Evaluation of International Endometrial Tumor Analysis Sonographic Criteria in diagnosis of Endometrial Carcinoma

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Abstract

Postmenopausal vaginal bleeding is a sign that should not be Ultrasound imaging has become an effective diagnostic tool of gynecological practice throughout the years. Endometrial diagnosis typically involves invasive investigational approaches. Today, however, with the advent of high-resolution transvaginal ultrasound and Doppler ultrasonography (non-invasive diagnostic tool), is an alternative candidate to replace invasive approaches.

The aim of this study is to evaluate the contribution of the terms and definitions described by the IETA group when designing a malignancy model for better diagnosis of malignancy in cases with postmenopausal uterine bleeding.

In the present study 120 patients with postmenopausal bleeding were included in the study. The study was conducted from April 2017 to April 2019 at Tanta University hospitals, Obstetrics & Gynecology and Diagnostic Radiology departments.

Both patients were subjected to the following: full history taking, general examination, local examination, 2D transvaginal ultrasonography, Doppler study, hysteroscopy examination, endometrial biopsy. Symptomatic postmenopausal women with endometrial thickness > 5 mm have been chosen because women with a lower endometrial thickness have a very low incidence of cancer and a prospective evaluation.

In this study:

- The best cut off value for endometrial thickness in predicting malignancy was ≥12mm.
- Doppler color content score > 2 showed differentiation between benign and malignant cases.
- IETA Doppler vascular pattern showed multiple vessel pattern was found in 70% in cases of endometrial cancers.
- An endometrial malignancy model was designed including the five significant variables with accuracy about 95% and AUC 0.9 consisted of Endo. thick. ≥12mm, heterogenous endometrium, irreg. endo. midline, ll defined endo. myo. interface, Doppler Score ≥2.
- The best cut off score that have the highest positive predictive value, highest +v likelihood ratio and the largest area under receiver operator curve was ≥10.

Conclusion: We may conclude that: applying a malignant model for postmenopausal bleeding cases allows for easy classification of cases into low and high risk, with the ability to restrict the invasive procedure on dangerous cases only for better diagnosis of endometrial cancer.

Key words: Endometrial Carcinoma; Endometrial Tumor

Introduction

Postmenopausal bleeding (PMB) in both the general and hospital settings is a serious clinical issue [1].

It is estimated that about 90-95% of postmenopausal women with endometrial cancer report a vaginal bleeding experience, while about 10% of postmenopausal women report an intrauterine malignancy. Therefore, a postmenopausal vaginal bleeding is a warning not to be ignored. [2]

In this regard a good clinical practice provides, as first diagnostic step, a transvaginal ultrasound in order to discriminate women at high or low risk of malignancy. But in order to obtain an efficient ultrasound report we must solve certain problems that will be discussed in the following.

Most reports describing uterine cavity ultrasonography are limited and sometimes contradictory, the lack of standardization of words and meanings used to define endometrial ultrasound results and uterine cavity makes the meta-analysis of small studies meaningless [3].

there is no absolute diagnostic consensus on the appearance of endometrial cancer. Sometimes abnormal appearing masses may not be carcinoma and small foci of carcinoma may be present in simple lesions [4,5].
The International Endometrial Tumor Analysis (IETA) group, established in Chicago in 2008, has created a common consensus to agree on terms and definitions to identify ultrasound findings in the uterine cavity and to establish guidelines to promote the prediction and diagnosis of endometrial disease [6]. Several studies try to use variables other than endometrial thickness e.g. the gray-scale ultrasound morphology of the endometrium, the vascularization of the endometrium as assessed by Doppler ultrasound and clinical variables, in order to discriminate between benign and malignant endometrium in women with postmenopausal bleeding and improve the diagnostic performance of the procedures [7].

Finally, trials including patient characteristics and sonographic characteristics were conducted to design a model for endometrial cancer and then to estimate its risk and clinical usefulness. Some authors are using, as study participants, all postmenopausal women with vaginal bleeding, whereas other authors included only symptomatic postmenopausal women with an endometrial thickness at risk of intrauterine malignancy, the majority of these studies showed fair outcomes with an improvement of diagnostic performance in detecting endometrial cancers. However, up to date, these models are not yet validated externally [8].

**Aim of the work:**

To detect the diagnostic accuracy of transvaginal ultrasound in detecting endometrial cancer has been questioned in the most recent meta-analysis that justifies further studies in order to get simple, no invasive and valuable method in screening women with post-menopausal bleeding.

**Patients and methods:**

It was Prospective cross-sectional study. The study was conducted from April 2017 to April 2019 at Tanta University hospitals, Obstetrics & Gynecology and Diagnostic Radiology departments. 120 patients with postmenopausal bleeding selected from the attendees of the outpatient Gynecology clinic of the Department was recruited in this study.

**Inclusion criteria:**

1. Natural menopause; defined as 1 year of absence of menstruation in women older than 40 years provided that the amenorrhea was not explained by medication or disease.
2. Postmenopausal bleeding; defined as any vaginal bleeding in a postmenopausal woman not on hormone replacement therapy.

**Exclusion criteria:**

- Hormonal therapy.
- Coagulation disorders.
- Thyroid gland disorders.
- Tamoxifen therapy.
- Liver diseases.
- Evidence of PID.
- Neglected IUD or pessary.
- Any cervical abnormality.

**Ethical consideration:** They were properly counseled & signed informed consent.

All patients were submitted to the following:

1. Full history taking;
2. Examination;
3. Investigations:

   - CBC, LFT, KFT, PT, PTT, INR, Viral marker.

4. Transvaginal sonography:

Examination was performed with endovaginal transducer of 4-7 MHz frequency on voluson 730 pro machine (GE Healthcare, Austria) after complete emptying of the urinary bladder.

**All pelvic organs were assessed as the following:**

- **The uterus:** its central location and large size in the pelvis was used as a landmark for orientation, it is a hollow thick muscular organ, pear shaped situated in true pelvis between urinary bladder anterior and rectum posterior, the wall of the uterus is composed of 3 layers: endometrium, myometrium, perimetrium.
- **Ovaries**, Fallopian tubes and Pelvis: TVS allowed us to assess the presence or absence of free fluid in Douglas pouch, and the presence of lesions within neighboring organs as the bladder or rectum.

5. **Doppler study:**

The endometrial vasculature was scored using the International Endometrial Tumor Analysis (IETA) color score (score of 1 is given when no color flow signals, score of 2 when only minimal color can be detected, score of 3 when the color is mild, score of 4 when the color is abundant), and also its pattern described in the (IETA) terms Single vessel, Multiple dominant vessels, Scattered vessels.

6. **Hysteroscopy:**

After the sonographic and Doppler tests, diagnostic hysteroscopy was performed for all patients. Hysteroscopic controlled biopsy was taken under local anesthesia (para cervical block) or general anesthesia from suspected endometrial areas where appropriate. The endometrial examination offers a tissue diagnosis that directs further management. Then sonographic findings have been compared to the final histopathology.

**Statistical analysis:**

Data collected throughout history, basic clinical examination, sonographic reports and histopathology reports were analyzed with (SPSS) version 20. Quantitative results were represented as mean±standard deviation (SD) data were analyzed by independent t-test, paired t-test, using univariate analysis. In malignant situations, the receiver operating characteristic (ROC) curve was done to determine the best cutoff value, P-value was deemed meaningful if < 0.05 and highly significant if < 0.001.

**Results:**

In this study (patient characters): mean values of the clinical variables (Table I) were: age 56.7, BMI 29.4, Duration since menopause 4.3.
66.8% of patients have no medical disease while, the most frequent medical disorder recorded in diseased patients was hypertension (16.6%) as in (Table 2).

The most common lesions were benign in nature (specially the endometrial hyperplasia with highest frequency about 33%) while the endometrial carcinoma was only 16.7% (Table 3). Including clinical variables (Age, Parity, BMI, HPN and Diabetes) shows a statistically significant difference between benign and malignant cases. While (duration since menopause, hepatic disease and combined disease) the table shows statistically non-significant differences (Table 4). The mean endometrial thickness in malignancy cases (18.6 ± 7.5). (Figure 1&2).

The most frequently identified sonographic variables with malignancy were endo-heterogenous. Echogenicity, and endo irregularity. Midline, the endo is poorly defined. end. myo. System, Doppler score > 2, multiple vessel patterns and all show a significant difference between table of benign and malignant cases (Table 5), Endo. Endo. Power. (1.2 cm), endometrium heterogeneous, irregular. Endo. Endo. Midline, endo is ill-defined. Myo. myo. Browser (Table 6). Score cut off (≥10) had the largest area under receiver operator curve and had the best accuracy for detection of malignancy Area under curve (AUC) =0.94 (Table 7).

| Variables          | Range  | Mean ±SD |
|--------------------|--------|----------|
| Age (years)        | (47-72)| 56.7 ± 5.7 |
| BMI                | (23-42)| 29.4 ± 3.4 |
| Duration since menopause (years) | (2-10) | 4.3 ± 3.3 |
| Parity             | No     | Percentage % |
| Nuli para          | 6      | (5%)      |
| Multi para         | 114    | (95%)     |

**Table 1**: Descriptive analysis for demographic and clinical variables of studied group. Total No. = 120

| Medical disease | No of patients | Percentage % |
|-----------------|----------------|--------------|
| Non diseased    | 80             | 66.8         |
| Diseased        |                |              |
| DM              | 4              | 3.3          |
| HTN             | 20             | 16.6         |
| Hepatic         | 4              | 3.3          |
| Combined disease| 12             | 10           |

**Table (2)**: Medical history of studied group (N=120)
Table 3: Lesions detected by histopathology in the studied group (N= 120):

| Lesion                      | Frequency | Percentage % |
|-----------------------------|-----------|--------------|
| Endometrial carcinoma       | 20        | 16.7         |
| Endometrial hyperplasia     | 40        | 33.3         |
| Atrophic endometrium        | 22        | 18.3         |
| Endometrial polyp           | 18        | 15           |
| Submucous fibroid polyp     | 6         | 5            |
| Non-significant finding     | 14        | 11.7         |

Table 4: Univariate analysis for comparing clinical variables between endometrial cancer cases (N = 20) and benign cases (N = 100).

| variables                             | Malignant | Benign | Statistical test | P value |
|---------------------------------------|-----------|--------|------------------|---------|
| Age(year)                             | Range     | Mean ±SD | (55-70)          | 2.87*   | 0.005 |
|                                       | Mean ±SD  |         | 61.1± 5.4        |         |       |
| Duration since menopause             | Mean (years) ±SD | 4.1±3.2 | 5.6±3.7          | 1.174* | 0.246 |
| Parity                               | Nulli n (%) | 3(30) | 0(0)             | 10.11* | 0.0014|
|                                       | Para n (%) | 7(70) | 50(100)          |         |       |
| BMI                                   | Range     | Mean ±SD | 29-42            | 6.5*    | < 0.001|
|                                       | Mean ±SD  |         | 34.3± 3.6        |         |       |
| HPN                                   | Yes n (%) | 2(10) | 80(80)           | 15.77* | <0.001|
|                                       | No n (%)  | 18(90) | 20(20)           |         |       |
| Diabetic                              | Yes n (%) | 10(50) | 92(92)           | 8.47*  | 0.003 |
|                                       | No n (%)  | 10(50) | 8(8)             |         |       |
| Hepatic                               | Yes n (%) | 2(10) | 2(2)             | 9.4*   | 0.09  |
|                                       | No n (%)  | 18(90) | 98(98)           |         |       |
| Combined disease                      | Yes n (%) | 10(50) | 2(2)             | 8.4*   | 0.06  |
|                                       | No n (%)  | 10(50) | 98(98)           |         |       |

(*) using Chi-square analysis, (*) using t-test, significant result (p<0.05).
Table 5: Univariate analysis comparing IETA sonographic variables between malignant cases (N = 20) and benign cases (N = 100).

| variables                                | Malignant  | Benign     | Statistical test | P value |
|-------------------------------------------|------------|------------|------------------|---------|
| **Endo.thick**                            | Range (mm) | 9(10)      | 18.6±7.5         | 5.9*    | <0.001  |
|                                           | Mean ±SD   | 2(10)      | 9.9±3.2          |         |         |
| **Endo. Echogenicity**                     | Hetero. n (%) | 18 (90)       | 8(8)             | 28.38*  | <0.001  |
|                                           | Homo. n (%) | 16 (80)       | 92(92)           |         |         |
| **Endo. Midline**                          | Ill-defined n (%) | 0 (0)        | 4(4)             | 8.86*   | 0.011   |
|                                           | Linear n (%) | 2 (20)        | 66(66)           |         |         |
|                                           | Irregular n (%) | 16 (80)      | 30(30)           |         |         |
| **Endo. Myomet. Interface**                | Regular n (%) | 4 (20)        | 92 (98)          | 33.8*   | <0.001  |
|                                           | Ill-defined n (%) | 16 (80)      | 4 (2)            |         |         |
| **Doppler score**                          | No flow (1) n (%) | 4 (20)        | 26 (26)          | 33.1*   | <0.001  |
|                                           | Min. (2) n (%) | 8 (40)        | 66 (66)          |         |         |
|                                           | Mod. (3) n (%) | 8 (40)        | 8 (8)            |         |         |
|                                           | Sever (4) n (%) | 0 (0)         | 0 (0)            |         |         |
| **Vascular pattern**                       | No n (%)    | 4(20)       | 64(23)           | 25.28*  | <0.001  |
|                                           | Single n (%) | 0(0)         | 20(20)           |         |         |
|                                           | Multiple n (%) | 14(70)      | 66               |         |         |
|                                           | Scattered n (%) | 2(10)        | 34(33)           |         |         |
|                                           | Circular n (%) | 0(0)         | 8(8)             |         |         |

Table 6: Validity of clinical and IETA sonographic variables which associated with intrauterine malignancy.
Table 7: Validity of model of risk scoring for study group

| Score cut off | Sensitivity | specificity | PPV  | NPV  | LR +v | LR −v | Accuracy |
|---------------|-------------|-------------|------|------|-------|-------|----------|
| <5            | 10          | 8.6         | 2.3  | 30.7 | 0.1   | 10.4  | 8.9      |
| ≥5            | 90          | 93          | 75   | 97.7 | 12.8  | 0.1   | 92.8     |
| ≥10           | 80          | 97.8        | 88.8 | 95.7 | 36.3  | 0.1   | 94.6     |

Score cut off (≥10) had the largest area under receiver operator curve and had the best accuracy for detection of malignancy

Area under curve (AUC) = 0.94 table (7) Confidence interval (95%)

Figure 1: Endometrial thickness 16.5 mm, regular endometrial myometrial junction with linear midline, no detected blood flow (score 1), homogenous endometrium Histopathology revealed endometrial hyperplasia.

Figure 2: Endometrial thickness measures 15 mm, minimal endometrial blood flow (IETA score2), scattered vessel pattern, homogenous endometrium, regular endometrial myometrial junction, linear endometrial midline. Histopathology revealed endometrial hyperplasia.

Discussion:

- In this study (patient characters): mean values of the clinical variables were age 56.7, BMI 29.4, Duration since menopause 4.3. Also, medical history of the patients showed 66.8% of patients have no medical disease while, the most frequent medical disorder recorded in diseased patients was hypertension (16.6%). In the univariate analysis clinical variables including age, parity, BMI, cases demonstrated a statistically significant difference between hypertension and hyperglycemia.

- Conversely, Friedenreich C.M. et al. (2011), Rosato V et al. (2011) reported that there was no significant value for presence of hypertension in prediction of intrauterine malignancy [9,10].

- Opolskiene et al. (2011) It was found that, in univariate analysis between women with and without cancer, there was no disparity in BMI and diabetes [11].

- Although Giannella et al. (2014) found that there were no significant differences in patient characteristics regarding menarche age, menopause age, BMI, parity, diabetes, use of tamoxifen, use of anticoagulants, and history of breast cancer [12].
In this study, histopathological examination revealed endometrial atrophy in 22 patients (18.3%), endometrial hyperplasia in 40 patients (33.3%), endometrial carcinoma in 20 patients (16.7%), endometrial polyp in 18 patients (15%) and submucous fibroid in 6 patients(5%) and a non-significant finding 14 patients (11.7%). Thus, the commonest cause of postmenopausal bleeding is in this study was endometrial hyperplasia.

Conversely, Good (2007) found that the mean pathological finding in patients complaining of abnormal uterine bleeding were endometrial polyp and submucous myoma [13].

Lee et al. (2011) found that the commonest lesion causing postmenopausal bleeding was endometrial atrophy [14].

In this study (IETA sonographic variables): the mean endometrial thickness was 13.6 ± 5.6 mm, the most frequent sonographic variables (in general) were homogenous endo. echogenicity, linear endo. midline, regular endo. myo. Interface and Doppler score 2 but scattered vascular pattern and no flow pattern with the same frequency.

Regarding malignancy: the mean endometrial thickness in malignancy cases was 18.6 mm, the most frequent sonographic variables were heterogeneous endo. midline, ill-defined endo. myo. interface, score doppler> 2 and multiple vessel pattern. All show difference significantly between different cases.

Also, heterogeneous endometrium and ill-defined endo. myo. interface was good for predicting endometrial cancer with positive LR (11.2, 40) respectively and odds ratio (2.7, 3.2) respectively.

Similar results were found by Epstein (2006), Opolskien et al. (2007) The single best ultrasound variable for predicting endometrial malignancy was heterogeneous endometrial echogenicity. It was superior to endometrial thickness, (positive LR 9.4, negative LR 0.3). The internal endometrial structure most suggestive of malignancy was subjectively perceived as being ‘moth eaten’ (heterogeneous endometrial echogenicity and irregular endometrial–myometrial borders) [15, 17].

Papadopoulos et al. (2015) stated that irregular echogenicity of the endometrium and irregular or disrupted endo-myometrial border are bad prognostic factors [16].

Conversely, Opolskien et al. (2007) found the irregular endo-myometrial border to be a poorer predictor of malignancy than heterogeneous endometrial structure. Also, Dueholm M. et al. (2014) designed a malignancy model and did not use heterogeneous endometrium in their model. Although, highly discriminative, it had a low specificity [7, 17].

In this study (IETA Doppler score) Doppler color content score>2 (mod., sever) show a significant result between benign and malignant cases.

Conversely, Suna et al. (2013) tried to assess the contribution of the terms and definitions described by IETA group when evaluating endometrial lesions on gray scale sonography and color flow imaging. They stated that endometrial Doppler color score was found not having a clinical value in distinguishing endometrial pathologies in their study [18].

In this study, IETA Doppler vascular pattern: multiple vessel pattern was found in 70% in cases of endometrial cancers showing a significant result between benign and malignant cases.

Alcazar et al. (2003) described three different vascular patterns: multiple vessel pattern (pattern A), single-vessel pattern (pattern B), scattered vessel pattern (pattern C) they described multiple vessel pattern in 81.3% of endometrial cancers cases, which was in line with this study [19].

Also, Epstein and Valentin (2006) noted that irregular vessel branching was more common in malignant than in benign endometrium [20].

In this study the best cut off value for endometrial thickness (predicting malignancy) was ≥12mm with sensitivity 90%, specificity 78.3% and positive likelihood ratio (LR+) 4.1.

Bruchim et al. (2004) showed that an endometrial thickness of 5–9mm Just 10 percent of cases reported cancer. The rate of cancer exceeded 18 per cent [21] for an endometrial thickness > 9 mm.

Opolskien et al. (2007) found that the best endometrial thickness cut-off value was about ~115 mm with 73 percent sensitivity, 77 percent precision and 3.1 positive probability ratio. And this was confirmed with the findings of Burbos et al. (2010), who pick the same cut-off value (7.9).

Dueholm M. et al. (2014) stated that cases with endometrium ≥ 10-12 mm had a positive likelihood ratio 3.5, and when ≥ 15 mm it was 5.5 [17].

Giannella et al. (2014) designed a malignancy model, where the best cut-off value for endometrial thickness was ≥ 9mm and was considered as one of their predictors associated with endometrial cancer [12].

All the previous studies agreed with the results of this study.

In this study the validity assessment (sensitivity, specificity, LR +v, LR–v) of each variable (correlating with malignancy) showed that there is a significant difference between the results of the likelihood ratio test (LR +v, LR–v) as regard endo. thick. ≥12 mm, hetero. endometrium, irreg. endo. midline, ill-defined endo. myo. interface, Doppler Score > 2. But other variables (Age ≥60, Parity, BMI ≥30, HPN, Diabetes and multiple Vessel Pattern) had a statistically non-significant results between the likelihood ratio test (LR +v, LR–v).

So, an endometrial malignancy model was designed including the five significant variables with accuracy about 95% and area under curve (AUC) 0.95. The odds ratio was calculated for each variable to estimate the risk of malignancy, in which the presence of the variable was given the assigned score and its absence was given zero.

The study population was classified according to their score, then the validity assessment was done revealing the best cut off score that had the highest positive predictive value, highest +v likelihood ratio and the largest area under receiver operator curve was ≥10. The scoring system used in this study and the subsequent model seemed to be more simple, applicable and reach accuracy about (95%).

Opolskien et al. (2011) compared different predictive models for endometrial cancer in postmenopausal women with vaginal bleeding and endometrial thickness of up to 4.5 mm. We concluded that the diagnostic efficiency of prediction models greatly increased by applying endometrial thickness and power Doppler information to the patient characteristics. With respect to their predictive model like endometrium (19).

The study by Giannella et al. (2014) showed that a risk-scoring model, including recurrent vaginal bleeding, endometrial thickness >8mm, presence of hypertension and age ≥65 years, called RHEA, provided moderate diagnostic accuracy for predicting intrauterine malignancies among symptomatic postmenopausal women at risk of endometrial cancer. At a cutoff score of 4, a probability of 35 after test

All the previous scoring systems tried to reach the best malignancy model with the highest validity in prediction of endometrial cancer but in more complicated fashion.

Conclusion:

We can conclude that:
• Words used to characterize endometrial sonographic characteristics identified by the (IETA group) are clinically useful and appropriate for endometrium evaluation using a standardized measuring technique.

• The implementation of a malignancy model for postmenopausal bleeding cases makes it easy to distinguish cases into low-risk cases with the ability to restrict the dangerous invasive procedure

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