



Ki-67 Expression in Urinary Bladder Carcinomas and Its Prognostic Role

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Abstract

Background: Transitional cell carcinoma is the commonest histological type of bladder malignancies. There is a need for good prognostic markers that help to decide which group of patients need to be subjected to chemotherapy. The present study determines the expression of the cell proliferative marker Ki-67 and correlates it with pathologic features and disease prognosis in patients with transitional cell carcinoma (TCC) of the urinary bladder.

Methods: Immunohistochemical staining for Ki-67 was done on tissue blocks of cystectomy specimens from patients with bladder TCC.

Results: Ki-67 expression was increased in 56% of cystectomy specimens. Ki-67 overexpression was associated with advanced pathologic stage, higher grade, and metastases to lymph nodes ($P = 0.001, 0.040, \text{ and } 0.036$, respectively).

Conclusion: Ki-67 overexpression is associated with features of aggressive bladder TCC and adds independent prognostic information to standard pathologic features for prediction of clinical outcome after radical cystectomy.

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Introduction

Radical cystectomy remains the most common treatment for bladder cancer. Despite advances in surgical technique and improved understanding of the role of pelvic lymphadenectomy, 5-year disease-specific survival remains 50% to 60% (1, 2). Moreover, while providing important prognostic information in transitional cell carcinoma (TCC) of the urinary bladder, current clinical and pathologic variables have a limited ability to predict tumor recurrence, progression, or patient survival. With availability of effective systemic chemotherapy, there is a clear need for accurate predictors of failure after local therapy with curative intent. Biomarkers may be helpful for selecting patients best suited for early systemic intervention and for sparing patients who have undergone cystectomy from the morbidity associated with local adjuvant or salvage radiation therapy. Ki-67 could be one such marker. Ki-67 is a nuclear protein expressed by proliferating cells and can be observed immunohistochemically. Nuclear Ki-67 antigen expression is a measure of cell growth fraction and hence biological aggressiveness of a malignancy (3). This marker has shown promise as an independent prognosticator of patient outcome in several malignancies (4–6). Most recently, investigations established Ki-67 antigen as an independent predictor of recurrence, progression, and response to immunotherapy in patients with TCC (7–10). To date, few studies explored the predictive role of Ki-67 after radical cystectomy for advanced TCC (11, 12).

We determined the association of Ki-67 expression with clinicopathologic characteristics in patients with TCC treated with radical cystectomy.

Materials and Methods

The study comprised 80 patients who underwent radical cystectomy with bilateral lymphadenectomy. The clinical stage was assigned by the operative surgeon according to the 1997 tumor-node-metastasis system. For each patient, comprehensive clinical and pathologic data elements were collected. We did Ki-67 immunohistochemical staining using serial sections from the paraffin-embedded tissue blocks.

Result

Our present study comprises majority of cases in T1s and T1 stage constituting 36.45% followed by 35% cases in T2 staging. Lymph node involvement is seen in 16% of cases and distant metastasis were seen in 5% of cases. Tumors with grade 1 constituted 28.7%, those with grade 2 constituted 37.5%, those with grade 3 constituted 33.7% of cystectomy specimens studied. Ki-67 expression varied from 0–92% in the samples studied with a mean of 18%. Ki-67 overexpression was defined as tumors with >20% of cells with positive nuclear reactivity (Fig. 1,2).

In the present study, Ki-67 overexpression was seen in 56% of cases. Ki-67 overexpression was correlated with pathological staging, grade of the tumor, lymph nodal metastasis. (tables 1,2,3).



Fig. 1 showing grade 1 transitional carcinoma showing weak staining for Ki-67 (<20%)

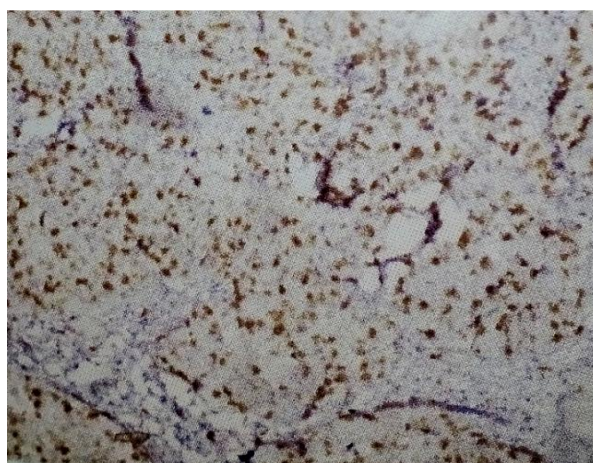


Fig 2 showing grade 3 TCC with Ki-67 overexpression (>20% tumor cells showing positivity)

TABLE-1 showing correlation between tumor stage and Ki-67 overexpression

Stage	No of cases	Those with ki-67 expression	Percentages
Tis, Ta	15	03	20%
T1	21	05	23%
T2	28	13	46.42%
T3	13	11	84.6%
T4	03	03	100%

TABLE-2 showing correlation between tumor grade and Ki-67 overexpression

Tumour grade	No of cases showing over-expression	Percentages
Grade 1 (n=23)	04	17%
Grade 2 (n=30)	16	53%
Grade 3 (n=27)	25	92%

TABLE-3 showing correlation between Nodal status and Ki-67 overexpression

Nodal status	No of cases showing over-expression	percentages
N0 (n=68)	38	55.9%
N1, N2 (n=12)	07	58.3%

Statistical association was calculated and it was found that there was a significant positive association between Ki-67 overexpression and stage, grade, metastasis. P value calculated was 0.001, 0.040, and 0.036, respectively

Disease recurred in 56% of patients, the mean follow-up was 36 months for those patients alive at the time of analysis. Kaplan-Meier analyses revealed that Ki-67 overexpression was significantly associated with an increased probability of disease recurrence and bladder cancer-specific mortality.

Discussion

Approximately 50% to 60% of patients diagnosed with muscle-invasive TCC of the urinary bladder will develop metastatic progression after local therapy with curative intent, resulting in ~12,000 deaths annually (1, 2). Although pathologic staging after local therapy is the most important prognosticator, its value for predicting clinical outcomes remains limited. A reliable predictor of metastatic progression would enhance our ability to identify patients who would benefit from adjuvant therapy and spare those who would not the toxicity associated with adjuvant therapies.

Several biomarkers, including proliferation-associated molecule Ki-67, have shown promise in their ability to stratify patients according to their risk for disease progression (15). Ki-67 is an established marker of cell proliferation, present during the G1, S, G2, and M stages of the cell cycle. In addition to Ki-67 antibody, MIB-1 antibody also detects the Ki-67 antigen but can be used on formalin-fixed, paraffin-embedded tissues. Staining for Ki-67 with MIB-1 is a simple and reproducible technique for assessing cell proliferation in bladder carcinoma and can be done on a small amount of tissue taken (3). Ki-67 expression is independently associated with clinical outcome after local therapy in several tumor types, such as breast, soft tissue, lung, cervix, melanoma, hepatocellular carcinoma, and prostate (4–6, 13).

Recently, investigators have established Ki-67 expression as an independent predictor of disease recurrence, progression, and response to intravesical therapy in patients with nonmuscle-invasive bladder cancer (7–10). Popov et al. (11), in a heterogeneous cohort of 114 patients treated with TUR or radical cystectomy, concluded that Ki-67 expression was independently associated with disease recurrence. Unfortunately, subgroup analysis of Ki-67 expression in patients with muscle-invasive and advanced TCC was not done. In a co-

hort of 75 patients treated with radical cystectomy, Suwa et al. (12) found that Ki-67 expression was an independent prognosticator of patient survival. However, most patients in that series had locally advanced or node-positive disease. Frank et al. (14) examined the expression of Ki-67 in the lymph node metastases from 139 patients who underwent cystectomy for TCC at their institution and found no association between Ki-67 and disease-related outcomes. However, when the analysis was limited to patients who were treated with adjuvant chemotherapy (n = 37 patients), there was a significant association between Ki-67 expression and distant metastases (P = 0.049).

We have shown that Ki-67 overexpression was significantly associated with advanced pathologic stage, higher tumor grade, lymphovascular invasion, and metastases to lymph nodes. Most importantly, Ki-67 expression was independently associated with both disease recurrence and bladder cancer-specific mortality. Patients with lymph node-positive disease are usually recommended to undergo adjuvant chemotherapy but it is not clear which patients with organ-confined disease will benefit from adjuvant therapies. As such identifying factors that may predict a worse outcome will improve our ability to counsel such patients about the best management strategy.

Conclusion

Ki-67 immunostaining adds significant and independent prognostic information in patients treated with radical cystectomy for bladder TCC. Ki-67 expression may help identify patients with pathologically organ-confined bladder TCC who are at increased risk for disease progression and may benefit from adjuvant therapies. The clinical usefulness of this marker prompts large, prospective, multi-institutional comparative studies using standardized immunohistochemical assessment techniques.

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Competing Interests

None declared.

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