

FACTORS ASSOCIATED WITH TUMOR RECURRENCE IN STAGE 1 BLADDER TRANSITIONAL CELL CARCINOMA IN SARDJITO HOSPITAL YOGYAKARTA

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ABSTRACT

Objective: This study is assigned to evaluate factors associated with tumor recurrence in patients with superficial transitional cell carcinoma (TCC) of bladder in Sardjito General Hospital Yogyakarta. **Material & methods:** A prospective observational study design is conducted to evaluate patients with T1 TCC of bladder between 2011 and 2012. Inclusion criteria was patients with T1 TCC of bladder from pathological report. The independent variables are ages, hemoglobin, albumin, creatinine level, urine cytology, tumor grade, tumor diameter, number of tumor, and intravesical chemotherapy. The outcome measure is tumor recurrence during cystoscopy at 3, 6, 9, and 12 month after first resection. This study used chi-square and logistic regression analysis as statistical methods with $p < 0.05$ and $\alpha = 5\%$ are considered significant. All analyses were performed with SPSS statistical software, version 20.0. **Result:** Sixty-two patients were participated in this study with mean age 60.62 ± 12.15 years. There were 32 patients (51.6%) who had tumour recurrence during first year that need to be resected. Of these patients, 9 patients (14.5%) had tumour recurrence more than one time during first year. In multivariate analysis, factors associated with tumour recurrence were tumour grade ($p = 0.041$, $CI = 0.008-0.908$), number of tumor ($p = 0.003$, $CI = 0.003-0.293$), and intravesical chemotherapy ($p = 0.022$, $CI = 0.015-0.719$). **Conclusion:** Degree of tumor differentiation, number of tumor and intravesical chemotherapy are factors affecting recurrence of stage 1 transitional cell carcinoma of the bladder.

Keywords: Superficial transitional cell carcinoma, recurrence.

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk mengevaluasi faktor yang berhubungan dengan kambuhnya tumor pada pasien dengan transitional cell carcinoma (TCC) kandung kemih dangkal di RSUP Sardjito Yogyakarta. **Bahan & cara:** Desain penelitian observasional prospektif diterapkan untuk mengevaluasi pasien dengan T1 TCC kandung kemih antara tahun 2011 dan 2012. Kriteria inklusi adalah pasien dengan T1 TCC kandung kemih dari laporan patologi. Variabel independen adalah usia, hemoglobin, albumin, level kreatinin, sitologi urine, grade tumor, diameter tumor, angka tumor dan kemoterapi intravesika. Hasil penilaian adalah kambuhnya tumor antara sistoskopi pada 3, 6, 9, dan 12 bulan setelah reseksi pertama. Penelitian ini menggunakan chi-square dan analisa regresi logistik sebagai metode statistik dengan $p < 0.05$ dan $\alpha = 5\%$ dianggap signifikan. Semua analisa dilakukan dengan software statistik SPSS, versi 20.0. **Hasil:** Sebanyak 62 pasien berpartisipasi dalam penelitian ini dengan rerata umur 60.62 ± 12.15 tahun. Terdapat 32 pasien (51.6%) yang kambuh tumornya antara tahun pertama yang diperlukan untuk diambil. Dari pasien ini, 9 pasien (14.5%) tumornya kambuh lebih dari sekali selama tahun pertama. Pada analisa multivariate, faktor yang berhubungan dengan kambuhnya tumor adalah grade tumor ($p = 0.041$, $CI = 0.008-0.908$), angka tumor ($p = 0.003$, $CI = 0.003-0.293$), dan kemoterapi intravesika ($p = 0.022$, $CI = 0.015-0.719$). **Simpulan:** Derajat diferensiasi tumor, angka tumor dan kemoterapi intravesika adalah faktor yang mempengaruhi kambuhnya stase 1 TCC kandung kemih.

Kata kunci: Transitional cell carcinoma dangkal, kekambuhan.

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INTRODUCTION

Bladder cancer is the most-common malignancy of the urinary tract. Mortality rates (age-standardized) among European countries are 8 for men and 3 for women per 100,000 populations. Seventy-five percent of bladder cancers are superficial, having a high recurrence rate, with low progression and a good survival in many cases.¹ Therefore, identifying factors affecting recurrence and strategy of management at high risk of cancer recurrence becomes important.

Publication of the study investigating factors associated with recurrence of bladder cancer is relatively limited, especially in our center. These factors could be used as the basic assessment of patients whether they had a low or high risk for recurrence of the tumor. Therefore, patients with a high risk had a different strategy of management and follow-up to those with a low risk of tumor recurrence. This study was expected to be the risk assessment material of recurrence in patients with transitional cell carcinoma of the bladder for better management.

OBJECTIVE

This study was intended to identify factors influencing the recurrence of transitional cell carcinoma of the bladder.

MATERIAL & METHOD

A prospective observational study was conducted on patients with transitional cell carcinoma of the bladder in the period of 2011-2013 at Sardjito General Hospital, Yogyakarta. The inclusion criterion was all patients diagnosed with T1 transitional cell carcinoma of the bladder from anatomical pathology results. Exclusion criterion was all patients with T2-T4 transitional cell carcinoma of the bladder.

Every patient who suspected bladder cancer performed evaluation procedures including clinical and additional evaluation. Clinical evaluation involved history of intermittent painless hematuria, symptoms of LUTS especially irritating complaint and symptoms of metastatic cancer. Physical evaluation included digital rectal examination, bimanual palpation of the kidneys and bladder. Additional Evaluation comprised of ultrasound, intravenous urography, and urine cytology. All

patients suspected bladder cancer underwent cystoscopy and if tumor was found, patients underwent transurethral tumor resection of bladder tumor (TURB). Results of tumor scrapings and tumor invasion were sent to pathology for evaluation of tumor type, invasion and degree of differentiation. Patients who had performed TURB were managed with intravesical chemotherapy for once after TURB. Some patients underwent intravesical chemotherapy within the first 24 hours after TURB, while other patients underwent intravesical chemotherapy more than 24 hours after TURB. All patients with anatomic pathology results of superficial bladder transitional cell carcinoma (T1) underwent cystoscopy evaluation at month 3, 6, 9, and 12 after the first TURB. The patient was categorized to have tumor recurrence when the tumor was found on cystoscopy evaluation.

The dependent factor analyzed in this study was tumor recurrence within the first year after TURB. The independent factors suspected to affect the dependent factor were age, hemoglobin level, albumin level, creatinine level, urine cytology, degree of tumor differentiation, tumor diameter and location, as well as intravesical chemotherapy within 24 hours after TURB. Statistical analysis used in this study was bivariate analysis using independent T-test for numerical variables and chi-square for nominal variables. Multivariate analysis was performed to evaluate the independent factors as prognostic factors of tumor recurrence. Statistical analysis was used through SPSS version 20 with a value of $p < 0.05$ and $\alpha = 5\%$ considered statistically significant.

RESULTS

This study included 62 patients with T1 transitional cell carcinoma of the bladder. Mean of age was 60.58 ± 12.01 years. Mean of hemoglobin, albumin, and serum creatinine levels were respectively 11.90 ± 2.04 g/dl, 3.26 ± 0.53 mg/dl, 1.65 ± 3.25 mg/dl. Based on the descriptive analysis, mean value of hemoglobin levels was below the normal value. Mean value of albumin and creatinine level was within normal values.

Based on the characteristics of the tumor, 27 (43.5%) patients had a poor degree of tumor differentiation (high grade) and 35 (56.5%) patients had a good degree of tumor differentiation (low grade). Urine cytology results showed that 22 (35.5%) were found to have malignant urothelial

cells and 40 (64.5%) were found no malignant cells. Most patients (71%) had tumor diameter of < 3 cm. A total of 36 (58.1%) patients had > 1 location of the tumor in the bladder. 33 (53.2%) patients underwent intravesical chemotherapy within 24 hours after TURB. Clinical features and tumor characteristics of patients were shown in table 1 and 2.

After TURB, a total of 32 (51.6%) patients had tumor recurrence. Of the 32 patients, a total of 9 (14.5%) patients had tumor recurrence more than once in the first year after TURB.

Multivariate logistic regression analysis was performed to evaluate the relationship between

clinical characteristics and tumor recurrence. Multivariate analysis showed that there was a statistically significant relationship between the degree of tumor differentiation, tumor number and intravesical chemotherapy for tumor recurrence with p values and 95% confidence intervals, respectively $p = 0.041$, CI of 0.008-0.908, $p = 0.003$, CI of 0.003-0.293 and $p = 0.022$, CI of 0.015-0.719.

Patients with high-grade tumors experiencing recurrence were 23 (85.2%) compared to those with low-grade tumors of 9 (25.7%) patients. Tumor recurrence was more frequent in the group of patients with high-grade tumors (85.2% versus

Table 1. General characteristics of participants.

Variable	N	Mean	Std. deviation
Age (year)	62	60.26	12.15
Hemoglobin level (g/dl)	62	11.90	2.04
Creatinine level (mg/dl)	62	1.65	3.25
Albumin level (g/dl)	62	3.26	0.53
Sex			
Men	34		
Women	28		

Table 2. Characteristics of transitional cell carcinoma of bladder.

Tumor characteristic	N	Percentage
Degree of tumor differentiation		
High-grade	27	43.5
Low-grade	35	56.5
Number of tumor		
> 1 location	36	58.1
1 location	26	41.9
Urine cytology		
Malignant cell	22	35.5
No malignant cell	40	64.5
Tumor diameter		
> 3 cm	18	29
3 cm	44	71
Intravesical chemotherapy		
Yes	29	46.8
No	33	53.2

Table 3. Multivariate analysis of factors associated with bladder tumor recurrence.

Variable	Constanta	Sig.	95% CI	Odds Ratio (OR)
Tumor grade	-2.460	0.041	0.008-0.908	3.313
Number of tumor	-3.527	0.003	0.003-0.293	6.981
Intravesical chemotherapy	-2.266	0.022	0.015-0.719	4.931

25.7%), the number of tumors > 1 location (80.6% versus 11.5%), and in the group of patients who did not undergo intravesical chemotherapy within 24 hours after TURB (89.7% versus 18.2%). The results of the multivariate analysis were shown in table 3.

DISCUSSION

The results of this study indicated that of the 62 patients who underwent TURB, 32 (51.6%) of those patients had recurrence and 9 (14.5%) of them experienced tumor recurrence more than once in the first year after TURB.

In the literature, malignant superficial urothelial cancer had a high recurrence rate reaching 80%. Based on the classification of bladder tumors described by World Health Organization (WHO) in 2004, the rate of recurrence of papillary neoplasm of low malignancy risk was 27-47%. Papillary carcinoma recurrence rate for low-grade and high-grade was respectively 48-71% and 55-58%.²

According to Sylvester RJ, et al (2006), the rate of tumor recurrence in TaT1 bladder cancer in the first year was approximately 15-61%. In the fifth year recurrence rate ranged from 31-78%. Research by the author showed that the recurrence rate of 51.6% was not quite different from the previous studies published.³

Based on multivariate analysis, factors associated with tumor recurrence involved the degree of tumor differentiation, number of tumor and intravesical chemotherapy. Research by Sylvester RJ, et al (2006) indicated that the factors predicting tumor recurrence were the number of tumors, tumor size, T category, grade of tumor, carcinoma in situ, and a history of previous recurrence. The results found by the authors did not differ from previous research that degree of tumor differentiation, number of tumor and intravesical chemotherapy associated with tumor recurrence. However, the size of the tumor, carcinoma in situ, and a history of tumor recurrence were not investigated as a factor associated with tumor recurrence.³

The degree of tumor differentiation was significantly associated with tumor recurrence. Patients with high-grade tumors experienced tumor recurrence at 23 (85.2%), while patients with low-grade tumors were at 9 (25.7%) ($p = 0.000$, OR = 3.313). Statistical analysis showed high-grade tumors had a significantly greater risk of tumor recurrence than low-grade tumors with an odds ratio of 3.313.

The number of tumors was one of the factors that affect tumor recurrence. In this research, patient with > 1 of tumor location on the bladder was significantly more prevalent than those with only one tumor location in the bladder (80.6% versus 11.5%). The results also indicated a greater risk of recurrence in patients with > 1 tumor location spotted on the bladder ($p = 0.000$, OR = 6.981).

Intravesical chemotherapy statistically was associated with tumor recurrence. The results showed that intravesical chemotherapy administration lowered the risk of tumor recurrence ($p = 0.000$, OR = 4.391). These results were consistent with studies that had been published previously that intravesical chemotherapy administration decreased the risk of tumor recurrence.

Research by Sylvester RJ, et al (2004) showed that immediate intravesical-chemotherapy administration significantly reduced the risk of recurrence at 39% in the odds ratio (OR) of recurrence after TURB in patients with TaT1 bladder cancer. In this study, a higher recurrence rate in multiple tumors (65.2%) compared to primary tumors (35.8%) after intravesical chemotherapy administration.⁴

Meta-analysis study by Perlis N, et al (2013) demonstrated that immediate intravesical chemotherapy after TURB prolonged recurrence-free interval and lowered the risk of early tumor recurrence in superficial bladder cancer. Intravesical chemotherapy prolonged recurrence-free interval of 38% and reduced the occurrence of early recurrence at 12%. This study analyzed 13 studies involving 2548 patients. However, the quality of the methodologies used in most studies was insufficient due to the high risk of bias.⁵

Kaasinen E, et al (2002) concluded that the timing of intravesical chemotherapy was a factor affecting tumor recurrence. The results showed that intravesical chemotherapy administered more than 24 hours after TURB would increase the relative risk of tumor recurrence more than 2 times than intravesical chemotherapy administered within 24 hours after TURB.⁶ The result of this study reinforced the result in our study as one of the predictor variables of tumor recurrence was intravesical chemotherapy within 24 hours after TURB.

This study had some limitations in terms of the number of samples and the time of the study. The number of samples in this study was small, 62 patients. Time of follow-up conducted in this study

was limited only one year. Therefore, further research was needed to study with larger sample size and a longer follow-up time.

CONCLUSION

Degree of tumor differentiation, number of tumor and intravesical chemotherapy are factors affecting recurrence of superficial transitional cell carcinoma of the bladder. However, further research was needed to investigate high-grade tumors and > 1 number of tumors because it had a higher recurrence rate so that management strategies and evaluation of bladder transitional cell carcinoma could be optimized.

REFERENCES

1. Babjuk M, Bohle A, Burger M, Comperat E, Kaasinen E, Palou J, et al. Guidelines on non-muscle-invasive bladder cancer (Ta, T1, and Cis) [Internet]. European Association of Urology Guidelines 2015 edition; 2014 [Cited 2015 May 12]. Available from: .
2. Jones JS, Larchian WA. Non-muscle-invasive bladder cancer (Ta, T1, and Cis), In Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters AC, Editor Campbell-Walsh Urology 10th edition. Philadelphia: Saunders Elsevier; 2012. p. 2335-54.
3. Sylvester RJ, Van der Meijden AP, Oosterlinck W, Witjes JA, Bouffoux C, Denis L, 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(3): 466-5. <http://www.ncbi.nlm.nih.gov/pubmed/16442208>
4. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol.* 2004; 171: 2186-90. <http://www.ncbi.nlm.nih.gov/pubmed/15126782>
5. Perlis N, Zlotta AR, Beyene J, Finelli A, Fleshner NE, Kulkarni GS. Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality of evidence review. *Eur Urol.* 2013; 64(3): 421-30. <http://www.ncbi.nlm.nih.gov/pubmed/23830475>
6. Kaasinen E, Rintala E, Hellstrom P, Viitanen J, Juusela H, Rajala P, et al. Factors explaining recurrence in patients undergoing chemoinmunotherapy regimens for frequently recurring superficial bladder carcinoma. *Eur Urol.* 2002; 42(2): 167-74.