ACCURACY OF ENDOMETRIAL THICKNESS MEASUREMENT IN DIAGNOSIS OF ENDOMETRIAL CARCINOMA

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ABSTRACT

BACKGROUND

Aim is to study the accuracy of endometrial thickness measurement in diagnosis of endometrial carcinoma using histopathological results as the gold standard.

MATERIALS AND METHODS

120 patients (with postmenopausal bleeding) referred to the Department of Radiodiagnosis were included in the study after applying inclusion and exclusion criteria. 2-D ultrasound was performed and endometrial thickness, echogenicity, were recorded on transvaginal ultrasonography. Cut-off was obtained after drawing ROC for endometrial thickness in differentiating benign and malignant pathology.

RESULTS

Using endometrial thickness as the diagnostic test, present study shows a sensitivity of 100% and specificity of 61.7% ($p<0.0001$) for differentiating benign and malignant endometrial lesions.

CONCLUSION

Endometrial thickness can be effectively used to differentiate between endometrial carcinoma and benign lesions.

KEYWORDS

Endometrial Thickness, Echogenicity, Endometrial Carcinoma, Benign and Malignant Endometrium, Postmenopausal Bleeding.

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BACKGROUND

Postmenopausal bleeding can be worrisome as sometimes it can be the first sign of endometrial carcinoma. Postmenopausal bleeding has been defined as vaginal bleeding occurring at least 6 months after complete cessation of periods in women not taking hormonal replacement therapy (HRT), or non-cyclic vaginal bleeding occurring in postmenopausal women who are receiving HRT.[1]

The common benign causes include atrophic endometrium, endometrial hyperplasia, endometrial polyp and malignant causes include endometrial carcinoma, cervical cancer and uterine leiomyosarcoma.[2] The most common cause of postmenopausal bleeding is reported to be atrophic endometrium.[3] However, recent studies indicate that leiomyomata and polyps are much more common than has been generally believed.[4]

A diagnosis of endometrial carcinoma should be considered in all women presenting with postmenopausal bleeding.[2] Postmenopausal bleeding is the initial symptom in most of the of patients with endometrial carcinoma.[5] Early diagnosis and treatment are important because the prognosis is generally good, the five-year survival rate for endometrial adenocarcinoma following appropriate treatment is 80%.[6]

Unfortunately, endometrium is not as accessible as cervix for screening tests. Dilation and curettage has been considered the gold standard for the diagnosis of endometrial carcinoma historically.

Imaging modalities like ultrasound have been used to differentiate between benign and malignant endometrial pathology.

Endometrial thickness has been reported to be a better predictor of endometrial pathology than Doppler indices.[6]

The present study was carried out to assess the accuracy of measurement of endometrial thickness in the diagnosis of endometrial carcinoma in Indian women presenting with postmenopausal bleeding while taking histopathological findings as the gold standard.

MATERIALS AND METHODS

This cross-sectional study was conducted in Department of Radiodiagnosis, Sree Avittom Thirunal Hospital, Thiruvananthapuram for eighteen months from May 2014 to October 2015. All patients above 50 years of age having history of postmenopausal bleeding, who have been referred to the Radiology Department of, Sree Avittom Thirunal Hospital, Government medical college, Thiruvananthapuram, Kerala, by consulting gynaecologists.

All patients with postmenopausal bleeding were included in the study.

Patients not willing to participate in the study, asymptomatic patients, perimenopausal and premenopausal patients, patients with fibroid uterus, patients with endometrial polyps, patients with endometrial cavitary fluid were excluded from the study.

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Study variables included are endometrial thickness, Endometrial Echogenicity and Endomyometrial junction.

Name, age and relevant details of the patient were recorded on a proforma. Patients were informed that data collected would be used in a study and that issues related to confidentiality and anonymity would be taken due care of.

After taking informed consent, Real-time ultrasonography was done with Phillips IU-22 ultrasound machine equipped with a 5 MHz vaginal transducer. The vaginal probe covered with a coupling gel, inserted into a condom, coated with gel was inserted into the vaginal fornix, with the subject in the lithotomy position. With the uterus imaged in the longitudinal plane, endometrial thickness were measured as from echogenic border to echogenic border across the endometrial cavity on midline sagittal image.

Endometrial biopsy of these patients was carried out in the Gynaecology Department and sent to the Pathology Department of the Government Medical College Hospital, Thiruvananthapuram and was recorded almost after 1 week.

RESULTS

Ultrasonography was done for the patients with postmenopausal bleeding and the results were tabulated. Following findings were observed.

Age Distribution of Patients

Age (years)	Benign		Malignant	
	No. of Patients	%	No. of Patients	%
51 – 55	24	20	12	10
56 – 60	28	23.2	13	10.7
61 – 65	13	10.8	7	5.8
66 – 70	8	6.6	2	1.6
>70	8	6.6	5	4.1
Total	**81**	**67.5**	**39**	**32.5**

Table 1. Age Distribution of Patients with Postmenopausal Bleeding

120 patients were imaged in total. 81 patients (67.5% of the study population) had benign aetiology and 39 patients (32.5% of the study population) had malignancy. Among the 39 patients, majority i.e., 10.7% come under age group 61-65. The oldest patient was aged 75 years.

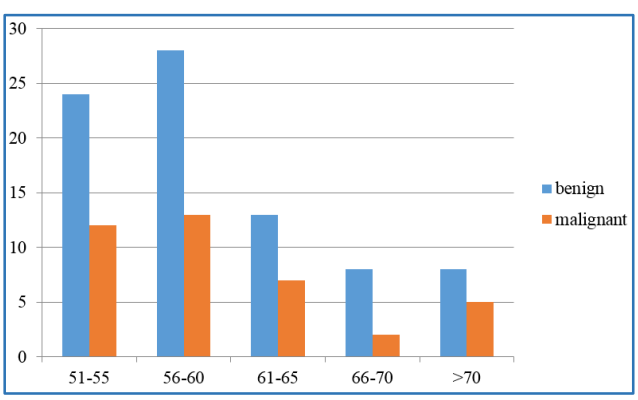

Image 1. Bar Diagram Showing Distribution of Benign and Malignant Cases According to Age

HPR Distribution

Among the malignant histopathological results, endometrioid type of adenocarcinoma constituted 76.93%, papillary serous adenocarcinoma was 15.3% and adenocarcinoma with squamous differentiation was 7.7%.

Subtype	Frequency	%
Endometrioid	30	76.93%
Papillary serous adenocarcinoma	6	15.30%
Adenocarcinoma with squamous differentiation	3	7.7%

Table 2. Frequency Distribution of Histopathological Findings in Malignancy

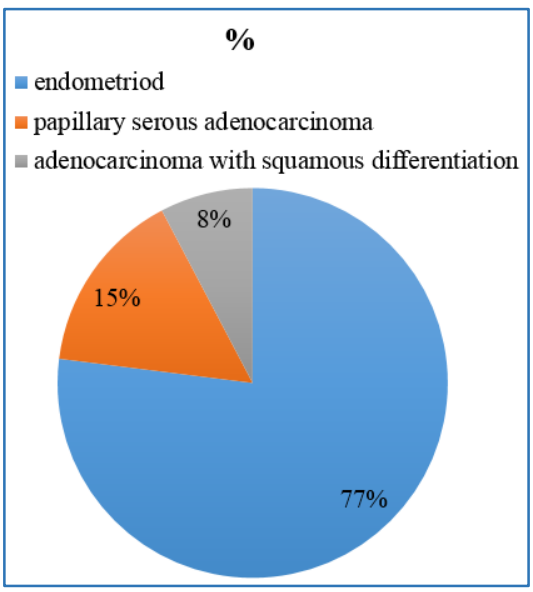

Image 2. Pie Chart Showing Distribution of Histopathological Findings in Malignancy

Out of the 81 benign patients, 68 patients had atrophic endometrium, 9 patients had hyperplasia, and 4 patients had proliferative type of endometrium.

	Frequency	%
Atrophic	68	84%
Hyperplasia	9	11%
Proliferative	4	5%

Table 3. Frequency Distribution of Histopathological Findings in Benign Cases

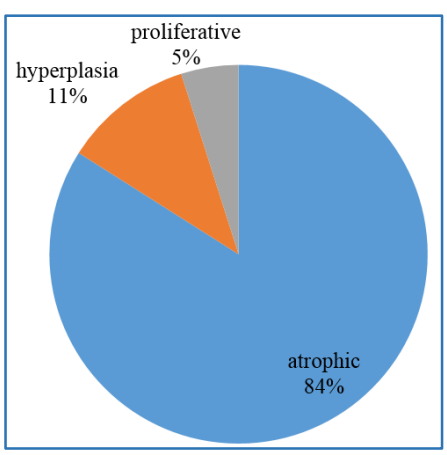

Image 3. Pie Chart Showing Frequency Distribution of HPR Findings in Benign Patients

Echogenicity of Endometrium

Among the 120 patients, the endometrium appeared heterogeneous in 31 patients, out of which 28 patients had malignancy and 3 patients had benign aetiology. Out of the 89 patients with homogeneous appearing endometrium, 78 patients had benign aetiology and 11 patients had malignancy.

The sensitivity of the test was 71.7% and specificity was 96.3% with positive predictive value of 90.32% and negative predictive value of 87.6% with diagnostic accuracy of 88.3%.

Echogenicity	Malignant	Benign	Total
Heterogeneous	28	3	31
Homogeneous	11	78	89
Total	**39**	**81**	

Table 4. Frequency Distribution of Patients According to Echogenicity of the Endometrium

Sensitivity	71.79%
Specificity	96.30%
AUC	0.84
Positive Likelihood Ratio	19.38
Negative Likelihood Ratio	0.29
Disease prevalence	32.50%
Positive Predictive Value	90.32%
Negative Predictive Value	87.64%

Table 5. Statistical Parameters of Echogenicity

Malignancy	
Proportion (%)	71.7
Number of Cases	39
Benign	
Proportion (%)	3.7
Number of Cases	81

Table 6. Comparison of Proportions of Patients with Heterogeneous Endometrium in Benign and Malignant Subgroups

Difference	68.00%
Chi-squared	60.084
Significance level	P < 0.0001

Comparison of proportions show a p value of <0.0001 which implies that the difference is statically significant and the presence of heterogeneous endometrium can reliably used as an indicator of carcinoma endometrium.

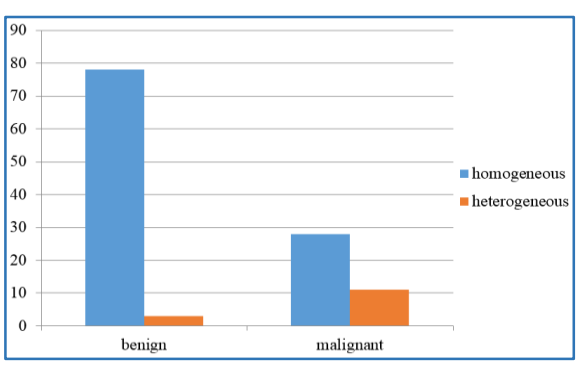

Image 4. Bar Diagram Showing Frequency Distribution of Echogenicity in Benign and Malignant Cases

Endometrial Thickness

B. Randelzhofer et al derived a cut-off of 5 mm for differentiating benign and malignant disease. With this cut-off, 2 x 2 Table was constructed to assess the diagnostic power of endometrial thickness with literature cut-off value.

Endometrial Thickness	Malignant	Benign	
>5 mm	39	31	70
<5 mm	0	50	50
	39	81	

Table 7. 2 x 2 Table in Assessing Diagnostic Power of Endometrial Thickness using Literature Cut-off Value (B. Randelzhofer et al)

The calculated parameters are as follows:

Sensitivity	100.00%
Specificity	61.73%
AUC	0.81
Positive Likelihood Ratio	2.61
Negative Likelihood Ratio	0.00
Disease prevalence	32.50%
Positive Predictive Value	55.71%
Negative Predictive Value	100.00%

Table 8. Statistical Parameters of Endometrial Thickness Obtained using Literature Cut-off Value (B. Randelzhofer et al)

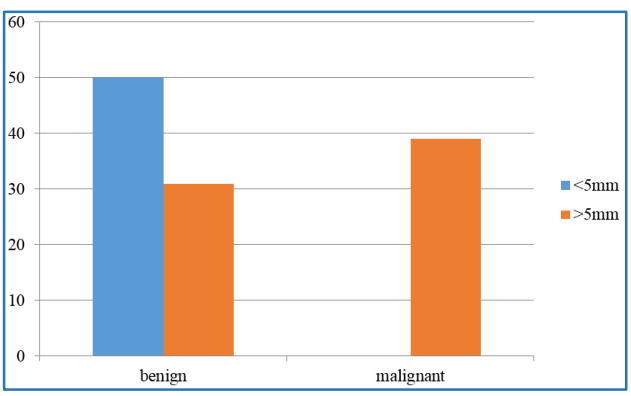

Image 5. Bar Diagram Showing Frequency Distribution of Endometrial Thickness

Parameters	Benign	Malignant
No. of cases	81	39
Mean	6.3	10.5
Median	5	11
Standard deviation	3.98	3.03
Maximum value	15	15
Minimum value	2	6
95% CI	5.4 - 7.2	9.5 - 11.5

Table 9. Statistical Analysis of Endometrial Thickness

Malignant	
Mean	10.5
Standard deviation	3.03
Number of cases	39
Benign	
Mean	6.3
Standard deviation	3.98
Number of cases	42
Results	
Difference	-4.2
Standard error	0.721
Test statistic t	-5.823
Significance level	P < 0.0001

Table 10. Comparison of Means (t-test) of Endometrial Thickness in Benign and Malignant Subgroup

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
≥2	100.00	91.0 - 100.0	0.00	0.0 - 4.5	1.00	
>5	100.00	91.0 - 100.0	61.73	50.3 - 72.3	2.61	0.00
>6	87.18	72.6 - 95.7	66.67	55.3 - 76.8	2.62	0.19
>7	76.92	60.7 - 88.9	69.14	57.9 - 78.9	2.49	0.33
>8	69.23	52.4 - 83.0	75.31	64.5 - 84.2	2.80	0.41
>9	61.54	44.6 - 76.6	75.31	64.5 - 84.2	2.49	0.51
>10	53.85	37.2 - 69.9	77.78	67.2 - 86.3	2.42	0.59
>11	41.03	25.6 - 57.9	82.72	72.7 - 90.2	2.37	0.71
>12	30.77	17.0 - 47.6	87.65	78.5 - 93.9	2.49	0.79
>13	20.51	9.3 - 36.5	91.36	83.0 - 96.5	2.37	0.87
>14	12.82	4.3 - 27.4	95.06	87.8 - 98.6	2.60	0.92
>15	0.00	0.0 - 9.0	100.00	95.5 - 100.0		1.00

Table 11. Receiver Operator Characteristic Curve Analysis of Endometrial Thickness

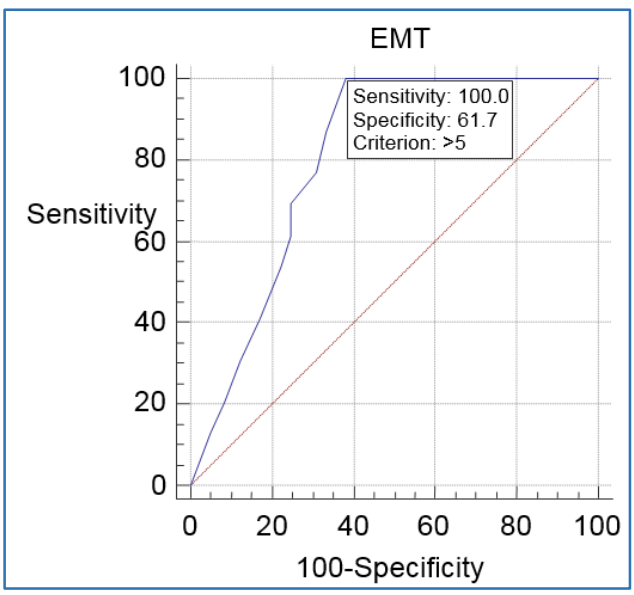

Image 6. Receiver Operator Characteristic Curve Analysis of Endometrial Thickness

From the graph, a cut-off value of 5 mm was derived. This cut-off has a sensitivity of 100% and specificity of 61.7%. Positive likelihood ratio with this cut-off is 2.61 and negative likelihood ratio is 0.0

Endometrial Thickness	Malignant	Benign	
>5 mm	39	31	70
<5 mm	0	50	50
	39	81	

Table 12. 2 x 2 Table in Assessing Diagnostic Power of Endometrial Thickness using Receiver Operator Characteristic Curve Cut-off Value

Area under the ROC curve (AUC)	0.803
Standard Error	0.0387
95% Confidence interval	0.721 to 0.870
z statistic	7.840
Significance level P (Area = 0.5)	<0.0001
Youden index J	0.6173
Associated criterion	>5
Sensitivity	100.00
Specificity	61.73
Accuracy	74.1%

Table 13. Parameters Obtained in Receiver Operator Characteristic Curve Analysis of Endometrial Thickness

Study	Cut off mm	Sensitivity %	Specificity %	PPV %	NPV %	+LR	-LR	P value
B. Randelzhofer	5	97.9	33.2	38.1	97.4	----	----	<0.0001
Applying in present study	5	100	61.7	55.7	100	2.61	0.0	<0.0001
Applying the cut-off derived from ROC	5	100	61.7	55.7	100	2.61	0.0	<0.0001

Table 14. Comparison of Endometrial Thickness Obtained in the Study and the Literature

Endomyometrial Junction

The endomyometrial junction was indistinct in 22 of the 39 malignant cases and had a sensitivity of 56.4% and was distinct in 80 of the 81 benign cases with a specificity of 98.7%.

	Malignant	Benign	
Indistinct	22	1	23
Distinct	17	80	97
	39	**81**	

Table 15. 2x2 Table Showing Distribution of Distinct and Indistinct of Endomyometrial Junction in Benign and Malignant Cases

Sensitivity	56.41%
Specificity	98.77%
AUC	0.78
Positive Likelihood Ratio	45.69
Negative Likelihood Ratio	0.44
Disease prevalence	32.50%
Positive Predictive Value	95.65%
Negative Predictive Value	82.47%
Accuracy	85%

Table 16. Statistical Parameters of Indistinct Endomyometrial Junction

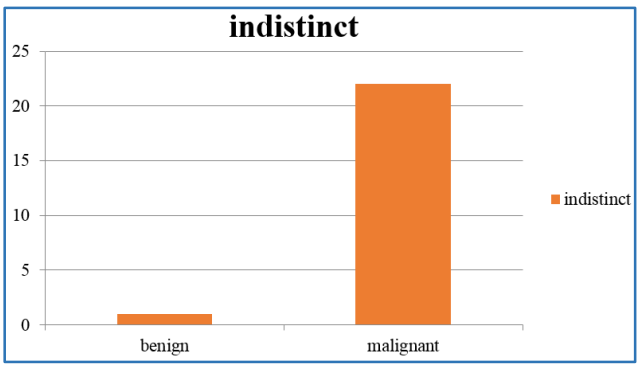

Image 7. Bar Diagram Showing Distribution of Indistinct Endomyometrial Junction in Benign and Malignant Cases

Malignant	
Proportion (%)	56
Number of Cases	39
Benign	
Proportion (%)	1.2
Number of Cases	81
Results	
Difference	54.80%
Chi-Squared	47.849
Significance Level	P < 0.0001

Table 17. Comparison of Proportions of Patients with Indistinct Endomyometrial Junction in Benign and Malignant Subgroups

Comparison of proportions show a p value of <0.0001 which implies that the difference is statistically significant, and hence indistinct endomyometrial junction can be used reliably as an indicator in identifying patients with carcinoma endometrium.

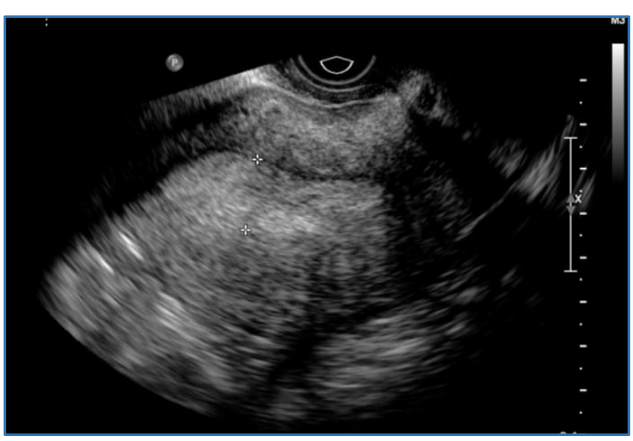

Figure 1. Thickened and Homogeneous Endometrium, with Distinct Endomyometrial Junction. HPR – Endometrial Hyperplasia

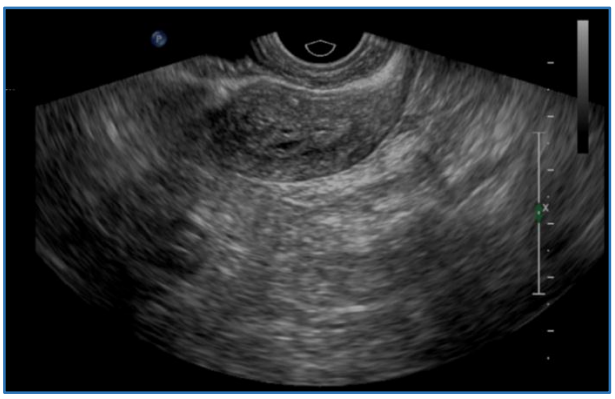

Figure 2. Thickened and Heterogeneous Endometrium, with Indistinct Endomyometrial Junction, Predominantly in the Anterior Aspect. HPR – Endometrial Carcinoma

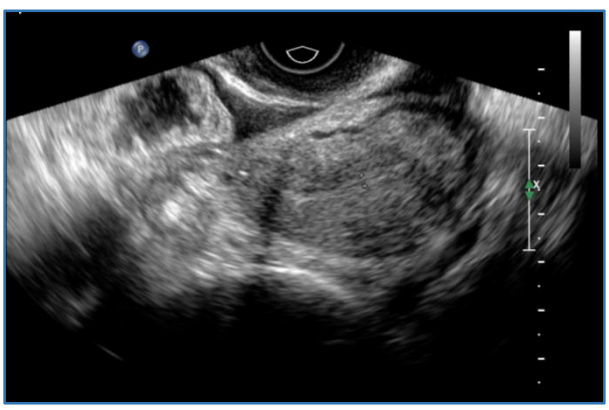

Figure 3. Thinned out Endometrium, with Distinct Endomyometrial Junction. HPR – Atrophic Endometrium

DISCUSSION

Age Distribution

Among the 120 patients studied, 39 patients proved to have malignancy and 30.7% belonged to age group 51-55, 32.9% belonged to age group 56-60, 17.8% belonged to age group 61-65, 4.9% to age group 66-70 and 12.6% to age group >70. According to the study by Amant F et al, endometrial carcinoma had a peak in 7th decade.[7]

Histopathological Results

76.9% of the patients had endometrioid type of adenocarcinoma on HPR. Next common subtype being papillary serous adenocarcinoma. As given by Sala et al in a journal published in AJR, adenocarcinoma arise from uterine epithelium and constitute 90% of endometrial cancers.

Among the benign conditions, atrophic endometrium constituted 83.9% of the cases, 11.1% had hyperplasia, 4.9% had proliferative type of endometrium.

In the study by B Randelzhofer, endometrial atrophy was seen in 45.1%, endometrial proliferation in 8.3%, endometrial hyperplasia in 16.3%, and endometrial polyps in 30%.[8]

Echogenicity

Among the 120 patients, the endometrium appeared heterogeneous in 31 patients, out of which 28 patients had malignancy and 3 patients had benign aetiology.

The sensitivity of the test was 71.7% and specificity was 96.3% with positive predictive value of 90.32% and negative predictive value of 87.6% with diagnostic accuracy of 88.3%.

Study by Opolskiene et al concluded that heterogenous endometrial echogenicity was the single best ultrasound variable for predicting endometrial malignancy.[9] The internal endometrial structure most suggestive of malignancy was subjectively perceived as being 'moth eaten'.

Comparison of proportions show a p value of <0.0001 which implies that the difference between benign and malignant subgroups is significant.

Endometrial Thickness

Among the 120 patients, all the patients with endometrial carcinoma had endometrial thickness of >5 mm. When the cut off value is set for 5 mm, the test proved to have a sensitivity of 100 %.

31 patients with benign aetiology also had endometrial thickness of >5 mm, which reduces the specificity to 61.7%. Positive predictive value of the test was 55.7%, negative predictive value 100 % with diagnostic accuracy of 74.1 %.

Mean endometrial thickness was found to be 6.3±3.98 mm in benign and 10.5 ± 3.03 mm in malignancy (t test, p<0.001).

B. Randelzhofer et al derived a cut-off of 5 mm for differentiating benign and malignant disease which had a sensitivity of 97.9%, specificity of 33.2%, positive predictive value of 38.1% and negative predictive value of 97.4%.[8]

In another study conducted by Mahmoud El-Morsi Aboul-Fotouha et al, taking an endometrial thickness of 5 mm as a cut off value for prediction of endometrial malignancy had 100% sensitivity, 51.9% specificity, 60.9% positive predictive value, 100% negative predictive value, and 48.7% diagnostic accuracy.[10]

Endomyometrial Junction

The endomyometrial junction was indistinct in 22 of the 39 malignant cases and had a sensitivity of 56.4 % and was distinct in 80 of the 81 benign cases with a specificity of 98.7%**.** Positive predictive value of the test was 95.6%, negative predictive value 82.4 % with diagnostic accuracy of 85%.

Comparison of proportions show a p value of <0.0001 which implies that the difference between the benign and malignant subgroups is significant.

Myometrial invasion is depicted as irregularity of the endometrium — myometrium border and disruption of the subendometrial halo. According to Teefey SA et al, the accuracy of US in diagnosing the depth of invasion is approximately 73% to 93%, but US is better for grade 2-3 tumours and should not be used as the sole criterion for the decision to perform extensive surgery.[11]

The study by Opolskiene et al concluded that Irregular endometrial–myometrial border was also a sign of endometrial cancer.[9]

In the study conducted by B Randelzhofer et al, the sensitivity of indistinct endomyometrial border had a sensitivity of 73.7% and specificity of 87.7%.[8]

Limitations of the Study

1. Subjective inference of endometrial morphology.
2. Small sample size. Similar results should be reproduced in larger numbers and in a different population prior to being introduced in a clinical setting.
3. These results are applicable to examinations carried out using similar ultrasound system and transducer.

CONCLUSION

Endometrial thickness can be effectively used to differentiate between endometrial carcinoma and benign lesions. Thus, a conservative approach can be recommended for women with endometrial thickness of <5 mm avoiding unnecessary dilation and curettage.

ACKNOWLEDGEMENTS

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