Influence of postoperative empyema on survival after pulmonary resection for bronchogenic carcinoma

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Summary and conclusions

Fifty patients who had developed empyema after pulmonary resection for primary carcinoma of the lung were individually paired with patients who had not suffered this complication. Pairs were matched as far as possible for age, sex, extent of operation, histology of tumour, extent of primary spread, extent of lymphatic spread, and use of postoperative radiotherapy. Analysis of survival times both for the matched pairs and for the two groups of patients showed no significant difference in long-term survival.

The results suggest that any immunological suppression of carcinoma cells due to sepsis in the pleural space is ineffective in prolonging survival.

Introduction

Le Roux[1] suggested that postoperative chronic empyema might prolong survival in some patients after resection for primary carcinoma of the lung. This was also Williams and Lewis's[2] impression when they reviewed the results of bronchopleural fistula at this hospital. If confirmed it could influence management and give credence to attempts to generate an anamnestic immunological response.

Several small studies have tried to compare survival in infected and uninfected cases but with conflicting results.[3-6] These studies, however, were based on relatively few patients with empyema and made no attempt to match individual patients in pairs. We have therefore carried out a study based on our hospital records in which each patient with empyema was accurately matched and paired with an uninfected patient.

Patients and methods

Out of the records of 3450 patients who had undergone thoracotomy for lung neoplasms at this hospital during 1950-76, only 50 cases were found suitable for the empyema group. Except for the initial infection, all these patients had made a satisfactory postoperative recovery and been discharged from hospital. These 50 patients were paired with patients from the parent group who had not developed empyema and who thereby served as controls.

Pairs were matched for the following variables: (1) age; (2) sex; (3) type of operation (pneumonectomy or lobectomy, including sleeve resection); (4) extent of growth of the primary neoplasm—namely, (*a*) confined to lung or invading as far as the visual pleura only, (*b*) extending to parietal pleura, (*c*) extending to parietal pleura, ribs, and intercostal muscles, and (*d*) invading mediastinum; (5) histology of the neoplasm—namely, (*a*) squamous-cell carcinoma, (*b*) undifferentiated carcinoma, (*c*) oat-cell carcinoma, (*d*) adenocarcinoma, and (*e*) alveolar-cell carcinoma; (6) extent of spread to lymph nodes (histological)—namely, (*a*) no deposits in lymph nodes, (*b*) deposits in intrapulmonary lymph nodes only, (*c*) deposits in hilar lymph nodes, and (*d*) deposits in mediastinal lymph nodes; and (7) use of postoperative radiotherapy.

Survival was measured from the date of operation. In the case of six patients who were still alive at the time of the study the survival period was taken as the date of operation to the date of the last outpatient attendance. Of these six patients, two in the empyema group were paired with live (at the time of the study) control patients who had been operated on in the same year. One other patient in the empyema group and one in the control group who were still alive at the time of the study were each paired with a patient who had had his operation in the same year.

The overall survival time and 10-year and five-year survival rates in the empyema group were compared with those in the control group. The overall periods of survival in the matched pairs were also compared. For statistical analysis both parametric (*t* tests) and non-parametric tests (Wilcoxon's rank sum and matched-pairs signed ranks tests) were used. The groups were compared both matched and unmatched. The χ^2 test was used to compare percentages. Sequential analysis of the data was also carried out with a closed sequential sign test according to the method described.[7]

Results

The durations of sepsis in the empyema group ranged from one to 181 months (mean 19 months, median 7·7 months—table I). In 40 cases the empyema was due to bronchopleural fistula.

The following results were obtained from analysis of the 50 matched pairs.

Age at time of operation—The mean ages (±SD) in the empyema and control groups at the time of operation were 58·78±6·85 and 58·60±6·54 years respectively (table II). This difference was not significant (P=0·89). In 41 matched pairs the age difference between the patients was five years or less (in half of these the patient with empyema was older); in eight the age difference was 6-12 years (the patient with empyema being older in five); and in one matched pair the patient with empyema was 41 and the control patient 61 years of age.

Sex—There were only two women in the series; these were paired.

Type of operation—Perfect match was achieved for all 50 pairs: 36 had undergone pneumonectomy, and 14 lobectomy.

Extent of growth of primary neoplasm—Forty-one pairs were matched perfectly. In 37 of these the carcinoma was confined to the lung or had invaded the visceral pleura; in one it had extended to parietal pleura; and in three it had invaded the mediastinum. There were nine imperfect matches, most of them differing in only one category.

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TABLE I—*Durations of sepsis in the 50 patients who developed empyema after thoracotomy for lung neoplasms*

	Duration of sepsis (months)														Total
	1-3	-6	-9	-12	-15	18-21	-24	34	36	48	66	71	180	181	
No of patients ..	8	10	8	6	7	2	2	1	1	1	1	1	1	1	50

TABLE II—*Ages at time of operation in the empyema and control groups*

	Age in years							Total
	40-	45-	50-	55-	60-	65-	70-75	
No in empyema group ..	2	2	7	17	10	8	4	50
No of controls	2	2	5	21	11	8	1	50

Histology of neoplasm—A complete match was possible in all except one of the pairs, in which a patient with empyema and alveolar-cell carcinoma was matched with a control patient with adenocarcinoma. Thirty-three pairs had squamous-cell carcinoma, eight undifferentiated carcinoma, five oat-cell carcinoma, and three adenocarcinoma.

Extent of spread to lymph nodes—There were 43 pairs who matched perfectly, 19 of whom did not have deposits in lymph nodes. Of the remaining pairs, one had deposits in intrapulmonary lymph nodes, 13 deposits in hilar lymph nodes, and 10 deposits in mediastinal lymph nodes. Most of the seven pairs of imperfect matches varied in only one category.

Postoperative radiotherapy—Four pairs of patients had received radiotherapy, and a complete match was possible.

In 32 matched pairs the same surgeon had performed the operation. At the time none of the patients had clinical or radiological evidence of secondary carcinoma, neuropathy, or myopathy. Altogether 30 pairs of patients matched perfectly for all seven variables and categories (matching for age being assumed to be perfect when the difference was five years or less). Of the remaining 20 pairs, 12 matched for six variables. In five of these pairs the mismatch occurred in the extent of growth of the primary tumour, in three it occurred in the extent of lymphatic spread, and four mismatched for age. In eight pairs there was a perfect match for five variables.

Table III gives the periods of survival in the matched pairs. The overall mean durations of survival in the empyema and control groups were 3·41 (median 1·60) and 3·02 (median 1·00) years respectively (table IV). This difference was not significant (P = 0·61). The two groups of 30 patients who matched for all seven variables differed even less in their durations of survival, the group means being 3·91 and 3·70 years respectively (P = 0·86). The 95% confidence limits of the mean difference were −1·1 and 1·9 years. If a log normal distribution is assumed, the 95% confidence limits were −1·3 and 1·8 (where −1·1 and −1·3 are in favour of the control group).

The five-year survival rates in the empyema and control groups were 24% (12 patients) and 22% (11) respectively. This difference was not significant ($\chi^2 = 0{\cdot}06$; P = 0·8). The 95% confidence limits of the mean difference were −15% and 19% (where −15% is in favour of the controls). The 10-year survival rates in the two groups were the same—10% (five patients).

Analysis of the 50 matched pairs with Wilcoxon's matched-pairs signed ranks test showed no significant difference in survival times between the patients with empyema and controls (P = 0·66). The same test applied to the 30 pairs matched for all seven variables produced a similar result (P = 0·62). As the distribution of survival times was very skew, logarithms of survival times were also used; again no significant differences were found. When the closed sequential sign test (the date of operation for the first member of each pair being used as the sequencing indicator) was used on the 50 pairs the middle boundary of the test was crossed after 40 pairs ($2\alpha = 0{\cdot}2$, $1\text{-}\beta = 0{\cdot}95$, $\sigma = 0{\cdot}75$), suggesting no significant difference in survival times.

The commonest organism cultured from the empyema fluid was *Staphylococcus pyogenes*. Others in order of prevalence were *Escherichia coli*, *Pseudomonas aeruginosa*, streptococci, and *Haemophilus influenzae*.

There were too few patients to permit a statistically meaningful assessment of survival according to type of organism. Our results however, suggested that the difference in survival in favour of the empyema group was greater in patients infected with *E coli* and *Ps aeruginosa*.

TABLE III—*Durations of postoperative survival (years) of the matched pairs of patients from the empyema and control groups*

Pair	Empyema	Control	Pair	Empyema	Control	Pair	Empyema	Control
1	0·14	0·40	18	0·90	1·64	35	2·93	1·51
2	0·14	1·25	19	1·97	0·30	36	2·96	20·82
3	0·16	0·78	20	1·20	2·76	37	3·13	1·89
4	0·20	0·85	21	1·21	0·60	38	3·51	0·64
5	0·35	0·49	22	1·27	0·61	39	5·07	7·02
6	0·36	2·33	23	1·31	1·94	40	5·12	0·39
7	0·37	0·22	24	1·31	2·39	41	5·59	5·44
8	0·53	0·91	25	1·56	18·04	42	5·92	0·54
9	0·57	0·20	26	1·64	0·48	43	6·00	5·10
10	0·63	0·66	27	1·93	0·31	44	7·47	13·21
11	0·64	0·65	28	2·05	1·08	45	8·34	10·33
12	0·75	0·79	29	2·06	0·16	46	10·63	0·18
13	0·77	5·14	30	2·10	5·30	47	15·24	0·60
14	0·79	1·39	31	2·12	0·36	48	15·24	2·19
15	0·79	2·45	32	2·52	0·57	49	15·99	6·39
16	0·86	0·65	33	2·61	4·44	50	18·93	10·49
17	0·85	0·93	34	2·67	1·51			

Discussion

The variables used for pairing patients were chosen because of their considered importance in influencing survival. Any possible effect of age and sex was excluded by matching individual pairs accordingly. Histology was considered to be a most important factor influencing survival, and in this respect matching was perfect in 49 pairs. In view of the diversity and number of variables considered it was not surprising that in 20 out of 50 pairs matching was less than perfect. Nevertheless, the non-correspondence in these cases was relatively minor.

Comparisons were made between groups as well as within pairs to ensure that any significant difference in survival times was not overlooked. None of the comparisons showed a significant difference in survival, and when the 30 pairs matched for all seven variables were considered the differences were even smaller. We therefore conclude that postoperative empyema does not influence survival in patients who have had pulmonary resection for bronchogenic carcinoma.

Our conclusions differ from those of Cady and Clifton,[3] Takita,[1] and Ruckdeschel *et al*[5] and agree with those of Lawton and Keehan.[6] Cady and Clifton analysed five-year survival rates in 40 patients with empyema and 333 patients without and found rates of 13% and 35% respectively. They concluded that this difference was significant at the 1% level (χ^2 6·72). Takita, who analysed five-year survival rates in only 14 patients with empyema compared with 178 patients without, found rates of 54% and 27% respectively and concluded that empyema may have a favourable influence on survival. Ruckdeschel *et al* compared the five-year survival rate in 18 empyema patients with that in 34 non-empyema patients. The patients were divided into four groups according to Feinstein's[8] clinicopathological classification. Survivals of patients in various combinations of these groups and in the four groups as a whole were compared. Differences in survival in favour of the empyema groups were considered to be significant. The largest difference was between patients with growth confined to lung and those with regional intrathoracic lymph nodes.

In our study there were 22 such pairs of patients who matched for all seven variables: the mean period of survival in the empyema group was 4·81 years and in the control group 4·85 years. This difference was not significant (P < 0·8).

Lawton and Keehan analysed the five-year survival rates in 34 empyema patients and 899 non-empyema patients and found rates of 17·6% and 25·2% respectively. They concluded that this difference was not significant.

TABLE IV—*Durations of postoperative survival in the empyema and control groups*

	Duration of survival (years)																	Total
	≤0·5	-1	-1·5	-2	-2·5	-3	-3·5	-4	-4·5	5-6	-7	-8	-9	10-12	-14	-16	18-20	-22	
No in empyema group..	7	12	5	3	4	5	1	1		4	1	1	1	1		3	1		50
No of controls	10	14	3	5	5	1			1	4	1	1		2	1		1	1	50

Several studies have suggested that stimulation of the immune system with non-specific agents, including bacteria such as BCG and *Corynebacterium parvum*, may help to delay or partially suppress the growth of some neoplasms,[9 11] especially if administered locally.[11-13] Lung cancers have tumour-associated antigens,[14-16] but some patients are immunosuppressed and cannot respond.[17] Khadzhiev and Kavaklieva-Dimitrova[18] administered BCG to patients with carcinoma of the lung and observed radiological evidence of regression in 28% of cases and an improvement in survival. Pimm and Baldwin[19] showed that intrapleural administration of BCG may suppress the pleural growth of transplanted rat tumour. Ruckdeschel *et al*[5] postulated a mechanism by which the reaction of the immune system, evoked by intrapleural sepsis, may destroy residual cancer cells.

Our findings suggest that any possible suppression of carcinoma cells due to sepsis in the pleural space is inadequate to prolong survival.

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Trial of high-titre human rubella immunoglobulin

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Summary and conclusions

To test the efficacy of passive antibody for protecting susceptible pregnant women who have been exposed to rubella high-titre human rubella immunoglobulin (HRI) was given to 20 seronegative male adult volunteers simultaneously with rubella vaccine. After receiving the intramuscular injections of HRI (750 mg of IgG) and vaccine ($10^{3.92}$ median tissue culture dose, Wistar RA27/3 subcutaneously) eight of the 20 volunteers failed to show seroconversion. Antibody responses—and thus presumably viraemia—in the remaining 12 volunteers were delayed and reduced when compared with those in 19 volunteers given the vaccine alone. No significant responses occurred in volunteers given only HRI.

We conclude that HRI may be of value for seronegative pregnant women who come into contact with clinical rubella, particularly when termination is likely to be refused.

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Introduction

Since laboratory tests for rubella[1] were introduced several studies[2-4] have shown that human normal immunoglobulin has no prophylactic or therapeutic value in natural rubella infections. Pepsin-treated human normal immunoglobulin given intravenously[5] and preparations of high-titre human rubella immunoglobulin[6] (HRI) given intramuscularly, however, have proved 100% effective when used for pre-exposure prophylaxis in in-vivo experimental studies. A useful immunising effect was also observed when HRI was given up to three days after experimental intranasal infection.[7] Shortage of HRI has limited further studies, but as a batch was prepared in 1974 by the protein fractionation centre of the Scottish Blood Transfusion Service we undertook a study to establish whether HRI modifies or prevents rubella infection in susceptible pregnant women who have been exposed to the infection. To simulate the natural infection and its prophylaxis we gave rubella vaccine alone, HRI alone or both simultaneously to rubella-susceptible male adult volunteers and followed them up clinically and serologically (GEDU and RJC) for 12 weeks.

Subjects and methods

Plasma specimens from about 1500 male blood donors aged under 30 were tested by the haemagglutination inhibition (HI) technique[8] for rubella antibody, and 52 out of the 238 who were susceptible volunteered to take part in the trial. Susceptible subjects were defined as those who had no detectable antibody on duplicate serum testing at a dilution of 1 in 8. Similarly, out of 80 male medical students, eight of 12 who were susceptible volunteered. All volunteers were given a detailed explanation of the study before they agreed to participate. None had any contraindication to the vaccine, and though there appear to be no risks from spread of vaccine virus they were advised to avoid close contact with any pregnant woman throughout the 12-week study period.