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MAINTENANCE BACILLUS CALMETTE-GUERIN IMMUNOTHERAPY FOR RECURRENT TA, T1 AND CARCINOMA IN SITU TRANSITIONAL CELL CARCINOMA OF THE BLADDER: A RANDOMIZED SOUTHWEST ONCOLOGY GROUP STUDY

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ABSTRACT

Purpose: Bacillus Calmette-Guerin (BCG) immunotherapy has been widely accepted as the optimal treatment for carcinoma in situ and high grade superficial transitional cell carcinoma. However, controversy remains regarding the role of maintenance therapy, and its long-term effect on recurrence and progression.

Materials and Methods: All patients in the study had transitional cell carcinoma of the bladder with carcinoma in situ or an increased risk of recurrence. The criteria for increased risk were 2 or more episodes of tumor within the most recent year, or 3 or more tumors within 6 months. At least 1 week following biopsy of carcinoma in situ and resection of any stage Ta or T1 transitional cell tumors 660 patients were started on a 6-week induction course of intravesical and percutaneous Connaught BCG. Three months following initiation of BCG induction therapy 550 consenting patients were stratified by purified protein derivative skin test and the presence of carcinoma in situ, and then randomized by central computer to receive BCG maintenance therapy (maintenance arm) or no BCG maintenance therapy (no maintenance arm). Maintenance therapy consisted of intravesical and percutaneous BCG each week for 3 weeks given 3, 6, 12, 18, 24, 30 and 36 months from initiation of induction therapy. The 384 eligible patients who were disease-free at randomization constitute the primary intent to treat analytic group because they could be followed for disease recurrence. All patients were followed for adverse effects of treatment, recurrence, disease worsening and survival.

Results: No toxicities above grade 3 were noted in the 243 maintenance arm patients. The policy of withholding maintenance BCG from patients with increased side effects may have diminished the opportunity to observe severe toxicity. Estimated median recurrence-free survival was 35.7 months (95% confidence interval 25.1 to 56.8) in the no maintenance and 76.8 months (64.3 to 93.2) in the maintenance arm (log rank $p < 0.0001$). Estimated median time for worsening-free survival, defined as no evidence of progression including pathological stage T2 disease or greater, or the use of cystectomy, systemic chemotherapy or radiation therapy, was 111.5 months in the no maintenance and not estimable in the maintenance arm (log rank $p = 0.04$). Overall 5-year survival was 78% in the no maintenance compared to 83% in the maintenance arm.

Conclusions: Compared to standard induction therapy maintenance BCG immunotherapy was beneficial in patients with carcinoma in situ and select patients with Ta, T1 bladder cancer. Median recurrence-free survival time was twice as long in the 3-week maintenance arm compared to the no maintenance arm, and patients had significantly longer worsening-free survival.

KEY WORDS: bladder; carcinoma, transitional cell; bladder neoplasms; carcinoma in situ, immunotherapy

Adjuvant intravesical chemotherapy and immunotherapy with bacillus Calmette-Guerin (BCG) result in significantly better time to first recurrence compared to no adjuvant treatment.[1–3] Previous large randomized clinical trials performed by the Southwest Oncology Group (SWOG) have demonstrated that BCG immunotherapy provides significantly longer time to first recurrence compared to chemotherapy

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with doxorubicin[4] or mitomycin.[5] We evaluate a refinement in the use of BCG.

By continuing on a fixed schedule with additional courses of treatment, maintenance therapy has been conjectured to extend the benefit of adjuvant intravesical therapy. In the animal model re-treatment with BCG effectively reduced the growth of transplanted transitional cell carcinoma but only when sufficient time had lapsed for the immune stimulation of previous BCG treatment to wane.[6] An early clinical trial using a single quarterly BCG instillation resulted in a 4-fold reduction in recurrence from 1.9 to 0.49 tumors per 100 patient-months.[7] Other studies designed to compare maintenance BCG intravesical therapy using quarterly or monthly instillations and a single 6-week induction course were unable to document a benefit.[8,9] However, these studies were too small (statistically under powered) and too immature to support the conclusion that maintenance therapy had no benefit.

It has been assumed but not demonstrated to our knowledge that prolonging the time to first recurrence will prolong the time to worsening disease (for example progression) and also possibly survival. This assumption designates the time to first recurrence as a potential surrogate for longer term outcomes. However, a recent combined analysis of randomized clinical trials of intravesical chemotherapy for large and mature superficial bladder cancer failed to confirm long-term outcome benefits, despite differences in recurrence.[3] Thus, there is now strong evidence against a surrogate status for the time to first recurrence outcome.[10] In 1985 SWOG investigators initiated a randomized clinical trial of adjuvant maintenance BCG immunotherapy to assess whether it is beneficial compared to no maintenance following standard induction therapy.

METHODS

Patient eligibility. Patients were required to have histologically confirmed transitional cell carcinoma of the bladder within 6 months before enrollment in the study. Papillary tumors had to have been completely resected and classified as stage Ta (noninvasive urothelial confined) or T1 (lamina propria invasion) disease. All patients were required to have an increased risk of recurrence defined as 2 tumors (primary and recurrent or 2 recurrences) within 1 year, 3 or more within the most recent 6 months and/or carcinoma in situ on at least 1 random biopsy. Patients with carcinoma invading the detrusor muscle (stage T2 or higher), those previously treated with radiation therapy for bladder cancer, those planning to undergo concomitant chemotherapy or radiation therapy and those who had received previous BCG treatment for bladder cancer were excluded from study. However, patients who had received other intravesical treatments were eligible to participate. Adequate liver function was required as determined by bilirubin less than 2.0 mg.%. All patients had to be available for long-term followup. Written informed consent describing the investigational nature of the protocol was signed in accordance with institutional and Food and Drug Administration guidelines.

Treatment. At least 1 week following tumor resection patients received induction therapy of 81 mg. (120 mg. wet weight, $10.5 \pm 8.7 \times 10^8$ colony-forming units) Connaught BCG. The lyophilized BCG was suspended in 50.5 cc physiological bacteriostatic-free saline for irrigation. After draining the bladder with a catheter 50 cc of the suspension were instilled and the catheter was withdrawn. Patients were instructed to lie on the abdomen for 15 minutes and retain the suspension if possible for 2 hours. At the same time percutaneous BCG was administered by cleansing the inner thigh with alcohol, applying 0.5 cc (containing approximately 10^7 colony-forming units) BCG suspension and puncturing the skin 3 times with a sterile 28 gauge needle. The alternate thigh was used for each subsequent treatment. Intravesical and percutaneous treatments were repeated each week for 6 weeks. In patients with transitional cell carcinoma of the prostatic urethra 5 cc BCG suspension were instilled in the prostatic urethra as the catheter was removed and a Cunningham clamp was applied for 2 hours.

Randomization. Patients who completed the induction course underwent purified protein derivative skin testing, were stratified by the outcome (less than 5 or 5 mm. or greater induration) and initial carcinoma in situ status (absent or present at study enrollment), and were then randomized to a BCG maintenance or no maintenance arm. It was intended that no maintenance arm patients receive no further therapy except for residual or recurring disease. The maintenance arm patients were treated with sets of 3 successive weekly intravesical and percutaneous administrations of BCG 3 months, 6 months and every 6 months to 3 years from the start of induction therapy. Randomization with dynamic balancing based on stratifications was performed using a central computer at the SWOG Statistical Center.[11]

Followup. Patients were followed for adverse response to treatment with limited history and physical examination before treatment and at cystoscopy, and as indicated. Purified protein derivative skin tests, complete blood counts, serum creatinine and liver function tests were repeated at cystoscopy. Patients with extant disease (primarily carcinoma in situ) were assessed for response to treatment with cystoscopy, urinary cytology and bladder biopsy. In tumor-free cases cystoscopy and urinary cytology were repeated at 3-month intervals for 2 years, 6-month intervals for 2 years and yearly thereafter. Patients with carcinoma in situ underwent bladder biopsy at 3 and 6 months, and thereafter only if indicated by suspicious urinary cytology or cystoscopy. Patients with visible recurrence underwent tumor resection with confirmation by pathological examination.

Efficacy end points. Complete response of carcinoma in situ was defined as histological disappearance of malignancy on bladder biopsy and resolution of abnormal cytology. In patients without carcinoma in situ and those with complete response of carcinoma in situ to BCG the primary criterion for treatment efficacy was recurrence-free survival. Disease progression was also assessed. Since therapeutic interventions were often instituted before biopsy confirmed stage progression, an outcome designated as disease worsening was used, which was defined as biopsy evidence of stage T2 or higher disease, or initiation of a change in treatment strategy implying impending progression or worsening. Evidence of the latter included cystectomy, systemic chemotherapy, radiation therapy or other therapy indicative of abandonment of strategies for treatment of superficial disease. All patients were followed until death.

Study design considerations. The study design included an induction therapy period of approximately 3 months, after which patients were randomized as described previously. Our goal was to assess whether maintenance therapy is beneficial for patients with superficial bladder cancer who have no evidence of disease following induction therapy. We focused on the primary efficacy assessment of maintenance therapy and, therefore, patients who had evidence of disease at randomization were not included in the primary analysis. Since no evidence of disease status at randomization was independent of the randomization process, focusing on patients with no evidence of disease at randomization did not bias our results.

Statistical methods. The primary end point for comparison of the treatment arms is recurrence-free survival. Median recurrence-free survival of approximately 2 years was observed in a previous SWOG study, and so this was used in the trial size computations for the no maintenance arm. Approx-

imately 400 patients would be required to detect a 50% or more improvement in median recurrence-free survival with a type 1 error probability of 0.05 (1-sided) and a power of 0.8.[12] The 3 interim analyses were planned for increments of 100 enrolled patients.[13] The levels of significance for formal interim analyses were 0.003, 0.004 and 0.005, and the significance level for the final analysis was to be 0.048 to preserve an overall type 1 error probability of 0.05. The study was not terminated before reaching its accrual goal.

The primary analyses were by arm (intent to treat) using the stratified 1-sided log rank test on the eligible patients with no evidence of disease at randomization.[14] The stratifications were carcinoma in situ at induction registration (yes/no) and purified protein derivative status at randomization (positive/negative). The 1-sided testing was used because the trial was designed to ascertain whether maintenance BCG improved outcome. Time to recurrence, worsening of disease and death were measured from the date of randomization. Exploratory analyses of failure time outcomes in the presence of covariates were performed using Cox proportional hazards regression.[14]

Previous presentations of trial results have emphasized the significant improvement in recurrence-free survival in the maintenance arm.[15–17] The present study updates and extends previously reported results, including an analysis of long-term outcomes not defined in the original protocol. The trial was closed to registration more than 10 years ago. Long-term outcomes allow clinicians to assess the trade-offs inherent in implementing maintenance therapy, namely greater toxicity and significant patient inconvenience.

RESULTS

Patient characteristics. Of the 660 patients from 81 SWOG institutions registered to undergo induction BCG immunotherapy from December 1985 to December 1988, 550 were subsequently randomized in our study. Of the patients 5 with no maintenance and 7 with maintenance therapy were declared ineligible based on information ascertained before randomization, and 78 and 76, respectively, had evidence of disease at randomization and, therefore, they were not included in the primary analyses. Thus, outcomes for the 192 eligible patients with no evidence of disease in each treatment arm were compared. Demographic and descriptive statistics for the 284 patients are shown in table 1. There was no evidence of significant randomization imbalance for race, age, presence of carcinoma in situ or positive purified protein derivative status.

Failure time analyses. Figure 1 shows the Kaplan-Meier plots of recurrence-free survival, worsening-free survival and survival by randomized arm. The stratified log rank statistic for recurrence-free survival was $p < 0.0001$, providing evidence that maintenance therapy provides benefit with respect to delaying recurrence. Death without recurrence was noted in 49 of the 250 recurrence or death events. Details of the analysis of recurrence-free survival, worsening-free survival and survival by arm are shown in table 2.

TABLE 1. *Demographic and descriptive statistics for the randomized eligible patients with no evidence of disease at randomization*

	No Maintenance		Maintenance	
No. pts.	192		192	
No. men (%)	173	(90.1)	159	(82.8)
No. black men (%)	8	(4.2)	6	(3.1)
Mean age at induction registration (quartile range)	67.0 (62–73)		66.8 (62–72.5)	
No. Ca in situ at induction (%)	66	(34.4)	64	(33.3)
No. purified protein derivative at randomization (%)	104	(54.2)	106	(55.2)

The stratified log rank statistic for worsening-free survival was $p = 0.04$ (table 2). Although the criterion for judging the significance of this value was not defined by the protocol, the small p value suggests that maintenance therapy may have a benefit with respect to a longer time to worsening disease. Further followup (more events) could lead to a stronger conclusion. For survival $p = 0.08$, providing a weak suggestion that further followup (more events) may lead to a significant difference in survival. The 5-year survival was 78% in the no maintenance compared to 83% in the maintenance arm.

Detailed exploratory analyses of these 3 event time outcomes were performed using proportional hazards regression modeling. Other than the previously noted relationships between outcome and randomized arm, there were no other notable covariate relationships. In particular, neither carcinoma in situ nor purified protein derivative status was significant in any model, indicating that these prospective stratification factors were not prognostic.

Toxicity. There were 2 previously reported BCG related deaths due to systemic infection among the 599 patients evaluated for induction period toxicities.[18] No toxicities above grade 3 were noted in the maintenance arm. Only 16% of the 243 maintenance cases received all 8 scheduled maintenance courses during 3 years.

Carcinoma in situ response. The trial was not specifically designed to evaluate the response of carcinoma in situ to maintenance therapy but the study design did permit evaluation of complete response rates between arms. A total of 278 eligible patients with carcinoma in situ were registered to undergo induction therapy, of whom 141 (50.7%) had no evidence of disease (complete response) at the 3-month evaluation following treatment. Of the 278 cases 116 were randomized to the no maintenance arm and 117 to the maintenance arm. At 3 months no evidence of disease was noted in 66 no maintenance (56.9%) and 64 maintenance (54.7%) arm patients. As expected the difference in the response rate with equal treatment was not significant ($p = 0.8$). Ultimately an additional 13 maintenance arm patients with carcinoma in situ had no evidence of disease, for an overall response rate of 68.1% (79 patients). An additional 34 maintenance arm patients had no evidence of disease as a result of additional therapy, for an overall response rate of 83.8% (97 patients). The between arm difference for the overall rate of carcinoma in situ response was significant at $p = 0.004$. Thus, for nonresponding carcinoma in situ there was strong evidence of the benefit of additional BCG instillations. The previously presented analysis of recurrence-free survival showed a benefit to giving additional BCG instillations to patients with carcinoma in situ with response after the first 6 weekly instillations.

Comparison to other SWOG studies. Figure 2 shows a Kaplan-Meier comparison of recurrence-free survival in patients without carcinoma in situ with arms designated OBS8507 (no maintenance) and BCG8507 (maintenance), the BCG arm of the SWOG previous study of BCG versus doxorubicin designated BCG8216 and the BCG arm of the SWOG subsequent study of BCG versus mitomycin C designated BCG8795.[4,5] Treatment for the BCG8216 arm consisted of intravesical and percutaneous Connaught BCG weekly for 6 weeks with single maintenance treatments every 3 months for 2 years. The BCG8795 arm received intravesical Tice BCG weekly for 6 weeks and then monthly for 11 months beginning at week 8. Except for the comparison between OBS8507 and BCG8507, there is no basis for assuming that patients in the arms are comparable except that they were enrolled by SWOG institutions using similar eligibility criteria. However, they are likely to be more similar than if they had come from independent sources because entry criteria and patient sources were similar among trials. The BCG8507 maintenance arm was clearly above all other arms and there are general similarities among the other 3

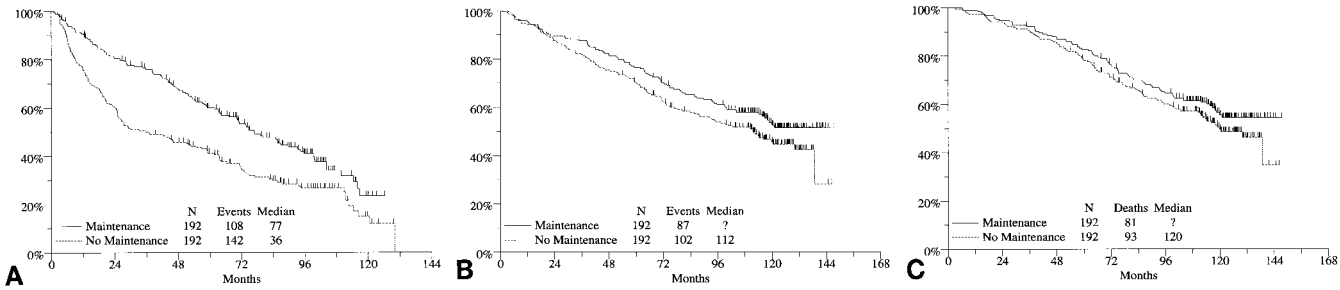

FIG. 1. Recurrence-free survival (*A*), worsening-free survival (*B*) and survival (*C*) in months by arm for eligible patients with no evidence of disease at randomization.

TABLE 2. *Results of time to event analyses for eligible patients with no evidence of disease at randomization*

	No Maintenance		Maintenance	
Recurrence-free survival (p <0.0001):				
Median mos. followup	91.4		87.7	
No. events	142		108	
Median mos. estimate (95% CI)	35.7	(25.1–56.8)	76.8	(64.3–93.2)
% 5-Yr. (95% CI)	41	(35–49)	60	(53–67)
Worsening-free survival (p = 0.04):				
Median mos. followup	120.3		119.1	
No. events	102		87	(too early)
Median mos. estimate (95% CI)	111.5	(too early)		
% 5-Yr. (95% CI)	70	(63–76)	76	(70–83)
Survival (p = 0.08):				
Median mos. followup	120.2		119.1	
No. events	93		81	(too early)
Median mos. estimate (95% CI)	119.8	(too early)		
% 5-Yr. (95% CI)	78	(72–84)	83	(77–88)

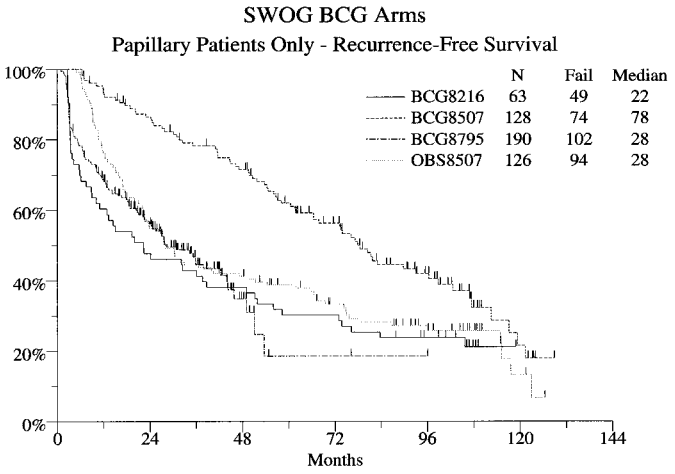

FIG. 2. Comparison of recurrence-free survival for patients without carcinoma in situ from various SWOG studies of BCG.

arms (fig. 2). This comparison suggests that previously reported results for monthly and quarterly single BCG instillations were not markedly different from those for our standard 6-week induction arm.

DISCUSSION

After Morales et al reported that adjuvant intravesical BCG reduced tumor recurrence in a historical study[19] randomized studies demonstrated that BCG was superior to surgery alone.[20,21] Previous SWOG studies have also demonstrated that BCG immunotherapy is superior to intravesical chemotherapy.[4,5] BCG is generally accepted as the treatment of choice for carcinoma in situ and rapidly recurrent or high risk stages Ta and T1 transitional cell carcinoma.

Previous randomized studies of maintenance schedules of intravesical chemotherapy[22,23] or BCG[8,9] have failed to demonstrate any significant advantage for maintenance schedules, although they were often too small for a negative conclusion. Our observation that 3-week maintenance BCG immunotherapy results in a disease-free survival more than twice as long (77 versus 36 months) provides evidence concerning the efficacy of BCG. This highly significant difference (log rank p <0.0001) in the disease-free survival time distributions demonstrates the superiority of the 3-week maintenance schedule compared to the commonly used 6-week induction.

Our extended followup provided an unusual opportunity to evaluate the long-term effects of maintenance BCG immunotherapy. In addition to a highly significant difference in recurrence, the maintenance arm had a significantly longer time to worsening disease or death (p = 0.04) and there was a suggestion of survival benefit (p = 0.08). In 2 randomized comparisons of induction or short maintenance BCG schedules versus surgery alone significant reduction in disease progression was also reported.[1,24] This finding is remarkable because the low hazards rate for progression in superficial bladder cancer cases makes it difficult to demonstrate disease progression effects.

Our demonstration of the long-term benefit of 3-week maintenance BCG is based on an intent to treat analysis. The significant results of our primary end point, recurrence-free survival, were previously reported.[15–17] Full publication of the extended results from this trial were postponed because early reports generated debate regarding the clinical significance of claims of patient benefit based on disease-free interval.[25] The long-term results of worsening-free survival were not based on protocol planned analysis but on the original randomized design. Nonetheless, under these circumstances there is an increased risk of type I error, that is finding significance when it does not exist. The complexity of the situation does not provide a basis for computing a suitable type I error level correction. Therefore, the reader must interpret the statistical results regarding worsening-free survival with some degree of caution.

The demonstrated long-term benefit of our 3-week maintenance schedule has major implications regarding the treatment of bladder cancer. Before the results from this trial were available treatment decisions focused on cost, convenience or patient preferences.[25] Demonstration of long-term benefit, including a longer progression-free interval, should dramatically change treatment recommendations. Currently many urologists give a 6-week induction treatment and a second 6-week course at recurrence. A randomized comparison of 6-week induction versus induction plus maintenance using 6 weekly instillations at 6-month intervals for 2 years showed no benefit.[26] Assuming as well that many no maintenance arm cases in our study received

a second 6-week course of BCG at recurrence, it appears that repeat 6-week courses of BCG immunotherapy are suboptimal.

There are many possible mechanistic explanations for the unique success observed with our 3-week maintenance schedule. Following exposure to an antigen the secondary immune response occurs more rapidly and is more vigorous. Immune stimulation measured by urinary cytokine excretion in patients receiving the initial course of intravesical BCG generally peaks at 6 weeks.[27,28] However, with subsequent instillations immune stimulation generally peaks at 3 weeks, and is suppressed with weekly instillations 4, 5 and 6.[29] The duration of immune stimulation and protection from recurrence following BCG instillation appears to be long term but lymphocytic infiltration,[18] delayed cutaneous hypersensitivity response,[30] HLA-DR[31] and immunoproliferative responses persist for as little as 6 months. Therefore, the 6-month maintenance schedule may have biological significance. The 3-year duration of maintenance was selected for convenience. To our knowledge there are no randomized comparisons of 3-week maintenance with single quarterly instillations, monthly instillations or treatment with further 6-week courses at recurrence. Future studies to improve BCG treatment techniques should consider convenience, safety and cost as well as the biology of the immune response.

Both treatment arms included percutaneous BCG administration as originally described by Morales et al[19] and used in the SWOG comparison of Connaught BCG and doxorubicin.[4] Based on subsequent favorable results with BCG given only intravesically[5,9,24,26] and small (under powered) controlled trials that failed to show significant benefit,[32,33] most urologists have now eliminated percutaneous administration. Our study clearly demonstrates the superiority of maintenance BCG using up to 3 weekly instillations. However, data condemning the use of percutaneous BCG are as weak as previous data condemning maintenance BCG. A large randomized trial would be required to determine definitively the benefit or futility of percutaneous BCG administration.

Our 3-week, 3-year BCG maintenance schedule can now be recommended as the treatment of choice for carcinoma in situ, and high risk Ta and T1 transitional cell carcinoma but caution must be taken to avoid undue side effects. Instillation 2 or 3 was withheld in our patients who had side effects, such as severe or prolonged dysuria, fever or malaise with maintenance instillation 1 or 2. The practice of withholding treatment for increased side effects may be responsible for the lack of severe toxicity during maintenance in this trial as evidenced by the small number of patients (16%) who received all scheduled maintenance treatments. Studies evaluating the safety and efficacy of reduced dose BCG are planned or under way but until they are complete we recommend continuing to suspend instillation 2 or 3 in patients with increased side effects.

REFERENCES

1. Herr, H. W., Laudone, V. P., Badalament, R. A. et al: Bacillus Calmette-Guerin therapy alters the progression of superficial bladder cancer. J Clin Oncol, **6:** 1450, 1988
2. Lamm, D. L.: Long-term results of intravesical therapy for superficial bladder cancer. Urol Clin North Am, **19:** 573, 1992
3. Pawinski, A., Sylvester, R., Kurth, K. H. et al: A combined analysis of European Organization for Research and Treatment of Cancer, and Medical Research Council randomized clinical trials for the prophylactic treatment of stage TaT1 bladder cancer. J. Urol, **156:** 1934, 1996
4. Lamm, D. L., Blumenstein, B. A., Crawford, E. D. et al: A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guérin for transitional-cell carcinoma of the bladder. N Engl J Med, **325:** 1205, 1991
5. Lamm, D. L., Blumenstein, B. A., Crawford, E. D. et al: Randomized intergroup comparison of bacillus Calmette-Guerin immunotherapy and mitomycin C chemotherapy prophylaxis in superficial transitional cell carcinoma of the bladder: a Southwest Oncology Group study. Urol Oncol, **1:** 119, 1995
6. Reichert, D. F. and Lamm, D. L.: Long term protection in bladder cancer following intralesional immunotherapy. J Urol, **132:** 570, 1984
7. Lamm, D. L.: Bacillus Calmette-Guérin immunotherapy for bladder cancer. J Urol, **134:** 40, 1985
8. Hudson, M. A., Ratliff, T. L., Gillen, D. P. et al: Single course versus maintenance bacillus Calmette-Guerin therapy for superficial bladder tumors: a prospective, randomized trial. J Urol, **138:** 295, 1987
9. Badalament, R. A., Herr, H. W., Wong, G. Y. et al: A prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette-Guerin therapy of superficial bladder cancer. J Clin Oncol, **5:** 441, 1987
10. Prentice, R. L.: Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med, **8:** 431, 1989
11. Pocock, S. J. and Simon, R.: Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics, **31:** 103, 1975
12. Rubinstein, L. V., Gail, M. H. and Santner, T. J.: Planning the duration of a comparative clinical trial with loss to follow-up and a period of continued observation. J Chronic Dis, **34:** 469, 1981
13. Fleming, T. R., Harrington, D. P. and O'Brien, P. C.: Designs for group sequential tests. Control Clin Trials, **5:** 348, 1984
14. Cox, D. R. and Oakes, D.: Analysis of Survival Data. New York: Chapman and Hall, 1984
15. Lamm, D. L., Sarosdy, M. F., Grossman, H. B. et al: Maintenance vs. nonmaintenance BCG immunotherapy of superficial bladder cancer: a Southwest Oncology Group Study. J Urol, suppl., **143:** 341A, abstract 610, 1990
16. Lamm, D. L., Crawford, E. D., Blumenstein, B. et al: Maintenance BCG immunotherapy of superficial bladder cancer: a randomized prospective Southwest Oncology Group Study. J Urol, suppl., **147:** 274A, abstract 242, 1992
17. Lamm, D. L., Crawford, E. D., Blumenstein, B. et al: Maintenance BCG immunotherapy of superficial bladder cancer: A randomized prospective Southwest Oncology Group Study. Presented at American Society of Clinical Oncology Annual Meeting, San Diego, California, May 17–19, 1992
18. Rawls, W. H., Lamm, D. L., Lowe, B. A. et al: Fatal sepsis following intravesical bacillus Calmette-Guerin administration for bladder cancer. J Urol, **144:** 1328, 1990
19. Morales, A., Eidinger, D. and Bruce, A. W.: Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol, **116:** 180, 1976
20. Lamm, D. L., Thor, D. E., Harris, S. C. et al: Bacillus Calmette-Guerin immunotherapy of superficial bladder cancer. J Urol, **124:** 38, 1980
21. Pinsky, C. M., Comacho, F. J., Kerr, D. et al: Treatment of superficial bladder cancer with intravesical BCG. In: Immunotherapy of Human Cancer. Edited by W. D. Terry and S. T. Rosenberg. North Holland, New York: Elsevier, pp. 309–313, 1982
22. Flamm, J.: Long-term versus short-term doxorubicin hydrochloride instillation after transurethral resection of superficial bladder cancer. Eur Urol, **17:** 119, 1990
23. Huland, H., Klöppel, G., Feddersen, I. et al: Comparison of different schedules of cytostatic intravesical instillations in patients with superficial bladder carcinoma: final evaluation of a prospective multicenter study with 419 patients. J Urol, **144:** 68, 1990
24. Pagano, F., Bassi, P., Milani, C. et al: A low dose bacillus Calmette-Guerin regimen in superficial bladder cancer therapy: is it effective? J Urol, **146:** 32, 1991
25. Blumenstein, B. A.: Editorial comment. J Urol, **156:** 1940, 1996
26. Palou, J., Laguna, P., Algaba, F. et al: High grade superficial transitional cell carcinoma of the bladder and/or CIS treated with BCG: Control vs. maintenance treatment. Br J Urol, suppl., **80:** 32, 1997
27. Ratliff, T. L., Haaff, E. O. and Catalona, W. J.: Interleukin-2 production during intravesical bacille Calmette-Guerin therapy for bladder cancer. Clin Immunol Immunopathol, **40:** 375, 1986
28. DeBoer, E. C, De Jong, W. H., Steerenberg, P. A. et al: Induction

of urinary IL1, IL2, IL6 and TNF during intravesical immunotherapy with BCG in superficial bladder cancer. Cancer Immunol Immunother, **33:** 306, 1991

29. DeBoer, E. C., De Jong, W. H., Steerenberg, P. A. et al: Induction of urinary interleukin-1 (IL-1), IL-2, IL-6, and tumour necrosis factor during intravesical immunotherapy with bacillus Calmette-Guerin in superficial bladder cancer. Cancer Immunol Immunother, **34:** 306, 1992
30. Winters, W. D. and Lamm, D. L.: Antibody responses to Bacillus Calmette-Guérin during immunotherapy in bladder cancer patients. Cancer Res, **41:** 2672, 1981
31. Prescott, S., James, K., Hargreave, T. B. et al: Immunopathological effects of intravesical BCG therapy. Prog Clin Biol Res, **310:** 93, 1989
32. Lamm, D. L., DeHaven, J. I., Shriver, J. et al: Prospective randomized comparison of intravesical with percutaneous bacillus Calmette-Guerin versus intravesical bacillus Calmette-Guerin for superficial bladder cancer. J Urol, **145:** 738, 1991
33. Lüftenegger, W., Ackermann, D. K., Futterlieb, A. et al: Intravesical versus intravesical plus intradermal bacillus Calmette-Guerin: a prospective randomized study in patients with recurrent superficial bladder tumors. J Urol, **155:** 483, 1996