

Use of BCG as an immunostimulant after resection of carcinoma of the lung: a two-year assessment of a trial of 500 patients*†

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ABSTRACT BCG (Glaxo) ($0.5 \text{ ml} = 5 \times 10^6$ organisms) was given subdermally to 250 patients ten days after resection of a lung carcinoma to stimulate the immune system. Increased activity of lymphocytes and macrophages could possibly result in the destruction of small extrapulmonary tumour deposits that were previously unidentified. The two-year survival of this group of patients was compared with 250 controls not receiving BCG after operation. A comparative analysis of the sex, histological types, and lymph node involvement in relation to the survivals occurring in these two groups showed that the administration of BCG by the method described produced a numerically greater survival rate, which was particularly noticeable in the women. None of these figures, however, is statistically significant. It would be unwise to draw any final conclusion until a five-year survey has been completed.

That some immunological control over the growth of cancer cells in the body might be obtained by increasing the number and activity of lymphocytes and macrophages has been shown from experiments in animals undertaken by many investigators. Various agents—zymosan (Bradner *et al* 1958), phytohaemagglutinin (Oppenheim *et al*, 1965), *Corynebacterium parvum* (Halpern *et al*, 1966), oestrogen (Biozzi *et al*, 1957) Bacille Calmette-Guérin (BCG) (Old *et al*, 1959), and others—have been shown to be active stimulators for this purpose.

Clearly whatever agent was used it or the stimulated lymphocytes and macrophages had to be carried to the neoplasm by the blood stream. Because of the relative ischaemia of most tumours, the agent or cells could therefore be brought into effective contact with only isolated or small agglomerations of tumour cells. It was thus mandatory that the main mass of tumour should be removed at operation and then the immunostimu-

lant agent should be administered to control the growth of isolated non-demonstrable metastases, which would probably have been ultimately responsible for death. In view of the active cellular content of lymph nodes it might be that after operation small deposits left behind in these locations could be more adequately dealt with by the body after the use of an immunostimulant agent.

Of the materials available, BCG seemed to be the most acceptable as a supplement to the surgical resection of carcinoma of the lung. BCG could be given in one dose, and its action could persist for three to four months. It was unlikely to produce any serious side effects, and if it did these could be controlled by isoniazid (INAH).

Method of administration of BCG

It was considered that the standard technique of BCG inoculation by intradermal puncture or scarification could not be used satisfactorily in these rather elderly postoperative patients as it would require weekly or fortnightly visits, often from a distance. Accordingly, it was decided to give 0.5 ml of BCG (Glaxo) (5×10^6 organisms) subdermally in the deltoid region 10 days after operation. This resulted in an active lesion presenting as a subcutaneous swelling 2–3 cm in diameter,

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which nearly always broke down into a series of sinuses or an ulcer 1–2 cm across. This type of resection was relatively painless and required only a dry dressing that could be managed by the patient's family. Healing would not take place for four to six months. In only one case did a flagrant and spreading lesion develop and this was controlled by INAH. In a few secondary infection occurred, which was treated by an oral antibiotic.

Establishment of the trial

To discover the possible effects of giving BCG in the postoperative stages a pilot study was made of 60 consecutive surviving patients who had undergone lung resection by one surgeon between October 1970 and December 1971 and had been given BCG by the method described. The survival rate was compared with the previous 60 consecutive surviving patients, operated on by the same surgeon, who had not received BCG. Two-year and five-year follow-up reports of this series have been published (Edwards and Whitwell, 1974, 1978). As no serious complication followed the use of this technique, it was considered safe and a larger fully randomised trial was started in December 1971. It was considered that only a large number of cases of resection of lung carcinoma could eliminate those factors that influence small series. In view of the difficulties of assessing and analysing signs and symptoms in the months after operation, the only feature that would give a factual estimate of the effects of BCG would be the length of survival after operation. The determination of the survival rate at two years and five years after operation in the BCG and the control group was the purpose of this trial.

It was not possible to determine the exact cause of death in such a large group of cases, and the death certificate could not be accepted as a reliable explanation of the death of the patient. While most patients would die as a direct result of the extension of the malignant disease, quite a number would die of unrelated causes in view of the age of the group. It was assumed that in 500 cases the number would be similar in both groups.

Five hundred consecutive patients who survived resection of a carcinoma of the lung and who were discharged from hospital were selected for this trial. They were all operated on by members of the surgical staff of the Liverpool Regional Cardiothoracic Surgical Centre. The selection of cases for operation and the operative and postoperative management were similar for all surgeons. It is an agreed policy to undertake resection of the

lung for carcinoma only if all macroscopic disease can be extirpated. The presence of affected lymph nodes is not considered a contraindication to resection provided they can be removed. A patient with an oat cell carcinoma diagnosed by bronchoscopic biopsy or sputum cytology was not considered unsuitable for surgery, and was given a preoperative assessment similar to patients with other histological types. "Palliative" resection in the presence of irremovable extension of the tumour or distant metastases is undertaken only in the most exceptional circumstances, and any such cases were not entered into the trial.

Two hundred and fifty patients were to receive BCG in the postoperative phase, and 250 patients were used as a control. The choice of the group in which the patient was to be entered was based on alternation by a disinterested person at the time of registration, which was three days after the operation. In the event 561 patients were registered of whom 61 were rejected because of death before leaving hospital, change of diagnosis, or non-administration of BCG.

The BCG was given on the tenth day after the operation, and the patient then attended the routine follow-up in the outpatient department. Adjuvant radiotherapy or chemotherapy was given to those patients who developed a late metastatic lesion causing symptoms.

Any patient who did not leave hospital after operation was rejected from the trial as the cause of death was probably related to the operation rather than the carcinoma.

All resected specimens were submitted to one of three pathologists, and the histological reports used in the trial were those on the resected specimen and the associated lymph nodes.

All patients were registered with the Mersey Regional Cancer Registry who undertake an annual follow-up of all cancer cases. The survival of patients at two years was obtained with the help of this organisation. Five patients were untraceable, two in the control group and three in the BCG group, and these patients were assumed to be dead.

Results

Table 1

Table 1 shows that the two groups were closely matched as to sex, type of operation, and histological type.

Table 2

The overall survival rate at two years was 114/250

Table 1 Comparison of control and BCG groups

	Control		BCG	
No of patients	250	Average age	250	Average age
Men	204	60.1	206	60.0
Women	46	60.4	44	56.9
Operations				
Pneumonectomy	119		119	
Lobectomy, bilobectomy, or sublobectomy	131		131	
Histology		M		M
Squamous cell	152	132	152	131
Adenocarcinoma	51	40	47	39
Oat cell carcinoma	15	9	20	13
Carcinoma simplex	21	15	23	17
Mixed cell	5	3	4	4
Alveolar cell	4	3	1	0
Clear cell	2	2	3	2

Table 2 Two-year survival rate of histological types in control and BCG groups

	Control			BCG		
	Total No	Survivors	%	Total No	Survivors	%
Squamous cell	152	83	54.6	152	77	50.6
Adenocarcinoma	51	15	29.4	47	20	42.6
Oat cell carcinoma	15	4	26.7	20	6	30.0
Carcinoma simplex	21	8	38.1	23	14	60.9
Mixed cell carcinoma	5	1	20.0	4	1	25.0
Alveolar cell carcinoma	4	1	25.0	1	1	100
Clear cell carcinoma	2	2	100	3	0	0
Total	250	114	45.6%	250	119	47.6

(45.6%) in the control group and 119/250 (47.6%) for the BCG group.

Table 3

Comparing the two-year survival rate in the two sexes the number of male survivors was about the same in the two groups—(control 46.1%; BCG 45.6%). There were however more female survivors in the BCG group (control 43.5%; BCG 56.8%). $\chi^2=1.6$.

Table 4

Positive lymph nodes were found in 109 of the control group and 108 of the BCG group (table 4).

In the control group 26.6% of those with positive nodes and 60.3% of those with negative nodes survived two years, while in the BCG group 34.5% of those with positive nodes and 57.7% of those with negative nodes survived two years ($\chi^2=1.5$).

Table 5

Analysis of the sex distribution of the two-year survival of the positive and negative node groups shows that while the male survival rates were similar, there was a contrast, which however was not significant, in the survival rate of the women with positive nodes when comparing the two groups:

Table 3 Two-year survival rate in men and women in control and BCG groups

	Control					BCG				
	Total	Male survivors		Female survivors		Total	Male survivors		Female survivors	
	No	No	%	No	%	No	No	%	No	%
Squamous cell	152	73/132	55.3	10/20	50.0	152	66/131	50.4	11/21	52.4
Adenocarcinoma	51	11/40	27.5	4/11	36.4	47	15/39	38.5	5/8	62.5
Oat cell carcinoma	15	2/9	22.2	2/6	33.3	20	3/13	23.1	3/7	42.8
Carcinoma simplex	21	5/15	33.3	3/6	50.0	23	9/17	52.9	5/6	83.3
Mixed cell	5	1/3	33.3	0/2	0.0	4	1/4	25.0	0/0	—
Alveolar cell	4	0/3	0.0	1/1	100	1	0/0	—	1/1	100
Clear cell	2	2/2	100	0/0	—	3	0/2	0.0	0/1	0.0
Total	250	94/204	46.1	20/46	46.1	250	94/206	45.6	25/44	56.8

Table 4 Two-year survival rate of patients with positive and negative nodes in different histological groups

	Control						BCG					
	Nodes positive			Nodes negative			Nodes positive			Nodes negative		
	Total		Alive	Total		Alive	Total		Alive	Total		Alive
	No	%		No	%		No	%		No	%	
Squamous cell	67	25	37.3	85	58	68.2	62	25	40.3	90	52	57.8
Adenocarcinoma	24	2	8.3	27	13	48.1	23	6	26.1	24	14	58.4
Oat cell carcinoma	9	1	11.1	6	3	50.0	12	2	16.7	8	4	50.0
Carcinoma simplex	6	1	16.7	15	7	46.7	8	3	37.5	15	11	73.3
Mixed cell	1	0	0.0	4	1	25.0	3	1	33.3	1	0	0.0
Alveolar cell	2	0	0.0	2	1	50.0	0	0	0.0	1	1	100.0
Clear cell	0	0	0.0	2	2	100.0	0	0	0.0	3	0	0.0
Total	109	29	26.6	141	85	60.8	108	37	34.3	142	82	57.7

Table 5 Two-year survival rate of men and women with positive and negative nodes

	Control								BCG							
	Nodes positive				Nodes negative				Nodes positive				Nodes negative			
	Men		Women		Men		Women		Men		Women		Men		Women	
	alive	%	alive	%	alive	%	alive	%	alive	%	alive	%	alive	%	alive	%
Squamous cell	23/58	39.7	2/9	22.2	50/74	65.5	8/11	72.7	20/50	40.0	5/12	41.7	46/81	56.8	6/9	66.7
Adenocarcinoma	1/17	5.9	1/7	14.3	10/23	43.5	3/4	75.0	3/19	15.8	3/4	75.0	12/20	60.0	2/4	50.0
Oat cell carcinoma	0/6	0.0	1/3	33.3	2/3	66.6	1/3	33.3	2/9	22.2	0/3	0.0	1/4	25.0	3/4	75.0
Carcinoma simplex	1/5	20.0	0/1	0.0	4/10	40.0	3/5	60.0	1/6	16.6	2/2	100.0	8/11	72.7	3/4	75.0
Mixed cell	0/0	0.0	0/1	0.0	1/3	33.3	0/1	0.0	1/3	33.3	0/0	0.0	0/1	0.0	0/0	0.0
Alveolar cell	0/2	0.0	0/0	0.0	0/1	0.0	1/1	100.0	0/0	0.0	0/0	0.0	0/0	0.0	1/1	100.0
Clear cell	0/0	0.0	0/0	0.0	2/2	100.0	0/0	0.0	0/0	0.0	0/0	0.0	0/2	0.0	0/1	0.0
Total	25/88	28.4	4/21	19.0	69/116	59.5	16/25	64.0	27/87	31.0	10/21	47.6	67/119	56.3	15/23	65.2

Female positive nodes control = $\frac{4/21}{10/21} = 19.0\%$
 Female positive nodes BCG = $\frac{10/21}{10/21} = 47.6\%$
 $(\chi^2=3.86$ with Yates's correction $\chi^2=2.68$).
 $(P=0.10)$.

Table 6 Survival in the main histological types of lung carcinoma

While no results based on survival can be fully accepted until a five-year survey is carried out, certain observations on the possible effect of BCG on the various histological types can be made as a result of the two-year survey.

Squamous cell carcinoma—In this differentiated group the total number of survivors who had received BCG (77/152=50.6%) was less than the controls (83/152=54.6%). The number of women with positive nodes alive at two years was nearly twice as many in the BCG treated cases (5/12=41.7%) as in the controls (2/9=22.2%).

Adenocarcinoma—The total survival rate in the BCG group was higher (20/47=42.6%) than in the controls (15/51=29.4%) $\chi^2=1.84$. All groups except women with negative nodes show more survivors when given BCG.

Table 6 Composite table of two-year survival of main histological groups

	Squamous cell carcinoma		Adenocarcinoma		Oat cell carcinoma		Carcinoma simplex	
	Control	BCG	Control	BCG	Control	BCG	Control	BCG
No of patients	152	152	51	47	15	20	21	23
Percentage two-year survival rate								
Men: Total	55.3	50.4	27.5	38.5	22.2	23.1	33.3	52.9
With positive nodes	39.7	40.0	5.9	15.8	0.0	22.2	20.0	16.6
With negative nodes	65.5	56.8	43.5	60.0	66.6	25.0	40.0	72.7
Women: Total	50.0	52.4	36.4	62.5	33.3	42.8	50.0	83.3
With positive nodes	22.2	41.7	14.3	75.0	33.3	0.0	0.0	100.0
With negative nodes	72.7	66.7	75.0	50.0	33.3	75.0	60.0	75.0
Total	54.6	50.6	29.4	42.6	26.7	30.0	38.1	60.9

Oat cell carcinoma (small cell carcinoma)—The two-year survival rate in all categories of patients with an oat cell carcinoma are similar whether BCG was given or not. It might be expected that in this active form of tumour the speed of cell multiplication would be much greater than could be coped with by cellular immunity, however much it was stimulated. It should be noted, however, that over a quarter of the patients in both groups survived two years (control group 4/15=26.7%, BCG group 6/20=30.0%). While these results are not good they do not justify the pessimism concerning surgery for oat cell carcinoma that has recently developed.

Carcinoma simplex (undifferentiated carcinoma)—The survival rate at two years of the BCG group is considerably better than that of the controls.

$$\frac{\text{Carcinoma simplex controls}}{\text{Carcinoma simplex BCG}} = \frac{8/21}{14/23} = \frac{38.1\%}{60.9\%}$$

$\chi^2=2.3$; with Yates's correction $\chi^2=1.1$.

This improved survival rate with BCG is reflected throughout all categories of the carcinoma simplex group, and the undifferentiated cell may be more susceptible to cellular immunity.

Mixed cell carcinoma, alveolar cell carcinoma (bronchiolar carcinoma, pulmonary adenomatosis), and **clear cell carcinoma**—The numbers in these three groups are too small for any discussion.

Although there are trends visible in the response of these different histological types to the administration of BCG, none of the figures are statistically significant. Similar trends were noticeable in our original pilot study at the two-year review, but they became less definite at five years (Edwards and Whitwell, 1974, 1978).

Table 7 Length of survival of patients dying at two years

There is a slightly longer average survival (six weeks) in the patients dying under two years who had received BCG. This was more noticeable in the squamous cell group (nine weeks) (table 8).

Table 7 Length of survival in months of patients dying in under two years after lung resection

	Control	BCG
No of patients	136	131
Months		
Men	8.8	10.3
Women	9.4	11.1
Total	8.9	10.4

Table 8 Length of survival in months of patients dying in under two years after lung resection—histological groups

	Control		BCG	
	No of patients	Months	No of patients	Months
Squamous cell carcinoma	69	8.8	75	11.0
Adenocarcinoma	36	8.9	27	10.6
Oat cell carcinoma	11	7.4	14	7.1
Carcinoma simplex	13	10.4	9	10.3
Others	7	9.9	6	10.4
Total	136	8.9	131	10.4

TYPE OF OPERATION

It was decided that a detailed analysis as to whether survival was affected by the type of operation would be of no value. The age and size of a tumour influences the surgeon in deciding whether a pneumonectomy or a lesser operation is required; similarly, the presence of hilar glands, even though the primary tumour was small, would encourage a more radical type of operation.

Conclusions

After resection for lung carcinoma the administration of BCG has resulted in a numerically improved survival rate in adenocarcinoma (29.4% to 42.6%) and carcinoma simplex (38.1% to 60.9%). The survival rate in women as a whole is improved (46.1% to 56.8%). There is a small increase in the survival of those with positive nodes at the time of operation (26.6% to 34.3%), but this is mainly due to a striking increase in the female survivors in this group (19.0% to 47.6%).

Patients dying within two years of operation have lived on average 1.5 months longer with BCG (8.9 to 10.4 months).

None of the above figures is statistically significant. The impression is gained, however, throughout this survey that BCG has a more specific action on women than men. Whether it is easier to stimulate the immune system in women, or whether there is some other factor is not clear. Further study of this aspect might be profitable.

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