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ORIGINAL ARTICLE

Immunological treatment of superficial bladder carcinoma

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Summary

Purpose: *To determine the effect of intravesical bacillus Calmette-Guerin (BCG) therapy in relation to recurrence of superficial bladder cancer after transurethral resection (TUR).*

Patients and methods: *During the period 1996-2001 patients who underwent TUR were randomized to have adjuvant BCG treatment (intravesically and subcutaneously) (43 patients) or TUR alone (43 patients). Eighteen patients of the latter group were crossed-over to BCG group because of frequent recurrences. These 61 BCG-treated patients were the focus of this report. All of them presented with papillary noninvasive (stage Ta) or superficially invasive (stage T1) tumours (grades 2 and 3), with or without associated carcinoma in situ (Tis).*

Results: *A total of 19 (31%) patients remain free of tumor, 17 (28%) had superficial recurrences and 25 (41%) had disease progression, first identified as muscle invasion in 12, prostatic involvement in 8 and metastasis in 5. Most tumors recurred or progressed within the first 5 years. Of the 61 patients 33 (54%) are disease-free and with intact bladder, 13 (21%) are disease-free after cystectomy, 2 (3%) died of other causes, 1 (2%) is alive with metastasis and 12 (20%) died of metastatic urothelial cancer.*

Conclusion: *BCG has been shown to be effective for prophylaxis against tumor recurrence and appears to be more useful in the treatment of patients with Tis. Intravesical BCG in conjunction with TUR may be effective in the treatment of patients with Tis involving the prostatic urethral mucosa. The mechanism by which BCG exerts its antitumor effect seems to be immunologically-mediated. Based upon our current data we believe the potential for long-term bladder preservation, progression-free and overall survival justifies the risk and cost of BCG therapy and frequent follow-up evaluations for most patients with superficial bladder cancer.*

Key words: BCG therapy, bladder cancer, recurrence, superficial, transurethral resection

Introduction

Bladder cancer is the second most common cancer of the genitourinary tract. The average age at diagnosis is 65 years. At that time, approximately 85% of the patients have disease localized to the bladder. At initial presentation, approximately 50-70% of bladder tumors are superficial-stage Tis or Ta [1]. Invasion into the lamina propria or muscle layer is identified in a smaller number of patients, approximately 28% and 24%, respectively; regional or distant metastases are found in approximately 15% of the patients [2].

Ninety-eight per cent of all bladder cancers are epithelial malignancies, with the majority (98%) being transitional cell carcinomas. These tumors commonly appear as papillary exophytic lesions; less commonly they may be sessile or ulcerated.

The most common presenting symptom of bladder cancer is painless hematuria, which occurs in about 85 % of the patients. The combination of bladder irritability with urinary frequency, urgency and dysuria is the second most common form of presentation. Other signs and symptoms of bladder cancer include flank pain from ureteral obstruction, lower extremity edema, and a pelvic mass. Occasionally patients present with symptoms of advanced disease, such as weight loss and abdominal or bone pain [3].

In the majority of patients with superficial bladder cancer, tumors recur. Because a certain percent-

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age of these are of higher stage or grade, attempts to reduce recurrence should be undertaken. Immuno- or chemotherapeutic agents can be instilled into the bladder directly via catheter, thereby avoiding the morbidity of systemic drug administration in most cases.

The treatment of superficial bladder cancer includes TUR and adjuvant therapies [4].

Transurethral resection: most patients with superficial bladder cancer can be adequately treated with TUR. The overall survival rate is excellent (5-year survival approximately 70%) [3,5,6].

Adjuvant therapies: a variety of treatments have been employed as adjuvant therapy in patients with superficial bladder cancer to prevent recurrence and progression of cancer. These include: intravesical chemotherapy; systemic chemotherapy; intravesical immunotherapy with interferon, BCG and other agents; photoradiation therapy; laser therapy; and vitamin therapy. Other treatments such as radiation, hyperthermia and hydrostatic pressure have been tested, but have not been adopted for general use [7].

Adjuvant intravesical therapy: either adjuvant intravesical chemotherapy or intravesical immunotherapy are indicated in patients who are at high risk for tumor recurrence by virtue of having recurrent tumors, multiple tumors, high grade tumors associated with urothelial atypia or Tis. Thiotepa and BCG are the least expensive intravesical agents available [8-10]. Doxorubicin has an intermediate cost [8,9,11,12] and mitomycin C is the most expensive [8,9,13]. BCG currently appears to be the most effective agent for intravesical use, but the optimum strain, dose schedule, and route of administration have not been determined. Patients who fail treatment with one intravesical agent may be managed successfully with a different agent. BCG is commonly given in three clinical settings: 1. Prophylaxis in tumor-free patients; 2. Treatment of residual tumor in patients with papillary transitional cell carcinoma other than Tis; 3. Treatment of patients with Tis [14].

The exact mechanism by which BCG exerts its antitumor effect is unknown, but it seems to be immunologically mediated. Mucosal ulceration and granuloma formation are commonly seen after intravesical instillation. Activated helper T lymphocytes can be identified in the granulomas and interleukin-2 reportedly can be detected in the urine of treated patients [8,15-19].

Patients and methods

The objective of this study was to determine the effect of BCG treatment on the recurrence of superficial bladder cancer after TUR. During the period 1996-2001 43 patients were randomized to have TUR plus BCG and 43 to TUR alone. Of the control group (TUR alone) 18 patients were crossed-over to the BCG arm after 6 months to 1 year because of frequent tumor recurrences. These 61 BCG-treated patients have been followed for a minimum of 5 years and were the focus of this report. All of them had papillary noninvasive (stage Ta) or superficially invasive (stage T1) tumors (grades 2 and 3), with or without associated Tis.

BCG (Armand Frappier substrain) was administered intravesically (120 mg in 50 ml saline) and percutaneously (5×10^7 units). Treatment begun 2-4 weeks after complete TUR of overt papillary lesions and continued weekly for 6 weeks. BCG treatments were repeated intravesically at the same induction dosage and schedule. No patient received maintenance BCG. Patients were followed every 3-4 months thereafter with cystoscopy, biopsy or TUR and urine cytology. After 5 years, disease-free patients were generally evaluated at 6-month intervals.

Endpoints selected for analysis included number of patients with and without superficial (stages Ta, Tis and T1) recurrences, number of patients with disease progression and the time to progression, and survival from the initial BCG treatment. Tumor progression was defined as muscle invasion (stage T2+), metastasis (M+) or prostatic involvement (stage T4p). Prostatic disease included noninvasive urethral and/or ductal carcinoma and stromal invasion.

For the collection of data a special file was constructed, and the following data were recorded: name, age, sex, anamnesis, symptomatology, date of clinical onset, results of laboratory examinations (full blood count, erythrocyte sedimentation rate, fasting blood sugar, serum urea and creatinine, urine examination, urine culture) and radiological investigations.

Results

Patient characteristics are listed in Table 1. Of the 61 patients 34 (56%) had stage Ta and 27 (44%) had stage T1 tumors. A total of 44 (72%) patients had coexisting Tis proved by biopsy and positive urine cytology, and they received BCG therapeutically. The other 17 patients underwent resection of papillary lesions only, and they had negative post-TUR cytology studies and received prophylactic BCG. Forty-one patients received 1 course of BCG, 14 received 2 and 6 patients received 3 6-week treatments. The average interval between BCG treatments was 26 months. Sequential BCG courses (i.e. 12 consecutive weeks) were not given.

A total of 19 (31%) patients remained free of recurrence and progression for more than 10 years after

Table 1. Patient, tumor and therapy characteristics (n=61)

Characteristic		
Age, yrs		
median (range)	63	(34-77)
Males / females	47/14	
Initial T stage (patients, n)		
Ta	11	
Ta + T1a	23	
T1	6	
T1 + T1a	21	
No. BCG treatment (patients, n)		
1	41	
2	14	
3	6	
Patients without tumor progression, n (%)		
no recurrence	19	(31)
recurrence	17	(28)
Stage on progression, n (%)		
T2+	12	(20)
T4 (p)	8	(13)
M+	5	(8)
Total	25	(41)
Follow up (yrs)		
median (range)	11.9	(10-13)

TUR and 1 course of BCG: 1 had stage Ta, 6 had stage Ta+Tis, 1 had stage T1 and 11 had stage T1+Tis disease. Another 17 (28%) patients had recurrent superficial bladder tumors but no progression during the 10-year period. These patients received BCG initially for stage Ta tumors (n=6), stage Ta+Tis (n=5) and stage T1+Tis (n=6).

The outcome of these 36 patients without progression is shown in Table 1. The number of patients with positive cystoscopic evaluations showing recurrent tumor indicates that the tumor recurred most often within the initial 5 years, (the majority were seen within 2 years). Eight patients had recurrence(s) before but none after 5 years, 2 had no recurrences within 5 years, only to suffer recurrent disease at 6 and 7 years, and 7 had sporadic recurrences during the entire 10^+ -year period. The trend was toward fewer recurrences among fewer patients after 5 and up to 10 years of follow up. Recurrences were generally easily controlled by TUR, which was supplemented in some patients with Tis by additional BCG. No patient underwent cystectomy for recurrent superficial bladder tumor alone. Only 1 patient in this group died of metastatic renal pelvis cancer. There was no difference in the initial T stage among patients who did or did not have superficial tumor recurrence.

Progression occurred in 25 (41%) patients: 12 (20%) with muscle invasion, 8 (13%) with prostatic involvement and 5 (8%) with distant metastasis (Table 1). The distribution in initial T stages (stage Ta in 5, stage Ta+Tis in 10, stage T1 in 4 and stage T1+Tis in 6) did not differ from those in patients without progression. Tumor progressed most often within 5 years, although 3 patients had muscle-infiltrating tumors at 6, 8 and 9 years, respectively. No tumor progressed after 10 years. Of the 25 patients 8 (32%) had superficial bladder recurrences at the time or within 6 months before disease progression was documented. The other 13 (52%) patients had *de novo* progression as this was not heralded by a pattern of prior recurrence. Of the 12 patients with stage T2+ tumors, 4 had superficial lesions 3-6 months previously, and in 3 this was a stage T1 tumor. Radical cystectomy (TUR in 1 patient) salvaged all but 1 patient with progression only in the bladder or prostate. None of the patients with metastasis (with or without local disease) survived beyond 5 years despite chemotherapy administration.

A muscle-infiltrating (stage T2+) tumor developed in 12 patients at an average of 33 months after BCG therapy. Four patients had metastases at the time or within 3 months of detection of the bladder cancer and 1 had metastases from an invasive bladder tumor after 8 years. The median interval to stage T2+ progression in this group was 26 months. Seven patients had no distant disease when stage T2+ bladder tumor occurred. The median interval to invasion among these patients was 45 months. All patients remain disease-free after salvage therapy with TUR and intravesical BCG.

Table 2 shows the outcome of 8 patients with progression in the prostate: prostatic transitional carcinoma was diagnosed within 5 years in 5, and 3 had disease at 5, 7 and 9 years, respectively. The presence or absence of concomitant bladder tumor recurrence was a poor predictor of subsequent prostatic disease, since the bladder was free of disease in 6 patients when the prostatic tumor was documented. One patient with stromal invasion died but the other 7 (5 with noninvasive ductal tumor and 2 with stromal invasion) were salvaged with cystoprostatectomy.

Table 3 shows characteristics of the 12 patients who died of urothelial cancer. All 12 patients died of metastases emanating from the bladder or upper urothelial tract. Five patients had metastases without an invasive bladder tumor, although 4 had had prior superficial recurrences. The other 7 patients had concomitant local and systemic progression, which in 5 was not heralded by a pattern of recurrent superficial tumors. If we assume that distant metastases appearing within 2 years of BCG therapy were from the original bladder tumor (4 patients), then 7 of these patients might have been saved if cystectomy had been performed initially.

Discussion

Assessing the impact of conservative management

Table 2. Outcome of patients with progression in the prostate

Initial T stage	*Type of progression*	*Time to progression (months)*	*Treatment of progression*	*P stage*	*Overall survival (yrs)*	*With bladder recurrence*
Ta+Tis	Noninvasive prostatic Ca involving urethra or ducts	14	Radical cystectomy	P0	13	No
T1	Stromal invasion	40	Radical cystectomy	P4	11	Yes
Ta+Tis	Noninvasive prostatic Ca involving urethra or ducts	16	Radical cystectomy	P0	12	No
Ta	Stromal invasion	10	Radical cystectomy	Pis, N+	11	No
Ta	Noninvasive prostatic Ca involving urethra or ducts	60	Radical cystectomy	P0	12	Yes
T1+Tis	Stromal invasion	48	Systemic chemotherapy	–	Dead of disease	No
T1+Tis	Stromal invasion	108	Radical cystectomy	P4	10	No
T1+Tis	Noninvasive prostatic Ca involving urethra or ducts	84	Radical cystectomy	Pis	10	No

on tumor recurrence, progression and survival in patients with superficial bladder tumors is compromised by the often long natural history of the disease, the competing mortality in the age groups concerned, and the lack of studies providing long-term follow-up. Can some patients be cured, or at least maintain a functioning bladder for more than 10 years? Are enough patients with progression salvaged to justify the initial conservative approach?

Of the 61 patients followed for at least 10 and up to 13 years 33 (54%) have a functioning bladder (albeit half required local therapy for tumor recurrence), 13 (21%) are disease-free after cystectomy, 2 (3%) are dead of unrelated causes, 1 (2%) is currently alive with metastatic disease and 12 (20%) died of metastatic bladder/prostate (11) or upper tract (1) urothelial cancer. Progression of bladder cancer was noted more often within the initial 5 years, suggesting that surveillance should be particularly intense during this interval even among patients without superficial recurrence. Tumor progression after 5 years and up to 10 years was sufficiently common to make lifelong surveillance for panurothelial cancer a necessity in such patients [20-22].

A total of 11 (18%) patients had upper urothelial tract tumors from 1.5 to 9 years after BCG treatment: in 2 metastasis originated from a renal pelvis tumor, while 9 were salvaged with either distal ureterectomy

Table 3. Patients dead of bladder cancer

Initial stage	*Superficial recurrence*	*Type of progression*	*Time to progression (months)*	*Treatment of progression*	*Overall survival (yrs)*
T1*	No	T2+M$^+$	32	Systemic chemotherapy	3.4
Ti	Yes	M$^+$	3	Systemic chemotherapy	1
Ta+Tis	No	M$^+$	15	Systemic chemotherapy	1.8
Ta+*	Yes	T2+M$^+$	24	Systemic chemotherapy	2.3
T1+Tis	Yes	M§	96	—	9
Ta+Tis*	Yes	TisM$^+$	72	Systemic chemotherapy	8
Ta+Tis	Yes	M$^+$	7	Systemic chemotherapy	2
T1*	Yes	M$^+$	24	Systemic chemotherapy	3
T1+Tis	No	T2+M$^+$	18	Systemic chemotherapy	2.5
Tis*	No	T2+M$^+$	96	Systemic chemotherapy	9
T1+Tis*	No	T4P†M$^+$	48	Systemic chemotherapy	5
Ta+Tis*	No	T1M$^+$	24	Systemic chemotherapy	2

*patients who might survive with earlier cystectomy; §Metastases from renal pelvis tumor; †prostate infiltration; M=distant metastasis

or nephroureterectomy. These patients will be the subject of a separate report.

The initial T stage and the presence or number of subsequent superficial bladder tumor recurrences did not correlate with progression. An average of 12 cystoscopy studies identified an average of 38 tumors among patients with superficial recurrences but no progression compared to 5 positive cystoscopy studies showing 14 superficial tumors among patients with progression. Furthermore, because so many of the patients (72%) had associated Tis, the impact of multifocal disease upon recurrence and progression rates cannot be well evaluated [23].

Why did these high risk patients have a progression rate of less than 50% during 10 years, a high rate of salvage when nonmetastatic progression occurred and a favorable overall survival?

An explanation might be the selection of patients with tumors having a long natural history and a low rate of metastasis, even in the event of local progression. Against this possibility is the fact that all of these patients entered into a randomized prospective trial in which 95% of the control population had progression (including 37% who had muscle-infiltrating tumor) within 12 months. This fact suggests that BCG may have conferred a durable protective effect against new tumor formation within regenerating bladder epithelium. In support to this observation is the decrease in tumor recurrence and progression rates in patients followed longer than 5 years, and the increasing detection with time of extravesical urothelial disease involving the upper urinary tract and prostate. Local BCG administration might not be expected to alter favorably neoplastic or preneoplastic events occurring at these sites.

The results of this study are due most likely to a combination of factors, including an initial vigorous transurethral resection and the use of prophylactic or therapeutic BCG directed against minimal (Tis) disease, careful surveillance, repeat complete TUR with adjunctive BCG as needed, and early detection of tumor progression. While not preserving bladder function, salvage cystectomy contributed significantly to improved survival. An alternative explanation is that patients who had progression with new muscle-infiltrating tumors after a history of recurrent superficial disease may have had a biologically more favorable tumor that is associated with *de novo* muscle invasion.

The short interval (average 33 months) to metastatic progression and the fact that not all patients (6 of 12) had evident cancer in the bladder at the time of metastasis suggest understaging of the primary tumor and/or unrecognized metastasis at initial diagnosis and treatment. Alternatively, it must be recognized that in some cases superficial tumors, especially stage T1 cancers, may not be adequately controlled with TUR and BCG, leading to undetected local progression and metastasis. That may have been the case in the patient who had relapse after 8 years with infiltrating disease in the bladder and concomitant distant dissemination. Thus, this patient coupled with the other 6 who had metastases after the development of progression in the bladder (5) or prostate (1) suggests, with an overall probability of 11% (7 of 61), that earlier cystectomy might have prevented a cancer death.

If we optimistically assume that early radical cystectomy in all 61 patients would have salvaged all 11 (18%) who had metastases from the bladder, and take into account the 13 (21%) who were saved with delayed cystectomy, there remain 37 (61%) patients who would have lost the bladder unnecessarily. Therefore, the overall risk of cancer death as a result of conservative bladder-sparing therapy in this high risk group was 18%. Against this risk must be weighed the cost of preserving bladder (and sexual) function, including frequent surveillance, multiple invasive diagnostic and therapeutic procedures, and risk of extravesical disease, which at least–in cases involving the distal ureters and prostate–probably would be prevented by cystectomy [24]. Based on our current data, we believe the potential for long-term bladder preservation, progression-free and overall survival justifies the risk and cost of BCG therapy and frequent follow-up evaluations for most patients with recurrent superficial bladder cancer [25].

The results of our study are concordant with those of other studies and the international literature.

In the majority of patients with superficial bladder cancer, tumors recur. Because a certain percentage of these are of higher stage or grade, attempts to reduce recurrence should be undertaken. Immuno- or chemotherapeutic agents can be instilled into the bladder directly via catheter, thereby avoiding the morbidity of systemic administration in most cases. BCG has been shown to be effective for prophylaxis against tumor recurrence [8,9,15,17,26].

It appears to be more useful in the treatment of patients with Tis. Intravesical BCG in conjunction with TUR resection may be effective in the treatment of patients with Tis involving the prostatic urethral mucosa [3,8,17,26].

The exact mechanism by which BCG exerts its antitumor effect is unknown, but it seems to be immunologically-mediated. Mucosal ulceration and granuloma formation are commonly seen after intravesical instillation. Activated helper T lymphocytes can be identified in the granulomas, and interleukin-2 reportedly can be detected in the urine of treated patients [8,17,27].

Therefore, the overall risk of cancer death as the

result of conservative bladder-sparing therapy in this high risk group was 18%. Against this risk must be weighed the cost of preserving bladder (and sexual) function, including frequent surveillance, multiple invasive diagnostic and therapeutic procedures, and risk of extravesical disease, which at least in cases involving the distal ureters and prostate probably would be prevented by cystectomy. Based upon our current data we believe the potential for long-term bladder preservation, progression-free and overall survival justifies the risk and cost of BCG therapy and frequent follow-up evaluations for most patients with recurrent superficial bladder cancer [8,17].

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References

1. Cutler SJ, Heney NM, Friedell OH. Longitudinal study of patients with bladder cancer: Factors associated with disease recurrence and progression. In: Bonney WW, Prout OR (eds). Bladder Cancer. AUA Monographs. Williams and Wilkins 1982; pp 124-132.
2. Liotta LA, Rao CN. Tumor invasion and metastases. Cancer Res 1986; 27: 183-192.
3. Farrow GM, Utz DC, Rife CC, Greene LF . Clinical observations in 69 cases of in situ carcinoma of the urinary bladder. Cancer Res 1977; 37: 2794-2798.
4. Badalament RA, Fair WR, Whitmore WF Jr, Melamed MR. The relative value of cytometry and cytology in the management of bladder cancer: The Memorial Sloan-Kettering Cancer Center experience. Semin Urol 1988; 6: 22-30.
5. Dretler SP. Ragsdale BD, Leadhetter WR. The value of pelvic lymphadenectomy in the surgical treatment of bladder cancer. J Urol 1973; 109: 414-416.
6. Montie JE, Straffon RA, Stewart BH. Radical cystectomy without radiation therapy for carcinoma of the bladder. J Urol 1984;131:477-482.
7. Housset M, Maulard C, Chretien Y et al. Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: A prospective study. J Clin Oncol 1993;11:2150-2157.
8. Herr HW, Laudone VP, Whitmore WF Jr. An overview of intravesical therapy for superficial bladder tumors. J Urol 1987;138:1363-1368.
9. Kowalkowski TS, Lantm DL. Intravesical chemotherapy of superficial bladder cancer. In: Resnick M (ed). Current Trend- Urology. Williams & Wilkins 1988, pp 153-154.
10. Prout GR, Koontz WW Jr, Coombs LJ, Hawkins IR, Friedell GH. Long-term fate of 90 patients with superficial bladder cancer randomly assigned to receive or not to receive thiotepa. J Urol 1983; 130: 677-680.
11. Logothetis CJ, Johnson DE, Chong C et al. Adjuvant cyclophosphamide, doxorubicin, and cisplatin chemotherapy for bladder cancer: An update. J Clin Oncol 1988; 6: 1590-1596.
12. Logothetis CJ, Samuels ML, Ogden S et al. Cyclophosphamide, doxorubicin and cisplatin chemotherapy for patients with locally advanced urothelial tumors with or without nodal metastases. J Urol 1985; 134: 460-464.
13. Soloway MS. Diagnosis and management of superficial bladder cancer. Semin Surg Oncol 1989; 5: 247-254.
14. Badalament RA, Gay H, Whitmore WF Jr et al. Monitoring intravesical BCG treatment of superficial bladder carcinoma by serial flow cytometry. Cancer 1986; 58: 2751-2757.
15. Badalament RA, Herr HW, Wong GY et al. A prospective randomized trial of maintenance versus non-maintenance intravesical bacillus Calmette-Guerin therapy of superficial bladder cancer. J Clin Oncol 1987; 5: 441-449.
16. Catalona WJ. Practical utility of specific red cell adherence test in bladder cancer. Urology 1981; 18: 113-117.
17. Herr HW, Pinsky CM, Whitmore WF Jr, Sogani PG, Oettgen HF, Melamed MR. Experience with intravesical bacillus Calmette-Guerin therapy of superficial bladder tumors. Urology 1985; 25: 119-123.
18. Hudson MA, Ratliff TL, Gillen DP, Haaff EO, Dresner SM, Catalona WJ. Single course versus maintenance bacillus Calmette-Guerin therapy for superficial bladder tumours: A prospective randomized trial. J Urol 1987; 138: 295-298.
19. Latnm DL. Complications of bacillus Calmette-Guerin immunotherapy. Urol Clin North Am 1992; 19: 549-565.
20. Fradet Y, Tardif M, Bourget L, Robert J. Clinical cancer progression in urinary bladder tumors evaluated by multiparameter flow cytometry with monoclonal antibodies. Laval University Urology Group. Cancer Res 1990; 50: 432-437.
21. Heney NM, Ahmed S, Flanagan MJ et al. Superficial bladder cancer: Progression and recurrence. J Urol 1983; 130: 1083-1086.
22. Herr HW, Badalament RA, Amato DA, Landone VP, Fair WR, Whitmore WF Jr. Superficial bladder cancer treated with bacillus Calmette-Guerin: A multivariate analysis of factors affecting tumor progression. J Urol 1989; 141: 22-29.
23. Herr HW. Progression of stage T1 bladder tumors after intravesical bacillus Calmette-Guerin. J Urol 1991; 145: 40-43.
24. Cummings KB, Mason JT, Correa RJ Jr, Gibbons RP. Segmental resection in the management of bladder carcinoma. J Urol 1978; 119: 56-58.
25. Brettun PR. Intravesical bacillus Calmette-Guerin therapy for in situ transitional cell carcinoma involving the prostatic urethra. J Urol 1989; 141: 820-853.
26. Cokson MS, Sarosdy M. Management of stage T1 bladder cancer with intravesical bacillus Calmette-Guerin therapy. J Urol 1992; 148: 784-797.
27. Haaff EO, Catalona WJ, Ratliff TL. Detection of interleukin 2 in urine of patients with superficial bladder tumors after treatment with intravesical BCG. J Urol 1986; 136: 970-974.