Predicting Recurrence and Progression in Non-Muscle-Invasive Bladder Cancer Using European Organization of Research and Treatment of Cancer Risk Tables

M Hammad Ather, Masooma Zaidi

Introduction: We determined the recurrence and progression at 1 year in patients with non-muscle-invasive urothelial carcinoma who underwent transurethral resection of bladder tumor (TURBT) and compared those with the calculated risk according to the European Organization of Research and Treatment of Cancer (EORTC).

Materials and Methods: Follow-up data of 92 patients with non-muscle-invasive bladder cancer who underwent TURBT were reviewed, and their 1st year recurrence and progression were recorded. The risk of recurrence and progression were calculated for 1 year according to the EORTC scoring system, using tumors' stage, grade, size, and multiplicity, and the presence of carcinoma in situ and previous recurrence episodes. The outcomes were compared with the EORTC's predictive scores.

Results: The patients were 75 men and 17 women with an age range of 31 to 91 years. Sixteen patients (17.4%) had a recurrent disease, 41 (44.6%) had a tumor larger than 3 cm in diameter, 35 (38.0%) had multiple lesions, 2 (2.2%) had carcinoma in situ, 73 (79.3%) had stage T1 lesions, and 8 (8.7%) had a high-grade disease. Recurrence was found in 34 patients (37.0%). The recurrence rates were 20.0%, 28.2%, 40.5%, and 83.3% in groups with the predicted EORTC risks of 15%, 24%, 38%, and 61%, respectively. There were 2 patients (2.2%) with progression of the diseases.

Conclusion: A significant concordance was noted between the EORTC's predicted risk and the actuarial recurrence rate of stage Ta T1 bladder cancer at 1 year. Progression was less than that predicted, probably due to our small sample size.

Keywords: urinary bladder neoplasms, disease progression, neoplasm recurrence, risk

Urol J. 2009;6:189-93.
www.uj.unrc.ir

INTRODUCTION

Bladder carcinoma is the most common malignancy of the urinary tract.[1] Data from tumor registry data analysis of the Armed Forces Institute of Pathology, in Rawalpindi, Pakistan, showed that bladder cancer was the 5th most common cancer in men during a period between 1992 and 2001.[2] In a minimal cancer incidence data for Karachi, the largest city of Pakistan, for the years 1998 and 1999 indicate that tobacco-associated cancers in Karachi were responsible for 38.3% of the tumors diagnosed amongst the men.[3] Approximately 75% to 85% of patients with bladder cancer present with the disease confined to the mucosa (stage Ta and carcinoma in situ) or submucosa (stage T1) with various grades of

Department of Surgery, Aga Khan University, Karachi, Pakistan

Corresponding Author:
M Hammad Ather, FCPS (Urol), FEBU
Dept of Surgery, PO Box 3500, Stadium Road, Karachi 74800, Pakistan
Tel: +92 21 486 4778
Fax: +92 21 493 4294
E-mail: hammad.ather@aku.edu

Received January 2009
Accepted May 2009

differentiation.[4] Non-muscle-invasive urothelial cell carcinoma of the bladder (UCC) accounts for about 80% of all the newly diagnosed cancers.[1] Transurethral resection of the bladder tumor (TURBT) is the gold standard for diagnosis and treatment.

Reported recurrence after TURBT is about 30% to 70%.[1] The classic way to categorize patients with stage Ta and stage T1 tumors is to divide them into risk groups based on prognostic factors derived from multivariate analyses. Using such a technique, it was proposed to divide patients into low-risk, intermediate-risk, and high-risk groups.[5] When using these risk groups, however, no difference is usually made between the risk of recurrence and progression. Although prognostic factors may indicate a high risk of recurrence, the risk of progression may still be low and other tumors may have a high risk of both recurrence and progression. In order to separately predict the short-term and long-term risks of both recurrence and progression in individual patients, the European Organization for Research and Treatment of Cancer (EORTC) developed a scoring system and risk tables.[6] The scores can be calculated for each patient according to the EORTC recurrence and progression predictor table and percentage risk calculated. We undertook this study to validate the scoring system on our patients with non-muscle-invasive UCC. Our aim was to compare the predicted (EORTC model) versus actual recurrence rate, without taking into consideration the maintenance therapy.

MATERIALS AND METHODS

Patients

This retrospective study was conducted on the records at a university hospital between March 1998 and December 2007, and 178 patients with non-muscle-invasive bladder cancer were evaluated. They were treated with TURBT and diagnosed with stage Ta or stage T1 transitional cell carcinoma (TCC) of the bladder based on the 2002 American Joint Committee on Cancer TNM staging system.[7] The grades were determined using the 1973 World Health Organization system. Patients with a history of muscle-invasive bladder cancer treated with a bladder-sparing protocol, non-TCC histology, primary carcinoma in situ, or a follow-up duration of less than 12 months were excluded. After exclusions, 92 patients were enrolled in this study.

Follow-up

Follow-up cystoscopies were done every 3 months for the first 2 years in all of the patients, followed by a protocol dictated by the risk stratification. After 2 years, the follow-up cystoscopies were done yearly for 5 years in low-risk patients. In high-risk patients, cystoscopies were done every 4 months during the 3rd year, and every 6 months during the 4th and 5th years. Prior to each follow-up cystoscopy, 2 free voided urine cytology tests were performed in order to determine the need for random biopsy.

We collected the clinical and pathological data, including sex, age, tumor size (< 3 cm or ≥ 3 cm), multiplicity (single or multiple), T category (Ta or T1), tumor grade, presence of concomitant carcinoma in situ or squamous differentiation, and intra vesical therapy (single instillation following TURBT and maintenance). Follow-up data were also obtained, including pathologically proven recurrence and time to the first recurrence, which was defined as the time period between the date of initial diagnosis and the date of recurrence. All pathological specimens were routinely assessed in the pathology department. Pathologists were not blinded to the results of initial pathology report or patients' clinical findings. Patients who were still alive or who had died before a recurrence were considered as censored at the date of the last available follow-up cystoscopy.

European Organization for Research and Treatment of Cancer Scoring

Scores of progression and recurrence risks at 1 year were calculated for each patient according to the EORTC (available from: http://www.eortc.be/tools/bladdercalculator/).[8] We assessed the impact of various clinical and pathological features on the outcome of the 1st year. Intravesical single instillation of chemotherapy (mitomycin C, 40 mg) was given to all patients

following initial transurethral resection. Maintenance intravesical treatment (either with mitomycin C or bacillus Calmette-Guerin) was given to the patients with intermediate or high risk of progression. In accordance with the EORTC model, the impact of either single instillation of chemotherapeutic agents following TURBT, maintenance intravesical chemotherapy, and immunotherapy were not specifically assessed. The provided software implements the EORTC Scoring System and Risk Tables for Stage Ta T1 Bladder Cancer based on the data published by Sylvester and colleagues.[6] They allow the user to estimate the probability of recurrence and progression in patients with stages Ta and T1 bladder cancer based on 6 different factors: number of tumors , tumor size, prior recurrence rate, T category, concomitant carcinoma in situ, and grade. The endpoint was comparison of predicted versus actual recurrence, irrespective of the intravesical maintenance therapy.

RESULTS

The median age of the patients was 56 years (range, 31 to 91 years), and their median follow-up duration was 38 months (range, 12 to 101 months). They were 75 men (81.5%) and 17 women (18.5%). Seventy-one patients presented with hematuria (77.2%), 15 with lower urinary tract symptoms (16.3%), and 6 with a combination of these symptoms (6.5%). Tumor characteristics, including primary or recurrent, size, number, and pathological characteristics are summarized in Table 1. After 1 year, there were 34 patients (37.0%) with recurrence of the tumor. The recurrence rates after 1 year are listed and compared with the predicted EORTC risks in Table 2. Progression of the cancer was seen in 2 patients (2.2%) during the first postoperative year. The predicted risks of progression by the EORTC in comparison with the progression cases are summarized in Table 3.

Table1. Bladder Tumor Characteristics

Characteristics	Value (%)
Bladder tumor	
Primary	76 (82.6)
Recurrent	16 (17.4)
Tumor size, cm	
< 3	51 (55.4)
≥ 3	41 (44.6)
Number of tumors	
1	57 (62.0)
2 to 7	28 (30.4)
≥ 8	7 (7.6)
Concomitant carcinoma in situ	2 (2.2)
Tumor stage	
Ta	19 (20.6)
T1	73 (79.3)
Tumor grade	
1	46 (50.0)
2	38 (41.3)
3	8 (8.7)

Table 2. Predicted Versus Actual 1-Year Recurrence Rate*

EORTC's Recurrence Prediction (Score)	Patients	Recurrence After 1 Year (%)
15% risk (0)	5	1 (20.0)
24% risk (1 to 4)	39	11 (28.2)
38% risk (5 to 9)	42	17 (40.5)
61% risk (10 to 17)	6	5 (83.3)

*Prediction scores were calculated according to the European Organization for research and Treatment of Cancer (EORTC).

Table 3. Predicted Versus Actual 1-Year Progression Rate*

EORTC's Progression Prediction (Score)	Patients	Progression After 1 Year (%)
0.2% risk (0)	5	0
1% risk (1 to 6)	33	1 (3.0)
5% risk (7 to 13)	51	1 (1.9)
17% risk (14 to 23)	3	0

*Prediction scores were calculated according to the European Organization for research and Treatment of Cancer (EORTC).

DISCUSSION

The clinical management of non-muscle-invasive UCC is challenging, as it has a marked tendency to recur and to progress. These recurrences are most frequent in the first 3 years, but sometimes are seen even after long periods of dormancy.[9] Regular urological follow-up assessments should be continued until at least 15 years of tumor-free status, especially in patients treated with intravesical chemotherapy or in those initially having multiple tumors. Prediction of progression is made by various tumor characteristics such as tumor size, number of tumors, prior recurrence, and grade and stage of the disease. These factors are incorporated in the EORTC's developed a risk scoring system.[6] Scores were calculated for each patient according to the EORTC recurrence

and progression predictor table and percentage risk. However, sometimes patients with non-muscle-invasive UCC are often observed without progression in the long-term follow-up period, although many of them experience recurrence of the disease. It is difficult to accurately predict the disease outcome of each patient with conventional prognostic criteria. In such situation, Fujikawa and colleagues[10] proposed that the use of the artificial neural network has a potential to improve the prediction. They noted that long-term progression-free survival of patients with noninvasive TCC of the urinary bladder can be precisely predicted using the artificial neural network, which would be one of the criteria for making decision about immediate or future total cystectomy.

The use of molecular markers and gene expression profiling provides a promising approach for improving the predictive accuracy of current prognostic indexes for predicting progression. In order to establish prognostic factors of recurrence and progression in stage T1 TCC, paying special attention to prognostic value of p53 and ki67 is suggested by some authors. A group from Spain[11] noted that solid microscopic pattern and p53 expression are the variables which best predict progression. A positive relationship was observed between p53 and progression: the greater the expression of p53, the greater the progression. Tumor multifocality and ki67 expression of greater than 27% are the main prognostic factors for recurrence.[11] Galectin-3 is a glycoprotein involved in various physiological cellular processes. Altered expression or loss of function of galectin-3 is suggested to be involved in the pathogenesis and further progression of various human cancer entities. Kramer and colleagues[12] studied the role of galectin-3 in the development and/or progression of non-muscle-invasive (pTa, pT1) TCC of the bladder. They noted that loss of galectin-3 appeared to be involved in the carcinogenesis of TCC and to serve as a valuable biological variable to identify a subgroup of patients with stage Ta bladder cancer at a high risk of the development of recurrent disease. Baak and colleagues[13] studied the predictive value for recurrence and stage progression of DNA ploidy and S-phase fraction by flow cytometry and highly automated ultrafast image cytometry in biopsies of stages Ta and T1 UCCs of the bladder. They observed that DNA image cytometric features predicted recurrence and stage progression more accurately than classic prognostic factors, independent of treatment modality. The clinical significance of various molecular markers in predicting prognosis is still being debated. Current recommendations of the European Association of Urology guidelines[14] are to use EORTC risk calculator incorporating.

CONCLUSION

The current work showed that the recurrence rates were found to be similar as compared to the EORTC model. Progression rates were found to be less than that predicted by the scoring system, most likely because of the limitations in this study, including the small sample size. We propose validation of EORTC table in a larger cohort for its global applicability.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM. Globcan 2002, Cancer Incidence, Mortality and Prevalence Worldwide, IARC CancerBase No 5, version 2.0. Lyon: IARCC Press; 2004.
2. Jamal S, Moghal S, Mamoon N, Mushtaq S, Luqman M, Anwar M. The pattern of malignant tumours: tumour registry data analysis, AFIP, Rawalpindi, Pakistan (1992-2001). J Pak Med Assoc. 2006;56:359-62.
3. Bhurgri Y, Bhurgri A, Hasan SH, et al. Cancer patterns in Karachi division (1998-1999). J Pak Med Assoc. 2002;52:244-6.
4. Heney NM, Ahmed S, Flanagan MJ, et al. Superficial bladder cancer: progression and recurrence. J Urol. 1983;130:1083-6.
5. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Algaba F, Vicente-Rodriguez J. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. J Urol. 2000;164:680-4.
6. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49:466-5.
7. Greene FL, Page DL, Fleming ID, et al. AJCC cancer staging Manual. 6th ed. New York: Springer Verlag; 2002.

8. European Organization for Research and Treatment of Cancer [homepage on the Internet]. EORTC risk tables for predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer [cited 2009 Aug 1]. Available form: http://www.eortc.be/tools/bladdercalculator/
9. Fujii Y, Fukui I, Kihara K, Tsujii T, Kageyama Y, Oshima H. Late recurrence and progression after a long tumor-free period in primary Ta and T1 bladder cancer. Eur Urol. 1999;36:309-13.
10. Fujikawa K, Matsui Y, Kobayashi T, et al. Predicting disease outcome of non-invasive transitional cell carcinoma of the urinary bladder using an artificial neural network model: results of patient follow-up for 15 years or longer. Int J Urol. 2003;10:149-52.
11. Rodriguez Alonso A, Pita Fernandez S, Gonzalez-Carrero J, Nogueira March JL. [Multivariate analysis of recurrence and progression in stage T1 transitional-cell carcinoma of the bladder. Prognostic value of p53 and Ki67]. Actas Urol Esp. 2003;27:132-41. Spanish.
12. Kramer MW, Kuczyk MA, Hennenlotter J, et al. Decreased expression of galectin-3 predicts tumour recurrence in pTa bladder cancer. Oncol Rep. 2008;20:1403-8.
13. Baak JP, Bol MG, van Diermen B, Janssen EA, Buhr-Wildhagen SB, Mestad O, Øgreid P, Kjellevold KH. DNA cytometric features in biopsies of TaT1 urothelial cell cancer predict recurrence and stage progression more accurately than stage, grade, or treatment modality. Urology. 2003;61:1266-72.
14. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Bohle A, Palou J. Guidelines on TaT1 (non-muscle invasive) bladder cancer. Arnhem (The Netherlands): European Association of Urology (EAU); 2008.