Influence of site of origin of lung carcinomas on clinical presentation and central nervous system metastases

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SUMMARY A retrospective survey of 100 patients dying from carcinoma of the lung showed that neurological presentation and central nervous system metastases are more frequently present when the primary carcinoma is situated in the peripheral lung tissue (including lung apex). The high incidence of cases presenting neurologically and the high incidence of single secondary deposits involving the central nervous system from peripheral or apical growths suggest a difference in the mode of spread or other properties of such growths compared with the more common central carcinoma.

The clinical behaviour and pathological features of cancer of the lung have been reported extensively. The tendency to metastasise widely is well established, and the frequency of metastases in the brain has been analysed in many necropsy series. Blood-borne secondary deposits occur most frequently in the liver and suprarenal glands, and brain is the third most common organ involved (Spencer, 1968). In most investigations cerebral metastases have been estimated, usually on macroscopic examination alone, to occur in between 15 and 40%. A Table summarising the findings in 21 reported series is given by Galluzzi and Payne (1956). In their own necropsy series the incidence of cerebral secondaries was approximately 26% but they suggested that if the brain had been examined in all their cases the incidence would have been about 30%. The incidence of cerebral metastasis is known to vary with histological type (Weiss *et al.*, 1970), undifferentiated and adenocarcinomas each metastasising to the brain about three times as frequently as squamous cell carcinoma.

The occurrence of single as opposed to multiple secondary deposits in the brain has also aroused some interest as has the possibility of attempting to recognise those cases with a "solitary" cerebral

metastasis—that is, a single cerebral metastasis in the absence of other secondary deposits. Single cerebral metastases are not rare. Meyer and Reah (1953) recorded 35 out of 106 cases of cerebral metastases as being single, but only two as solitary. On the other hand, Galluzzi and Payne (1956) found 23 solitary metastases out of a total of 166 lung carcinomas with secondary deposits in the brain.

The clinical incidence of brain metastases in carcinoma of the lung is higher than average in neurosurgical units (Galluzzi and Payne, 1956; Bachay, 1958) and in series analysed from hospitals with neurological interests. It is in such units or hospitals than one might expect to find cases with single, or perhaps solitary, cerebral metastases and in which the initial symptoms from lung carcinoma arise from central nervous system involvement. So far as we are aware, no report has examined the possibility that such cases may be associated with carcinomas which differ in the site of origin within the lung by comparison with the more numerous cases which present with pulmonary symptoms or with widespread blood-borne deposits. This investigation arose from an impression that cases presenting with neurological symptoms frequently have peripherally sited primary growths, particularly those at the lung apex, and that such patients often have only a single cerebral metastasis and die more frequently without other organ involvement than do those with car-

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cinoma arising in the main bronchi. A retrospective investigation was, therefore, undertaken to test these possibilities.

Materials and methods

The records of necropsies (mostly performed by BET) of 100 patients dying from carcinoma of the lung were extracted, sequentially, from our files. In addition to the standard necropsy findings the reports contained details of the clinical presentation and investigation of the patients. The following information was obtained: the age and sex of the patient, the unit to which they had been referred, the nature of the presenting symptoms, and the total duration of the illness. If the presenting symptoms included disturbances considered to result from involvement of the brain, cranial nerves, and spinal cord the presentation was classified as neurological. The size of the primary pulmonary tumour was noted and its site classified on the following basis: *apical*—arising in the apex of the upper lobe, involving either the pleural surface or the immediate subpleural tissues; *peripheral*—originating in the periphery of the lung tissue other than the apex of the upper lobe and, again, involving either the pleural surface or the immediate subpleural tissues; *intermediate*—arising between the periphery and the hilum but without a definable connection with, or origin in, a major bronchus; *bronchial*—arising within or enveloping and ulcerating a major bronchus or the carina.

Secondary deposits located at necropsy were divided into central nervous system metastases and those involving other organs. In addition to deposits within brain or cord, secondaries in the central nervous system included those occurring within the pituitary gland or its fossa, those attached to or within the dural membranes, and those within the confines of the spinal canal. Secondary deposits in skull bones or vertebrae which had not encroached into the intracranial cavity or compressed the cranial or spinal nerves or produced spinal cord symptoms were not grouped with central nervous system secondaries. Central nervous system deposits were further divided according to their site and number and the presence of secondaries elsewhere. They were thus classified as multiple or single but associated with deposits in other organs, or solitary—that is, a single secondary deposit in the central nervous system without involvement of other organs. In almost every case detailed examination of the brain had been undertaken after previous fixation but the spinal cord had only been examined where symptoma-

tology suggested its possible involvement. The histological type of the tumour was classified into adenocarcinoma, squamous carcinoma, small cell undifferentiated, large cell undifferentiated, and bronchiolar carcinoma.

Differences between groups were compared using the chi-squared technique.

Results

Table 1 shows the site of the primary tumour in the 100 cases related to the clinical presentation, the latter being divided into those with neurological and non-neurological symptoms. Forty-two cases presented neurologically; of these the primary tumour was located in a major bronchus in 18 (42.9%), the lung apex in 13 (31%), the periphery in eight (19.1%), and in an intermediate site in three (7.1%). Thus in 21 (50%) of these 42 cases the primary growth was in either the apical or peripheral lung. These 42 cases with a neurological presentation included three in which central nervous system metastases were not found at necropsy. Two of these had presented as acute confusional states, and one as a focal hemisphere lesion which proved to be ischaemic in origin. Thirty-nine cases, therefore, presented neurologically and were subsequently established as having central nervous system metastases. In all three cases without central nervous system metastases, the primary tumour was in a major bronchus. The percentage of cases presenting neurologically because of metastatic involvement of the central nervous system from apical or peripheral carcinomas was, therefore, slightly higher than recorded above. A fourth case presented with cerebellar dysarthria which subsequently proved to be due to a paraneoplastic cerebellar degeneration. The only intracranial secondary in this case was in the anterior pituitary gland, and the origin of the primary growth was, again, a major bronchus.

In the remaining 38 cases presenting neurologically, the predominant symptomatology was of raised intracranial pressure in 15, a focal cerebral

Table 1 Site of primary lung carcinoma related to mode of presentation

Tumour site	Number of cases	Clinical presentation	
		Neurological	Non-neurological
Apical	15	13	2
Peripheral	13	8	5
Intermediate	7	3	4
Bronchus	65	18	47
Total	100	42	58

hemisphere lesion in six, a cerebellar disturbance in six, spinal cord symptomatology in five, brain-stem involvement in two, multiple cranial nerve palsies in one, and an acute confusional state in three cases. In many instances there were other clinical features which suggested neurological involvement in addition to those listed above. All these 38 patients proved to have secondary deposits involving the central nervous system.

Comparison of the initial symptoms with the site of the lung carcinoma showed that a neurological presentation occurred in 86.6% of apical, 61.5% of peripheral, 42.9% of intermediate, and only 27.7% of tumours arising in the main bronchus. Neurological presentation was, therefore, significantly more frequent in carcinomas arising in the apex compared to the bronchus ($P < 0.001$), and in carcinomas arising in the lung periphery, other than the apex, compared to the bronchus ($P < 0.05$). If the primary tumour sites are arranged into central (intermediate+bronchus) and non-central (apical+peripheral) groups it can be seen that neurological presentation occurred significantly more frequently in the latter group ($P < 0.001$). The clinical presentation of apical and peripheral carcinomas was not significantly different.

When non-neurological presentation was related to the site of the primary carcinomas in the total series, 47 (81%) arose from the main bronchus, four (6.9%) from intermediate, five (8.6%) from peripheral, and two (3.5%) from apical primaries. Again, relating the primary site to non-neurological presentation, 72.3% of bronchial, 57.1% of intermediate, 38.5% of peripheral, and 13.3% of apical growths presented with non-neurological symptoms.

Table 2 shows the incidence and number (multiple, single, or solitary) of secondary deposits found within the central nervous system at necropsy related to the primary site of the carcinoma and relates the central nervous system secondaries to the mode of presentation and the site of the primary tumour. The column "single" refers to those cases in which only one secondary tumour

was present in the central nervous system, although others were present in the general organs. Again it is clear that apical and peripheral primary sites gave rise to single or solitary central nervous system involvement by growth far more frequently than growths arising in a main bronchus. A total of 13 single or solitary central nervous system secondaries arose from 28 apical or peripheral carcinomas, whereas in only six instances did single central nervous system deposits arise from the 72 cases of carcinomas arising in the bronchi or in intermediate sites. Data in Table 2 also demonstrate that cases presenting with neurological symptoms caused by single central nervous system secondaries arose frequently from apical and peripheral lung sites. Thus, of the 42 cases presenting neurologically, 39 were associated with carcinomatous involvement of the central nervous system, and of these 39, 15 were single or solitary central nervous system lesions. Twelve of these 15 cases arose from apical or peripheral lung sites.

At necropsy the spinal cord was involved by infiltration or compression in 11 cases—the primary lung site was apical in three, peripheral in four, intermediate in one, and main bronchus in three cases. Five of these 11 presented with symptomatology related to spinal cord infiltration or compression—the primary growth was apical in two, peripheral in one, and main bronchus in two cases. These figures are insufficient for statistical analysis but suggest that apical and peripheral primaries present with cord symptomatology, and involve the cord considerably more frequently, than do intermediate or bronchial primaries. If the primary sites are grouped into central (bronchus+intermediate) and non-central (apical+peripheral) cases, spinal cord involvement occurred in seven out of 28 non-central sites compared with four out of 72 central growths.

We considered that the higher incidence of spinal cord involvement with non-central primary lung carcinomas might have influenced the statistical analysis of the series relating to cerebral secondaries. However, even when cases with spinal

Table 2 Numbers of CNS metastases related to primary site and type of clinical presentation

Primary carcinoma site		Neurological presentation (42)			Non-neurological presentation (58)		
		CNS secondaries			CNS secondaries		
		Single or solitary ()	Multiple	None	Single	Multiple	None
Apical	15	7 (1)	5	0	1	0	1
Peripheral	13	3 (1)	4	0	0	1	4
Intermediate	7	0	3	0	1	0	3
Bronchus	65	3	12	3	2	6	39
Total	100	15	24	3	4	7	47

cord involvement were excluded from the group with neurological presentation (Table 3), apical and peripheral growths still gave rise to neurological presentation with striking frequency. Thus neurological presentation occurred in 10 out of 12 apical primaries compared with 15 out of 62 cases arising in the main bronchus ($P<0.001$). Similarly, in analysing the effect of the site of the lung growth on the incidence of single cerebral secondaries, exclusion of those cases with spinal cord involvement did not affect the increased incidence of single cerebral secondaries seen with apical and peripheral growths compared with central growths (eight out of 21 and five out of 68 cases with single cerebral secondaries in those groups respectively, $P<0.01$).

Other items which might be relevant to the clinical presentation or to theoretical explanations for the different behaviour of central and peripheral growths were extracted from the records in addition to the main items originally investigated. Thus it was noted that in 55 instances adhesions were found over the lobe associated with the carcinoma. Adhesions over the immediate site of peripheral or apical growths were present in 20 out of 28 cases. In 30 cases they were present elsewhere in the pleural cavity, and on 10 occasions adhesions were present both over the affected lobe and elsewhere in the pleural cavity. The possible relevance of adhesions over peripherally sited growths to their spread to other tissues is discussed later. The recorded size of the primary tumour (usually the greatest diameter) was used to classify carcinomas into those greater and those less than 25 mm. No correlation was found between the size of the primary tumour (at necropsy) and the presence or absence of central nervous system secondaries. Twenty-four tumours were below 25 mm in size, and of these central nervous system secondaries were present in 12 cases. The total incidence of central nervous system metastases in the 100 cases was 50%. Adenocarcinomas are known to originate particularly at the lung periphery, and they frequently remain silent until the appearance of signs and symptoms caused by distant metastases (Spencer, 1968). A preponder-

ance of adenocarcinomas at the lung periphery could, therefore, be an explanation for the increased incidence of central nervous system metastases arising from non-central primaries. Table 4 contains a list of the histological type in relation to central and non-central primary sites and the incidence of central nervous system spread. Five, out of a total of 28 non-central primary tumours, were adenocarcinomas, and all had metastases in the central nervous system, four being single deposits. Of nine adenocarcinomas which arose at central sites, five metastasised to the central nervous system and four of these produced multiple deposits. Thus the same tendency for single cerebral metastases to be associated with non-central primary sites is apparent and, in the group of adenocarcinomas, the site of origin again appears to influence its metastatic behaviour.

Metastatic spread to general organs was broadly in agreement with that recorded by other authors (listed in Table 20.3, Spencer (1968)), although in the present series the adrenal gland involved in 34% of cases had a slightly higher incidence of secondary deposits than the liver which was involved in 33%. However, adrenal secondaries were not frequent in those cases which had single central nervous system secondaries. Thus of 19 cases with single central nervous system secondaries only three had adrenal deposits (15.8%) compared with 16 adrenal deposits in the 31 cases which had multiple central nervous system secondaries.

Table 4 Histological type related to site of primary tumour and central nervous system metastases

Histological type	Site	Central nervous system secondaries		
		Single	Multiple	Absent
Adenocarcinoma	Non-central	4	1	0
	Central	1	4	4
Small cell undifferentiated	Non-central	2	3	1
	Central	1	8	12
Large cell undifferentiated	Non-central	5	3	1
	Central	2	6	8
Squamous cell	Non-central	2	3	2
	Central	2	2	20
Bronchiolar carcinoma	Non-central	0	0	1
	Central	0	1	1

Table 3 Site of primary lung carcinoma related to clinical presentation and incidence of cerebral secondaries (excluding cases with spinal cord involvement)

Site	Clinical presentation		Cerebral secondaries		
	Neurological	Non-neurological	Single	Multiple	Present
Apical	10	2	6	5	11
Peripheral	5	4	2	3	5
Intermediate	2	4	1	2	3
Bronchus	15	47	4	16	20

(51.6%). These figures are not statistically significant but they suggest that the mechanism of metastatic spread may differ between those cases with single and those with multiple cerebral secondaries.

The length of survival (duration of illness from the first symptoms) of those cases which presented neurologically or had cerebral secondaries was not significantly different from cases with a non-neurological presentation or cases in whom central nervous system secondaries were absent. Thus, although cases with central nervous system involvement usually presented neurologically and, therefore, probably had central nervous system metastases at an early or intermediate stage of the disease, the occurrence of central nervous system metastases did not appreciably shorten the length of the illness. This finding, however, may be biased by a tendency for those patients in which the disease progresses rapidly to die in hospital while those with a more slowly progressive illness are likely to be discharged from hospital and to die elsewhere.

Discussion

Our data strongly support the notion that carcinomas originating in the lung periphery, whether apical or elsewhere, spread to the central nervous system with significantly greater frequency than the more commonly occurring carcinomas which arise centrally, most of which have their origin in a major bronchus. Of more clinical significance is the evidence that apical or peripheral carcinomas of lung present much more frequently with neurological disturbances than carcinomas of the major bronchus. Clearly, in the clinical and radiological examination of patients suspected of metastatic central nervous system involvement, particular attention should be paid to the lung apex and periphery.

It cannot, unfortunately, be maintained that the figures in this series are representative of the true incidence of neurological presentation in carcinoma of the lung, since a major medical and surgical neurological unit in the hospital results in a high degree of referral of patients with neurological disturbances. The hospital, nevertheless, has a large general medical and chest diseases unit, and out of the 100 cases analysed 63 first presented to these units. Of these 63 cases, 13 presented with neurological symptoms, the primary growth being apical or peripheral in seven (five apical and two peripheral), and the main bronchus in six. The same tendency for neurological presentation to be associated with peripheral or apical growths is still,

therefore, evident. Unfortunately the literature is no guide as to how biased our series is in relation to the incidence of patients with lung cancer presenting with neurological disturbances. We could find no report of a large series, unbiased by hospital type, and particularly investigating this point, despite the fact that there are several publications on cerebral metastases in lung carcinoma (Hazra *et al.*, 1972; Pedersen *et al.*, 1973; Newman and Hansen, 1974; Jaenisch and Zimmermann, 1975; Modestic and Feldman, 1975). That our series is biased towards patients with central nervous system metastases is suggested by the high incidence of central nervous system secondaries. Of the 100 cases, 50 (50%) had secondary central nervous system deposits at necropsy. This compares with figures which vary from 18% in the massive series reported by Jaenisch and Zimmermann (1975) to between 25 and 40% by most other authors. The latter figures, however, refer to brain secondaries, whereas in the present series spinal cord involvement has been included. Further, detailed examination of the brain after fixation (which occurred in the great majority of cases in this series) is likely to yield a higher percentage of secondary cerebral deposits than assessments based on examination of the unfixed brain, and many reported series could well underestimate the true incidence of central nervous system involvement. While we acknowledge that our series is over-represented by cases presenting with neurological symptoms, it is still probable that, regardless of the percentage of cases so presenting, a high proportion will be found to be associated with peripheral primary growths.

The high incidence of cases presenting neurologically and the high incidence of single secondary deposits involving the central nervous system from peripheral or apical growths suggest a difference in the mode of spread or other properties of such growths compared with the more common central carcinoma. Isolated or early involvement of the spinal cord clearly may arise from peripheral or apical growths by direct extension. From the more centrally located growths such direct extension only appears likely after involvement of bronchial or posterior mediastinal lymph nodes. Analysis of the details of growths in our cases supports this possibility since of those with spinal cord compression or invasion, six were associated with peripheral (three) or apical (three) growths, and all were adherent to the thoracic cage or paravertebral tissues by dense adhesions or obvious direct extension of the growth. The formation of adhesions between the visceral and parietal pleura over the site of a peripheral or apical carcinoma may result

in spread via direct extension (in tissue planes) or indirect spread via newly formed lymphatic and vascular channels. Spread of tumour to the spinal canal may involve either of these mechanisms, and the proximity of the primary apical growths, particularly, to the spinal canal and cord increases the probability of such a mode of spread. No such explanation is readily available to account for the frequency with which apical or peripheral growths spread to the brain by comparison with central growths, or for the tendency for such growths to be single or, occasionally, solitary.

The central nervous system may provide an encouraging medium for tumour emboli arising from lung carcinomas and small tumour emboli, which would not be viable in other organs, may survive in the immunologically isolated environment of the brain. The capacity for haematogenous tumour emboli to produce metastatic deposits is thought to be a reflexion of the size of the embolic aggregates rather than a function of the total number of tumour cells released (Watanabe, 1954; Spencer, 1968). Lung carcinomas which arise at central sites are close to major vessels, lymph nodes, and the thoracic lymphatic duct. Involvement of these structures by tumour may well result in frequent, and perhaps large, haematogenous emboli which produce multiple secondary deposits. In contrast, carcinomas at the lung periphery, which often arise in scar tissue, involve mediastinal lymph nodes only at a late stage in growth. It seems possible that invasion of large vessels with resulting large tumour emboli are, therefore, less frequent in peripheral lung carcinomas than in central growths which reach mediastinal lymph nodes. Emboli which arise from peripheral carcinomas are likely to consist mainly of small tumour aggregates, only viable in tissue particularly susceptible to tumour growth. Adrenal metastatic deposits from lung carcinoma are thought to arise via lymphatic spread (Onuigbo, 1957). In 23 cases with cerebral metastasis which arose from peripheral or apical primaries the incidence of adrenal secondaries was one and five out of 13 cases with single and 10 cases with multiple cerebral metastases, respectively. This association between multiple cerebral and adrenal metastases, which was also reflected in the series as a whole, may be explained by a common involvement of the mediastinal lymphatic system which predisposes to adrenal metastasis and, via haematogenous emboli, to multiple cerebral deposits. One explanation, therefore, for the association between single cerebral metastases and tumours situated at the apex and periphery, may be the reduced tendency for apical and peripheral carcinomas to involve medias-

tinal lymphatic structures compared to centrally arising carcinomas.

It has been suggested (Anderson, 1951) that embolic spread through vertebral venous channels may be an explanation for the occurrence of cerebral metastasis from lung carcinoma. A similar route has been proposed by Batson (1942) to account for the spread of pelvic tumours to the vertebral column. The vertebral venous network is known to be extensive (Wack *et al.*, 1958) and, theoretically, invasion and continuous spread could result in tumour reaching the brain or cord. In addition a reversal of blood flow within the network may occur during periods of increased intrathoracic pressure, for instance through coughing, with resultant spread of venous emboli to the central nervous system. However, the infrequency of secondary deposits in the cervical vertebral column, the scalp, skull, and dura mater (en route to the brain) suggest that such a mechanism is unlikely unless tumour emboli which lodge in structures adjacent to the vertebral venous system find this tissue inimical to further tumour growth, and the brain an encouraging growth medium.

The explanation for the propensity of peripherally sited lung carcinomas to be associated with single or solitary cerebral metastasis is not obvious, and has not been revealed by this retrospective investigation. An attempt to demonstrate spread by venous and lymphatic channels is necessary, and the ability of central nervous tissue to act as an encouraging growth medium for metastases from lung carcinoma also requires investigation.

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