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Postoperative intrapleural BCG in lung cancer: lack of efficacy and possible enhancement of tumour growth

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ABSTRACT Fifty-six patients out of a group of 99 with lung cancer received postoperative intrapleural BCG (Pasteur strain) in three different dosages (16×10^6 culturable particles (cp), 32×10^6 cp, and 64×10^6 cp). When comparing the whole group of 99 patients with a historical control group of 126 patients no statistically significant differences were found in survival and disease-free interval. The two groups were well matched in respect of age, sex, histology, stage of disease, and type of operation. Patients with epidermoid carcinoma stage I receiving BCG, however, did significantly worse than those who had not received BCG in terms of disease-free interval. This unfavourable trend was caused by earlier local recurrences rather than metastases. The possible phenomenon of enhanced tumour growth noted in our patients with epidermoid carcinoma stage I might be related to the dosages used in this study, but the different BCG strain used hinders comparison with other studies. We conclude that BCG has no beneficial effect on survival or on disease-free interval; possible enhancement of tumour growth in stage I epidermoid carcinoma was found.

Since the promising results of McKneally *et al*,[1-3] there has been renewed interest in immunotherapy as an adjunct to surgery in patients with lung cancer. Their approach to immunotherapy with intrapleural administration of BCG after operation was based on the clinical observation of improved survival in patients developing empyema after resection.[4 5] In contrast to intradermal and subdermal BCG,[6 7] intrapleural BCG comes into close contact with the tumour cells possibly left after operation, which might favour optimal immune stimulation.[8]

We initiated a study primarily designed to determine the safety of intrapleural administration of different dosages of BCG after surgery. This report presents the survival data of patients receiving postoperative BCG compared with those of a historical control group.

Methods

The study group (n = 99) consisted of all patients with lung cancer operated upon in Leyden University Hospital from 1 November 1977 until 15 August 1979, excluding those with a previous or concomitant carcinoma (see table). Fifty-six consenting patients from this study group were selected to receive intrapleural BCG postoperatively. The remaining 43 patients did not receive immunotherapy with BCG for various reasons—for example, an unfavourable cardiovascular or pulmonary condition.

A historical control group was formed consisting of all 126 patients operated on for lung cancer from 1 October 1975 until 31 October 1977, excluding those with a previous or concomitant carcinoma.

All operations were carried out by the same surgical team, using standard indications for the type of operation and a uniform surgical technique. Resected tumours were histologically typed according to the WHO criteria,[9] and staged according to the UICC.[10]

BCG-treated patients were given a single pleural injection of BCG on the fifth or sixth day after operation. Six patients received 16×10^6 culturable particles (cp), 28 patients received 32×10^6 cp, and 30 patients 64×10^6 cp. The injection was given through a chest tube and flushed in with saline before the tube was removed. The lyophilised BCG (lot 048) was provided by the Rijks Instituut voor de Volksgezondheid, Bilthoven, The Netherlands.

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Table *Characteristics of study group and control group (figures in brackets indicate percentages)*

	Study group (operated 1/11/77-15/8/79)			*Control group (operated 1/10/75-31/10/77)*
	Whole group	*BCG-treated*	*No BCG*	*No BCG*
Number	99	56	43	126
Age (mean ± SD)	62·0 ± 7·8	62·3 ± 6·9	61·7 ± 8·9	60·9 ± 8·7
Sex male	96 (97)	54 (96)	42 (98)	119 (94)
female	3 (3)	2 (4)	1 (2)	7 (6)
Histological type				
epidermoid	68 (69)	42 (75)	26 (60)	82 (65)
adeno	22 (22)	9 (16)	13 (30)	20 (16)
anaplastic	7 (7)	4 (7)	3 (7)	22 (17)
unknown	2 (2)	1 (2)	1 (2)	2 (2)
Stage I	66 (67)	40 (71)	26 (60)	79 (63)
II	19 (19)	10 (18)	9 (21)	28 (22)
III	11 (11)	4 (7)	7 (16)	18 (14)
not certain	3 (3)	2 (4)	1 (2)	1 (1)
Type of operation:				
segment resection	3 (3)	3 (6)	0 (0)	1 (1)
lobectomy	60 (60)	34 (61)	26 (60)	78 (62)
bilobectomy	8 (8)	4 (7)	4 (9)	11 (9)
pneumonectomy	28 (28)	15 (27)	13 (30)	36 (29)

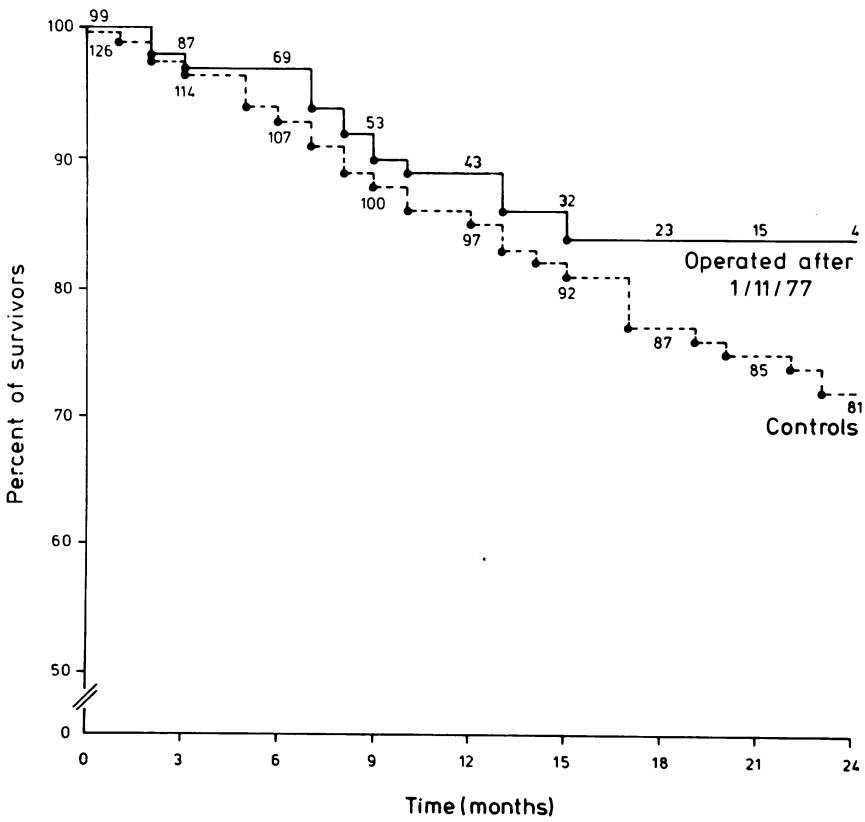

Fig 1 *Survival of patients with lung cancer, all histological types (99 operated on after 1/11/77 including 56 who received BCG and 126 controls operated on before 1/11/77). The number of patients remaining at risk is written along each graph. No significant difference is observed.*

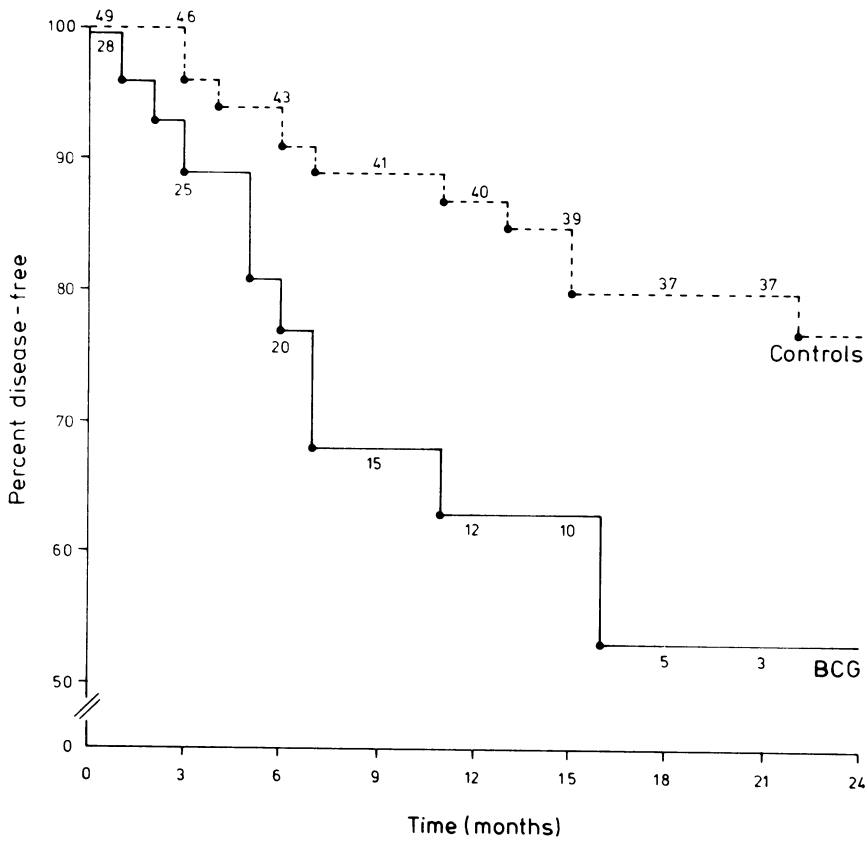

Fig 2 *Disease-free interval of patients with epidermoid carcinoma stage I (28 treated with BCG, 49 controls). The number of patients remaining at risk is written along each graph. The difference is statistically significant ($p < 0.05$).*

The vaccine was grown as a homogeneous culture using a seed lot derived from BCG Pasteur (Strain 1173). Isoniazid 300 mg/day was started three weeks after the BCG and continued for three months.

All patients were followed up by their chest physicians. No patient was lost to follow-up. Local recurrences and metastases were treated by radiotherapy or other palliative measures, as appropriate.

The two groups were compared with respect to age by Student's two sample t test. The chi-square test for contingency tables was used to test whether the two groups were equivalent in regard to sex, age, histology, stage of disease, and type of operation. The overall survival, recurrence-free interval, metastasis-free interval, and disease-free interval within the two groups and within subgroups were compared with the log rank test,[11] and two-sided p values were derived. Survival time was defined as the time elapsing between operation and death. A patient's follow-up was considered to be censored at the time of his death in case this death was not the result of carcinoma or in case the cause of death was unknown. Disease-free interval was defined as the time elapsing between operation and the first local recurrence or metastasis or both.

Results

The study group and control group turned out to be alike in respect of age, sex, histology, stage of disease, and type of operation (see table). A higher proportion of anaplastic tumours in the control group was found, explained by the fact that a more extensive search for metastases since 1977 has resulted in non-surgical treatment in a higher number of these patients.

The median time of follow-up in the study group and control group was 10 and 28 months respectively. The survival curves of the study group and the control group did not differ significantly (log rank

test $\chi^2 = 1{\cdot}11$, $p > 0{\cdot}1$, fig 1). Furthermore, the shape of the survival curves did not differ materially in the two groups, and when comparing the disease-free intervals there were no significant differences between the two groups.

Removal of patients with anaplastic carcinoma and unknown histology did not influence these results. Subgroups of the study group consisting of all patients with epidermoid carcinoma stage I, or stage I plus stage II, showed no differences from the equivalent subgroup of the controls in respect of survival and disease-free interval. Other subgroups according to histology and stage were too small for statistical analysis.

In a subsequent analysis patients with epidermoid carcinoma stage I who received BCG (28 out of the total BCG group of 56) were compared with the equivalent subgroup out of the controls (n= 49). It was found that the disease-free interval was significantly shorter in patients who received BCG ($\chi^2 = 4{\cdot}540$, $p < 0{\cdot}05$, fig 2). This effect was mainly caused by the earlier appearance of local recurrences and to a lesser extent by the appearance of distant metastases in the BCG-treated patients. As for survival, there were six deaths from carcinoma among the 28 BCG receivers and five among the 49 controls at 24 months follow-up ($0{\cdot}05 < p < 0{\cdot}10$, median time of follow-up 15 and 32 months respectively).

When comparing the 36 BCG-treated patients with epidermoid carcinoma stage I plus stage II with the equivalent subgroup of the controls (n = 67) comparable results were obtained: a statistically significantly shorter disease-free interval in the BCG receivers was seen ($p < 0{\cdot}05$), mainly because of the earlier appearance of local recurrences, and a trend towards a shorter survival ($0{\cdot}05 < p < 0{\cdot}10$).

After removal of patients with epidermoid carcinoma stage I no differences were found between the BCG receivers and the controls. Other subdivisions of the BCG-treated patients resulted in groups too small for analysis. The time of follow-up was too short to evaluate a dose-dependent effect of the BCG.

Discussion

The study group and the control group turned out to be sufficiently alike for it to be likely that differences in survival and disease-free interval between the two groups are caused by the BCG treatment. Since a patient had to be in a relatively good condition to be selected for BCG treatment, any bias should expectedly have favoured the BCG receivers. However, our results show no evidence of any benefit and even suggest an adverse effect of BCG in epidermoid tumours.

The observation that BCG had an even more unfavourable influence on local recurrences than on the occurrence of metastases might indicate that intrapleural BCG causes enhancement of local tumour growth. This phenomenon has been demonstrated in some experimental animal tumour systems after excessive doses of BCG.[12 13] We are not aware of any previous studies documenting the alarming occurrence of tumour enhancement after intrapleural BCG in patients with lung cancer.

McKneally *et al* reported a significant reduction in the incidence of recurrences and increased survival in patients with stage I carcinoma treated with postoperative intrapleural BCG, but subsequent trials have raised serious questions about the efficacy of intrapleural BCG.[3 14–17]

Our BCG treatment differs on several points from McKneally's, the main ones being that we used a different BCG strain (Pasteur versus Tice) and a different dosage (16, 32, and 64×10^6 against 10×10^6 cp). Moreover, we instituted isoniazide treatment three weeks after BCG administration whereas McKneally *et al* started it two weeks after. It has been clearly shown in animal studies that different BCG vaccine products show a different immunostimulating potency depending on the method of preparation.[18] This aspect of BCG adjuvant therapy hinders proper comparison of studies with different BCG strains and preparations.

We have observed serious side-effects caused by the intrapleural administration of BCG.[19] The strong specific inflammatory reaction apparently evoked failed to produce the desired non-specific immunostimulative action.

We conclude that postoperative intrapleural BCG in lung cancer, as used in this study, has no beneficial effect on survival or on disease-free interval. Evidence to the contrary has been presented hinting to a possible enhanced tumour growth in patients with stage I epidermoid carcinoma.

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