Intratumoral Bacillus Calmette-Guérin Immunotherapy prior to Surgery for Carcinoma of the Lung: Results of a Prospective Randomized Trial

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ABSTRACT

A prospective randomized trial of preoperative intratumoral therapy with Bacillus Calmette-Guérin (BCG) was conducted in non-small cell lung cancer patients. Eighty-eight patients (48 BCG-treated and 40 control subjects) were entered into the study; three control subjects were removed from data analysis because histology revealed pathology other than non-small cell lung cancer. There were no differences between BCG-treated and control patients in sex, age, cigarettes smoked per day, pack-years of cigarette smoking, white blood cell count, or number of peripheral blood lymphocytes. Toxicity of BCG was limited to transient malaise and fever (average peak temperature, 38.7°C). There was no significant difference in outcome (recurrence or survival) between BCG-treated and control groups with Stage I or Stage III tumors; there were too few Stage II tumors for separate statistical analysis. Outcome was not affected within or between the two treatment groups by tuberculin skin test status. Combining both treatment groups, Stage III patients had a worse outcome than did Stage I–II patients, non-squamous cell tumor patients (large cell and adenocarcinoma) had worse outcomes than did squamous cell tumor patients, and men had a worse outcome than women. We conclude that, although preoperative intratumoral BCG therapy is safe, it does not lengthen disease-free interval or prolong survival in patients with non-small cell lung cancer.

INTRODUCTION

Lung cancer, the most common and one of the most aggressive forms of carcinoma, kills 95% of its victims within 5 years. Despite surgical intervention and radiotherapy, only about 40% of patients with resectable Stage II disease survive 5 years (1), and response of non-small cell lung cancer to chemotherapy remains under 50% in most studies of patients with established metastatic disease. With the continued prevalence of smoking, the incidence of lung cancer is likely to remain high and may increase.

Immunocompetence may be a determining factor in surviving lung cancer. Cell-mediated and humoral immunity are compromised in cancer patients (1–5). Patients with advanced disease and a good delayed hypersensitivity response (skin test) to dinitrochlorobenzene are likely to survive longer than patients with a poor response to dinitrochlorobenzene (5). Likewise, lung cancer patients who respond to recall antigens have a better prognosis than those who do not (4, 6).

Specific and nonspecific stimulation of the immune system has been investigated in animals and humans to determine whether the host’s natural resistance to tumor could be enhanced, thus extending disease-free intervals (7–9). BCG is a nonspecific adjuvant isolated by Calmette and Guérin through progressive attenuation of a virulent strain of Mycobacterium bovis (10). BCG is a mainstay of active immunotherapy; it stimulates thymus-derived (T)-lymphocytes, macrophages, and “bursa-dependent” (B)-lymphocytes and has been effective against cutaneous neoplasms (10–12). However, the regression of multiple intradermal metastases of malignant melanoma after intraslesional injection of viable BCG probably best demonstrates the efficacy of this adjuvant (13).

McKneally et al. (14, 15) reported that intrapleural BCG significantly increases the survival of surgically resected Stage I lung cancer patients compared with concurrent randomized controls. However, this therapy did not augment survival or disease-free intervals in patients with Stage II or Stage III disease. These investigators suggested that regional immunotherapy with BCG eliminates small numbers of residual tumor cells in the lymphatics and draining lymph nodes of the chest. Other trials with intrapleural BCG failed to confirm these positive results in lung cancer patients (16, 17), perhaps because of differences in the source of the microorganism.

The principal objectives of this prospective randomized trial were to determine whether transbronchoscopic injection of BCG into lung tumors before resectional surgery is safe and whether this form of therapy improves survival or at least prolongs the disease-free interval after surgery. Preliminary results were published (18) after about one-half of the patients had entered the study. Preliminary data suggested that intratumoral injection of BCG in lung cancer was safe. This report corroborates the initial findings of safety and describes the outcome of all patients studied.

PATIENTS AND METHODS

Patient Selection and Experimental Design

Patients with potentially resectable non-small cell carcinoma of the lung were considered for this study. Before surgery, tumor cell type was established by sputum cytology, fiberoptic bronchoscopy with forceps, and/or brush biopsy (11, 19) or transthoracic needle aspiration biopsy with fluoroscopy as a guide to needle placement. Patients suspected of having lung cancer were excluded if a definite diagnosis had not been established before thoracotomy. Additional exclusion criteria included: (a) evidence of extrathoracic metastases, (b) previous irradiation of the thorax and/or chemotherapy, (c) cancers metastatic to the lung from another nonpulmonary site, (d) culture positive tuberculosis, (e) age of 80 or more years, and (f) inability to tolerate pneumonectomy or lobectomy due to severity of pulmonary function abnormalities (or due to other disease such as severe atherosclerotic cardiovascular disease).

Informed consent was obtained from patients who met the criteria for inclusion in the study. Skin test response to the following recall antigens was determined: 5 TU of PPD (Connaught), 0.1 ml of mumps skin test antigen (Eli Lilly), 50 PNU (0.1 ml) of trichophytin (Hollister-Stier), and 0.1 ml of streptokinase-streptodornase (Varidase; Lederle).

The abbreviations used are: BCG, Bacillus Calmette-Guérin; PPD, purified protein derivative; INH, isoniazid.
Patients were divided into 2 groups according to a table of random numbers and sealed-envelope technique in strict numerical order of entry into BCG and surgery, or surgery only (control). Before surgery, patients were classified into Stage I or II (20) by a stratified block randomization method. This technique randomizes patients separately based upon their being Stage I or II; random assignments are made in blocks of 11 persons so that 6 persons were assigned to BCG and surgery and 5 persons were assigned to surgery only. We anticipated that in some patients BCG would not be successfully injected into the tumor and that this subgroup would not be evaluated in the BCG treatment group. Therefore, the randomization was constructed so that the BCG treatment group would be slightly larger. As the study progressed, it became evident that tumors could all be reached successfully with BCG, but we decided to retain the original randomization scheme, so there were more BCG-treated than control patients.

We injected BCG (Tice strain; Chicago Research Foundation, University of Illinois) 10⁵ viable organisms for PPD skin test-negative patients (14, 15, 21) and 5 x 10⁵ for PPD-positive patients (22), into the tumor mass by passing a flexible fine needle (Meditech Corp., Watertown, MA) through the fiberoptic bronchoscope. Peripherally located lesions, not visible through the bronchoscope, were entered with flurosscopic guidance, and needle position was checked by viewing the lung from two vantages, supine and lateral.

We obtained chest radiographs 3 days after BCG injection and 2–3 weeks later (just before surgery) to determine whether BCG had caused a pulmonary infiltrate.

All control patients underwent thoracotomy immediately following randomization, and all BCG-treated patients underwent thoracotomy 2–3 weeks after intratumoral injection of BCG. Standard criteria for resection and uniform technique were used. Immediately after surgery, a 12-week course of 300 mg INH daily was given to all patients. Liver function was tested serially to monitor INH side effects. The control group underwent surgery promptly after randomization. After surgery, all patients were restaged according to the American Joint Committee on Cancer Staging as modified by Mountain et al. (20). One of us (D. C.) in the Department of Pathology established the cell type in each case. Patients classified as Stage III (20) and those who developed metastases or local recurrences were treated by irradiation (300 rads x 10 treatments) to all known tumor-bearing areas. Local recurrence and/or peripheral metastases were established by physical examination, sputum cytology, chest radiograph, and repeat bronchoscopy, when necessary and by lung tomography or radionuclide scanning as indicated.

Statistical Analysis. Survival and time interval from resection to disease recurrence were analyzed in BCG and control groups by tumor cell type and stage using standard statistical techniques (23, 24). The cumulative probabilities of survival and nonrecurrence were calculated by the actuarial method of Berkson and Gage. Survival and recurrence times were compared with the proportional hazard model of Cox (10). This model also allows the influence of covariants (e.g., tumor cell type, stage) to be evaluated and adjusted for when comparing the survival probabilities of the two treatments. This covariant analysis was repeated only with patients receiving BCG to include a covariant for post-BCG temperature in the patient. The Cox regression models were fit using PROC PHGLM in the SAS statistical package (10). The best fitting model was determined by the iterative process. Information was incomplete for some patients on some of the covariants, and these cases were automatically eliminated in the Cox procedure. Covariants that were clearly nonsignificant were then eliminated and a new model was fit, which usually included a large number of individuals. This step was repeated until most subjects were entered into the analysis. The forward stepwise option was used to find the model that contained only significant terms (P < 0.05). At this point, further models were fit that included interaction terms of the significant main effects or of the main effects with other factors of special interest. The main effects corresponding to any interaction term were always included in the model, whether significant or not. Insignificant interaction terms were eliminated from the model until a final model was produced.

RESULTS

Characteristics and Outcome of BCG-treated Patients and Controls. Eighty-eight patients entered the study; 48 BCG-treated and 40 control patients. Three control patients were removed from data analysis because the histology of the resected specimen at surgery revealed small cell carcinoma, a benign adenoma, and metastatic bladder carcinoma. Therefore, results are reported on 85 patients: 62 men and 23 women.

Of the 85 patients evaluated, 48 were treated with BCG and 37 were controls. The unequal numbers in the two groups favored the BCG group due to study design. In Stage I, there were 23 BCG treated and 20 control patients; Stage II, 3 BCG and 6 controls; Stage III, 22 BCG and 11 controls. Among all three stages, there were 44 squamous cell cancers (29 BCG, 15 controls), 31 adenocarcinomas (12 BCG and 19 controls), 9 large cell carcinomas (7 BCG and 2 controls), and one adenosquamous cell (one control). Tumor cell type did not differ significantly between BCG-treated and control patients at any of the three stages.

Table 1 shows comparative characteristics and outcome of BCG-treated and control patients in all three stages. There were no differences between BCG-treated and control patients in sex, age, cigarettes smoked per day, pack-years of cigarette smoking, white blood cell count, or number of peripheral blood lymphocytes. The two groups did not differ in mean follow-up time (entry to censorship) or in mean interval between entry and recurrence or death. Median time to recurrence was 237 days in BCG-treated patients and 288 days in controls (NS), whereas the median survival was 345 days in BCG-treated patients and 433 days in controls (NS).

Similarly, there was no statistically significant difference between BCG-treated and control patients at any of the three stages in sex, age, average number of cigarettes smoked per day, package years of cigarettes, PPD skin test status, skin test anergy, remote or recent hemoptysis, or absolute (pre-BCG) lymphocyte count. There was also no difference in outcome between BCG-treated patients and controls due to any of the aforementioned variables.

Table 2 and Figs. 1–4 illustrate the outcome of BCG and control patients by stage. In the Stage I group, the recurrence rate has been the same: 7/23 (30.4%) among BCG-treated patients and 6/10 (30%) among controls. The cumulative non-recurrence probability curve depicted in Fig. 1 was the same for both groups (59% in controls, 61% in BCG patients at 48 months). There have been 10 deaths in the Stage I BCG group (43.5%) and 8 deaths in the control group (40%). Moreover, the cumulative survival probabilities were the same in the BCG-treated and control groups (Fig. 2).

Since there were only 9 Stage II patients (3 BCG and 6

<table>
<thead>
<tr>
<th>Sex</th>
<th>BCG</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>38</td>
<td>24</td>
</tr>
<tr>
<td>Women</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Age</td>
<td>61 ± 9</td>
<td>61 ± 10</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>29 ± 12</td>
<td>32 ± 14</td>
</tr>
<tr>
<td>Cigarettes (pack-yr)</td>
<td>53 ± 28</td>
<td>58 ± 37</td>
</tr>
<tr>
<td>WBC/mm³</td>
<td>9600 ± 2086</td>
<td>8765 ± 2714</td>
</tr>
<tr>
<td>Lymphocytes/mm³</td>
<td>1954 ± 966</td>
<td>1949 ± 714</td>
</tr>
<tr>
<td>Entry to censorship (days)</td>
<td>986 ± 412</td>
<td>1062 ± 390</td>
</tr>
<tr>
<td>Entry to recurrence (days)</td>
<td>411 ± 433</td>
<td>388 ± 388</td>
</tr>
<tr>
<td>Entry to death (days)</td>
<td>482 ± 413</td>
<td>542 ± 365</td>
</tr>
</tbody>
</table>

*In none of the categories was the number for the BCG-treated group significantly different from the number for the control group.

* Mean ± SD.
Intratumoral BCG Immunotherapy

Table 2 Recurrences and deaths by treatment and stagé*

<table>
<thead>
<tr>
<th>Stage</th>
<th>BCG</th>
<th>C</th>
<th>BCG</th>
<th>C</th>
<th>BCG</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>23</td>
<td>20</td>
<td>6</td>
<td>3</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Recurrences</td>
<td>(30.4%)</td>
<td>(30%)</td>
<td>(0%)</td>
<td>(0%</td>
<td>(50%)</td>
<td>(72.7%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>10</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>(43.5%)</td>
<td>(40%)</td>
<td>(67%)</td>
<td>(67%)</td>
<td>(91.9%)</td>
<td>(72.7%)</td>
</tr>
</tbody>
</table>

* In neither of the categories (recurrences or deaths) was the number significantly different between BCG-treated and control groups at any of the three stages.

C, Control group.

In Stage I patients, overall recurrence rate has been 30% in each group (Table 2). Moreover, the cumulative nonrecurrence probabilities shown in Fig. 3 do not differ significantly in the two groups. Twenty (90.9%) BCG patients and 8 (72.7%) control patients have died. The cumulative survival probabilities are not significantly different in the BCG and control Stage I patients (Fig. 4).

Covariant Analysis. Besides a variable for treatment (BCG versus control), potential covariants used in the Cox regression model were stage of cancer, use of two dummy variables (Stage I versus Stage II-III versus Stage III), cell type (squamous versus all other types), largest tumor diameter, age, sex, number of lymphocytes, percentage of lymphocytes, and dummy variables for presence of positive tuberculin skin test (PPD), hemoptysis, chest pain, other pain, anorexia, weight loss, anergy, and peak temperature post-BCG. Smoking variables (e.g., smoker versus nonsmoker) were also examined but did not give meaningful results because of the small number of nonsmokers in the study.

Table 3 provides the final model when fitting survival time and disease-free interval in all 85 patients in the study. The influence of the type of treatment (BCG or control) had no significant influence in the presence of the covariants. Survival did not differ significantly between Stages I and II, but Stage III resulted in significantly worse survival than did Stage I-II. The risk of death per unit of time was 3.39 times greater for Stage III patients than for Stage I-II patients. Also, men had a poorer survival (3.74 relative risk) than women did as did persons with cell types other than squamous cell carcinoma (1.99 relative risk). Similar results held for disease-free interval,
except that cell type (other versus squamous cell) was not significant. Again, patients with Stage III lung cancer had a much greater risk (5 times) of recurrence than those with Stage I–II. For both outcome variables (survival time and disease-free interval) there were no significant interactions among these main effects (stage, sex, and cell type). However, for survival time, one interaction (sex x cell type) was marginally significant (P = 0.064) in the presence of the 3 main effects, although sex and cell type were no longer significant. Therefore, the model with only the main effects was felt to be the best and most easily interpreted.

To illustrate the effect of each of the 3 significant covariants on survival time, plots of the estimated survival probabilities for the various combinations of these factors are shown in Figs. 5 and 6. Fig. 5 shows the survival probabilities for Stage I and II lung cancer for the four combinations of cell type and sex. Men with non-squamous cell lung carcinoma had the worst prognosis while women with squamous cell lung cancer had the best survival.

![Fig. 5. Survival probabilities for Stage I and II lung cancer for four combinations of cell type and sex. Men with non-squamous cell lung carcinoma had the worst prognosis while women with squamous cell lung cancer had the best survival.](image)

In a model including the interaction of these two effects, the interaction term was significant (P = 0.016) whereas the two main effects were no longer significant. Although this model fit somewhat better than the main effect model, the interaction model is more difficult to interpret.

Since different covariants were important depending upon the treatment given, further models were fit on the whole set of patients to allow for interactions of treatment with sex and cell type. Neither of these interactions was significant. Furthermore, other interactions were allowed in the model but were nonsignificant. These interaction terms included stage x hemoptysis, stage x skin test results, cell type x hemoptysis, and cell type x skin tests results.

Moreover, the presence of a positive tuberculin skin test did not affect outcome (death or recurrence) in BCG-treated or control patients at any stage or for any tumor cell type.

**Toxicity and Histological Response to BCG.** BCG was successfully injected into the tumor in each case. One of the 48 BCG-treated patients with a peripheral lung lesion developed a pneumothorax after BCG injection and required a chest tube. Otherwise, toxicity was limited to transient malaise and fever. The peak temperature ranged from 37.8–41.1°C and was reached within 48 h of BCG injection. The mean peak temperature in PPD-positive and PPD-negative patients did not differ significantly (39.4 ± 0.7 versus 38.9 ± 0.6°C, mean ± SD, respectively). In each patient, including those with a febrile response as high as 41.1°C, the fever was controlled promptly with acetaminophen, administered every 4 h for a temperature higher than 38.4°C.

Chest radiographs of most of the BCG-injected patients showed a transient peritumoral infiltrate. Histological examination of specimens from BCG-treated patients showed a lymphocytic, granulomatous peritumoral infiltrate in most cases. Draining hilar lymph nodes in some BCG-injected patients contained tubercules. Also, acid-fast bacilli were seen on specially stained sections and/or grown from sputum, tumor, or regional lymph nodes. Perhaps due to the 50% reduction in BCG dose to tuberculin skin test-positive patients, this latter group did not differ from tuberculin-negative individuals in treatment results.

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**Table 3** Cox regression models for survival and disease-free interval in lung cancer patients—BCG-treated and controls combined

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Prognostic variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Significance level (P)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival time</td>
<td>Stage III vs. I–II</td>
<td>1.22 ± 0.30</td>
<td></td>
<td>&lt;0.0001</td>
<td>3.39</td>
</tr>
<tr>
<td>Survival time</td>
<td>Male vs. female</td>
<td>1.32 ± 0.43</td>
<td></td>
<td>0.002</td>
<td>3.74</td>
</tr>
<tr>
<td>Survival time</td>
<td>Other vs. squamous cell type</td>
<td>0.69 ± 0.32</td>
<td></td>
<td>0.029</td>
<td>1.99</td>
</tr>
<tr>
<td>Disease-free interval</td>
<td>Stage III vs. I–II</td>
<td>1.61 ± 0.35</td>
<td></td>
<td>&lt;0.0001</td>
<td>5.00</td>
</tr>
<tr>
<td>Disease-free interval</td>
<td>Male vs. female</td>
<td>0.94 ± 0.45</td>
<td></td>
<td>0.038</td>
<td>2.56</td>
</tr>
</tbody>
</table>

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**Fig. 6. Survival probabilities for Stage III lung cancer for four combinations of cell type and sex. Men with non-squamous cell lung carcinoma had the worst prognosis while women with squamous cell and nonsquamous cell tumors had the highest probability of short-term survival.**
histological response to BCG. BCG did not adversely affect lung resection or healing.

Patients received 300 mg INH daily for 12 weeks to prevent intra- and extrathoracic dissemination of BCG organisms, and there was no evidence of M. bovis dissemination after intraleisional injection. Serum glutamic-oxalacetic transaminase increased 5-fold, and lethargy developed in 2 patients. When INH was discontinued in these patients, the serum glutamic-oxalacetic transaminase returned to normal and the lethargy reversed.

DISCUSSION

This study confirms other reports (3, 22, 25) that preoperative intratumoral injection of BCG in patients with non-small cell lung cancer is both feasible and safe. However, this prospective, randomized study also shows that BCG therapy neither prolongs survival nor extends the interval between surgery and tumor recurrence.

BCG was successfully injected into all lung tumors, including peripheral tumors as small as 2 cm in diameter. Moreover, a pneumothorax requiring insertion of a chest tube developed in only one of the 48 BCG-injected patients (2%). This contrasts markedly with the 33% pneumothorax rate reported by Holmes et al. (3), who used the percutaneous transthoracic technique to administer BCG into peripheral lung tumors. Fever developed in all BCG-treated patients and a postinjection, transient peritumoral infiltrate was evident on the chest radiograph in most. The peak temperature was the same in PPD-positive and PPD-negative patients, probably because the former group received one-half the dose of BCG (5 x 10^6 organisms). When Holmes et al. (3, 22) injected Glaxo strain BCG into pulmonary tumors, the highest, most prolonged fever occurred in patients with a PPD-positive skin test. Accordingly, they recommended a lower BCG dose in PPD-positive patients (22). We followed this recommendation, and as a result the clinical and histological response to BCG was identical among PPD-positive and PPD-negative patients. In most patients, an inflammatory response consistent with tuberculous pneumonitis was adjacent to or infiltrating the tumor. Special stains and/or culture showed tuberculin organisms in the inflammatory lesions.

The therapeutic efficacy of BCG has been ascribed to its activation of the lymphoreticular system. A number of studies have demonstrated increased immunological reactivity of lymphocytes (26, 27), macrophages (12, 28, 29), and nonadherent spleen cells resembling monocytes (30) after administration of BCG. Together, these BCG-activated cells might assist in tumor regression. However, recently Bennett et al. (31) showed that BCG administered i.v. to mice activates "natural" suppressor cells in normal bone marrow. Thus, by augmenting suppressor cell activity, BCG may suppress tumor immunity, thereby enhancing tumor growth. However, results from studies using intraleisional BCG in cutaneous melanoma and other malignancies (13, 32, 33), as well as endobronchial non-small cell lung carcinomas (22), indicate that this agent causes tumor regression, rather than growth. Nonetheless, adverse affects of BCG on the immune system (e.g., an increase in suppressor cells) may be partially responsible for the failure of this agent to improve outcome in our study. In fact, in the Stage III group, the poorer outcome among BCG-treated individuals approached statistical significance.

The failure of intratumoral BCG to augment disease-free interval or survival in this study also may have been associated with differences in biological activity among batches of Tice strain BCG. Mokyr et al. (34) found striking differences in the ability of various strains of BCG to augment or decrease immune responses in vitro. Bennett et al. (35) reported that batches of BCG that protected mice against circulating tumor cells have greater sensitivity to INH and higher viability than do batches that did not elicit this antitumor activity. Moreover, the cumulative disease-free interval in Stage I lung cancer patients was longer with batches that protected mice against circulating tumor cells than with batches that did not afford this protection. A possible solution to this "batch" problem would be use of a nonviable immunostimulant with predictable, nonvarying antitumor activity.

Another possible reason for failure of intraleisional BCG to improve outcome, particularly in the Stage III group, was the large tumor burden. McKnealy et al. (14, 15, 21) reported similar negative results with postoperative intrapleural BCG in Stage III lung cancer patients and attributed the results to the wide extent of tumor.

A type II error (36) may have affected our results. According to this statistical concept, there may not have been enough patients in the Stage I or Stage III group to establish conclusively that preoperative, intraleisional BCG improves or worsens the outcome of patients with lung cancer. We doubt that a type II error prevented us from identifying beneficial effects of BCG because there was no evident trend favoring BCG therapy in the Stage I or Stage III group. However, in the Stage III group, a type II error may have prevented the demonstration of statistically significant adverse effects of BCG.

McKnealy and colleagues (21) have suggested that PPD-negative patients with Stage I squamous cell lung carcinoma may benefit from postoperative intrapleural administration of BCG. Accordingly, in our study we assessed outcome according to skin test status and three variables—treatment (BCG versus control), stage, and cell type. Skin test status (PPD positive or PPD negative) did not significantly affect survival or recurrence for either treatment group, any stage, or any cell type.

The Cox regression model results show (a) that Stage III patients have worse outcomes than Stage I-II patients do, (b) that non-squamous cell (large cell and adenocarcinoma) tumors have worse outcomes than squamous cell lung carcinomas do, and (c) that men have a worse prognosis than women do.

We conclude that although preoperative intratumoral BCG therapy is well tolerated and safe in lung cancer patients, it does not alter the outcome of the disease. Improved understanding of the ways of selectively manipulating the host's immune response to his tumor, utilization of a tumor-associated antigen(s), and targeted monoclonal antibodies may all lead to improved results.

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REFERENCES

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