Determining Good Practice For BCG Therapy Of Urinary Tract Cancer By Using A Knowledge Model

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ABSTRACT:

This study aimed to predict the recurrence of carcinoma following Bacillus Calmette-Guérin (BCG) therapy, an effective treatment for urothelial carcinoma. In everyday practice, cytodiagnosis of cells of the whole urinary tract is performed because it is not possible to identify and isolate the bladder or the cancerous cells of the upper urinary tract and the affected sites. We performed statistical analysis on the entire urinary tract using urine cytology specimens of patients with urinary tract cancer who had undergone BCG therapy. Subsequently, we developed a formula for predicting the recurrence of urothelial carcinoma by statistical analysis of 17 parameters in each patient. Validation based on this prediction formula yielded a hitting ratio of 80.4%. The number of BCG injections was minimized to avoid excessive side effects, and we determined the relationship between cancer recurrence, treatment and side effects. These results provide good practice guidelines for the treatment of individual patients.

Keywords: *Good practice, Knowledge model, BCG therapy, Recurrence, Urinary tract cancer*

1. Background

Bacillus Calmette-Guérin (BCG) therapy is regarded as one of a number of effective treatments for urothelial carcinoma and has been used in many patients as a gold standard. (Japanese Urological Association , The Japanese Society of Pathology , 2001) However, BCG causes severe side effects and therefore many patients prematurely terminate their treatment. Several studies have investigated the relationship between BCG dose and adverse events, and reported that a high dose (80 mg) causes more severe side effects than a lower dose (40 mg). However, many centers continue to use the highdose of BCG, based on previously established treatment guidelines, because a lower dose of BCG may result in recurrence. In this study, we used urinary cytology samples from patients with urothelial carcinoma who received BCG therapy and statistically analyzed 17 parameters to establish a formula for recurrence prediction. The formula that we established using "number of BCG dose"and "last positive time of cytology" (Okubo, 1997; Rishmann, 2006) was considered to be simple and useful.

2. Materials And Methods

2.1. Data Collection For Establishing A Formula For Recurrence Prediction

We selected those patients with urothelial carcinoma from all patients who had been treated at the Department of Urology, University of Occupational and Environmental Health, Japan between 1990 and 2004, and we then selected those patients who also received BCG treatment. Subsequently, we collected data from 650 medical records and 1632 urinary cytology samples, and determined 102 cases that could be statistically analyzed.

2.2. Collected Information And Establishment Of Parameters As Data Preprocessing

The following 17 variables were used (Table 1): "recurrence", "gender", "age", "BCG dose", "number of BCG doses", "last positive time of cytology", "BCG infusion into the bladder", "BCG infusion into the upper urinary tract", "histologic type of cancer", "cancer grade", "pain (side effect)", "pyrexia (side effect)", "bladder irritation (side effect)", "withdrawal of BCG treatment due to side effect", "status of urothelial carcinoma 2 or more years after the start of BCG therapy (prognosis)", "death due to diseases other than urothelial carcinoma 2 or more years after the start of BCG therapy (prognosis)", and "combination with other therapy". The recurrence rate after BCG therapy was investigated in order to assess the validity of the above variables for our patients. According to the Japan BCG Laboratory, among patients in Japan with bladder cancer who have received BCG therapy, 7–33% (Japan BCG Laboratory,1990) have a recurrence of their disease. Our data showed a recurrence rate of 26.2%; indicating that the results of the statistical analysis based on the above variables would be highly reliable. Cancer that recurred within 2 years after the start of BCG therapy was regarded as "recurrent". In addition, we regarded the appearance of tumor cells within 6 months of the start of BCG therapy as "residual tumors".

Table 1: Details Of 102 Experimental Cases

		Total	Non-recurrence	Recurrence
Gender	Male	84	40	44
	Female	18	8	10
BCG dose	40 mg	55	27	28
	80 mg	47	20	27
Cancer grade	Grade 2	32	18	14
	Grade 3	70	29	41
Histologic type of cancer	UC	88	10	78
	UC+others	14	4	10

Last positive time of cytology	40 mg	47	16	31
	80 mg	55	29	26

UC: urothelial carcinoma

3. Results

3.1. Multiple Linear Regression Analysis Using A Variety Of Parameters: Formula For Recurrence Prediction

In a multiple linear regression analysis, the presence and absence of recurrence was expressed as “0” and “1”, respectively, and a discriminative point as “0.5”. The independent variable that showed the highest coefficient of multiple determination in a multiple linear regression analysis with SPSS (SPSS 13.0 for Windows) was “last positive time of cytology”. Furthermore, the highest coefficient was obtained when both “last positive time of cytology” and “number of BCG doses” were used as independent variables in a regression model. The value of R^2 was 0.477, indicating that 47.7% of cases can be explained by these two independent variables. The two regression models, one with “last positive time of cytology” as an independent variable and the other with “last positive time of cytology and number of BCG infusions” as independent variables, were both statistically significant at the 0.01 level (Table 2).

The standard partial regression coefficient of “last positive time of cytology” had a positive influence (0.672), and its p value was very high (7.26E-05). The standard partial regression coefficient of “number of BCG doses” had a significant negative influence (-0.184), and its p value was high (0.013). The following formula for recurrence prediction was obtained through multiple linear regression analysis using SPSS:

Y = 0.661+0.133 * “last positive time of cytology” – 0.092 * “number of BCG doses”

Table 2: Established Parameters

Variables	Actual number	Dummy variable: 0
Presence of recurrence		Absent
Gender		Female
Age	Actual number	
BCG dose	Actual number	
Number of BCG doses	Actual number	
Last positive time of cytology	Actual number	
BCG infusion into the bladder		No
BCG infusion into the upper urinary tract		No
Histologic type of cancer		Single
Cancer grade	Actual number	
Pain (side effect)		Absent
Pyrexia (side effect)		Absent
Bladder irritation (side effect)		Absent
Withdrawal due to side effect		Absent
Conditions of urothelial carcinoma 2 or more years after the start of BCG therapy (prognosis)		Favorable
Death due to diseases other than urothelial carcinoma 2 or more years after the start of BCG therapy (prognosis)		Favorable
Combination with other therapies		TUR or biopsy alone

TUR: Transurethral resection of the bladder tumor

3.2. Evaluation Of The Validity Of The Formula For Recurrence Prediction

The validity of the formula for recurrence prediction was evaluated by statistical analysis of the data from the 102 cases. The formula was established based on the data from these 102 cases; however, we could not perform a true validation using these data alone. Therefore, to prove the robustness of our formula, the evaluation was performed using stored data from another 37 cases receiving BCG therapy at our center or other hospitals (Munakata Suikokai General Hospital, n=1; Kushu Rosai Hospital, n=10; Nippon Steel Yawata Memorial Hospital, n=4; Moji Rosai Hospital, n=8; and University Hospital of Occupational and Environmental Health, n=14). The hitting rate in these 37 cases was 86.5% (32/37), and in the 102 cases used for statistical analysis it was 80.4% (82/102). The hitting rate in all cases was 82.0% (114/139).However, we feared complications when using predictive discriminate in actual clinical settings and therefore developed a simplified chart (Table 3). The hitting ratio of recurrence prediction using this simplified chart for verification, statistical analysis, and all examples were 34/37 (91.9%), 91/102 (89.2%) and 125/139 (89.9%), respectively, and higher hitting ratio results were obtained than when using the formula for predicting the recurrence of cancer.

3.3. Recurrence And Side Effects Of BCG Therapy

Data about the three side effects of pain, fever, and bladder irritation symptom come from a previous investigation (Table 4). The number of BCG injections and the appearance of side effects is given in each case, and the presence or absence of recurrence is noted. If no side effects were reported, the side effect level was considered to be level 0, whereas it was considered to be level 3 if all three side effects.

Table 3: Simplified Chart

Last positive time / Injection time	0	1	2	3	4	5	6	7	8
1	0.753	0.702	0.835	0.968	1.101	1.234	1.367	1.500	1.633
2	0.577	0.610	0.743	0.876	1.009	1.142	1.275	1.408	1.541
3	0.462	0.518	0.651	0.784	0.917	1.050	1.183	1.316	1.449
4	0.354	0.426	0.559	0.692	0.825	0.958	1.091	1.224	1.357
5	0.248	0.334	0.467	0.600	0.733	0.866	0.999	1.132	1.265
6	0.142	0.242	0.375	0.508	0.641	0.774	0.907	1.040	1.173
7	0.036	0.150	0.283	0.416	0.549	0.682	0.815	0.948	1.081
8	-0.070	0.058	0.191	0.324	0.457	0.590	0.723	0.856	0.989
9	-0.176	-0.034	0.099	0.232	0.365	0.498	0.631	0.764	0.897
10	-0.282	-0.126	0.007	0.140	0.273	0.406	0.539	0.672	0.805
11	-0.389	-0.218	-0.085	0.048	0.181	0.314	0.447	0.580	0.713
12	-0.495	-0.310	-0.177	-0.044	0.089	0.222	0.355	0.488	0.621

Table 4 shows the relationship between cancer recurrence and side effects of BCG treatment. This table may be used for determining the next injecton in treatment with BCG.

4. Discussion

An inappropriate decision was made in five out of 37 investigated cases. Among them, three cases received radical cystectomy after BCG treatment (within 2 years after the start of BCG treatment), and it was highly probable that recurrence would have occurred in these cases if they had not received surgery.

Table 4: Relationship Between BCG Side Effect And Number Of The Appearances Of Positive Time

Side effect level	Recurrence	Number of the appearances of positive time								
		Last positive time of cytology								
		0	1	2	3	4	5	6	7	8
0	No	2	1	4	1	1	2	2	1	1
	Yes	0	0	0	1	0	0	0	0	7
1	No	3	2	5	5	1	3	0	1	0
	Yes	0	0	1	2	2	4	1	1	5
2	No	2	1	1	7	1	0	0	0	0
	Yes	0	0	0	3	1	1	4	1	2
3	No	0	0	3	2	0	0	0	0	0
	Yes	0	0	0	1	2	3	3	1	4

Urinary cytology was performed once a week during BCG therapy, and once every 6 months after the treatment. The inappropriate decision was made in the remaining two cases because the cytology finding at the last positive time did not meet the diagnostic criteria. In particular, a difference in classification between class III and IIIb was thought to result from the observers' subjective criteria of diagnosis based on the cytology results. It was very important to have a consensus of diagnostic criteria among observers making the diagnosis (e.g., which cellular findings should be taken into account for diagnosis).

As the recurrence prediction model established in this study was expressed as a linear function, its outcome differed from that of the sigmoid logistic curve that is generally used clinically. (Zlotta ,1994) reported that six or more BCG infusions are unnecessary because immunoreactions are maximized after the fourth infusion. However, immunoreactions differed among individuals in general. Table 5 shows the probability of side effects after each BCG injection. Urinary cytology represents the individual reaction of each patient to BCG. Therefore, it might be appropriate to individually determine the optimal number of BCG doses based on the results of cytology.

Table 5 Relationship Between Cancer Recurrence And BCG Side Effects

BCG injection time	Judgment of cytology	Probability of side effect appearing	Actual probability of recurrence	Prediction probability of recurrence	Recommended injection time and predictive
1	0	0.064	0.000	0.000	(4) 0.293
	1	0.073	0.000	0.000	(4) 0.426
2	0	0.276	0.000	0.058	(4) 0.426
	1	0.016	0.000	0.191	(5) 0.467
3	0	0.319	0.333	0.191	(5) 0.467
	1	0.127	0.333	0.324	(7) 0.416
4	0	0.064	0.833	0.324	(7) 0.416
	1	0.091	0.833	0.457	(8) 0.457
5	0	0.106	0.769	0.457	(8) 0.457
	1	0.145	0.769	0.590	(9) 0.498
6	0	0.043	0.900	0.590	(9) 0.498

	1	0.145	0.900	0.723	(11) 0.447
7	0	0.043	1.000	0.723	(11) 0.447
	1	0.546	1.000	0.764	(12) 0.488
8	0	0.021	1.000	0.764	(12) 0.488
	1	0.327	0.000	0.989	(14) 0.427

5. Conclusions

The results of this study could be used to determine the optimal number of BCG doses for prevention of cancer recurrence, while minimizing the side effects of treatment. As a method of resolving the drawbacks of using the same therapy for all patients, we recommend tailor-made medication based on our model for recurrence prediction. With regard to BCG dose, generally 40 or 80 mg is selected, and 80 mg has traditionally been preferred even though more severe side effects are reported; the issue of optimal BCG dose is still controversial. In our study, BCG dose was not a significant variable and there was no significant difference in the results of multiple linear regression analysis between the two doses (40 and 80 mg). We performed a chi-squared test between 40 and 80 mg, and the probability of cancer recurrence was slightly lower with 40 than with 80 mg. Therefore, we highly recommend the use of 40 mg BCG (see Table1). This suggested the multiple low-dose infusion of BCG as an optimal BCG therapy protocol.

The relationship between cancer recurrence and treatment side effects has been investigated in this study.

6. References

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