Global Journal of Medical Research: E
Gynecology and Obstetrics
Volume 18 Issue 1 Version 1.0 Year 2018
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Do We Need More than Ultrasound Endometrial Thickness to Predict Malignancy?

By Adly Nanda Al Fattah, Tricia Dewi Anggraeni, Bella Aprilia & Muhammad Ikhsan
Faculty of Medicine Universitas

Abstract- Endometrial thickness (ET) ultrasound measurement has high diagnostic performance for detection of endometrial cancer in symptomatic postmenopausal women. Identified clinical risk factors, Doppler or 3D ultrasound parameters to predict endometrial malignancy had been proposed in several studies. This article is comparing the accuracy of ultrasound endometrial thickness with scoring system/index involving both of clinical and ultrasound parameters to predict endometrial malignancy. Eight eligible diagnostic studies were appraised to assess the accuracy of ultrasound ET and/or ultrasound-based index to predict malignancy. The incidence of endometrial malignancy confirmed by histopathology examination was ranging from 10.5 to 58% from 8 studies. Ultrasound-based index to predict endometrial malignancy had good accuracy (AUC 75%- 98%). The addition of endometrial volume/ uterine corpus volume ratio (EV/UCV) and Doppler to clinical parameters had increased the prediction accuracy of the index. While ultrasound ET alone has also high sensitivity, respectively 90.6% and 96.9% using the cut-off 4 mm and 3 mm with low accuracy.

Keywords: doppler endometrial cancer, ultrasound, clinical.

GJMR-E Classification: NLMC Code: WP 390

Strictly as per the compliance and regulations of:

Do We Need More than Ultrasound Endometrial Thickness to Predict Malignancy?

Adly Nanda Al Fattah [α], Tricia Dewi Anggraeni [σ], Bella Aprilia [ρ] & Muhammad Ikhsan [ω]

Abstract- Endometrial thickness (ET) ultrasound measurement has high diagnostic performance for detection of endometrial cancer in symptomatic postmenopausal women. Identified clinical risk factors, Doppler or 3D ultrasound parameters to predict endometrial malignancy had been proposed in several studies. This article is comparing the accuracy of ultrasound endometrial thickness with scoring system/index involving both of clinical and ultrasound parameters to predict endometrial malignancy. Eight eligible diagnostic studies were appraised to assess the accuracy of ultrasound ET and/or ultrasound-based index to predict malignancy. The incidence of endometrial malignancy confirmed by histopathology examination was ranging from 10.5 to 58% from 8 studies. Ultrasound-based index to predict endometrial malignancy had good accuracy (AUC 75% - 98%). The addition of endometrial volume/uterine corpus volume ratio (EV/UCV) and Doppler to clinical parameters had increased the prediction accuracy of the index. While ultrasound ET alone has also high sensitivity, respectively 90.6% and 96.9% using the cut-off 4 mm and 3 mm with low accuracy.

Ultrasound-based index to predict endometrial malignancy had better accuracy compared to ultrasound ET alone. Combination of ultrasound including Doppler parameters and clinical parameters had increased the prediction accuracy of the endometrial malignancy prediction index.

Keywords: doppler endometrial cancer, ultrasound, clinical.

I. Introduction

Endometrial cancer is one of the most common gynecological malignancies. It develops in about 142,000 women worldwide, and lead to approximately 42,000 of mortality [1]. Transvaginal ultrasound followed by endometrial biopsy is the most cost-effective diagnostic approach in the population with post-menopausal bleeding [2]. We therefore consider TVU as the first step in any woman presenting with postmenopausal bleeding [3]. Ultrasonography is a non-invasive method that could assess the morphologic structures of endometrium [4,5]. Sonographically determined endometrial thickness measurement shows high diagnostic performance for detection of endometrial cancer in symptomatic postmenopausal women[6].In addition, there is no universally accepted sonomorphologic criteria to define benign or malignant structure on the endometrium. In order to make the prediction accuracy better, some studies created a scoring system involving clinical and ultrasound parameters [7,8].This article was aimed to appraise studies that assess the accuracy of endometrial malignancy prediction system or index which involving ultrasound as one of the predictors.

Author α: Departemen Obstetri dan Ginekologi, Rumah Sakit Cipto Mangunkusumo, Jl. Diponegoro No. 71, Jakarta Pusat, Indonesia.
e-mail: adlynanda@yahoo.com
Author σ ρ ω: Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Indonesia, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia.

II. Methods

a) Search Strategy

The search was conducted on the Cochrane Library®, PubMed® and EMBASE® with the keywords of "endometrial" AND "malignancy" AND "scoring" OR "prediction" OR "index" on each databases with certain techniques (figure 1). Search focused on articles in diagnostic type showing diagnostic values of the studies. Reference lists of relevant articles were searched for other possibly relevant studies. After obtaining a result, a first selection was done by screening the study titles and abstracts. Eight articles were available as full text, and all of them included in our analysis.

b) Critical Appraisal

Appraisal of 8 diagnostic studies involving 5543 patients underwent clinical and ultrasound for predicting endometrial malignancy confirmed with the histopathology result was conducted finding of the diagnostic values (Se, Sp, PPV, NPV). Review study or study without diagnostic values reported were excluded. We used diagnostic appraisal questions developed by Centre of Evidence-Based Medicine (CEBM), University of Oxford (available at: http://www.cebm.net/critical-appraisal/).

III. Result

Eight eligible studies were appraised to assess the accuracy of ultrasound and/or ultrasound index to predict malignancy. The incidence of endometrial malignancy confirmed by histopathology examination was ranging from 10.5 to 58% from 8 studies. The accuracy of ultrasound-based index to predict endometrial malignancy was ranging from 75% - 98% from eight studies. Opolskiene, et al conducted a consecutive study of 729 post-menopausal bleeding, to evaluate the diagnostic performance of models predicting endometrial cancer. They stated that the

accuracy was increased significantly when endometrial thickness and power Doppler assessment are added to clinical variables. Clinical model including the variables age, use of warfarin and use of hormone replacement therapy had the largest area under the receiver–operating characteristics curve (AUC), with a value of 0.74 (95% confidence interval (CI), 0.67–0.81). A model including age, use of warfarin and endometrial thickness had an AUC of 0.82 (95% CI, 0.76–0.87), and one including age, use of hormone replacement therapy, endometrial thickness and vascularity index had an AUC of 0.91 (95% CI, 0.87 – 0.95)[9].

Dueholm, et al concluded that simple Doppler score (which considered only presence of vascularity and not presence of single/double dominant vessel, multiple vessels, large vessels, color splash or densely packed vessels) had an AUC of 0.83 in the prediction of endometrial cancer. Prediction index including endometrial thickness, Doppler score and interrupted endomyometrial junction on unenhanced TVS predicted endometrial cancer with an AUC of 0.95 (95% CI, 0.92 – 0.99) and, with addition of irregular surface on GIS, the AUC was 0.97 (95% CI, 0.94 – 0.99)[10].

In further study [11] they compare the offline and real time evaluation during scanning to assess efficiency of two-dimensional (2D) and three-dimensional (3D) TVU, power Doppler angiography (PDA) and gel infusion sonography (GIS) to detect endometrial malignancy. Diagnostic efficiency of 3D analysis may be improved by use of risk of endometrial cancer (REC)-scoring systems, without the need for calculation of vascular or endometrial volume. The REC consisted of: (1) body mass index ≥ 30 (+1 point), (2) total endometrial thickness ≥ 10 mm (+1 point), (3) total endometrial thickness ≥ 15 mm (+1 point), (4) interrupted endomyometrial junction (+1 point) and (5) irregular surface at gel instillation sonography (GIS) (+1 point). The first model included BMI, endometrial thickness, presence of an interrupted endomyometrial junction and Doppler score, had AUC of 0.879. Evaluation of 3D-GIS with BMI, an interrupted endomyometrial junction, Doppler score and irregular endometrial surface at 3D-GIS, had the highest diagnostic efficiency on multivariate regression, with an AUC of 0.908. Application of the REC-score system at 3D-PDA or 3D-GIS had comparable efficiency compared with their respective 2D models [11].

Burbos, et al created a model to predict endometrial carcinoma in postmenopausal women called DEFAB (Diabetes, Endometrial thickness, Frequency of bleeding, Age, and BMI). In the DEFAB criteria, presence of diabetes in a patient scores 2; endometrial thickness ≥ 14mm scores 1, recurrent episodes of bleeding scores 4; age ≥64 years scores 1; and BMI ≥31 $\mathrm{kg}\,m^2$ scores 1. The value ≥3 has a positive predictive value (PPV) of 7.78% and negative predictive value (NPV) of 98.2%, whereas a score equal to or greater than 5 has a PPV of 11.9% and NPV of 97.8% [12].

Seek in, et al investigated the accuracy of endometrial thickness in predicting endometrial pathologies in both of symptomatic (group 1) and asymptomatic (group 2) postmenopausal women. The best cut-off point for endometrial thickness in predicting endometrial carcinoma in group 1 was 8.2 mm, which provided 75% sensitivity and 74% specificity; area under the AUC of 0.88; 95% CI, 0.76– 1.00%. In group 2, the AUC was 0.76 (95% CI, 0.46–1.00; p 5 0.114). [6]. In other study, Patel, et al stated that threshold of 4 mm, the sensitivity is 90.6% and increases to 96.9% when decreasing the threshold to 3 mm[13].

Mansour, et al evaluated the role of endometrial/uterine corporeal volume ratio (EV/UCV) assessment in the prediction of endometrial cancer. EV/UCV of a cutoff value 0.017 was predictive of malignancy. Endometrial/uterine volume ratio was more sensitive than endometrial volume and endometrial thickness for prediction of endometrial cancer[7].

Mihajovic, created the transvaginal ultrasound score for endometrial malignancy prediction consisted of: thickness of endometrium (up to five mm = 0, from five to eight mm = 1,> eight mm = 2), echogenicity of the endometrium compared to the myometrium: normal echogenicity = 0, hyperechogenous = 1, hypoechogenous = 2 , the border of the endometrium towards the myometrium - subendometrial hypoechogenous zone (whole = 0. intermittent = 1), homogeneity of the texture of the endometrium (homogenous = 1. inhomogeneous = 2), presence of the colored signals in the endometrium (present = 2. absent = 1), index of resistance in newly-formed blood vessels in the endometrium (> 0.4 = 1. < 0.40 = 2), volume of the endometrium by an ultrasound check-up (< 13 ml = 1. > 13 ml = 2). Score system showed that the value 8 had the best validity for the detection of endometrial malignity, with the sensitivity of 0.857 and specificity of 0.785[4].

IV. Discussion

In our study, the incidence of endometrial malignancy was varied among studies. It could possibly explain by the variation of the population. In some studies, they included women with a complaint of postmenopausal bleeding who has endometrial thickness ≥ 4.5 mm[9], while other studies included subjects without considering the ET.[12,14] We found the incidence of endometrial malignancy from 5 to 58%. It was similar with the finding from The Gynecologic Oncology Group (GOG) that found 42.6% of endometrial malignancy, 123 of 289 specimens [14].

Sorosky in their review stated that the positive predictive value and negative predictive value of an

office biopsy are greater than 90% [14].TVS screening for endometrial cancer has good sensitivity in postmenopausal women [15]. In addition, in certain conditions in which the cervical canal could not be accessed by curettage, the role of ultrasound will be useful to predict malignancy.

Monsour had the highest appraisal score, because they show all the diagnostic parameters of their result. Transvaginal 3D render mode ultrasound was used to assess the volume of the uterus in the coronal plane using manual lining technique. Volumes were manually calculated in the coronal plane with 30° rotation steps. They found that EV/UCV had the best in prediction of malignancy compared to endometrial thickness and endometrial volume; AUC (area under the curve) for endometrial thickness, volume and EV/UCV was respectively 75, 92 and 100%. However, further studies should be conducted with a larger number of subjects to support these findings.[7] The interobserver and intraobserver reproducibility of 3D ultrasound for assessment of endometrial volume measurements in patients with postmenopausal bleeding was well proved, showing better reproducibility than 2D measurement of endometrial thickness [7].

Using ultrasound parameter, the accuracy of prediction index was higher compared to the non-ultrasound based index. In our study, the accuracy of prediction index involving ultrasound parameters was ranging from 0,75 to 0.98. It was higher compared to the clinical-based prediction index. Burbos, et al created a clinical predictive model called FAD 31 (F for the frequency of bleeding episodes, A for the age of the patient, D for diabetes, and number 31 represents the BMI cut-off value). The AUC was 0.73. Among 14 recognized indexes in our appraisal study, only 3 indexes had the AUC below 0.8 [8].

V. Conclusion

Ultrasound-based index to predict endometrial malignancy had good accuracy. Addition of endometrial thickness and power Doppler to clinical parameters had increased the prediction accuracy. EV/UCV had the best in prediction of malignancy compared to endometrial thickness and endometrial volume. Further larger study should be conducted to assess the effectivity and eligibility of several ultrasound parameters.

Conflict of Interest

None to declare.

References Références Referencias

1. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. The Lancet. 2005 Aug; 366(9484): 491–505.
2. Breijer MC, Van Doorn HC, Clark TJ, Khan KS, Timmermans A, Ben W J Mol, et al. Diagnostic strategies for endometrial cancer in women with postmenopausal bleeding: cost-effectiveness of individualized strategies. Eur J Obstet Gynecol. Elsevier Ireland Ltd; 2012 Jul 1; 163(1): 91–6.
3. Dijkhuizen FPHLJ, Mol BWJ, Br lmann HAM, Heintz APM. Cost-effectiveness of the use of transvaginal sonography in the evaluation of postmenopausal bleeding. Maturitas. 2003 Aug; 45(4): 275–82.
4. Mihajlovic S, Vasiljevic M, Jurisic A, Kisic-Tepavcevic, Dimitrijevic D, Nejkovic L. Predictive value of transvaginal ultrasound score for detection of endometrial malignancy. 2016 Oct 30: 1–6.
5. Clark TJ. Outpatient hysteroscopy and ultrasonography in the management of endometrial disease. Curr Opin Obstet Gynecol. 2004 Aug; 16(4): 305–11.
6. Seckin B, Cicek MN, Dikmen AU, Bostanc EI, Muftuoglu KH. Diagnostic value of sonography for detecting endometrial pathologies in post menopausal women with and without bleeding. J Clin Ultrasound. 2016 Feb 9; 44(6): 339–46.
7. Mansour GM, El-Shalakany A. Endometrial/uterine corporeal volume ratio (EV/UCV) as predictor of malignancy in women with postmenopausal bleeding. Arch Gynecol Obstet. 2nd ed. 2011 Aug 24; 285(3): 831–8.
8. Burbos N, Musonda P, Duncan TJ, Crocker SG, Morris EP, Nieto JJ. Estimating the Risk of Endometrial Cancer in Symptomatic Postmenopausal Women. Int J Gynecol Cancer. 2011 Apr; 21(3): 500–6.
9. Opolskiene G, Sladkevicius P, Valentin L. Prediction of endometrial malignancy in women with postmenopausal bleeding and sonographic endometrial thickness? 4.5 mm. Ultrasound Obstet Gynecol. 2011 Jan 19; 37(2): 232–40.
10. Dueholm M, M ller C, Rydbjerg S, Hansen ES, rtoft G. An ultrasound algorithm for identification of endometrial cancer. Ultrasound Obstet Gynecol. 2014 May 2; 43(5): 557–68.
11. Dueholm M, Christensen JW, Rydbjerg S, Hansen ES, rtoft G. Two- and three-dimensional transvaginal ultrasound with power Doppler angiography and gel infusion sonography for diagnosis of endometrial malignancy. Ultrasound Obstet Gynecol. 2015 Jun 2; 45(6): 734–43.
12. Burbos N, Musonda P, Giarenis I, Shiner AM, Giamougiannis P, Morris EP, et al. Predicting the risk of endometrial cancer in postmenopausal women presenting with vaginal bleeding: the Norwich DEFAB risk assessment tool. British Journal of Cancer. Nature Publishing Group; 2010 Mar 30; 102(8): 1201–6.
13. Patel V, Wilkinson EJ, Chamala S, Lu X, Castagno J, Rush D. Endometrial Thickness as Measured by Transvaginal Ultrasound and the Corresponding Histopathologic Diagnosis in Women With Postmenopausal Bleeding. International Journal of Gynecological Pathology. 2017 Jul; 36(4): 348–55.

14. Sorosky JI. Endometrial Cancer. Obstet Gynecol. 2008 Jan 11; 111: 1–12.
15. Jacobs I, Burnell M, Manchanda R, Singh N, Sharma A, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncology. Elsevier Ltd; 2010 Dec 18; 12(1): 38–48.

Table 1: Eight Eligible Studies

Reference	Eligible for analysis	Design	Required parameters	Endometrial malignancy rate (%)	Result (accuracy for endometrial malignancy)
Opolskiene (2011)	729	Cross-sectional	- Age, use of warfarin and endometrial thickness. - Age, use of hormone replacement therapy, endometrial thickness and vascularity index.	24%	AUC 0.82 Sens 84%, Spec 66%, LR+ 2,49, LR 0,24 AUC 0, 91. Sens 90%, Spec 77%, + LR 3.14, - LR 0.13.
Dueholm (2014)	432	Cross-sectional	- Presence of vascularity and not presence of single/double dominant vessel, multiple vessels, large vessels, color splash or densely packed vessels - Endometrial thickness, Doppler score and interrupted endomyometrial junction on unenhanced TVS - Endometrial thickness, Doppler score and interrupted endomyometrial junction on unenhanced TVS with addition of irregular surface on GIS	41%	AUC 0.83 AUC 0.95 AUC 0.97
Burbos, et al (2010)	3047	Cross-sectional	Norwich DEFAB prediction: - Diabetes - Endometrial thickness (ET) - Age - Frequency of bleeding - BMI	58%	AUC 0.77 ET Cut-off ≥3 mm PPV 7.78% NPV: 98.2% ET Cutoff ≥ 5 mm PPV 11.9% NPV: 97.8%
Dueholm (2015)	169	Prospective cohort	- BMI, interrupted endomyometrial junction, Doppler score, irregular endometrial surface at 3D-GIS (Model 4) - REC score 3D-PDA (BMI≥30, ET≥10mm, ET≥15mm, interrupted endomyometrial junction, Doppler score) - REC score 3D-GIS (BMI≥30, ET≥10mm, ET≥15mm, interrupted endomyometrial junction, Doppler score, irregular surface at 3D-GIS)	40,8%	AUC: 0.908, Sens 85.3% Spec 89.3% AUC: 0.88, Sens 86.9%, Spec 81% AUC: 0.894, Sens: 85.3% Spec: 86.9%
Mihajlovic (2015),	100	Cross-sectional	- Thickness of endometrium - Echogenicity of the endometrium compared to the myometrium - The border of the endometrium towards the myometrium - subendometrial hypoechogenous zone - Presence of the coloured signals in the endometrium - Index of resistance in newly-formed blood vessels of the endometrium - Volume of the endometrium by an ultrasound check-up	21%	Cutoff: 8 Sens 85.7%, Spec 78,5%

Mansour (2012)	160	Cross-sectional	An endometrial/ uterine volume (EV/UCV) ratio Endometrial thickness Endometrial volume in cc	16,87%	Cutoff: 0.017, Accuracy: 98%, Sens: 99%, Spec: 98%, PPV: 98%, NPV: 99% Cutoff: 5mm, Accuracy: 75%, Sens: 68%, Spc: e 82%, PPV: 77%, NPV: 74% Cutoff: 1.4 cc, Accuracy: 86%, Sens: 81%, Spec: 90%, PPV: 88%, NPV: 84%
Seekin, (2015)	602	Cross-sectional	Endometrial thickness	Symptomatic group: 2,9% Asymptomatic group: 0,9%	Cutoff ≥ 8.2 mm Sens 75%, Spec 74%, AUC: 0.88 Cutoff ≥ 5 mm AUC: 0.76
Patel et al (2017)	304	Cross-sectional	Endometrial thickness	10,5%	Cutoff 4 mm, Sens: 90.6% Cut off 3 mm, Sens: 96.9%

BMI, body mass index; ET, endometrial thickness; TVS, trans-vaginal ultrasound; GIS, gel infusion sonography; PDA, power Doppler Angiography; EV/UCV, endometrial volume/uterine corporeal volume; REC score, risk of endometrial cancer score; Sens., sensitivity; Spec., specificity; LR+, positive likelihood ratio; LR–, negative likelihood ratio; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

Table 2: Appraisal Table

No.	Study	Population	Validity			Result					Applicability	Total Score
			1	2	3	4 (Sn)	5 (Sp)	6 (PPV)	7 (NPV)	8 AUC	9	
1.	Opolskiene (2011) Clinical parameters, ET Clinical parameters, ET and vascularity index	729	+	+	+	84 % 90%	66 % 77%	- -	- -	0.82 0.91	+	7/9 7/9
2.	Dueholm (2014) Presence of vascualrity ET, Doppler, TVS parameter ET, Doppler, TVS parameter + irregular surface on GIS	432	+	+	+	-	-	-	-	0.83 0.95 0.97	+	4/9 4/9 4/9
3.	Burbos, et al (2010) Cutoff ≥3 mm Cutoff ≥ 5 mm	3047	+	+	+	- -	- -	7.78% 11.9%	98.25% 97.8%	0.76	+	4/9 4/9
4.	Seekin, (2015) Cutoff ≥ 8.2 mm Cutoff ≥ 5 mm	602	+	+	+	75%	74%	-	-	0.88 0.76	+	4/9 4/9
5.	Dueholm (2015) Moedl 4 REC score 3D-PDA REC score 3D-GIS	169	+	+	+	85.3% 86.9% 85.3%	89.3% 81% 86.9%	- - -	- - -	0.90 0.88 0.89	-	6/9 6/9 6/9
6.	Mansour (2012) EV/UCV Endometrial thickness Endometrial volume in cc	160	+	+	+	99% 68% 81%	98% 82% 90%	98% 77% 88%	99% 74% 84%	0.98 0.75 0.86	+	9/9 5/9 9/9
7	Mihajovic (2015)	100	+	+	+	85.7%	78.5%	-	-	-	+	5/9
8.	Patel et al (2017) Cutoff 4 mm Cutoff 3 mm	304	+	+	+	90.6% 96.9%	- -	- -	- -	- -	+	5/9 5/9

1, representative patients; 2 reference standard; 3, blind & independent; 4, sensitivity; 5, specificity; 6, positive predictive value; 7, negative predictive value; 8,area under the curve; 9 detail methods to permit replication;US, ultrasound; +, adequate; −, inadequate; ?, unknown, no information given'. Every item was scored based on diagnostic study appraisal questions developed by CEBM (available at: http://www.cebm.net/critical-appraisal/)