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Prognostic features of large cell anaplastic carcinoma of the bronchus

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ABSTRACT The clinical features of 208 patients with large cell anaplastic carcinoma of the bronchus are reviewed. Of the sample 47·6% had disseminated disease at presentation, and 95% were cigarette smokers. The median survival was 6·0 months and five-year-survival was 5·9%. Twenty-seven per cent of the patients had surgical resection of tumour. The median survival of resected patients was 13·0 months and five-year-survival was 21%. Radiotherapy was ineffective in controlling the disease in this series.

Large cell carcinoma of the bronchus accounts for 7–14% of all bronchogenic carcinomas.[1–3] In 1948 Willis[4] proposed a unitary view of bronchogenic carcinoma as he found that in a series of 84 cases, 19 (23%) had features of more than one cell type. A different conclusion was reached by Walter and Pryce[3] who reviewed 207 resection specimens and material from 159 postmortems. They divided the tumours into oat cell, squamous cell, adenocarcinoma, and a fourth anaplastic group that lacked squamous or glandular features and that did not resemble oat cell carcinoma. They suggested that this group might represent either anaplastic squamous carcinoma or adenocarcinoma. They found no convincingly mixed tumours. The cellular variability they did find in individual tumours was the result of secondary change within the tumour, and they concluded that histological types of bronchogenic carcinoma were distinct and not degrees of a spectrum.

For practical purposes a modified World Health Organisation classification[5] is used by most histopathologists, the four common tumours being epidermoid, adenocarcinoma, small cell anaplastic carcinoma, and large cell carcinoma. This last group consists of large undifferentiated cells lacking features of the other three common tumours and lacking the special features of the rare pulmonary neoplasms. Prognosis and response to treatment depend on the histological type of tumour,[6 7] and although there are many general large retrospective studies of bronchogenic carcinoma,[2 8 9] the natural history of each histological type is often not described separately. This is particularly so for large cell carcinoma which is usually considered together with small cell carcinoma. This is inappropriate, as small cell carcinoma is now understood to have a distinct cell of origin and biological behaviour.[10 11] On the other hand prospective studies of various treatments for carcinoma of the bronchus have focused attention on epidermoid, adeno, and small cell carcinoma of the bronchus.

This study was, therefore, undertaken to clarify the natural history of large cell carcinoma of the bronchus.

Methods

Case records of all patients with a diagnosis of large cell, anaplastic, or unclassified carcinoma of the bronchus were selected and the histology was reviewed.

Two hundred and eight patients with large cell carcinoma were diagnosed at Brompton Hospital from September 1968 to September 1978. This represents approximately 9% of all classified bronchogenic carcinomas diagnosed during that period. They were followed from first admission until death or until September 1978. Fifteen were lost to follow-up. Histology was reviewed by a consultant histopathologist (JB) and only cases fulfilling the following criteria were included: (1) cells greater than 12 μm in diameter; (2) no evidence of keratinisation; (3) no evidence of tubule formation or mucin production; (4) the sample

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examined was considered adequate to exclude the possibility of differentiation elsewhere in the tumour; (5) no features of the rare pulmonary neoplasms.

Clinical features

One hundred and fifty-nine patients were men and 49 were women, the male to female ratio being 3·2 : 1. The age range was from 36 to 82 years with a mean age of 59·6 years; 79·3% were between 50 and 70 years old. The mean ages for women and men were 56·8 years and 60·9 years respectively. Eleven of the patients stated that they were non-smokers and information on smoking was not available in a further seven. Of the smokers 9·4% smoked up to 10 cigarettes a day, 17·4% smoked 10–20 a day, 38·5% smoked 20–30 a day, 13·9% 30–40 a day, and 20·8% smoked in excess of 40 a day. The mean number of cigarettes smoked was 24·5 per day. At diagnosis, 159 had not stopped smoking, 26 gave up smoking over one year before diagnosis, and 16 gave up during the year before diagnosis. There was no record of asbestos exposure in any of the patients; 26 worked in the engineering or electrical industries.

The symptoms are summarised in table 1. Only nine patients (4·3%) were asymptomatic. Of the 41 (19·7%) patients who had other symptoms not mentioned in the table, seven had malaise, three had hoarseness, three complained of lumps in the neck, five had cerebral symptoms, two had dysphagia, one had abdominal pain, one had hypertrophic pulmonary osteoarthropathy, and one had fever.

Table 1 *Symptomatology of large cell carcinoma*

Symptoms	*Patients affected (%)*
Cough	61·5
Chest pain	48·0
Short of breath	44·2
Sputum	35·5
Haemoptysis	30·2
Weight loss	27·4
Other symptoms	19·7
Upper respiratory tract infection	8·6
Asymptomatic	4·3

Table 2 *Physical signs in large cell carcinoma*

Sign	*Patients affected (%)*
Chest signs (wheeze, crackles, effusion, etc.)	61·6
Cervical lymph node enlargement	27·5
No physical signs	22·6
Hepatomegaly	17·8
Clubbing	17·4
Pleural effusion	13·0
Superior vena cava obstruction	5·7
Central nervous system signs	4·8

The physical findings are summarised in table 2. One patient had a metastasis in the orbit. There were no cases of carcinomatous neuromyopathy. Only three (1·4%) patients had clinical evidence of bone involvement.

Investigations

Chest radiography revealed a right-sided abnormality in 112 patients (54%), and of these, 62 (30%) also had mediastinal involvement. Left-sided abnormality was present in 91 patients (44%) and 52 (25%) of these also had mediastinal involvement. Two patients had a normal chest radiograph, one had bilateral changes, and in two the records were lost. Twenty-three (14·2%) of 161 patients had positive sputum cytology. One hundred and forty-three patients had bronchoscopy and there was a visible abnormality in 88 (61·5%).

Seventy-two (71%) patients had an FEV_1/FVC ratio of less than 75%. Liver scintiscans were performed in 31 patients and were abnormal in four; two of them had an enlarged liver on palpation, and the other two had abnormal liver function tests. Bone scintiscans were performed in 19 patients. Of these, 12 had bone pain, and of these six had abnormal scans. Brain scintiscans were performed in eight patients, five of whom had central nervous system symptoms or signs. Only one scan was abnormal.

Forty-four (22·5%) patients out of 195 had a haemoglobin of less than 12 g. Fifty-five (29·7%) had a total WBC of less than 5×10^9/l, and 23 (13·5%) had a count of greater than 10×10^9/l. Seventy-five (48%) had a relative lymphocyte count of less than 20%. Eight (5·1%) patients had a relative monocyte count of greater than 10%. One hundred and seventeen patients (68·8%) had an ESR of greater than 20 mm in one hour. Only one patient had a plasma sodium level of below 125 mEq/l, 37 (20·3%) had plasma sodium below 132 mEq/l (normal range 132–145 mEq/l). Nineteen (10·4%) had plasma potassium below 3·5 mEq/l. Serum calcium was below 2·2 mEq/l in three (4%) of 72 patients, and above 2·6 mEq/l in 11 (15%). Liver function tests as measured by alkaline phosphatase, gamma glutamyl transpeptidase, and aspartate transaminase were measured in 123 patients; 83 (67%) were normal, 34 (27·6%) had a rise in alkaline phosphatase alone, and six

(4·8%) had raised values for all three enzymes. The mode of diagnosis is summarised in table 3.

At presentation each patient was placed in one of three groups: (1) disease confined to one hemithorax without lymph node involvement; (2) unilateral thoracic disease with mediastinal lymph node involvement; (3) extensive disease (including chest wall involvement). Stage at presentation and extent of disease at death are summarised in table 4. Post-mortem examination was performed in 24 patients and three (12·5%) had adrenal involvement.

Table 3 *Method of diagnosis in large cell carcinoma*

Method	*Patients (%)*
Bronchoscopy	42·3
Thoracotomy	20·1
Supraclavicular node biopsy	19·7
Percutaneous needle biopsy	3·3
Mediastinotomy	3·3
Sputum cytology alone	3·1
Pleural biopsy	2·9
Mediastinoscopy	2·4
Postmortem	2·4
Drill biopsy	0·5

Table 4 *Spread of disease in large cell carcinoma*

Spread of disease	*Patients (%)*
At presentation	
Stage 1 Local disease	19·2
Stage 2 Local disease with mediastinal involvement	33·1
Stage 3 Extensive disease	47·6
At death	
Local disease in the chest	93·7
Lymph node involvement	90·1
Liver involvement	62·3
Bone involvement	55·9
Central nervous system involvement	54·3
Skin metastases	4·4

Survival

Survival figures as actuarial survival were calculated by the life table method. The median survival for the whole group was 6·0 months. One-year-survival was 27·9%, and five-year-survival was 5·9% for the whole group. Shortened survival (Spearman's rank correlation coefficient) correlated with the features listed in table 5. Symptoms did not correlate with survival, apart from weight loss. There was no difference in survival between patients with peripheral lung opacity alone and those with lung opacity and mediastinal involvement. Survival figures are compared between those with disease limited to the chest, and those with clinical evidence of dissemination—namely, lymph node enlargement, palpable liver, superior vena cava obstruction, pleural effusion, bone involvement, or central nervous system involvement. Survival data are summarised in table 6.

Table 5 *Factors affecting survival in large cell carcinoma*

Shortened survival correlated with	*p value*
Lymph node enlargement	< 0·001
Abnormal chest signs	< 0·001
Elevated ESR	< 0·001
Elevated WBC	< 0·001
Decreased lymphocyte count	< 0·005
Abnormal liver function tests	< 0·005
Raised polymorph count	< 0·025
Increasing age	< 0·05
Low haemoglobin	< 0·05
Weight loss	< 0·05

Table 6 *Survival of patients with large cell carcinoma*

Group	*Number*	*Mean age (yr)*	*Disease staging*		*% Survival*				*Median survival (months)*
			Stage 1+2	*Stage 3*	*4 mo*	*6 mo*	*12 mo*	*5 yr*	
Untreated	58	62·6	21 (36%)	37	37	25·4	11	0	2·5
Radiotherapy	45	58	24 (53%)	21	65·5	46·8	18·8	0	6·0
Palliative radiotherapy	28	59	8 (29%)	20	64·3	44·2	20·2	0	5·9
Surgery	55	58	42 (76%)	13	78·1	70·6	53·5	21·2	13·0
Chemotherapy	8	60	0 (0%)	8	—	—	—	—	4·4 (range 1·4–12·0)
Chemotherapy and radiotherapy	4	61	0 (0%)	4	—	—	—	—	2·9 (range 2–16·4)
Surgery and radiotherapy	4	60	4 (100%)	0	—	—	—	—	6·2 (range 6–19·8)
All groups	202	59·6	99	103	60·7	46·6	27·9	5·9	6·0

Treatment

UNTREATED

Fifty-eight patients (28·7%) received no treatment, either because they were too ill, or physician or patient decided against treatment. None of these patients was asymptomatic. Twenty-one (36%) had no clinical evidence of dissemination, and 37 (63%) had extrathoracic disease. The median survival was 2·5 months (range four days to 21·2 months), one-year-survival was 11·0%, and five-year-survival was zero. There was no difference in median survival between those with and those without disseminated disease.

RADIOTHERAPY

Forty-five patients (22·3%) received radiotherapy to the primary lesion and the mediastinum if this was also involved. Doses ranged from 3500 to 5000 rads. Twenty-four patients (53%) had limited disease (stage 1 and 2) and 21 (46%) had clinical evidence of dissemination. The median survival of the whole group was 6·0 months (range 20 days to 47 months). Median survival for limited disease was 6·2 months, and for extensive disease 4·1 months. One-year-survival was 18·8%, five-year-survival was zero.

PALLIATIVE RADIOTHERAPY

Twenty-eight patients (13·9%) received palliative radiotherapy. Twenty had clinical evidence of dissemination (stage 3). Median survival was 5·9 months (range: nine days to 19·4 months), one-year-survival was 20·2%, five-year-survival was zero. Those with disseminated disease had a median survival of 4·7 months and those with limited disease 6·6 months.

SURGERY

Eighty-four patients (41%) underwent thoracotomy; 29 were found to be inoperable and 55 (27·2%) underwent pneumonectomy or lobectomy. Thus 34·5% of patients submitted to surgery were inoperable. The 29 inoperable patients either had radiotherapy or no further treatment. Of the group that had resections, 41 (74·5%) had limited disease (stage 1 and 2)and 14 (25·5%) had extensive disease (stage 3). There was no significant difference in age between surgical treatment and no treatment. The median survival was 13 months (range: 14 days to 3900 days), one-year-survival was 53·5%, and five-year-survival 21·2%.

CHEMOTHERAPY

Eight patients received chemotherapy. A variety of drug combinations was used. Median survival was 4·4 months (range: 1·4 to 12·0 months).

RADIOTHERAPY AND CHEMOTHERAPY

Four patients received combination treatment. Median survival was 2·9 months (range: 2 to 16·4 months).

SURGERY AND RADIOTHERAPY

Four patients received postoperative radiotherapy. Median survival was 6·2 months (range: 6 to 19·8 months).

Treatment records were unavailable in a further six patients.

Survival and treatment

There was a statistically significant difference in survival between radiotherapy to the primary lesion and mediastinum, and patients receiving no treatment ($<0·05$, Mann-Whitney U test), but no statistically significant difference between palliative radiotherapy and patients receiving no treatment was observed. The difference in survival between patients receiving no treatment and those receiving surgery was highly significant ($<0·001$). The numbers in the other treatment groups were too small to allow statistical analysis.

Discussion

Ninety-five per cent of the patients in our series were smokers suggesting that large cell carcinoma is a smoking related disease. The age distribution was similar to other series of all histological types although women (mean age 56 years) were significantly younger than men (mean age 61 years) ($<0·002$). Four per cent of patients were asymptomatic. In those with symptoms 50% had dull intermittent chest pain and nearly one-third had haemoptysis. There were no physical signs in 23% at presentation. This may reflect the tendency of the disease to arise in the lung periphery[12 13] Clinically, bone and CNS involvement were rare at presentation but common at death. Ninety-eight per cent of patients had an abnormality on chest radiograph and of these 43% had a peripheral abnormality alone. This confirms Byrd's and colleagues finding of a solitary peripheral abnormality in 40% of 93 patients with large cell carcinoma, in contrast to squamous cell carcinoma where only 24% had peripheral abnormality alone.[12 13] In our series, site and extent of chest radiograph abnormality did not affect survival. Forty-two per cent were diagnosed at

bronchoscopy and 14% had positive sputum cytology. These figures are low compared with series of other histological types and may reflect the peripheral nature of the disease, and, in the case of sputum cytology,[14] possibly large cell carcinoma does not exfoliate as readily as epidermoid and small cell carcinoma.

The five-year-survival figure for the whole group of 5·9% is lower than that reported for squamous carcinoma or adenocarcinoma,[6 7] but similar to that reported for small cell carcinoma.[11] The median survival for patients who received no treatment was 2·5 months, similar to small cell carcinoma, 2·3 months, and survival was not affected by staging at presentation. This group cannot be used as a control as they were a selected group either because they were too ill to receive treatment, declined treatment, or were found to be inoperable at thoracotomy. Radiotherapy produced very poor survival figures. Large cell carcinoma has been reported to be more radiosensitive than epidermoid or adenocarcinoma.[15] It is, therefore, surprising that there were no five-year radiotherapy survivors, as long-term survival has been reported with epidermoid and small cell carcinoma.[16] Radiotherapy prolonged survival when compared with untreated patients but, as already pointed out, the untreated group cannot be used as a control, and treatment with radiotherapy presupposes a minimum of four weeks survival from diagnosis. The poor radiotherapy results in this series suggest that the tumour is not very radiosensitive.

No conclusion can be drawn from the chemotherapy group because of the small numbers of patients and varied drug regimens used. However, large cell carcinoma has similarities with small cell carcinoma (which has been reported to be responsive to chemotherapy[17]) as the untreated survival time is short, and both are disseminated in the majority of cases at presentation.

In 27% of patients it was possible to resect tumour surgically. These patients had a five-year-survival of 21% which compares favourably with epidermoid carcinoma[6 18] and offers the only possibility of useful survival.

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