The Significance of Cell Types in Bronchogenic Carcinoma*

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Physicians dealing with diseases of the thorax have long been aware that carcinoma of the lung varies greatly in its clinical manifestations, and that certain types of bronchogenic carcinoma are much more amenable to surgical eradication than others. The great frequency with which bronchogenic carcinoma occurs and its apparent increasing incidence make it essential to determine as far as possible the various factors that may influence the course of the disease.

In discussing bronchogenic carcinoma, it is first essential to define what is included by the term. Bronchogenic carcinoma is a primary carcinoma of the lung which is presumed to originate in the mucosa of the bronchi. Metastatic carcinoma of the lung, adenoma of the bronchus, and alveolar cell tumor must be distinguished from bronchogenic carcinoma, for not only are their clinical course and prognosis different from those of bronchogenic carcinoma, but they have an entirely different source of origin.

The results of early studies that were carried out to classify carcinoma of the lung solely on the basis of grade of malignancy of the tumor according to the method of Broders were soon found to be of little or no clinical, surgical or prognostic value. It has long been recognized that true bronchogenic carcinoma may assume a variety of forms, and many terms have been utilized by pathologists to describe these various changes. This lack of uniformity in terminology has made an understanding of the significance of cell types in carcinoma of the lung difficult. It is only since sufficient surgical and necropsy material has become available that it is possible to study and correlate the clinical course of the disease with survival following operative intervention and to devise a workable histologic classification.

In order to study the problem of the significance of cell types of bronchogenic carcinoma, the records of 1,000 cases of proved carcinoma of the lung, taken at random from the files of the Mayo Clinic, were reviewed. In each case, the diagnosis of carcinoma of the lung was based on the examination of bronchoscopic specimens, specimens taken for biopsy at the time of thoracotomy for inoperable neoplasms, and surgical specimens obtained by lobectomy or pneumonectomy. This series did not include any case in which there was evidence of carcinoma elsewhere in the body or in which there was a chance that the pulmonary lesion might be metastatic.

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Of the 1,000 patients in the cases in this series, 895 were men and 105 were women. The ratio of males to females, therefore, was 8.5:1. The ages of the patients ranged from 22 to 80 years. Operation for the bronchogenic carcinoma was performed in 479 of the 1,000 cases.

Some bronchogenic carcinomas are not made up of a single cell type but have a mixed cellular pattern. Part of the tumor may be of one cell type and another part may be of a different type. In attempting to classify tumors of this kind, the dominant type of cell present in the available histologic material was selected, and the tumor was classified as of that type. The minor histologic pattern was disregarded.

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Number</th>
<th>Per cent</th>
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<tr>
<td>Small cell carcinoma</td>
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<td>9.0</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>137</td>
<td>13.7</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>378</td>
<td>37.8</td>
</tr>
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<td>Squamous cell carcinoma</td>
<td>395</td>
<td>39.5</td>
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<td><strong>TOTAL</strong></td>
<td><strong>1,000</strong></td>
<td><strong>100.0</strong></td>
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**FIGURE 1:** Small cell bronchogenic carcinoma. The cells are very small and are not forming glands. (Hematoxylin and eosin stain; x 200).
One of us (McDonald) and his associates\textsuperscript{1-5} have divided bronchogenic carcinomas into four groups: (1) small cell carcinomas, (2) adenocarcinomas, (3) squamous cell carcinomas, and (4) large cell carcinomas.

\textit{Small Cell Carcinoma}

A small cell carcinoma (Figure 1) is one in which the cells are small, with little cytoplasm surrounding the nucleus. The nucleus makes up almost 90 per cent of the cell. Nucleoli are not a prominent feature of this type of cell. This type of tumor is often designated as the "oat-cell type of cancer," "spindle-cell cancer," or "sarcoma."

The various types of bronchogenic carcinoma produce a gross picture which is more or less characteristic. In cases of small cell bronchogenic carcinoma, the involved bronchus is a large one, either the main stem bronchus or a primary division of the lobe bronchi (Figure 2). The lumen of the bronchus is stenotic, and the growth does not tend to produce a polypoid tumor mass in the bronchial lumen. The carcinoma extends beyond the involved bronchus to adjacent tissues. Oftentimes, the extrabronchial tumor mass is much larger than the part within the lung. In its most characteristic form, this type of bronchogenic carcinoma simulates a mediastinal tumor in the roentgenogram.

In 90, or 9 per cent, of the entire series of 1,000 cases the tumor was a small cell carcinoma (Table I). Although it was the least common of the bronchogenic carcinomas, it had the gravest prognosis. It is a disease that possesses a peculiar predilection for males. Eighty-seven of the patients were men and only three were women. The ratio of males to females, therefore, was 29:1. The average age of the patients was 46 years. The youngest patient was 36 years of age and the oldest was 75 years. All of the patients with small cell carcinoma had symptoms referable to the
thorax. Such symptoms were not present in all of the cases of the other types of carcinoma. The symptoms were indistinguishable from those of other types of bronchogenic cancer with the single exception that, on the average, the duration of symptoms before the diagnosis was established was of slightly shorter duration, being but 5.9 months. The sedimentation rate of the erythrocytes was not found to be of any value in distinguishing one type of bronchogenic carcinoma from another, and was elevated, on the average, in all types of carcinoma. In all of the 90 cases of small cell carcinoma, roentgenographic examination of the thorax disclosed changes which might be interpreted as indicative of a tumor.

The study of the gross surgical specimens revealed that most of the small cell carcinomas were of large size. With one exception, the tumor was situated either in the main stem or in a major secondary bronchus. If one divides the lung into two portions so that the primary and secondary bronchi are regarded as the central portion of the lung and the tertiary and distal bronchi are regarded as the peripheral portion, small cell carcinoma is essentially a tumor of the central portion of the lung.

In 84 of the 90 cases of small cell carcinoma, accurate information was available concerning the lobe of the lung involved. It was found that the lesion was on the right side in 51 cases and on the left side in 33 cases. The distribution according to lobe is shown in Figure 3. With almost all the small cell carcinomas arising from the central portion of the lung, one would anticipate being able to visualize the lesion bronchoscopically and to obtain tissue for microscopic examination in a high percentage of cases. This proved to be true. Bronchoscopy was performed in 81 of the 90 cases, and it disclosed a tumor in 67, or 82.7 per cent, of the 81 cases. In 62, or 76.5 per cent, of the 81 cases, microscopic examination of tissue which was removed by bronchoscopy revealed that the lesion was a carcinoma.

Cytologic examination of the sputum and bronchial secretions was found to be highly effective in the diagnosis of small cell bronchogenic carcinoma. It disclosed malignant cells in 93.5 per cent of the cases in which it was employed.

The tumor was considered operable in only 30 of the 90 cases. An exploratory operation was performed in 30 cases, but it was possible to remove the tumor in only 15 of these cases. Pneumonectomy was performed in all of these 15 cases. Study of the surgical specimens showed involvement of the hilar nodes in every case. Of the 15 patients who underwent pneumonectomy, only three were living two years after operation. One was living five years later. This would seem to indicate that the prognosis with respect to surgical eradication is extremely poor in cases of small cell carcinoma.

**Adenocarcinoma**

Adenocarcinoma (Figure 4) is characterized by cells which are forming glands or producing secretion. The diagnostic criterion is the presence of definite alveolar, acinar or papillary structures, or the formation of extracellular or intracellular mucus with columnar or cuboidal configuration of the cells.
Grossly, an adenocarcinoma of the lung is usually a peripheral tumor, oftentimes sharply circumscribed and situated subjacent to the pleura (Figure 5). In a small percentage of cases, a small bronchus can be traced into the tumor mass. In most cases, however, it is impossible to identify an involved bronchus intimately associated with the tumor.

In 137, 13.7 per cent, of the entire series of 1,000 cases of primary bronchogenic carcinoma, the tumor was an adenocarcinoma. Although adenocarcinoma occurs more frequently in men than in women, the predilection was not as great as in cases of the other types of bronchogenic carcinoma. One hundred and six of the patients were men and 31 were women. The ratio of males to females, therefore, was 3.4:1. The average age of the patients was 53 years. The youngest patient was 31 years of age and the oldest was 71 years. When the patients were divided into groups according to their ages by decades, those in the largest group were found to be in the sixth decade. The symptoms of adenocarcinoma were essentially the same as those of other types of bronchogenic carcinoma. However, in an occasional case, the patient was asymptomatic. The average duration of symptoms in the cases of adenocarcinoma was 7.9 months. Roentgenologic examination of the thorax disclosed evidence of an abnormality in all of the 137 cases.

FIGURE 4: Bronchogenic carcinoma, adenocarcinoma type. The carcinoma cells are forming acini. (Hematoxylin and eosin stain; x 200).
Adequate surgical specimens were available for examination in 65 of the 137 cases. The distribution of the tumors in the 65 cases is shown in Figure 6. In 34 of the cases the tumor involved the right lung, and in 31 cases it was situated in the left lung. The tumor originated in the peripheral portion of the lung in 43 (66.2 per cent) of the 65 cases, and in the central portion of the lung in 22 cases (33.8 per cent).

In contrast to small cell carcinomas which are primarily central in origin, adenocarcinomas are almost twice as common in the peripheral portion of the lung. One, therefore, would not anticipate being able to visualize the lesion as frequently as small cell carcinoma on bronchoscoptic examination. This indeed proved to be the case. Bronchoscopy was performed in 57 of the 137 cases, and it disclosed a tumor in only 22, 38.5 per cent, of the 57 cases. Microscopic examination of tissue removed by bronchoscopy, disclosed carcinoma in only 13 or 22.8 per cent of the cases in which bronchoscopy was performed.

Cytologic examination of sputum or bronchial secretions was performed in 82 of the 137 cases of adenocarcinoma. In 40 or 48.8 per cent of the 82 cases, it disclosed malignant cells.

Eighty-four of the patients were regarded as suitable candidates for exploratory thoracotomy. In 56 cases it was possible to resect the tumor. This figure in many respects is misleading as to the operability of adenocarcinoma. Because of the great strides that have been made in thoracic surgery, the percentage of cases of adenocarcinoma in which resection can be performed successfully is much higher today than it was 10 years ago. In the period from 1945 through 1949, an exploratory operation was performed in 68.7 per cent of the cases of adenocarcinomas observed at the Mayo Clinic, and resection was performed successfully in 70.9 per cent of cases in which exploratory thoracotomy was performed. The surgical prognosis
in the cases of adenocarcinoma was somewhat better than it was in the cases of small cell carcinomas. At the end of two years, 33.3 per cent of the patients who had undergone resection of adenocarcinoma were living and well.

**Squamous Cell Carcinoma**

In a squamous cell carcinoma (Figure 7), at least some of the malignant cells show evidence of epidermoidization, usually, the production of keratinized or cornified material in at least some of the cells. The presence of prickle cells is accepted as sufficient evidence to classify a tumor as a squamous cell carcinoma.

Bronchogenic carcinoma of the squamous cell type is usually found in a large bronchus (Figure 8). Characteristically, it either produces a polypoid tumor mass projecting into the bronchus from the wall, or it produces a cicatricial narrowing of the bronchial lumen. There usually is not as much peribronchial extension as is seen in cases of small cell bronchogenic carcinoma. Cavitation is more commonly seen in cases of bronchogenic carcinoma than in cases of the other types of carcinoma.

Squamous cell carcinoma was the most frequent type of bronchogenic carcinoma in this series of 1,000 cases. In 395, or 39.5 per cent of the cases, the tumor was of the squamous cell variety. It was found to affect men predominantly, as 380 of the patients were men and only 15 women. The ratio of males to females, therefore, was 25.3:1. The average age of the patients was 52 years. When the patients were divided into groups according to their ages by decades, those in the largest group were found to be in the sixth decade. In only eight of the 395 cases were the patients less than 40 years of age, and only one was less than 30 years of age. The symptoms produced by squamous cell carcinoma were essentially the same as those observed in cases of the other types of bronchogenic carcinoma, and the average duration of symptoms before the diagnosis was established was six months. Roentgen examination of the thorax was highly informative, as it disclosed abnormal findings in 99 per cent of the 395 cases.

Exploratory thoracotomy was performed in 245 or 62 per cent of the 395 cases and resection was performed in 182 of the 245 cases. During the past five years, resection has been performed in 71 per cent of the cases in which the tumor was of the squamous cell type. Figure 9 shows the distribution of the tumors in the 182 cases in which resection was performed. The tumor was situated in the right lung in 96 or 52.7 per cent of the cases, and in the left lung in 86 or 47.3 per cent. Study of the surgical specimens showed that the tumors involved primarily the central portion of the lung, and in only four of the 182 cases was the tumor truly peripheral in situation in that it was more than 4 cm. from the main stem bronchus or its continuation as the lower lobe bronchus.

As one might anticipate from the site of most squamous cell carcinomas of the bronchial tree, bronchoscopy was highly effective in visualization of the lesions. Bronchoscopy was performed in 382 of the 395 cases, and it disclosed a lesion in 322 or 84.2 per cent of the 395 cases. In 306 or 80 per
cent of the 382 cases in which bronchoscopy was performed, biopsy disclosed that the lesion was a squamous cell carcinoma.

Cytologic examination of the sputum or bronchial secretions was performed in 221 of the 395 cases of squamous cell carcinoma. It disclosed carcinoma cells in 160 or 72.3 per cent of the 221 cases.

In 68 of the 182 cases in which resection was performed, the patients were traced for two years after the operation. Of the 68 patients in these

FIGURE 7 (top): Bronchogenic squamous carcinoma with definite evidence of squamatization. (Hematoxylin and eosin stain; x 200).—FIGURE 8 (bottom): Bronchogenic carcinoma, squamous type, involving the upper lobe bronchus. The carcinoma has produced narrowing of the bronchial lumen, but there is very little evidence of peribronchial extension, unlike a small cell carcinoma.
cases, 38 or 55.8 per cent were alive at the end of this period. Of 27 patients who were traced for five or more years after the operation, 14 or 51.9 per cent were alive when the last follow-up data were obtained. It should be pointed out that none of the patients who did not undergo operation were living at the end of three years. It is obvious, therefore, that squamous cell carcinoma is by far the most responsive to surgical eradication of all the types of bronchogenic carcinoma. It was found that those patients with involvement of the regional lymph nodes had less than half as good a chance of surviving five years following pulmonary resection as those without such involvement.

Large Cell Carcinoma

In a large cell carcinoma (Figure 10) the neoplastic cells do not show any evidence of epidermoidization, glandular formation, or the production of secretion. The cells are considerably larger than those seen in small cell carcinoma, and have more abundant cytoplasm. Large cell carcinoma in many respects represents a more or less negative diagnosis. There has been a tendency by many pathologists to group carcinomas of this type with those of the small cell type under the mysterious term, "undifferentiated carcinoma." Such a classification does not seem justified, since the clinical outlook in cases of large cell carcinoma is different from that in cases of small cell carcinoma.

The gross appearance of a large cell carcinoma is not as characteristic as that of other varieties of bronchogenic carcinoma. It becomes obvious that this might be expected when one realizes that some large cell carcinomas are, in reality, highly undifferentiated forms of squamous carcinoma, while others represent highly undifferentiated forms of adenocarcinoma.

Figure 9: Distribution of squamous carcinomas in 121 cases in which resection was performed. — Figure 10: Bronchogenic carcinoma, large cell type. The cells are considerably larger than those of the small cell type. However, there is no evidence of glandular formation or squamatization. (Hematoxylin and eosin stain; x 200).
Some of these tumors are found in large bronchi and others are found near the periphery of the lung.

In 378 or 37.8 per cent of the entire series of 1,000 cases, the tumor was of the large cell type. Of the 378 patients, 322 were men and 56 were women. The ratio of males to females, therefore, was slightly less than 6:1. The ages of the patients ranged from 22 to 80 years, and the average age was 55 years. When the patients were divided into groups according to their ages by decades, those in the largest group were found to be in the sixth decade. The symptoms were essentially the same as those in cases of the other types of carcinoma, and the average duration of symptoms before diagnosis was made was the same as it was in the cases of adenocarcinoma. In more than half of the cases, the symptoms had been present for less than four months. In eight of the 378 cases, roentgenographic examination of the thorax did not reveal any abnormality.

In 130 of the 378 cases of large cell carcinoma, surgical specimens were examined in order to determine the site of origin of the tumor. In 75 or 57.7 per cent of the 130 cases, the tumor was situated in the central portion of the lung. In the remaining 55 cases (42.3 per cent), it was situated in the peripheral portion of the lung. Figure 11 shows the distribution of

![Figure 11: Distribution of large cell carcinomas in 130 cases.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21235/)
the tumors according to the involved lobe in this group of 130 cases. The tumors were approximately evenly divided between the right and left lungs. As one might anticipate, when such a large percentage of tumors occur in the peripheral portion of the lung as they did in this group of 130 cases, bronchoscopy would be less likely to disclose a lesion than it would in cases in which a large majority of the tumors were situated in the central portion of the lung. Bronchoscopy was performed in all of the 130 cases in which resection was performed, and it disclosed a tumor in 65 or 50 per cent of the cases. Biopsy disclosed carcinoma cells in 59 or 45.4 per cent of the 130 cases.

Cytologic examination of the sputum or bronchial secretions was performed in 170 of the 378 cases of large cell carcinoma. This diagnostic procedure disclosed the presence of carcinoma cells in 122 or 71.8 per cent of the 170 cases.

Exploratory thoracotomy was performed in 186 or 49.2 per cent of the 378 cases. Pulmonary resection was possible in 108 or 58.1 per cent of the 186 cases in which an exploratory operation was performed. In 43.6 per cent of the cases in which resection was performed, the patients were alive two years after the operation.

SUMMARY

This report is based on a study of 1,000 cases of proved bronchogenic carcinoma which were observed at the Mayo Clinic. The cell type of the tumors was as follows: small cell carcinoma in 90 cases (9 per cent), adenocarcinoma in 137 cases (13.7 per cent), large cell carcinoma in 378 cases (37.8 per cent), and squamous cell carcinoma in 395 cases (39.5 per cent).

Small cell carcinomas and squamous cell carcinomas occur much more frequently in men than in women. The ratio of males to females was 29:1 in the 90 cases of small cell carcinoma and 25.3:1 in the 395 cases of squamous cell carcinoma. The difference in the sexual incidence was not so great in the cases of adenocarcinoma or large cell carcinoma. The ratio of males to females was 3.4:1 in the 137 cases of adenocarcinoma and slightly less than 6:1 in the 378 cases of large cell carcinoma. The average age of the patients was slightly lower in the cases of small cell carcinoma than it was in cases of the other types of tumor.

The duration of symptoms was shorter in the cases of small cell carcinoma than it was in cases of the other types of tumor. In all of the cases of small cell carcinoma, the patients had symptoms that were referable to the thorax. Such symptoms were not present in all of the cases of the other types of carcinoma. With the exceptions noted, the symptoms were essentially the same in all cases.

Roentgenographic examination of the thorax disclosed an abnormality in all but 12 of the entire series of 1,000 cases. Bronchoscopy was not performed in all of the cases in the respective groups, but it was a very effective diagnostic procedure in cases in which the tumor arose from the central portion of the lung, that is, in cases of small cell carcinoma and in cases of squamous cell carcinoma. Cytologic examination of the sputum or bron-
chial secretions was more effective in the cases of small cell carcinoma and least effective in the cases of adenocarcinoma.

The results of surgical treatment were more satisfactory in cases of squamous cell carcinoma than they were in cases of the other types of carcinoma. The results of surgical treatment were least satisfactory in the cases of small cell carcinoma.

RESUMEN

Esta comunicación se basa en el estudio de 1,000 casos de carcinoma bronquiogénico comprobado que fueron observados en la Clínica Mayo. El tipo celular de los tumores fue como sigue: Carcinoma de celdillas pequeñas 90 casos (9 por ciento); adenocarcinoma en 137 casos (13.7 por ciento), carcinoma de celdillas grandes en 378 casos (37.8 por ciento) y carcinoma de celdillas escamosas 395 casos (39.5 por ciento).

Los carcinomas de celdillas pequeñas y escamosas ocurren mucho más frecuentemente en el hombre que en la mujer. La relación de hombres a mujeres fue de 29:1 en los 90 casos de carcinoma de pequeñas celdillas y de 25:1:1 en los 378 casos de carcinoma de celdillas escamosas. La diferencia en la incidencia sexual no fue tan grande en los adenocarcinomas o en los carcinomas de celdillas grandes. La relación de hombres a mujeres fue de 3.4:1 en 137 casos de adenocarcinoma y ligeramente menor que 6:1 en 387 casos de carcinomas de celdillas grandes. La edad media de los enfermos fue ligeramente más baja en los casos de carcinoma de pequeñas celdillas que en los casos de otros tipos de tumor.

La duración de los síntomas fue más corta en los casos de carcinoma de pequeñas celdillas que en los casos de otros tipos de tumor. En todos los casos de carcinoma de celdillas pequeñas los enfermos tenían síntomas que podían referirse al torax. Tales síntomas no se encontraron en todos los casos de otros tipos. Con las excepciones señaladas los síntomas fueron esencialmente los mismos en todos los casos.

El examen roentgenográfico del torax denotó anormalidad en todos menos 12 casos de los 1,000. La broncoscopia no fue llevada a cabo en todos los casos de los grupos respectivos pero fue un procedimiento de diagnóstico muy efectivo en los casos en que el tumor emergía de la porción central del pulmón, esto es, en los casos de carcinomas de celdillas pequeñas y en casos de carcinoma de celdillas escamosas. El examen citológico del esputo o de las secreciones bronquiales fue más efectivo en los carcinomas de pequeñas celdillas y menos efectivo en los adenocarcinomas.

El resultado del tratamiento quirúrgico fue más satisfactorio en casos de carcinoma de celdillas escamosas que en los otros tipos de carcinoma. Los resultados del tratamiento quirúrgico fueron menos satisfactorios en los casos de carcinoma de celdillas pequeñas.

RESUME

Le rapport est basé sur une étude de 1,000 cas de cancers bronchiques observés à la Mayo Clinique. Les différentes formes histologiques des tumeurs furent les suivantes: dans 90 cas, cancer à petites cellules (9%),
CELL TYPES IN BRONCHOGENIC CARCINOMA 633
dans 137 cas, adénocarcinomes (13.7%), dans 378 cas, cancer à grandes
cellules (37.8%) et cancers épidermoides dans 395 cas (39.5%).
Les cancers à petites cellules et les cancers épidermoides survinrent
beaucoup plus fréquemment chez les hommes que chez les femmes. La pro-
portion des hommes par rapport aux femmes fut de 29 pour une, dans les
90 cas de cancer à petites cellules et de 25.3 pour un dans les 378 cas de
cancers épidermoides. Dans les adénocarcinomes ou dans les cancers à
grandes cellules, il n'y a pas une différence aussi nette selon les sexes. Dans
les 337 cas d'adénocarcinomes, la proportion fut de 3.4 hommes pour une
femme; et un peu moins de six hommes pour une femme dans les 378 cas
de cancers à larges cellules.
L'âge moyen des malades fut nettement plus bas dans les cas de cancer
à petites cellules que dans les autres formes de tumeurs.
La période symptomatologique fut plus courte dans les cas de cancers à
petites cellules que dans les autres types de cancers. Dans tous les cas de
cancers à petites cellules, les malades ont présenté une symptomatologie
thoracique. De tels symptômes étaient loin d'être présentés dans tous les
cas, dans les autres types de cancer. Mis à part ces caractères particuliers,
les symptômes furent en gros les mêmes dans tous les cas.
L'examen radiologique du thorax révela une anomalie dans tous les cas
de la série des 1,000 observations, sauf dans 12 d'entre eux. La bronchosco-
pe ne fut pas pratiquée dans tous les cas, mais elle se montra un procédé très
efficace de diagnostic lorsque la tumeur s'était constituée dans une zone
centrale, c'est-à-dire dans les cas de cancer à petites cellules et les cancers
épidermoides. L'étude histologique des crachats ou des sécrétions bron-
chiques fut le plus efficace dans les cas de cancers à petites cellules et le
moins efficace dans les cas d'adénocarcinomes.
Les résultats du traitement chirurgical furent plus satisfaits pour les
cancers épidermoides que dans les autres types de cancer. C'est dans les
cancers à petites cellules que le traitement chirurgical à donné les moins
bons résultats.

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