

E-Cadherin Expression as a Prognostic Factor in Transitional Cell Carcinoma of the Bladder After Transurethral Resection

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Purpose: To analyze the role of negative versus positive immunoexpression of E-cadherin in recurrence rate of low-grade bladder tumors.

Materials and Methods: A total of 180 patients with unifocal, superficial, low-grade, papillary transitional cell carcinoma of the bladder were included in this study. The E-cadherin expression was evaluated using E-cadherin antibody. The patients were followed up for 36 months. Thereafter, recurrence rate of the tumor was compared between E-cadherin positive and negative groups.

Results: Of 180 low-grade carcinomas, E-cadherin immunoexpression was negative in 101 (56%) and positive in 79 (44%) patients. The recurrence rate in negative and positive groups was 65.6% and 37.9%, respectively. Negative in comparison with positive E-cadherin expression was associated with more disease recurrence ($P = .045$).

Conclusion: There is an association between decreased E-Cadherin immunoexpression and tumor recurrence in low-grade and non-muscle invasive transitional cell carcinoma of the bladder.

Keywords: urinary bladder neoplasm, transitional cell carcinoma, cadherins, recurrence

INTRODUCTION

Recurrence is common in all patients with non-muscle-invasive urothelial cancer after transurethral resection (TUR). This risk is more prominent in patients with high-grade tumors. Intravesical chemotherapy or immunotherapy can be used to prevent recurrence in these subjects.⁽¹⁾

Factors other than grade, such as E-cadherin (E-CD) expression, have been proposed as a prognostic factor. The cadherins are a group of membrane glycoprotein and the mediators of cell to cell adhesion. E-cadherin, which is an epithelial-specific cadherin, plays a major role in the selective adhesion of cells in epithelial tissue and is necessary for the maintenance of normal epithelial cells integrity.⁽¹⁾

Loss of E-CD expression causes separation of the cells from cohesive epithelial tissues and leads to undifferentiation and invasiveness in a group of solid tumors, showing the important role of E-CD as a suppressor for malignant cells invasion and metastasis.^(2,3) Several studies have demonstrated that decreased expression of E-CD, as determined by immunohistochemistry, is associated with high grade and advanced stage in transitional cell carcinoma (TCC) of the bladder.⁽⁴⁻¹⁰⁾ The aim of this study was to assess the role of E-CD expression in initial specimen of low-grade TCC in identifying patients at risk for disease recurrence.

MATERIALS AND METHODS

Of 256 patients with an initial diagnosis of bladder tumors who had undergone transurethral resection of bladder tumor (TURBT), 191 subjects were identified as low-grade tumors using WHO/ISUP classification system. Their specimens were sent for immunohistochemistry assay of E-CD by Link StreptAvidin-Biotin method. Mouse monoclonal antibodies to human E-CD were purchased from Dako Laboratories Inc., Denmark.

Of 191 patients, 11 (4 in positive and 7 in negative groups) missed the complete follow-up period and were excluded from the study. One hundred and eighty formalin-fixed, paraffin-embedded TCC samples were obtained from patients. Individual tumor sections of 4 to 5 mm were deparaffinized and heated in a 10 mol/L citric acid monophosphate buffer (pH = 6.0) for 30 minutes in a 1.35-kW microwave oven at

high power.

Immunohistochemical staining was performed with biotinylated secondary antibodies for 10 minutes at room temperature. Slides were washed thoroughly with phosphate buffered saline again. Diaminobenzidine chromogen 1 was added for 5 minutes at 25 °C. After being stained with hematoxylin, tissues were dried out and watched under optical microscope. A pathologist counted the cells and compared them with a normal sample. Normal and increased cell counts were considered as positive and decreased ones as

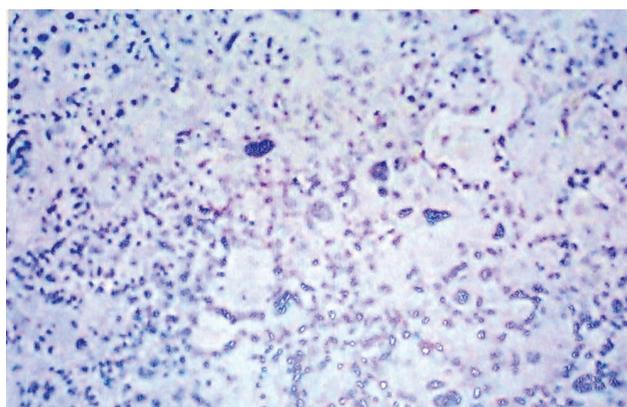


Figure 1. Decreased E-cadherin immunoreactivity.

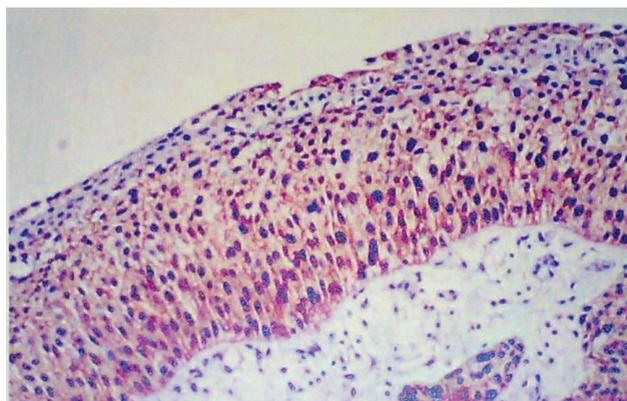


Figure 2. Increased E-cadherin immunoreactivity.

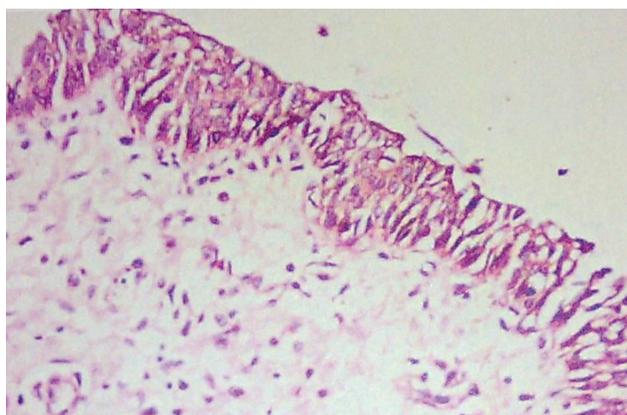


Figure 3. Normal E-cadherin immunoreactivity.

Comparison of findings between positive versus negative E-cadherin immunoexpression groups.

Parameters	E-cadherin negative	E-cadherin positive	P
Recurrence rate, n(%)	65 (65.6%)	30 (37.9%)	.045
Progression rate, n(%)	15 (14.8%)	9 (11.3%)	NS
Male/female	81/20	70/9	NS
Tumor size, cm	3 to 4	2.5 to 3.5	NS
Mean recurrence time, month	15	22	.035
Mean age, y	64	66.5	NS
High-grade recurrence, n	15	9	NS
Radical cystectomy, n	5	2	NS

NS indicates non-significant.

negative immunoexpression (Figures 1 to 3).

Cystoscopic follow-up was performed every 3 months for the first year and every 6 months for the second year. If the tumor recurrence occurred during the follow-up period, TURBT was performed and immediate instillations of 40 mg intravesical mitomycin C were done. The patients were followed up for at least 20 months. Median follow-up period of patients was 26 months. At the end of the follow-up period, 180 patients remained in the study and were evaluated.

The recurrence rates were compared between patients with negative and positive E-CD immunoexpression, with Kaplan-Meier recurrence survival analysis using SPSS software (the Statistical Package for the Social Sciences, Version 16.0, SPSS Inc, Chicago, Illinois, USA).

RESULTS

Of 180 low-grade bladder carcinomas, negative and positive E-CD immunoexpression were reported in 101 (56%) and 79(44%) patients, respectively.

One hundred and fifty-one patients were men, 81 in negative and 70 in positive E-CD groups. The median age was 64 and 66.5 years in negative and positive E-CD groups, respectively. The median follow-up period was 26 months (range, 20 to 36 months); 26.7 ± 6.3 months in negative and 26.08 ± 6.6 months in positive immunoexpression groups ($P = .522$).

Overall recurrence rate was 53.3%. Recurrence was de-

tected in 65 (65.6%) patients in negative and in 30 (37.9%) subjects in positive group. Negative E-CD expression was significantly associated with disease recurrence ($P = .021$). Test positive and negative predictive values were 38.0% and 35.6%, respectively.

Of 65 patients in negative E-CD group who recurred in 2-year follow-up, 15 had high-grade tumor in re-TUR and underwent intravesical immunotherapy. In 5 patients, there was muscle invasion in the specimen and radical cystectomy was recommended.

In positive E-CD group, 9 patients with high-grade tumor were reported in the follow-up period. Radical cystectomy was carried out in 2 patients in this group (Table). E-cadherin negative group had more progression in this study; however, it was not statistically significant.

DISCUSSION

Patients with bladder TCC prone to recurrence and progression are candidate for more comprehensive treatments, such as intravesical immunotherapy or chemotherapy. The most important cellular marker of unfavorable prognosis is tumor grade. Other parameters include tumor stage, presence of carcinoma in situ, tumor appearance, etc.⁽¹⁾

E-cadherin plays a critical role in maintaining intercellular junctions in epithelial tissues. In general, adhesion between normal epithelial cells is strong and stable. For malignant cells to separate from each other, invade, and metastasize from their native tissue, cell-to-cell associations have to be destroyed.^(11,12)

Immunohistochemical studies have revealed that loss of E-CD expression in a tissue is often associated with increased biological aggressiveness, such as high degree of invasiveness, more metastatic disease, poor histological differentiation, and a lower survival rate in patients with oral,⁽¹³⁾ breast,⁽¹⁴⁾ hepatocellular,⁽¹⁵⁾ bladder,⁽¹⁶⁾ prostate,⁽¹⁷⁾ renal,⁽¹⁸⁾ pancreatic,⁽¹⁹⁾ esophageal,⁽²⁰⁾ thyroid,⁽²¹⁾ head and neck,⁽²²⁾ and gastric carcinomas.⁽²³⁾

In this study, we evaluated the immunohistochemical expression of E-CD in formalin-fixed, paraffin-embedded tissue specimens in primary low-grade bladder tumors. Although the prognostic value of E-CD in bladder tumor needs to be confirmed in a larger number of patients, our

results indicate that the immunohistochemical assessment of E-CD into negative versus positive expression in low-grade bladder carcinomas may be valuable to predict the recurrence. This information can be used to stratify patients for therapeutic strategies.

CONCLUSION

This study demonstrates that there is an association between E-CD immunoexpression and bladder tumor recurrence rate. Further studies with larger sample sizes are needed to confirm our results.

CONFLICT OF INTEREST

None declared.

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