Criteria for the Histologic Diagnosis of Bronchogenic Carcinoma*

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The reliance on biopsy as a definitive diagnostic procedure has been challenged by reports of simulation of bronchogenic carcinoma by metastases from carcinomas of the stomach, kidney, adrenal, ovary, colon, rectum, pancreas and other sites. Bronchial, lymph node and lung metastases from carcinoma of the tail of the pancreas have been particularly involved in the mimicry because of the silent characteristics of the primary lesion. It has also been found that metastases from ductal or glandular carcinomas may present features of undifferentiated squamous cell carcinoma and that metastases to the periphery of the lung may show the typical appearance of bronchioloalveolar carcinoma.

The erroneous interpretation of metastatic lesions by pathologists from varied institutions makes it apparent that the differentiation between primary and secondary lung cancer is not always feasible. It was therefore deemed desirable to compare the histologic features of a large number of primary and metastatic cases, confirmed by necropsy, with the objective of establishing more definitive criteria.

Material and Methods

The material available for investigation consisted of 224 necropsy cases of metastatic lung cancer and 124 necropsy cases of bronchogenic carcinoma. All of the metastatic cases and 44 of the bronchogenic carcinomas had been observed at the Doctors Hospital during the period, 1946-1965. There were 80 necropsy cases of bronchogenic carcinoma observed at the City Hospital during the period, 1936-1956. The slides were reviewed according to a definite schema and, when indicated, additional sections were cut from the blocks. The sections were routinely stained with hematoxylin and eosin and, in particular instances, with periodic acid-Schiff, alcin blue, mucicarmine, Wilder's reticulum and Weigert's elastic tissue stains.

Results

The distinguishing features of the 124 cases of bronchogenic carcinoma and the 224 cases of metastatic lung cancer were compared in the following categories: (1) site of origin, (2) cytostucture and (3) lymph node metastases.

Site of Origin

Bronchogenic Carcinoma: Origin of the tumor from bronchial epithelium could be demonstrated in only 22 (28.5 per cent) of the 78 cases of primary squamous cell carcinoma. The outstanding feature was abrupt replacement of high columnar ciliated epithelium by malignant squamous cells in varying stages of differentiation. Intervening areas of squamous metaplasia were not observed. Non-malignant columnar ciliated epithelium bordered on both sides of the tumor (Fig. 1). In the other 59 cases of squamous cell carcinoma, extensive involvement and necrosis precluded identification of the site of origin. In a study of surgical material, previously reported, it was possible to determine bronchial epithelial origin in more than 50 per cent of the cases.

There were 28 adenocarcinomas of which 26 showed extensive involvement in the peripheral portions of the lung. In 14...
of the cases there could be demonstrated one or more areas of abrupt change from non-malignant low columnar or cuboidal epithelium to malignant tall columnar cells with eosinophilic cytoplasm and basally situated nuclei. The site of origin, when demonstrable, was limited to the terminal bronchi or bronchioles (Fig. 2). There were 18 cases of oat-cell carcinoma of which 12 showed complete replacement of the bronchial wall by tumor. In six of the cases, sites of origin could be demonstrated in the segmental bronchi from the basal layer of the epithelium.

Metastatic Carcinoma: Involvement of the segmental and subsegmental bronchi was present in 121 (54 per cent) of the 224 metastatic cases. The degree of implication ranged from multifocal invasion of the peribronchial lymphatics to replacement of the entire bronchial wall by tumor tissue. The outstanding characteristic of metastatic bronchial involvement was the intact epithelium overlying the tumor masses in the distended lymphatic spaces (Fig. 3). This feature could be consistently demonstrated even in cases in which massive tumor replacement of the bronchial wall simulated bronchogenic carcinoma. Metastases to the peripheral portions of the lung showed similarity to the transitional areas between non-malignant bronchial epithelium and tumor cells found in primary adenocarcinoma of the lung. Lymphatic invasion from the pleura by way of the interlobular septa was noted frequently in association with bronchiolar metastases.

Cytostucture
Bronchogenic Carcinoma: Of the 78 cases of primary squamous cell carcinoma, only 16 (20.5 per cent) could be described as well-differentiated. In the remaining 62 cases (79.5 per cent) keratinization, pearl formation, cell nests and intercellular bridges were relatively inconspicuous features. The distinguishing structural feature of the squamous cell carcinomas was related to their origin from the larger bronchi. The tumors extended along the bronchial surfaces with a marked tendency to polypoid formation. The adjacent non-malignant epithelium was displaced in a manner resembling the surface extension found in Paget's disease of the nipple. Invasion of the peribronchial lymphatics and alveolar structures occurred secondarily. Another distinguishing feature of the primary squamous cell carcinomas was the extensive desmoplastic reaction around the

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**Figure 1:** Section of segmental bronchus showing site of origin of squamous cell carcinoma. The abrupt line of demarcation between the columnar ciliated epithelium and the malignant squamous cells is very evident (X 200).

**Figure 2:** Section of bronchiolar bifurcation showing origin of adenocarcinoma. There is an abrupt transition from the non-malignant cuboidal epithelium to the tall malignant columnar cells; pappilation is prominent (X 150).
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Figure 3:
(a) Features of metastatic bronchial carcinoma. The primary carcinoma was located in the stomach (X 150). (b) The tumor-filled lymphatic spaces have collected in the peribronchial lymph nodes. (c) The primary bronchial carcinoma shows no malignant invasion. The primary bronchial carcinoma was located in the esophagus (X 90).

The lymphatic spaces are distended with proliferating malignant epithelial cells. The cells are columnar, forming large sub-epithelial spaces around the bronchial wall. In one area, the tumor has ulcerated through the bronchial wall and projects into the lumen.
segmental bronchi. In the smaller bronchi the fibrous tissue adjacent to the tumor was far less abundant. Productive endarteritis was observed on numerous occasions in areas adjacent to the tumor, but arterial invasion was a rarity.

The 28 primary adenocarcinomas showed, in varying degrees of involvement, structural formations having the appearance of ducts or glands and cluster arrangements of columnar or spheroidal cells with abundant cytoplasm and basally situated nuclei. In 14 of the cases, (50 per cent) propagation of the malignant cells could be followed from the terminal bronchi or bronchioles to the alveolar structures where they lined the stroma to produce a glandular effect. Origin from mucous glands was not evident. In areas of more extensive involvement, the malignant cells filled the alveoli producing a solid or nodular appearance. Crowding of the columnar cells in the alveoli often resulted in loss of identity as the cells assumed squamoid features (Fig. 4).

The prominent feature of the oat cell carcinomas was the extensive invasion into the subepithelial lymphatics and bronchial mucous glands. This was particularly notable in the six cases (33.3 per cent) in which extension of the tumors could be followed from their origin in the basal layer of the epithelium. In most sections the tumor cells had the appearance of small round cells with hyperchromatic nuclei, but spindle and ovoid forms were also conspicuous. The structural pattern of the tumor was frequently in the form of streams or ribbons within which could be seen formations resembling ducts and tubules.

Metastatic Carcinoma: The distinctive architectural features of the metastatic cases were related to the patterns of pulmonary invasion and the inherent characteristics of the primary extrathoracic tumors. The predominant findings were: (1) intralymphatic tumor masses encircling the larger bronchi with multifocal penetration of the epithelium, (2) pleural invasion with extension of the tumor into the lung along the interlobular septa, and (3) malignant emboli lodged in the small arteries and arterioles, indicative of hematogenous invasion.

The cytologic appearance of the metastases from extrapulmonary ductal or glandular carcinomas was mostly compatible with undifferentiated carcinoma and, in many sections, showed features resembling squamous cell carcinoma (Fig. 5). The notable exceptions were: (1) peri-

Figure 4: Section from primary adenocarcinoma of the lung showing crowding of alveolar spaces with malignant columnar cells to produce an effect simulating squamous cell carcinoma (X 135).

Figure 5: Metastatic lung cancer secondary to carcinoma of breast. Section shows areas of malignant columnar cells in linear and ductal formation adjacent to masses of undifferentiated malignant cells with squamoid features (X 90).
pheral metastases which showed histologic features simulating primary adenocarcinoma (Fig. 6), and (2) intrapulmonary metastases which showed features indigenous to the primary tumor, such as duct formation and cells typifying the primary site, i.e., clear and opaque cells from renal cancers, colloid containing cells from thyroid cancers and syncitial cells from testicular cancers (Fig. 7).

There were eight cases (3.5 per cent) with pulmonary metastases from squamous tumors of the tongue, esophagus and skin, respectively. Sections from the secondary growths in these cases exhibited a far greater degree of epidermoidalization than was present in the bronchogenic squamous cell carcinomas. The areas of keratinization and pearl formation were very extensive and uniformly distributed throughout the tumor mass (Fig. 8). The contrast between the secondary and primary squamous cell carcinomas was often marked with the primary tumors usually showing keratinized cells in patchy clusters irregularly distributed between areas of poorly differentiated squamous cells.

LYMPH NODE METASTASES

In 22 (18 per cent) of the primary cases and 46 (20.5 per cent) of the secondary cases, there were sufficient data available to study the anatomic distribution of intrathoracic lymph node metastases.

Bronchogenic Carcinoma: The patterns of spread in the primary cases generally followed the normal channels of lymphatic drainage. The left upper lobe carcinomas metastasized to the anterior mediastinal, left paratracheal, or subcarinal nodes; the left lower lobe tumors spread to the subcarinal and right paratracheal nodes; the right upper and middle lobe tumors to the right paratracheal or subcarinal nodes; and the right lower lobe tumors to the subcarinal and right paratracheal nodes.

The histologic features of the malignant lymph nodes generally reflected the morphologic appearance of the primary tumors. There were, however, many areas in sections of metastatic lymph nodes from oat cell carcinomas which simulated lymphosarcoma. The major points of differentiation were found to be: (1) morphologic variation of cells in oat cell carcinoma, (2) monotonous homogeneity of cells in lymphosarcoma, (3) involvement of entire gland in lymphosarcoma, and (4) intercellular distribution of reticulum in lymphosarcoma.

**Figure 6:** Metastatic lung cancer secondary to carcinoma of duodenum. The tall, columnar, malignant cells with basally situated nuclei line the alveolar walls to present the typical adenomatous appearance of adenocarcinoma of the lung (X 150).

**Figure 7:** Metastatic lung cancer secondary to carcinoma of the thyroid. The alveolar walls are lined by malignant cells simulating peripheral adenocarcinoma; the distinguishing feature is the distention of the alveolar spaces by colloid material (X 150).
Metastatic Carcinoma: The pulmonary metastases which were located mainly within one lobe showed patterns of lymph node involvement similar to those of the primary carcinomas. In the disseminated metastatic cases, the intrathoracic distribution varied considerably. The outstanding feature of lymph node spread in the metastatic cases was the frequent presence of malignant nodes in sites incompatible with the normal channels of lymph drainage i.e., the coexistence of a right lower lobe metastasis and malignant left cervical nodes.

The histologic features of the malignant lymph nodes found in the cases of metastatic lung cancer showed considerable morphologic variation. The appearance of the tumor generally reflected the ductal or glandular characteristics of the primary site, but there were also many areas resembling undifferentiated squamous cell carcinoma (Fig. 9). It was very apparent from these findings that examination of only a few areas of a section may readily contribute to erroneous interpretation.

DISCUSSION

The results of this study clearly indicate that the establishment of more definitive criteria for the histologic diagnosis of bronchogenic carcinoma involves recognition of the varied manifestations of bronchial, pulmonary and lymph node metastases from occult extrapulmonary carcinomas. Cumulative studies have shown that the differentiation between primary and secondary lung cancer is not always feasible.
The diagnosis of squamous cell carcinoma may be made unequivocally when
the bronchial biopsy shows origin from columnar ciliated epithelium. Considerable
reservation should exist if the epithelium is intact and the squamous appearance of
the tumor is caused by crowding of malignant cells in distended or coalescent sub-
epithelial lymph spaces. It was also observed in this study that complete replace-
ment of the bronchial wall by differentiated squamoid malignant cells occurred
in both bronchogenic carcinoma and metastatic lung cancer. Bronchial biopsy show-
ing adenocarcinoma should be suspect of metastatic origin because primary adeno-
carcinomas arise peripherally and are generally inaccessible to bronchoscopic visual-
ization. Tumors having the appearance of oat-cell carcinoma should be studied
for morphologic variations, tubule formation and distribution of reticulum to exclud
the possibility of lymphosarcoma.

In the study of the cytologic features of primary lung cancer it was noted that
few of the squamous cell carcinomas exhibited the classic features of epidermo-
idalization. Most of the tumors were classified as undifferentiated squamous cell car-
cinomas and the appearance was often simulated by metastatic cancers. Of consid-
erable interest was the finding that pulmonary metastases from extrapulmonary squamous cell carcinomas showed far more extensive keratinization and pearl forma-
tion than the primary squamous cell carcinomas.

The histologic differentiation between primary and secondary lung cancer will be
facilitated by consideration of the characteristics of metastases. In the larger bron-
chi, metastatic tumors are located chiefly in the subepithelial lymphatics. Metastatic
invasion of the terminal bronchi or bronchioles may result in a histologic picture
resembling primary adenocarcinoma and distinction may not be possible. An impor-
tant clue to the recognition of metastatic tumors is that they invariably retain some
of the features indigenous to the primary site. These may include duct or gland
formation or the presence of cells typical of the primary tumor. The demonstration
of malignant emboli in the small arteries is a significant finding indicative of hemato-
genous invasion of the lung.

**Summary**

1. Cumulative reports have established that bronchogenic carcinoma may be simu-
lated, histologically, by bronchial, lung and lymph node metastases from extrathoracic carcinomas.

2. A necropsy study of 124 cases of bronchogenic carcinoma and 224 cases of metastatic lung cancer revealed that histo-
logic differentiation was not always feasible.

3. The definitive criteria for the diagnosis of squamous cell and oat-cell carcino-
moma consisted of (a) demonstration of the site of epithelial origin and (b) exclu-
sion of features indigenous to metastatic tumors.

4. The histologic resemblance of periph-
eral metastases to adenocarcinoma pre-
cluded a positive diagnosis of primary lung cancer without necropsy.

5. The characteristic features of meta-
static bronchial carcinoma in the early
stages were involvement of the subepithelial lymphatics and preservation of the epite-

6. Pulmonary metastases from extrathoracic ductal or glandular carcinomas often
presented as squamoid tumors containing few identifiable ductal structures.

7. Pulmonary metastases from extrathoracic squamous cell carcinomas usually
showed a higher degree of keratinization and pearl formation than the primary squamous cell carcinomas of the lung.

8. A definitive clue to the diagnosis of metastatic tumors was the presence of cells
typifying the site of origin.

9. The presence of carcinomatous emboli in the small arteries occurred predominant-
ly in the cases of metastatic lung cancer.

10. Lymph node invasion presented problems in differential diagnosis because
of the pleomorphic features of extrathoracic metastases and the simulation of oat-cell carcinoma by lymphosarcoma.

**Resumen**

1. Numerosos reportes indican que las metástasis bronquiales, pulmonares y ganglionares de carcinomas extratorácicos pueden simular el carcinoma broncogén.

2. El estudio necrásico de 124 casos de carcinoma broncogén y 224 de cáncer pulmonar metastásico revelan que la diferenciación no es siempre factible.

3. El criterio definitivo para el diagnóstico de carcinoma de células escamosas y "oat cell" carcinoma consiste en: a) Determinación del punto de origen epitelial, b) Exclusión de características propias de tumores metastásicos.

4. Semejanzas histológicas de las metástasis periólicas con el adenocarcinoma excluye el diagnóstico de cáncer pulmonar primitivo cuando no se ha practicado la necropsia.

5. Las características de ca. bronquial metastásico en las etapas iniciales eran la invasión de los linfáticos subepiteliales con preservación del epitelio.

6. Las metástasis pulmonares de los carcinomas extratorácicos canalulares o glandulares frecuentemente presentan apariencia escamosa con escasas estructuras canalulares identificables.

7. Las metástasis pulmonares de ca. de células escamosas extratorácicas generalmente exhiben un grado de queratinización y formación de perlas epidermoideas mayor que el ca. epidermoide primitivo del pulmón.

8. La clave definitiva del diagnóstico de tumores metastásicos fue la presencia de células típicas del punto de origen.

9. La presencia de embolización carcinomatosa en las pequeñas arterias ocurre, predominantemente, en los casos de cáncer pulmonar metastásico.

10. La invasión de los ganglios linfáticos presenta problemas de diagnóstico diferencial debido a las características pleomórficas de las metástasis extratorácicas y la similitud del linfosarcoma con el oat cell carcinoma.

**Zusammenfassung**


2. Die Sektionsanalyse von 124 Fällen von Bronchuskarzinomen und 224 Fällen metastatischer Lungenkarzinome ergab, daß eine histologische Differenzierung nicht in jedem Fall möglich war.


4. Die histologische Ähnlichkeit peripherer Metastasen zu Adenokarzinomen schlossen eine positive Diagnose eines primären Lungenkarzinoms ohne Sektion aus.


6. Pulmonale Metastasen extrathorakaler kana
culärer oder glannulärer Karzinome stellen sich oft als Plattenzell-Tumoren dar und enthalten identifizierbare Wandstrukturen.


10. Lymphknotenbefall stellt ein besonders Problem dar bei der Differentialdiagnose in Hinblick auf die pleomorphe Gestalt extrathorakaler Metastasen und der Simulation von Pflasterzellkarzinomen durch Lymphosarkome.

**References**


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PALLIATIVE SURGERY IN COMPLETE TRANSPOSITION OF GREAT VESSELS

During the years 1960-63 inclusive, 53 infants with complete transposition of the great vessels were seen at the Royal Children's Hospital, Melbourne. Of these, 36 were investigated by venous angiography or by cardiac catheterization with selective angiography. An attempt was made to create an atrial septal defect in 30 infants, either under direct vision during inflow occlusion, or by the technique of Blalock and Hanlon. There were 11 operative deaths and 15 infants appeared to be improved by the procedure. Of these improved survivors, 13 patients have been followed up for up to four years with one death following an attempt at complete repair. The degree of improvement varied, but most infants could be classified as having had good functional results.


COMPLICATIONS ASSOCIATED WITH DISPLACEMENT OF BRONCHI AFTER PARTIAL RESECTION

On the basis of 141 bronchographic investigations, the regularity of bronchial displacement after different types of partial resection is described. The most unfavorable displacement of bronchi with their flexion is noted after superior and inferior lobectomy, which is conducive to the development of atelectasis and exacerbation of the inflammatory process at late periods. The author recommends fixation of the anteroinferior region to the pericardial adipose tissue for the prevention of excessive displacement of the remaining pulmonary lobes and segments.