

Histology of lung cancer in relation to prognosis

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The differences in microscopic appearance which characterize the main histological types of lung cancer suggest associated differences in biological behaviour. For example, their growth rates might be expected to increase as the degree of cell differentiation decreases, in which case the least differentiated tumours would be the most malignant.

One method of assessing the relative behaviour of different types of tumour is by studying the survival rates of untreated patients in whom they occur. However, among untreated patients with lung cancer the course of the disease is so short that survival differences between the histological types are small. A more useful index of relative biological behaviour is provided by comparative survival rates after treatment. Many papers have been written about this, mainly on the relation between tumour histology and survival after surgery, and these have been reviewed by Bignall (1958). From the data included in this review, and from other more recent publications, several apparent associations emerge.

Squamous-cell carcinoma has been found by most authors to confer the best prognosis, both for surgically treated patients (McDonald, McBurney, Carlisle, and Patton, 1951; Gifford and Waddington, 1957; Ochsner, Ochsner, H'Doubler, and Blalock, 1960; Shinton, 1963; Taylor, Shinton, and Waterhouse, 1963) and for those not treated surgically (Lea, 1952; Ballantyne, Clagett, and McDonald, 1957; Whitwell, 1961).

The prognosis associated with adenocarcinoma of the lung is less certain, largely because too few cases have been available for study. Some authors report survival rates similar to those for squamous-cell carcinoma (Kirklin, McDonald, Clagett, Moersch, and Gage, 1955; Bignall and Moon, 1955; Cleland, 1958; Spjut, Roper, and Butcher, 1961; Siddons, 1962); others record rates lower than for squamous or undifferentiated tumours (McDonald *et al.*, 1951; Gifford and Waddington, 1957; Ochsner *et al.*, 1960), whereas

in one surgical series adenocarcinoma was found to confer the best prognosis of all types (Barrett, Day, O'Rourke, Chapman, Sadeghi, Perry, and Tuttle, 1963).

Survival rates after surgery for undifferentiated carcinoma are reported to be lower than for squamous-cell or adenocarcinoma (Kirklin *et al.*, 1955; Bignall and Moon, 1955; Cleland, 1958; Spjut *et al.*, 1961; Barrett *et al.*, 1963). Oat-cell carcinoma, previously included with undifferentiated tumours, in more recent series has been classified separately and appears to confer the worst prognosis of all cell types (Kirklin *et al.*, 1955; Rienhoff, King, and Dana, 1958; Nicholson, Fox, and Bryce, 1957; Reid and Carr, 1961; Whitwell, 1961; Siddons, 1962; Shinton, 1963; Sensenig, Rossi, and Ehrenhaft, 1963).

In contrast to these studies, a small number of authors have found no significant correlation between tumour histology and prognosis (Overholt and Bougas, 1956; Ederer and Mersheimer, 1962).

The variation of results in some of these papers may be due to differences in the definition of histological types. This source of error is inevitable while pathologists fail to agree on a uniform system of classification. The purpose of the present paper is to support a system of histological classification which is shown to be related to the survival of patients, although the criteria of definition of cell types differ from those most widely in use.

CASE MATERIAL AND METHODS OF STUDY

A retrospective survey was undertaken of all patients who attended Sully Hospital during the period 1 January 1954 to 1 October 1960, and who were thought to have primary carcinoma of the lung. Cases in which the diagnosis, on review, seemed doubtful were excluded. The material was analysed by age, sex, tumour histology, method of treatment, and survival.

The histological classification of tumours was performed by one pathologist (Dr. R. M. E. Seal) and was not specially reviewed for this study. Classification was according to the predominant cell type. Tumours consisting mainly of well-differentiated cells

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TABLE I
HISTOLOGICAL TYPE OF TUMOUR ACCORDING TO AGE AND SEX OF PATIENT

	Squamous-cell		Undifferentiated		Oat-cell		Adenocarcinoma		Unclassified		Unknown
	No.	%	No.	%	No.	%	No.	%	No.	%	
All patients	224	37.3	173	28.8	135	22.5	42	7.0	27	4.5	145
Male	219	39.3	163	29.3	112	20.1	38	6.8	25	4.5	133
Female	5	11.4	10	22.7	23	52.3	4	9.1	2	4.5	12
Under 40	1	7.1	3	21.4	10	71.4	0	0	0	0	2
40-49	19	29.7	19	29.7	19	29.7	5	7.8	2	3.1	14
50-59	106	41.4	71	27.7	51	19.9	16	6.2	12	4.7	58
60-69	85	35.7	71	29.8	53	22.3	19	8.0	10	4.2	57
Over 70	13	44.8	9	31.0	2	6.9	2	6.9	3	10.3	14

were classed as squamous-cell carcinoma or adenocarcinoma, according to their characteristic features. Tumours consisting mainly or wholly of undifferentiated cells, which lacked specific characteristics, were grouped together as undifferentiated carcinoma; these included tumours which contained areas suggesting differentiation and which had been classified by the pathologist as poorly differentiated squamous-cell carcinoma or poorly differentiated adenocarcinoma. Tumours consisting of small cells with scanty cytoplasm and hyperchromatic nuclei were classed as oat-cell carcinoma.

There were some tumours which could not be placed into one of these four categories, often because of inadequate pathological material, and these were termed unclassified; they included a small number of mixed pathology. Bronchiolar carcinoma was excluded from the series.

A histological or cytological report was obtained on 601 cases or 81% of the total. The sources of pathology were resected tumours in 250 cases, biopsies taken at exploratory thoracotomy in 112, biopsy specimens and sputum in 186 inoperable cases, and 57 necropsy specimens. The commonest tumour was squamous-cell carcinoma (37.3%) and the least common was adenocarcinoma (7.0%). The frequency of the histological types is analysed according to age and sex in Table I. Of special interest is the high proportion of oat-cell tumours among women and younger patients and the preponderance of squamous-cell tumours among men and older patients.

Survival was measured up to 1 October 1960, so that all patients were followed for at least two years. Survival rates were analysed according to tumour histology and method of treatment, but deaths from lung cancer were not distinguished from the small number of deaths from other causes. The follow-up was completed on all 746 patients in the series.

RESULTS

The numbers of patients with each type of tumour that was operable and resectable are given in Table II. In the three largest groups the rates of pulmonary resection were highest for squamous-cell (45.5%) and undifferentiated carcinoma (47.4%) and lowest for oat-cell carcinoma (2.6%).

TABLE II
OPERABILITY IN RELATION TO HISTOLOGICAL TYPE OF TUMOUR

Type of Tumour	Total	Clinically Inoperable*		Submitted to Thoracotomy		Pulmonary Resection	
		No.	%	No.	%	No.	%
All cases	746	379	50.8	367	49.2	250	33.5
Squamous-cell	224	89	39.7	135	60.3	102	45.5
Undifferentiated	173	58	33.5	115	66.5	82	47.4
Oat-cell	135	65	48.2	70	51.8	40	29.6
Adeno-carcinoma	42	9	21.4	33	78.6	26	61.9

* Includes patients who refused operation

Of the patients with oat-cell carcinoma on whom thoracotomies were performed, only 57.1% were found to have resectable growths, a much lower proportion than for the other types of tumour.

The survival rates of patients treated by pulmonary resection are given in Table III. Deaths within four weeks of operation have been excluded, as they are unlikely to have been influenced by the tumour histology. It is seen that the two years' and five years' survival rates differ considerably according to the histology. The highest rates are recorded for squamous-cell carcinoma, intermediate rates for undifferentiated carcinoma, and the lowest for oat-cell and adenocarcinoma. Of special interest is the comparatively high five years' survival rate after resection for

TABLE III
SURVIVAL AFTER SURGICAL RESECTION ACCORDING TO HISTOLOGICAL TYPE OF TUMOUR, EXCLUDING 'OPERATIVE' DEATHS

Type of Tumour	Two Years*			Five Years		
	At Risk	Survivors	Survival (%)	At Risk	Survivors	Survival (%)
Squamous-cell	95	52	54.7	41	17	41.5
Undifferentiated	71	32	45.1	33	4	12.1
Oat-cell	33	8	24.2	19	1	5.3
Adenocarcinoma	21	4	19.0	7	0	0.0
All cases	220	96	43.6	100	22	22.0

* Two-year follow-up on patients resected during 1954-60. Five-year follow-up on patients resected during 1954-57

squamous-cell carcinoma, namely 41.5% compared with only 5.3% for oat-cell carcinoma.

The survival of patients not treated surgically is given for the first two years after diagnosis (Table IV). This includes patients who were found to have unresectable tumours at thoracotomy, those treated by radiotherapy or chemotherapy, and the remainder who received no specific treatment. The same trend is evident as for the surgical series, namely the highest survival rates associated with squamous-cell tumours and the lowest with oat-cell tumours. However, the correlation of survival with histology, although pronounced at six months and one year, is much less so at two years. Thus for squamous-cell, undifferentiated, and oat-cell carcinoma the six months' survival rates were 38%, 30%, and 15% respectively, whereas the two years' rates were 2.5%, 2.2%, and 1.1% respectively. The numbers of adenocarcinoma were too few for the associated survival rates to be reliable.

TABLE IV
SURVIVAL OF PATIENTS NOT TREATED SURGICALLY,
RELATED TO HISTOLOGICAL TYPE OF TUMOUR

Type of Tumour	Total	Survival ¹					
		Six Months		One Year		Two Years	
		No.	%	No.	%	No.	%
Squamous-cell	122	46	37.7	20	16.4	3	2.5
Undifferentiated	91	27	29.7	6	6.6	2	2.2
Oat-cell	95	14	14.7	1	1.1	1	1.1
Adenocarcinoma	16	4	25.0	1	6.3	1	6.3
Unclassified or unknown	166	45	49.0	20	24.5	3	5.6
All cases	490	136	27.8	48	9.8	10	2.0

¹ From the time of diagnosis

The combined experience of all patients in whom the tumour histology was known, whatever the method of treatment, is given in Figure 1. This summarizes the data relating prognosis to tumour histology which is detailed in Tables II, III, and IV.

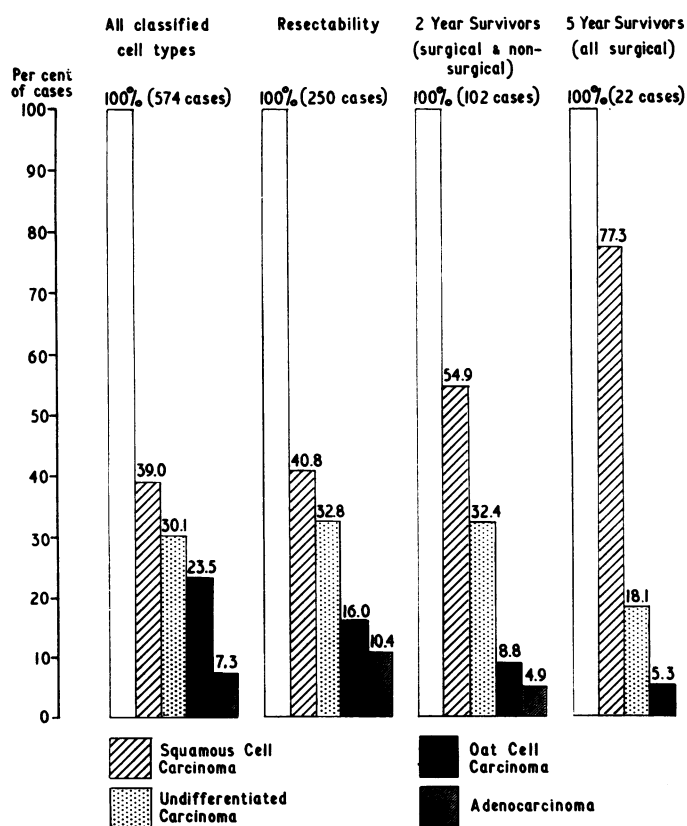


FIG. 1. Resectability and survival rates of 746 patients with lung cancer, related to histology.

DISCUSSION

'In addition to the fundamental histogenetic classification by which tumours are grouped solely according to the kinds of tissue from which they spring and of which they consist, it is also necessary to have a further grouping, biologically less fundamental but of great practical value, according to their behaviour and clinical progress' (Willis, 1960). In this paper a system of histological classification of lung cancer has been followed which it was thought would serve the second purpose and provide information about the relative clinical behaviour of different types of tumour.

The growth rate of normal tissues appears to vary inversely with cell differentiation. Thus mitoses are rarely observed in highly differentiated tissues, such as neurones or muscle, whereas in continuously proliferating tissues like the skin or bone marrow, mitotic activity is largely confined to zones of undifferentiated cells. It seems reasonable to suppose that the growth rate and cell differentiation of tumours are also inversely related. For survival studies it seemed best therefore to group

together all predominantly undifferentiated tumours irrespective of their apparent origin. This differs from current pathological practice, for lung cancer is generally typed according to the most differentiated tissue. For example, according to Kreyberg (1961), 'If anywhere in a tumour a definitely specific differentiation is found, however limited, this finding decides the type, undifferentiated areas being disregarded'. It seemed to the author that this results in the grouping together of tumours which may be of common origin but probably differ in their clinical behaviour.

The analysis of survival in 746 patients with cancer of the lung which has been presented shows the best prognosis to be associated with squamous-cell carcinoma. The high rates of resectability and of survival after surgical treatment are in accord with the findings of most other investigators. Of particular interest is the high survival rate after surgery, namely 37.8% at five years, or 41.5% excluding operative deaths. This figure is similar to that reported by Cleland (1958), who found a 42% survival for this group, but most other authors have recorded lower rates. Thus Taylor and colleagues (1963) reviewed the results of surgery in their own and 11 other series and found the five years' survival rates for patients with squamous-cell carcinoma were all below 40% and mostly below 30%. It seems likely that the survival rates associated with this type of tumour were especially favourable in the present series because only well-differentiated tumours were included.

The prognosis associated with adenocarcinoma remains undetermined because of its relative infrequency. In the present study there were only 42 classified cases, of which a high proportion were treated surgically (62%). This probably reflects the difficulties of obtaining the histology except at thoracotomy, for most of these tumours are peripheral and beyond the range of the bronchoscope. The survival experience of this small group of patients suggests a prognosis after surgery inferior to that associated with squamous-cell carcinoma.

The survival rates of patients with undifferentiated carcinoma were found to be intermediate between those of patients with squamous-cell and oat-cell tumours. A high proportion of the patients had resectable tumours (47.4%) and their two years' survival rate after resection was relatively high (45.1%), but at five years the rate had fallen to 12.1%, which is well below the figure for squamous carcinoma. Other investigators have recorded five years' survival rates after surgery for undifferentiated carcinoma (excluding oat-cell

tumours) ranging between 29% (Deal and Belcher, 1963) and 0% (Paulson, 1957), with a wide scatter between these two extremes. Although the pathological definition of this group varies greatly according to different authors, there is overall agreement that the prognosis associated with undifferentiated carcinoma is worse than that for squamous-cell carcinoma.

The finding of other authors that oat-cell carcinoma is associated with a relatively poor prognosis has been confirmed, both for surgical and non-surgical patients. The proportion of patients with this tumour who were submitted to thoracotomy was small (52%), which might partly reflect the reluctance of surgeons to operate on this type of case. However, at thoracotomy nearly half of these patients were found to have unresectable growths, a much higher proportion than in the other histological groups.

Oat-cell carcinoma, as distinct from undifferentiated or anaplastic carcinoma, has only been recognized in the last few years. It is now regarded as a pathological entity, and some of these tumours show signs of differentiation such as tubular or rosette formation (Azzopardi, 1959; Walter and Pryce, 1960). Only four patients in this series with oat-cell carcinoma survived for three years or more; the histology was reviewed, and in three of them there was rosette formation and palisading of cells suggesting differentiation. It would be interesting to determine, by means of a larger investigation, whether these characteristics are significantly associated with an improved prognosis.

The poor outlook of patients with oat-cell carcinoma after surgery has raised the question whether this is a better method of treatment than radiotherapy. If treatment is to be determined by the tumour histology it is important that it should be reported with accuracy. However, a bronchoscopic biopsy specimen is not always satisfactory and may suggest a different histology from that of the main part of the growth. Several investigators have compared the histological reports on bronchial biopsies with subsequent reports on the resected tumours. Reid and Carr (1961) found agreement between the two sets of reports in most cases of oat-cell carcinoma but in a small proportion of other types of lung cancer. In similar studies, Siddons (1962) recorded agreement between the reports in 93% of cases, and Taylor and colleagues in 90%. However, Deal and Belcher (1963) found that in only two-thirds of the cases of oat-cell and undifferentiated carcinoma was the report on the bronchial biopsy the same as that on the operation specimen. It

seems therefore that a bronchial biopsy provides information about tumour histology with only moderate accuracy, so that the choice of method of treatment should not be based on this information alone.

The association between histology and prognosis in cancer of the lung is not necessarily causative, for there may be other factors which vary with the histology and which influence survival. For example, the age of patients varies between the histological groups, in particular between those with oat-cell and squamous-cell carcinoma. Possibly this difference in age structure determines the difference in survival rates, although as yet no simple relation has been demonstrated between prognosis and age (Bignall, 1958). To test this hypothesis, the survival of patients with each type of tumour would have to be analysed by age, an investigation which, to attain significance, would require a much larger series of cases than the present one.

SUMMARY

The experience of 746 patients with lung cancer has been related to tumour histology. The survival rates in both surgical and non-surgical cases indicate that squamous-cell carcinoma is associated with the best prognosis, oat-cell carcinoma with the worst prognosis, and undifferentiated carcinoma with a prognosis intermediate between these two. In the small proportion of cases of adenocarcinoma the survival rates after surgery were comparatively low.

The criteria of definition of cell types are discussed in relation to the association between histology and prognosis. For clinical use it is suggested that the labels 'squamous-cell carcinoma' and 'adenocarcinoma' be confined to well-differentiated tumours and that poorly differentiated tumours are best grouped together.

Oat-cell carcinoma is a distinct clinical and pathological group which includes tumours with varying degrees of cell differentiation. There is a suggestion that the prognosis associated with these tumours may vary with this differentiation.

I wish to thank Dr. L. R. West for his encouragement and help with this work. I am also grateful to Dr. R. M. E. Seal for valuable discussions on the pathology of lung cancer and to Mr. C. E. Rossiter,

of the Pneumoconiosis Research Unit, Llandough, for statistical advice. Permission to publish was granted by Dr. H. M. Foreman, Physician Superintendent of Sully Hospital. Miss G. Smith kindly undertook much secretarial work in connexion with the follow-up of patients.

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