benign and malignant pathologies based on endometrial thickness, endometrial-myometrial junction (EMJ), and homogeneity of endometrial echogenicity (Table 3). An endometrial thickness of more than 20 mm, irregular EMJ, and heterogenous endometrium were significantly correlated with malignancy. On the other hand, presence of bright edge, midline echo and internal endometrium structures, did not show significant correlation with a benign or malignant pathology.

Doppler examination showed that the number of blood vessels present and its size were significant predictors of malignancy. However, there was no correlation with vessel branching nor area of densely packed vessels based on the given sample size.

Ten parameters were identified as basis for the scoring model. Each showed a significant p-value, thus demonstrating a statistically significant correlation

Table 3. Diagnostic performance of image parameters based on IETA features for prediction of endometrial cancer

Parameter		N	(%)	Endometrial Pathology		P value
Gray Scale Imaging				Benign N(%)	Malignant N(%)	
Thickness	5-10 mm	44	44.9	43 (97.7)	1 (2.3)	.006
	10-15 mm	31	31.6	28 (90.3)	3 (9.7)	
	15-20 mm	12	12.2	11 (91.7)	1 (8.3)	
	> 20 mm	11	11.2	7 (63.6)	4 (36.4)	
Bright edge	Yes	19	19.4	18 (94.7)	1 (5.3)	.510
	No	79	80.6	71 (89.9)	8 (10.1)	
Midline echo	Yes	76	77.6	71 (93.4)	5 (6.6)	.097
	No	22	22.4	18 (81.8)	4 (18.2)	
Endometrial-myometrial border	Regular	88	89.8	82 (93.2)	6 (6.8)	.016
	Irregular	10	10.2	7 (70)	3 (30)	
Internal endometrial structure	Hyperechogenic	62	63.3	59 (95.2)	3 (4.8)	.133
	Hypoechogenic	8	8.2	7 (87.5)	1 (12.5)	
	Mix	28	28.6	23 (82.1)	5 (17.9)	
Homogeneity of endometrial echogenicity	Homogenous	45	45.9	45 (100)	0	.004
	Heterogenous	53	54.1	44 (83)	9 (17)	
Power Doppler						
Number of blood vessels	None	56	57.1	53 (94.6)	3 (5.4)	.033
	One	37	37.8	33 (89.2)	4 (10.8)	
	Multiple	5	5.1	3 (60)	2 (40)	
Size of blood vessels	None	56	57.1	53 (96.4)	2 (3.6)	.001
	Small	28	29.6	27 (93.1)	2 (6.9)	
	Large	14	14.3	9 (64.3)	5 (35.7)	
Vessel branching	None	56	57.1	55 (96.5)	2 (3.5)	.072
	Yes	6	6.1	5 (83.3)	1 (16.7)	
	No	36	36.7	29 (90.8)	6 (9.2)	
Area with densely packed vessels	None	56	57.1	55 (96.5)	2 (3.5)	.060
	Yes	1	1	1 (100)	0	
	No	41	41.8	33 (90.8)	7 (9.2)	

between score point numbers and histopathological findings. The different features were rated on a scale from 0 to 3 points depending on the degree of manifestation observed for the individual characteristics (Table 4). Simple addition of points gave the predictive endometrial cancer risk score. The ROC curve had an AUC 0.974 giving the best cut-off value of more than or equal to 9, with 100% sensitivity and 89% specificity.

DISCUSSION

We have created a scoring system to predict endometrial cancer risk on the basis of five demographic characteristics and five ultrasound features using the IETA description. Age group ranges from < 30, 30-40, 41-50 and > 50 years; OB Score is classified as nulligravid, gravida 1 to 4, and multigravid (> 5 pregnancies); body

Table 4. Scoring Model for prediction of endometrial cancer risk

Parameters	0	1	2	3
PATIENTS CHARACTERISTICS				
Age group	< 30	30-40	41-50	>50
OB Score	≥ G5	G1-G4	G0	
BMI	18.5-24.9	25-29	≥ 30	
Hypertension	Absent	Present		
Diabetes Mellitus	Absent	Present		
IETA FEATURES				
Endometrial Thickness	5-10 mm	10-15 mm	15-20 mm	> 20 mm
Endometrial-myometrial Junction	Regular	Irregular		
Homogeneity	Homogenous	Heterogenous		
Number of Blood Vessels	None	One	Multiple	
Size of Blood Vessels	None	Small	Large	

*Cut-off score for endometrial cancer risk ≥ 9

mass index ranges from normal (18.5 to 24.9), overweight (25-29), and obese (≥ 30); and whether the patient has a medical history of hypertension and/or diabetes mellitus. Sonographic findings based on the IETA features include the following: endometrial thickness ranging from 5-10 mm, 10-15 mm, 15-20 mm and > 20 mm; regular or irregular endometrial-myometrial junction; homogenous or heterogenous endometrium; absence or presence of one or multiple blood vessels; and small or large blood vessel size. Each is given a score of 0 to 3 and a score of 9 and above classifies the patients to be at high risk for endometrial malignancy.

Several studies show correlation of individual parameters to endometrial cancer risk such as thickened endometrium, postmenopausal women and presence of vascular pattern on ultrasound.[6,7,8,10] A study by Mandic included 122 patinets with postmenopausal bleeding and a scoring system called ONCO 1 was created. This study is similar to ours such that the parameters included the patient's age, clinical examination, ultrasonographic findings and results of post curettage histopathology report. Our study, though similarly non-invasive, covers for a wider array of subjects as it is not limited to postmenopausal women, but to all subjects with aubnormal uterine bleeding. Several reports have suggested incidence of endometrial cancer even in the premenopausal or reproductive age women.

Antoher study by Giannella, and others suggested an algorithm for management of symptomatic postmenopausal women with endometrial thickness of > 4 mm. Their first objective is to decrease the number of missed cancer. The RHEA risk-model designates a score for age > 65 years (1), endometrial thickness > 8 mm (1), hypertension (2), and recurrent bleeding (3) and a score of more than 4 means that an outpatient hysteroscopy or sonohysterography should be performed. With this model, there is moderate diagnostic accuracy in detecting intrauterine malignancies.

The REC scoring system proposed by Duoholm and others studied 174 postmenopausal women with endometrial thickness of > 5 mm. Similar parameters were observed as compared to our study. The advantage of their study is that it included gel infusion sonography which provided an enhanced assessment of the endometrium. For the same reason, our study is advantageous due to its non-invasive in nature, and included clinical parameters contibutory to endometrial cancer risk.

Currents studies are coming out to prove that one parameter is superior to the other. The beauty of this scoring system is that it included the most significant parameters, score it based on points, without having to consider which parameter is more superior to the other.

One of the strengths of this study is that being prospective in nature, it allowed standardization of data collection using coded parameters thus producing reliable data for prediction of malignancy risk. We are also able to provide an optimal reference standard based on the histopathological results obtained in the same institution.

On the other hand, since the IETA system is still subjective in nature, description is highly dependent on operator interpretation of visual evaluation, thus there should be adequate training in pattern recognition.

Moreover, a high resolution ultrasound equipment might be a factor in future reproducibility of results, which may not be possible for substandard machines, even in the hands of experts.

This is a simplified scoring system not based on the most optimal mathematical calculation. But simple as it is, the overall objective is not to subject those at low risk (Score = < 9) for unnecessary operative procedure, and on the other hand, high risk patients (Score ≥ 9) should not delay a reliable diagnostic and/or surgical procedure. The prediction of endometrial cancer risk using this scoring system needs to be tested prospectively prior to use in clinical practice since results cannot be generalized and needs to be validated. ■

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