Original Article

Diagnostic Accuracy of E-Cadherin Expression in Diagnosis of Endometrioid Carcinoma in Females

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ABSTRACT

Objective: To determine the diagnostic accuracy of E-cadherin expression for diagnosis of endometrioid carcinoma in females with abnormal uterine bleeding taking histopathology as gold standard

Study Design: Cross sectional validation study.

Place and Duration of Study: This study was conducted at the Pathology Department at the Pakistan Institute of Medical Sciences in Islamabad from February to July, 2016.

Materials and Methods: Patients were selected using a non-probabilistic, consecutive sampling method. To examine their morphology, the specimens were grossly examined after being fixed in 10% buffered formalin and stained with Hematoxylin and Eosin. E-cadherin staining was evaluated by immunohistochemistry and categorized as "positive" or "negative." Results of E-cadherin and histopathology were compared.

Results: In our study the mean age of the patients was 55.31±9.023 years. The E- cadherin diagnoses positive endometrial cancer in 183(77.9%) patients and the histopathology diagnoses positive endometrial cancer in 144(61.28%) patients. the sensitivity of E-cadherin for diagnosing endometrial cancer was 81.94%, specificity was 28.57% and the diagnostic accuracy was 61.28%.

Conclusion: According to our study results E-cadherin expression is good and reliable test for diagnosis of endometrioid carcinoma in females with abnormal uterine bleeding taking histopathology as gold standard.

Key Words: E-cadherin, Expression, Histopathology, Endometrioid, Carcinoma.

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INTRODUCTION

Endometrial cancer ranks first among gynecological malignancies in industrialized nations and second in low-income regions.[1] India and the rest of South East Asia have the world's lowest recorded rates.[2, 3] Women in Pakistan over the age of 45 have a higher incidence of endometrial carcinoma than any other genital tract cancer.[4] There is substantial evidence that endometrial cancer is increasing in incidence in post-menopausal women.

Endometrial carcinoma's two histopathological subtypes– endometrioid adenocarcinomas with good prognosis and non-endometrioid carcinomas having an aggressive behavior and worse prognosis. It has been hypothesized that a lack of cohesion among tumor cells contributes to the aggressive aggressiveness of certain endometrial carcinomas.[5] More aggressive high grade endometrial cancers almost always have features like myometrial invasion, distant metastasis, poor differentiation, worse prognosis and tendency to recur after treatment.[6]

The patients of endometrial carcinoma mostly present with abnormal uterine bleeding. Abnormal uterine bleeding can also be seen in endometrial polyp, adenomyosis, endometrial hyperplasia and atypia.[7] Specimens usually encountered are endometrial curettings or hysterectomy specimens. Morphology remains the gold standard for diagnosis in most of the cases. E-cadherin is an epithelial trans-membrane glycoprotein and a calcium dependent epithelial adhesion molecule. It maintains intercellular cohesion and epithelial tissue structure. It also suppresses further tumor invasion. E-cadherin loss is an important event in the evolution of gynecological tumors and is seen in a wide variety of human malignancies.[8, 9] The majority of adenocarcinomas (80%) are endometrioid. This carcinoma has a better prognosis than others since it is less invasive.[10]

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According to research by Shaco-Levy et al., E-cadherin expression is lower in endometrioid cancer than in proliferative endometrium.[11] Recent work on E-cadherin by Carico et al concluded strong homogeneous staining of E-cadherin in normal endometrium and simple hyperplasia. In contrast, minimum or no staining was observed in atypical hyperplasia and endometrioid carcinomas.[9] Negative expression of E-cadherin is associated with neoplastic transformation in endometrium and is inversely related to patient's prognosis.[12, 13] The research found that E-cadherin has a sensitivity of 78.3% and a specificity of 77.8% (n=32) for diagnosing endometrioid.[4]

Rationale of this study is to find the diagnostic accuracy of E-cadherin for diagnosis of endometrioid in females taking histopathology as gold standard. So far, there is no established data available in Pakistan regarding E-cadherin use on endometrium.So we want to conduct this study to compare E-cadherin expression in normal and neoplastic endometrium to evaluate the utility of E-cadherin in routine histopathology. This research will use a larger sample size than the above-mentioned studies did in order to provide more trustworthy findings for the potential future use of E-cadherin for the diagnosis of endometrioid in a local environment.

MATERIALS AND METHODS

Study design: Cross sectional validation study.

Setting: Department of Pathology, Pakistan Institute of Medical Sciences, Islamabad.

Duration: 6 months i.e. February to July 2016.

Sample size: The sample size of 235 patients was determined using a 95% confidence level, an estimated proportion of endometrioid of 80%, a sensitivity of E-cadherin of 78.3% with a 10% margin of error, and a specificity of E-cadherin of 77.8% with a 10% margin of error, using histology as the gold standard.

Sampling Technique: Non Probability, Consecutive sampling

Sample Selection:

Inclusion Criteria: Female patients of age 40 to 70 years presenting with endometrial pathology undergoing endometrial curettings and hysterectomy were enrolled.

Exclusion Criteria: All poorly preserved and poorly fixed specimens, already diagnosed cases or cases in which histopathology not possible were excluded from the sample,

Data collection procedure: Endometrial curettages and hysterectomy specimens of 235 females fulfilled selection criteria, referred to Pathology Department, were enrolled. An informed consent was obtained from all the patients. Demographic details such as name, age and parity was noted. To examine their morphology, the specimens were grossly examined after being fixed in 10% buffered formalin and stained with Hematoxylin and Eosin. E-cadherin staining was scored as +ve or –ve in a blinded immunohistochemical analysis. Results of E-cadherin and histopathology were compared by researcher herself in consultation with histopathologist to establish the diagnosis. A positive result for E-cadherin staining was defined as the presence of positive staining in more than 5% of tumor cells and a negative result was defined as the absence of positive staining in less than 5% of tumor cells, independent of pattern. On histopathology, it was labeled as positive if there was myometrial invasion, tumors architecture show non-squamous solid areas with presence of necrosis inside tumor glands, otherwise it was labeled as negative. All this information was recorded in proforma.

Data analysis: The collected information was entered and analyzed by using computer software SPSS version 26. Using histology as the reference standard, a 2x2 table was created to compute sensitivity, specificity, PPV, NPV, and diagnostic accuracy.

RESULTS

In this present study total 235 cases participated. The mean age of the patients was 55.31±9.023 years with minimum and maximum ages of 40 & 70 years respectively. In our study the patients with parity two were 38(16.17%), the patients with parity three were 32(13.62%), the patients with parity four, five and six were 42(17.87%) respectively, the patients with parity seven were 38(16.17%) and the patients with parity eight were 1(0.43%).

Table No. 1: Demographics of patients

Feature	Mean ± SD, F (%)
n	235
Age (years)	55.31 ± 9.02
Parity	
2-3	38+32
4-5	42+42
6-8	42+38+1
Histopathology findings	
Benign endometrial polyp	13 (5.5%)
Clear Cell adenocarcinoma non-endometroid carcinoma	13 (5.5%)
Complex hyperplasia with atypia	39 (16.6%)
Endometroid Adenocarcinoma grade 1	53 (22.6%)
Endometroid Adenocarcinoma grade 2	52 (22.1%)
Endometroid Adenocarcinoma grade 3	26 (11.1%)
High grade papillary serous carcinoma non-endometroid carcinoma	13 (5.5%)
Simple hyperplasia without atypia	13 (5.5%)
Well-differentiated endometroid adenocarcinoma grade 1	13 (5.5%)

In our study Benign endometrial polyp, Clear Cell adenocarcinoma non-endometroid carcinoma, High grade papillary serous carcinoma non-endometroid carcinoma, Simple hyperplasia without atypia and Well-differentiated endometroid adenocarcinoma grade 1 was noted in 13(5.5%) patients respectively, Complex hyperplasia with atypia noted in 39(16.6%) patients, Endometroid Adenocarcinoma grade 1, grade 2 and grade 3 was noted in 53(22.6%), 52(22.1%) and 26(11.1%) respectively. Table 1

The study results showed that the sensitivity of E-cadherin for diagnosing endometrial cancer was 81.94%, specificity was 28.57%, PPV value was 64.48%, NPV value was 50%, diagnostic accuracy was 61.28% and Likelihood ratio of a Positive Test was 1.147 taking histopathology as gold standard. Table 2

Table No. 2: Accuracy of E-cadherin keeping Histopathology as gold standard

		Histopathology		Total	p-value
		Positive	Negative		
E-cadherin	Positive	118	65	183	0.059
	Negative	26	26	52	
Total		144	91	235	

Table No. 3: Overall Accuracy of E-cadherin keeping Histopathology as gold standard and for age strata

		Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
E-cadherin	Overall	81.94%	28.57%	64.48%	50%	61.30%
Age (years)	≤55	77.94%	23.91%	60.20%	42.30%	56.14%
	>55	85.53%	33.33%	68.40%	57.70%	66.12%

The study results showed that in ≤ 55 years patients, the sensitivity, specificity and diagnostic accuracy was 77.94%, 23.91% and 56.14% respectively, similarly in >55 years patients the sensitivity, specificity and diagnostic accuracy was 85.53%, 33.33% and 66.12% respectively. Table 3

DISCUSSION

The epithelial phenotype relies on persistent cell-cell interactions and adherens junctions, both of which are maintained by the cadherin E. control of apoptosis in tumor cells depends on E-cadherin expression, which is also essential for the control of intercellular cohesion. Calcium regulates the activity of E-cadherin, an epithelial adhesion protein.[14, 15] The American Cancer Society estimates that 43,470 new cases of endometrial cancer will be diagnosed in 2010.[16]. In 2010, endometrial cancer was predicted to have caused 6,665 new cases in Japan. As a result, it is the fourth most common kind of cancer affecting women in the United States.[17]

In our study low sensitivity and diagnostic accuracy was found of E-cadherin expression for diagnosis of endometrioid carcinoma. In this study the sensitivity of E-cadherine for diagnosing endometrial cancer was 81.94%, specificity was 28.57% and the diagnostic accuracy was 61.28% and Likelihood ratio of a Positive Test was 1.147 taking histopathology as gold standard. Schlosshauer PW et al. analyzed 17 FIGO Grade III endometrioid adenocarcinomas and 17 serous carcinomas histologically and immunohistochemically using commercially available monoclonal antibodies against beta-catenin and E-cadherin. High-grade endometrial cancers have been reported to have a strong correlation between beta-catenin and E-cadherin expression and histological subtype.[18]

Based on these findings, Jee Hyun Park et al. propose that hypermethylation of the E-cadherin promoter region plays a significant role in the development of endometrial cancer. E-cadherin promoter methylation was also observed to be substantially linked with endometrial cancer stages beyond Ic.[19]

The expression of E-cadherin is negatively correlated with endometrial neoplasia and poor patient outcomes.[12, 13] The research found that E-cadherin has a sensitivity of 78.3% and a specificity of 77.8% (n=32) for diagnosing endometrioid. [5] Researchers Saito T. et al. discovered that endometrioid adenocarcinoma's hypermethylation of the E-cadherin gene promoter downregulates E-cadherin expression, which in turn corresponds with tumor development, tumor dedifferentiation, and the degree of myometrial invasion.[20]

Research by Osogami H et al. demonstrated a statistically significant difference in E-cadherin immunohistochemistry between Negative and AGC or AC, providing more evidence that E-cadherin is connected to cytological findings in endometrial cancer.[21] Multivariate examination of primary tumors in the United Kingdom revealed that the lack of E-cadherin was a poor predictor of survival, ranking third behind node positive and higher depth of invasion but ahead of grade. In the complex process of adhesion between cells and the extracellular matrix, E-cadherin plays just a little role. It may be rare for a single anomaly in a complex system to have a significant prognostic impact on its own.

CONCLUSION

According to our study results E-cadherin expression is good and reliable test for diagnosis of endometrioid carcinoma in females with abnormal uterine bleeding taking histopathology as gold standard.

Author's Contribution:

Concept & Design of Study: Farzana Habib

Drafting:	Ahmareen Khalid Sheikh
Data Analysis:	Salma Iltaf, Shakila Khadim
Revisiting Critically:	Farzana Habib, Ahmareen Khalid Sheikh
Final Approval of version:	Farzana Habib

Conflict of Interest: The study has no conflict of interest to declare by any author.

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