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Study of Ki-67 and E-Cadherin Expression in Cervical Cancer as Marker of Proliferation and Invasiveness

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Abstract: **Introduction:** Cervical carcinoma is one of the most frequent cancers in women all over the world, especially in the developing countries. Increased cell proliferation and decreased cell adhesion are implicated in tumor development. Ki-67 is a well-known cellular proliferation marker and E-cadherin is an important cell adhesion protein related to tumor invasion and metastasis. **Aims:** The aim of this study was to evaluate the expression of Ki-67 and E-cadherin in cervical cancer for assessment of tumor growth and invasion and to find out their correlation. Also their association with histopathological grade and stage, detection of cervical cancer patients and use of these biomarkers as a sign of proliferation and invasion are also discussed. **Materials and methods:** The present study was a descriptive cross-sectional observational study. The study was conducted in Department of Pathology, N.R.S. Medical College and Hospital, Kolkata, Sealdah, Raja Bazar, Kolkata, West Bengal 700014 for a period of 18 months. The study population consisted of 62 individuals. **Result:** High Ki-67 expression was significantly associated with poorly differentiated tumors and advanced FIGO stage ($p = 0.001$ and $p = 0.002$, respectively). E-cadherin expression significantly decreased with increasing tumor grade and stage ($p = 0.003$ and $p = 0.001$ respectively). A statistically significant inverse association was observed between Ki-67 and E-cadherin expression ($p = 0.0001$) suggesting that increased proliferation is associated with decreased cell adhesion and increased invasiveness. **Conclusion:** Ki-67 and E-cadherin are important markers for assessing tumor behavior in cervical cancer. Their combined evaluation could provide valuable prognostic information and assist the identification of aggressive tumors.

Keywords: Cervical carcinoma, Ki-67, E-cadherin, proliferation, invasion, immunohistochemistry, prognostic markers.

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INTRODUCTION

Carcinoma of the uterine cervix is a major cause of cancer morbidity and mortality in women worldwide and remains a major public health problem, especially in developing countries. More than 25% of the worldwide burden of cervical cancer is in low- and middle-income countries. Breast and cervical cancers are the two major cancers seen in women in India [1].

Cervical cancer is the fourth most common cancer in women globally, both in terms of incidence and mortality. More than 570,000 women were diagnosed with cervical cancer and it killed about 311,000 women in 2018. It is estimated that around 84% of cases and 88% of deaths occur in resource limited countries indicating that there are huge disparities in the availability of screening, early detection and treatment facilities [2].

Cancer is a major health problem in India with over 120,000 new cases being reported every year. It is responsible for about 15.2% of all deaths from cervical cancer in the world and is the second most frequent malignancy in women, after breast cancer. It is highly prevalent in rural areas though its prevalence has declined in urban areas due to increased awareness and screening programs [3].

Clinically, cervical cancer usually presents as abnormal vaginal bleeding, bleeding after intercourse, foul-smelling vaginal discharge, and lower abdominal pain. Although asymptomatic early-stage illness can occur, advanced cases may present with ureteral obstruction leading to hydronephrosis, anuria, and uraemia [4].

In India the highest prevalence is seen in the age group of 55-59 years. The regional differences indicate higher prevalence in some parts of southern India and Tamil Nadu [5].

Cervical carcinogenesis is a multistep process involving the accumulation of genetic and epigenetic alterations that interfere with the pathways of cellular growth regulation. Recurrence and disease progression remain important challenges, despite the progress in diagnostic and therapeutic modalities. Several known prognostic factors such as tumor size, stromal invasion, lymph node status, lymphovascular space involvement, surgical margin, histological type and grade of tumor have been identified. Nevertheless, reliable biomarkers are still needed to better predict tumor behavior and clinical outcomes, especially in earlystage disease.

In this context, there has been an increasing focus on the biomarkers associated with tumor growth and invasion as possible prognostic markers. Some of the most studied biomarkers in cervical cancer are Ki-67 and E-cadherin.

-67 is a nuclear antigen expressed in all active phases of the cell cycle except for the G0 phase, and is a widely used marker for cell proliferation. This expression is a measure of the rate of proliferation of a tumor. A high Ki-67 labeling index is often associated with aggressive tumor characteristics and poor prognosis [6].

E-cadherin is a calcium-dependent transmembrane glycoprotein required for the maintenance of epithelial cell-cell adhesion and tissue architecture. Loss or down-regulation of E-cadherin disrupts cell–cell adhesion, promotes detachment of tumor cells and increases invasion and metastasis. Changes in the E-cadherin/β-catenin complex are thought to play a crucial role in tumor progression [7].

The purpose of this study is to analyze the expression of Ki-67 and E-cadherin to study tumor growth and invasion in cervical cancer and to identify its association. The study also shows the association of these biomarkers with the histopathological grade and stage of the tumor. In addition, it includes the diagnosis of cervical cancer cases and evaluation of Ki-67 and Ecadherin expression as proliferation and invasion markers, respectively.

MATERIALS AND METHODS

Type of study: Descriptive Cross-Sectional Observational study.

Place of study: Department of Pathology, N.R.S Medical College and Hospital Kolkata, Sealdah, Raja Bazar, Kolkata, West Bengal 700014.

Study duration: 18 months **Sample size: 62 cases.**

Inclusion Criteria: Newly diagnosed cases of invasive carcinoma of cervix in any age group **Exclusion Criteria:**

- Patients with malignancy of other organ systems.
- Patients with benign cervical lesions.
- Specimens showing necrotic/ gangrenous/ autolytic changes.
- Post chemotherapy carcinoma cervix.

Study Variables

- Histopathological Grade
- FIGO Stage
- Ki-67
- E-cadherin Expression

Statistical Analysis

Data were entered into Excel and analysed using SPSS and GraphPad Prism. Numerical variables were summarized using means and standard deviations and categorical variables using counts and percentages. Two-sample t-tests were used to compare independent groups, and paired t-tests were used to account for correlations in paired data. Chi-squared tests were used for categorical data (including Fisher's exact test for small sample sizes). A value of $p \leq 0.05$ was considered statistically significant.

RESULTS

Table 1: Association of Histopathological Grade with Ki-67 Expression

Grade	Ki-67 Low n (%)	Ki-67 High n (%)	Total n (%)	P-Value
Well differentiated	14 (22.58)	4 (6.45)	18 (29.03)	0.001
Moderately differentiated	10 (16.13)	16 (25.81)	26 (41.94)	
Poorly differentiated	3 (4.84)	15 (24.19)	18 (29.03)	

Table 2: Association of FIGO Stage with Ki-67 Expression

Stage	Ki-67 Low n (%)	Ki-67 High n (%)	Total n (%)	P-Value
Stage I	10 (16.13)	2 (3.23)	12 (19.35)	0.002
Stage II	12 (19.35)	16 (25.81)	28 (45.16)	
Stage III	5 (8.06)	17 (27.42)	22 (35.48)	

Table 3: Association of Histopathological Grade with E-cadherin Expression

Grade	E-cadherin Retained n (%)	E-cadherin Lost n (%)	Total n (%)	P-Value
Well differentiated	15 (24.19)	3 (4.84)	18 (29.03)	0.003
Moderately differentiated	14 (22.58)	12 (19.35)	26 (41.94)	
Poorly differentiated	5 (8.06)	13 (20.97)	18 (29.03)	

Table 4: Association of FIGO Stage with E-cadherin Expression

Stage	E-cadherin Retained n (%)	E-cadherin Lost n (%)	Total n (%)	P-Value
Stage I	10 (16.13)	2 (3.23)	12 (19.35)	0.001
Stage II	18 (29.03)	10 (16.13)	28 (45.16)	
Stage III	6 (9.68)	16 (25.81)	22 (35.48)	

Table 5: Correlation between Ki-67 and E-cadherin Expression

Ki-67 Expression	E-cadherin Retained n (%)	E-cadherin Lost n (%)	Total n (%)	P-Value
Low Ki-67	21 (33.87)	6 (9.68)	27 (43.55)	0.001
High Ki-67	13 (20.97)	22 (35.48)	35 (56.45)	

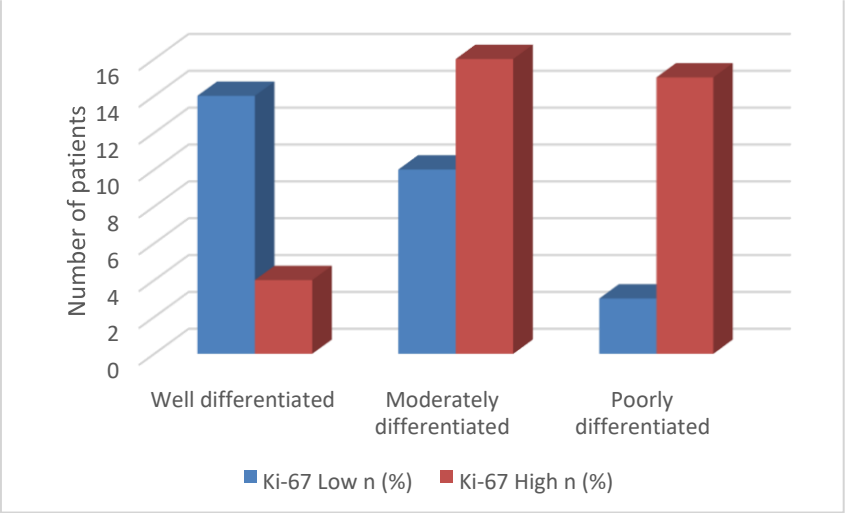

Fig: 1 Association of Histopathological Grade with Ki-67 Expression

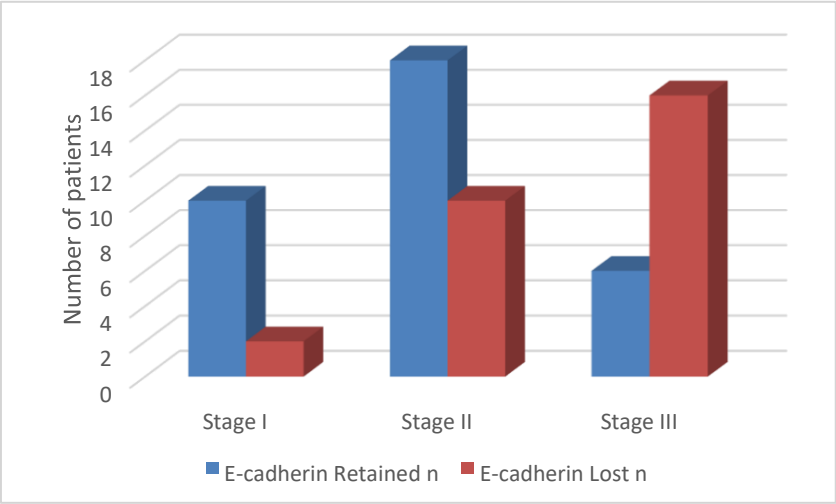

Fig: 2 Association of FIGO Stage with E-cadherin Expression

In the present study comprising 62 cases of cervical carcinoma, Ki-67 expression showed a significant association with histopathological grade. High Ki-67 expression was observed predominantly in poorly differentiated tumors (15 cases, 24.19%), followed by moderately differentiated tumors (16 cases, 25.81%), whereas well-differentiated tumors showed mainly low Ki-67 expression (14 cases, 22.58% low Ki-67). This association between increasing tumor grade and higher Ki-67 expression was statistically significant (p = 0.001), indicating increased proliferative activity with poor differentiation.

With respect to FIGO stage, Ki-67 expression showed a significant increasing trend with disease progression. High Ki-67 expression was more common in Stage III (17 cases, 27.42%) and Stage II (16 cases, 25.81%) than in Stage I (2 cases, 3.23%). Low expression of Ki-67 was mainly observed in Stage I (10 cases, 16.13%). This association was statistically significant (p = 0.002), indicating that proliferative activity increases with increasing stage.

E-cadherin expression was inversely correlated with tumor grade and stage. Loss of Ecadherin was more common in poorly differentiated (13 cases, 20.97%) and moderately differentiated tumors (12 cases, 19.35%). Retained expression was more common in well differentiated tumors (15 cases, 24.19%). Similarly, advanced stage tumors were associated with increased loss of E-cadherin (Stage III, 16 cases, 25.81% as compared to Stage I, 2 cases, 3.23%). These associations were statistically significant (p=0.003 for grade and p=0.001 for stage) and indicated a decrease in cell adhesion with increasing tumor aggressiveness.

Furthermore, an inverse correlation between Ki-67 and E-cadherin expression was observed. High Ki-67 expression was associated with loss of E-cadherin in 22 cases (35.48%), whereas low Ki-67 expression was mainly associated with retained E-cadherin in 21 cases (33.87%). This correlation was statistically highly significant (p = 0.0001), suggesting that increased tumor proliferation is associated with reduced cell adhesion and greater invasiveness.

DISCUSSION

The present study was Descriptive Cross-Sectional Observational study. This Study was conducted from 18 months at Department of Pathology, N.R.S Medical College and Hospital Kolkata, Sealdah, Raja Bazar, Kolkata, West Bengal 700014. Study population 62.

In the present study, Ki-67 expression showed a significant association with histopathological grade, with higher expression predominantly observed in poorly differentiated tumors. Similar findings were reported by Fan Y *et al.* [8], who demonstrated that Ki-67 labeling index increases significantly with tumor dedifferentiation, indicating aggressive biological behavior. Likewise, Arunachalam S *et al.* [9] observed significantly higher Ki-67 expression in poorly differentiated tumors compared to well-differentiated ones, supporting its role as a proliferation marker.

With respect to FIGO stage, our study demonstrated a significant increase in Ki-67 expression with advancing disease stage. This is in agreement with the findings of Wu J *et al.* [10], who reported that elevated Ki-67 expression is associated with advanced-stage disease and poor prognosis. Similarly, Mehdi HK *et al.* [11] found significantly higher Ki-67 expression in Stage II and III tumors compared to Stage I, indicating increased tumor proliferation with disease progression.

E-cadherin expression in the present study showed an inverse relationship with tumor grade and stage, with loss of expression more frequently observed in poorly differentiated and advanced-stage tumors. These findings are consistent with Jiang J *et al.* [12], who demonstrated that reduced E-cadherin expression is associated with increased tumor invasiveness and higher grade lesions. Similarly, Shang L *et al.* [13] reported that loss of Ecadherin correlates significantly with advanced FIGO stage and lymph node metastasis.

Furthermore, the present study showed a statistically significant inverse correlation between Ki-67 and E-cadherin expression. High Ki-67 expression was associated with loss of Ecadherin, suggesting that increased proliferative activity is accompanied by reduced cell adhesion and enhanced tumor invasiveness. This observation is supported by Santoro A *et al.* [14], who found that tumors with high proliferative indices frequently exhibit reduced expression of adhesion molecules, contributing to tumor progression. Likewise, Khan RR *et al.* [15] demonstrated a significant inverse relationship between Ki-67 and E-cadherin expression, highlighting their combined role in tumor aggressiveness.

CONCLUSION

This study indicates that Ki-67 and E-cadherin are significant indicators in evaluating tumor behavior in cervical cancer. Increased Ki-67 expression was significantly correlated with higher histopathological grade and advanced FIGO stage, reflecting increased proliferative activity in poorly differentiated and advanced tumors. A progressive decrease in E-cadherin expression was observed with increasing grade and stage, indicating less cell adherence and increased tumor invasiveness. A significant inverse correlation was observed between Ki-67 and E-cadherin expression indicating that increased proliferative activity is associated with decreased cellular adhesion and increased tumor aggressiveness. The results highlight the synergistic role of Ki-67 and E-cadherin in understanding the biological behavior of cervical cancer. Therefore, the combined assessment of these biomarkers may give important prognostic information

and help to identify patients at high risk of progressive disease. This may improve risk stratification and guide appropriate treatment care in cervical cancer patients.

DECLARATION

Conflict of interest: No Conflict of interest is found elsewhere considering this work.

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