Lung cancer

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• Carcinoma of the lung has become very frequent during the past 60 years.
• The American Cancer Society has estimated that in 2010 there will be 222520 new cases and 157300 deaths from lung cancer.
• The rate of increase in men has declined over the past 5 years.
• Male: female ratio is 1.5:1. More than 90% of the patients are over 40 years of age at the time of diagnosis, but cases have also been reported in young adults and adolescents.
• **Risk Factor:**

  - Exposure to asbestos (5%) of all lung cancer deaths; polycyclic aromatic hydrocarbons; arsenic, nickel, and chromium compounds; bis(chloromethyl)ether (BCME); chloromethyl methyl ether (CMME); vinyl chloride; radiation.

  - The fact that smokers living in urban areas and/or exposed to asbestos are at a higher risk for lung carcinoma.

  - The relationship of cigarette smoking with malignant, dysplastic, and metaplastic alterations of the tracheobronchial tree.
• However, approximately 10–15% of cases of lung carcinomas occur in never-smokers. Among them, three-fourths are women, and a high proportion of cases show an adenocarcinoma histology, more prevalent in Asian populations.

• Another factor is pulmonary fibrosis, 22% were associated with – and presumably preceded by – honeycombing and atypical epithelial proliferation. Most of these tumors were in the upper lobe, and one-third of them were adenocarcinomas.

• Malignant tumors arising at the site of scars resulting from bullets or other foreign bodies have been well documented.

• Carcinomas arising adjacent to old granulomomas are also on record.
• A typical adenomatous hyperplasia of type 2 alveolar cells or bronchioloalveolar cell adenomas as precursors of adenocarcinoma.
• A few cases of lung carcinoma have been found to originate from a malignant transformation of papillomatosis of the respiratory tract.
• Lung carcinoma is multiple (either synchronous or metachronous) in about 2–5% of the cases.
• Associated with independent cancer of the head and neck region in about 20% of the cases.
• Most lung cancers are of considerable size when first detected, and about 60% are incurable as a result of extensive local spread and/or distant metastases.
• Symptoms and signs develop relatively late in the course of the disease, are usually related to partial or complete bronchial obstruction, and may lead to confusion with a primary inflammatory process.
• The most common symptoms, in decreasing order of frequency, are cough, weight loss, pain, increased sputum production, hemoptysis, malaise, fever, and those resulting from paraneoplastic manifestations.

• Peripherally located lesions are clinically silent until they reach a sufficient size to ulcerate into a bronchus or to involve the pleural space.

• Carcinomas located in the superior pulmonary sulcus result in a clinical picture peculiar to their location, known as Pancoast syndrome.

• About 35–50% of pulmonary coin lesions in adults represent lung carcinoma, the percentage is higher for patients older than 60 years and for non calcified lesions. The incidence of malignancy in coin lesions exhibiting obvious calcification is less than 1%.
<table>
<thead>
<tr>
<th>Systemic effect and hormone responsible</th>
<th>Tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing syndrome (ACTH)</td>
<td>Small cell carcinoma, Bronchial carcinoid</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>Bronchial carcinoid, Small cell carcinoma</td>
</tr>
<tr>
<td>Hyponatremia (ADH)</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Hyperparathyroidism (parathormone)</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Gynecomastia (hCG)</td>
<td>All tumor types</td>
</tr>
<tr>
<td>Clubbing of fingers and hypertrophic pulmonary osteoarthropathy</td>
<td>Unrelated to tumor type; mainly dependent on proximity to pleural surface</td>
</tr>
<tr>
<td>Mental syndromes (i.e., toxic confusional psychosis)</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Cortical cerebellar degeneration</td>
<td>All tumor types</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Myopathic–myasthenic syndrome (Lambert–Eaton syndrome)</td>
<td>Small cell carcinoma</td>
</tr>
</tbody>
</table>
• HISTOLOGIC CLASSIFICATION
• The one most widely used derives from the scheme originally proposed by Kreyberg and by the WHO Committee and the authors of the *Third Series Atlas of Tumor Pathology*. It includes the following major categories:
  • Squamous cell carcinoma (including some types of clear cell carcinoma).
  • Small cell carcinoma.
  • Adenocarcinoma (including bronchoalveolar carcinoma and some types of clear cell carcinoma).
  • Large cell carcinoma.
  • Adenosquamous carcinoma.
  • Sarcomatoid carcinoma/ carcinosarcoma (including pulmonary blastoma and pulmonary endodermal tumor)
• **HISTOLOGIC CLASSIFICATION**

• Adenocarcinoma; in particular, papillary adenocarcinoma was found to be composed of several carcinomas of the following different cell types:
  • Mucus-producing (goblet) cell type.
  • Bronchiolar non ciliated cell (Clara cell) type.
  • Type II alveolar epithelial cell type.
  • Bronchial surface epithelial cell type producing either no mucin or only scant amounts of it.
  • The last type of cell appears to have a tendency to differentiate as a ciliated columnar cell.
• In the third edition of the WHO histologic typing several new categories, such as atypical adenomatous hyperplasia as one of the preinvasive lesions, large-cell neuroendocrine carcinoma, and carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements, and the subtyping of four major histologic types (squamous cell carcinoma, adenocarcinoma, large-cell carcinoma, and small-cell carcinoma).

• Small-cell carcinoma with a large-cell component be considered a subtype of small-cell carcinoma.

• Large-cell carcinomas are poorly differentiated adenocarcinoma, squamous cell carcinoma, neuroendocrine carcinoma, or undifferentiated carcinoma.

• Large-cell neuroendocrine carcinoma has become a subtype of large-cell carcinoma.
MALIGNANT EPITHELIAL TUMORS

• Squamous Cell Carcinoma
  • Is the most frequently occurring lung cancer in Western countries, and is the type of cancer most strongly related to cigarette smoking.
  • A marked male predominance in its incidence is seen, with a male-to-female ratio of between 6.6 and 15 to 1.
  • At least 50% of all squamous cell carcinomas arise in a major bronchus (main to segmental bronchus), where the tumor shows both endobronchial and invasive growth into the peribronchial soft tissue, lung parenchyma, and nearby lymph nodes; it often compresses the pulmonary artery and vein.
• **Grossly**, squamous cell carcinoma of peripheral origin can be roughly divided into the following two types:

• (a) tumor with central or subpleural fibrosis with anthracosis, with which pleural indentation is often associated (although the indentation is not as sharp or conspicuous as that seen in adenocarcinoma because of a dense fibrotic tissue reaction at the site of indentation).

• (b) tumor without scar, in which the cut surface reveals either no anthracotic pigments or only a scant amount. The former is the result of a growth characteristic involving the filling of alveolar spaces, whereas the latter is formed through compression-type tumor growth.
• **Macroscopical types:**
  - Polypoid type (frequently arising at the bronchial spur).
  - Nodular type (arising at any site and having a tendency to form a localized tumor and to show vertical invasive growth).
  - Superficially infiltrating type (in situ and microinvasive-type growth often involving a wide area but exhibiting little tendency to produce bronchial stenosis).
  - Combination of these types.
Microscopically:

The diagnosis of malignancy is based on cell atypia and invasiveness, and the diagnosis of squamous cell type on the detection in hematoxylin–eosin sections of keratinization and/or intercellular bridges. Keratin formation may be seen in isolated cells or, more commonly, in the form of ‘keratin pearls’. Isolated necrotic cells should not be confused with keratinized cells. Whorl formation and definite stratification of tumor cells have been used by some as presumptive evidence of squamous differentiation in the absence of the features listed, but according to the WHO classification, these tumors should be placed in an undifferentiated large cell category.
• Other morphologic features that can be encountered in squamous cell carcinoma include:
  • Oncocytoid appearance of the tumor cells (due to increased mitochondrial density); giant cell foreign body reaction to keratin; palisaded granulomas; extensive infiltration by neutrophils and other inflammatory cells (the so-called malignant fibrous histiocytoma-like pattern); and lepidic type of growth into air spaces at the tumor periphery.
  • In addition, morphologic features may be present that are distinctive enough to place the tumor into a special subset, as follows:
    • Small cell variant.
    • Clear cell variant.
    • Well differentiated papillary.
    • Basaloid (more aggressive).
    • Spindle cell(sarcomatoid)/carcinosarcoma.
• **Immunohistochemically:**

• There is consistent reactivity for low and high molecular weight keratins and involucrin, the latter is a precursor of the cross-linked envelope protein or marginal band present in the stratum corneum.

• Immunoreactivity can also be found for vimentin, EMA, human milk fat globule (HMF6-2), S-100 protein, Leu-M1, CEA, desmocollin-3, and glypican-3.

• CK7 and TTF-1 are usually negative.

• P63 (a member of the p53 family involved in the development of epithelial tissues) is expressed in nearly all pulmonary squamous cell carcinomas but also in a significant subset of other types, including the majority of small cell carcinomas.
• Claudins (a family of tight junction proteins) are said to distinguish pulmonary squamous cell carcinomas from adenocarcinomas through the expression of claudin-1 in the former and claudin-5 in the latter.

• Presence of HPV has been documented in close to 20% of squamous cell carcinomas.

• At the genetic level, common alterations include allelic loss of 3p (implicating many tumor suppressor genes), TP53 alteration (point mutation or homozygous deletion), and P16/CDKN2A inactivation. These findings are similar to those found in pulmonary adenocarcinomas, while KRAS and EGFR mutations characteristic of the latter are rare. A characteristic and common genetic alteration in pulmonary squamous cell carcinoma is gain of 3q24-qter.
**Adenocarcinoma**

- Adenocarcinoma of the lung is the most frequent lung cancer occurring in Japan and some Asian countries, and is said to be increasing in the United States.
- The male-to-female ratio is about 2:1, and the average age at the time of diagnosis is somewhat lower than that for squamous cell carcinoma.
- Grossly, most adenocarcinomas arise in the periphery of the bronchial tree, and differentiated adenocarcinoma often penetrates the pleura to disseminate into the pleural cavity, frequently producing effusion; conversely, poorly differentiated adenocarcinoma directly invades the thoracic wall through fibrous adhesion.
• Adenocarcinoma also frequently involves the lymphatic.
• Among the various histologic types of lung cancer, the incidence of intrapulmonary metastasis is highest in adenocarcinoma, occurring not only through the lymphatics and blood vessels but also through the airway.
• Hematogenous metastasis is also frequently seen in many organs.
• Adenocarcinoma is subdivided histologically into acinar (tubular), papillary, bronchioloalveolar, and solid carcinoma with mucus formation by the WHO classification.
Experience shows that many adenocarcinomas that are less than 1.5 cm in diameter are composed of tumor cells of a single cell type, whereas larger tumors often consist of two cell types or more, because of metaplastic changes in tumor cells from one cell type to another, such as Clara cell type to mucus-producing cell, which are complicated by anaplastic changes in tumor cells.

Adenocarcinoma cells are supposed to differentiate toward any of the various epithelial cells seen in the bronchus and bronchioloalveoli.

For the sake of convenience, we subclassify adenocarcinoma of the lung into the following six cytologic types:
• Bronchial surface cell type with little or no mucus production

• This cell type arises either in cartilage-bearing bronchus showing endobronchial polypoid growth or in the distal airway. It is composed of tall columnar cells arranged in a papillary and tubular fashion; these cells resemble ciliated columnar cells, although no cilia are visible. Ultrastructurally, the cytoplasm is rich in mitochondria and smooth surfaced vesicles but is devoid of secretory granules. Although cilia are very rarely observed, basal bodies may be seen at the free cell border, a finding indicating that the cells differentiate toward ciliated cells. This type of adenocarcinoma comprises about 8% of our adenocarcinoma cases.
• **Goblet cell type.**
  
  • The tumor cells resemble goblet cells of the bronchial epithelium, in which the cytoplasm is filled with mucus, frequently displacing the nuclei to the basal portion.

  • They are most frequently arranged in a bronchiolo-alveolar pattern with a lobar pneumonia-like gross feature; infrequently, they are arranged in a papillary pattern with nodular tumor growth.

  • Immunohistochemically, this cell type is negative for lactoferrin, a bronchial gland marker, but is often positive for lysozyme.
Adenocarcinoma of bronchial surface epithelial cell type, showing endobronchial growth
Histology of the true papillary adenocarcinoma. Papillary growth is made up of tall columnar cells with no cilia that somewhat resemble ciliated columnar cells and their own fibrous stroma.
• **Bronchial gland cell type.**
  • Cuboidal or polygonal cells often containing mucin are arranged in acini, tubules or ductal structures, cribriform patterns, or solid nests.
  • In solid nests, individual mucin-containing cells may show a signet ring form.
  • Electron microscopically, the mucous granules vary in density, and granules suggestive of the serous type. Characteristically present in the cytoplasm of the gland cell-type tumor cells are oval fibrillar structures. The cells bordering the nests may resemble myoepithelial cells with myofibril-like fibrillar structures.
  • Immunohistochemically, this type of tumor is often positive for lactoferrin. It arises in the cartilage-bearing.
Bronchioloalveolar carcinoma of goblet cell type. Alveolar lining cells have been replaced by tall columnar cells with abundant mucus and basal nuclei.
• **Clara cell type.**
  - Peg-shaped cells or low columnar cells with tongue-shaped projections into the spaces are arranged in a papillary pattern. They form
  - (a) Tubular structures in and around the central or subpleural fibrotic focus.
  - (b) Papillary structures in the midzone of the tumor.
  - (c) A bronchioloalveolar pattern at the periphery or advancing border of the tumor.
  - In tumor cells with slight atypia, the nuclei are oval with a thick nuclear membrane, granular chromatin, and inconspicuous nucleoli; in tumors with increased atypia, the nuclei are irregular and pleomorphic with prominent nucleoli. The mitotic figures increase in number as the degree of cell atypia advances. Intranuclear eosinophilic inclusion bodies are frequently seen.
  - Clara cell 10-kd protein (CC10) is the dominant product from Clara cells, and it has been thought to have immunomodulatory and anti-inflammatory activity. Reports have indicated that the downregulation of CC10 contributes to carcinogenesis. Immunohistochemically, CC10 is detected in many Clara cell-type adenocarcinomas but not in atypical adenomatous hyperplasia.
Gross features of papillary adenocarcinoma of Clara cell type. A nodular tumor is centrally fibrotic and is associated with sharp pleural indentation. The border is blurred.
• Type II alveolar epithelial cell type.
  Individual cells are cuboidal to low columnar with a dome-shaped free cell border; their cytoplasm is often finely vacuolated, with the vacuoles probably corresponding to cytoplasmic lamellar inclusion bodies. These cells are arranged in papillary or bronchioalveolar patterns, and, grossly, the tumor reveals a solitary nodular form or, rarely, diffuse lobar distribution.

• Immunohistochemically, surfactant apoprotein is the marker substance, although it is also positively stained in tumors that are considered to be of the Clara cell type, the bronchial surface epithelial cell type with little or no mucus, or the bronchial gland cell type.

• Cytologic subtyping is often impossible in poorly differentiated adenocarcinoma
Adenocarcinoma of alveolar type II epithelial cell type. Cuboidal cells replace the alveolar lining, and the septa show slight fibrous thickening. Alveolar spaces contain many exfoliated tumor cells.
**NOGUCHI'S CLASSIFICATION.**

Among the five histologic subtypes of adenocarcinoma, bronchioloalveolar carcinoma is a special subtype because it mimics atypical adenomatous hyperplasia, which is a preinvasive form of adenocarcinoma and has a relatively favorable prognosis.

Noguchi et al. classified small-sized adenocarcinomas (less than 2 cm in diameter) into two groups, one group showing replacement growth and the other showing destructive growth of preexisting alveolar structures. Both of them are subdivided into three histological types as follows:

- **Tumors Showing Replacement Growth**
  - **Type A: Localized Bronchioloalveolar Carcinoma.**
  - Tumors of this type are solitary and show growth by replacement of alveolar lining cells with minimal or mild thickening of the alveolar septa
  - The tumors lack fibrotic foci. Histologically, they are well-differentiated localized bronchioloalveolar carcinomas, and the individual cells resemble Clara cells, type II pneumocytes, or goblet cells.
• **Type B: Localized Bronchioalveolar Carcinoma with Foci of Alveolar Structural Collapse**

  The overall microscopic appearance of these tumors is similar to that of type A, showing a replacement growth pattern. However, the tumors contain fibrotic foci due to alveolar collapse. This tumor type is sometimes difficult to distinguish from type C tumors. The fibrosis in this tumor is due to alveolar collapse without cellular growth and elastic fiber staining is very useful for diagnosis of this type.

• **Type C: Localized Bronchioalveolar Carcinoma with Foci of Active Fibroblastic Proliferation**

  This type constitutes the largest group of small-sized adenocarcinoma. Tumors also show a replacement growth pattern, but foci of active fibroblastic proliferation are detectable. In these foci, large nuclei of the proliferating fibroblasts and endothelial cells of small vessels are prominent. These actively proliferating fibroblasts are absent in the foci of alveolar collapse that are seen in type B. The nuclei of tumor cells located in the foci of active fibroblastic proliferation are larger and show a more atypical structure than those in the peripheral region where tumors show growth by replacement of alveolar lining cells. Type C is called focally (or minimally) invasive bronchioalveolar carcinoma.
• **Tumors Showing Non replacement Growth**
  • **Type D: Poorly Differentiated Adenocarcinoma**
    • These tumors show largely solid growth, papillary and tubular growth patterns are minor components. Histologically, their classification is almost the same as that of “solid adenocarcinoma with mucin” in the third WHO classification. Macroscopically, they show a clear boundary between the cancer and the non cancerous parenchyma.
  • **Type E: Tubular Adenocarcinoma**
    • This tumor type consists of acinar, tubular, and cribriform structures, and tumor cells with a signet ring appearance may be present. This type is classified as “acinar adenocarcinoma” in the third WHO classification.
  • **Type F: Papillary Adenocarcinoma with a Compressive Growth Pattern**
    • These tumors show papillary growth. However, they do not grow by replacing the alveolar lining cells, but instead show expansive and destructive growth. This type is classified as “papillary adenocarcinoma” in the third WHO classification.
Noguchi's classification is applied for small-sized adenocarcinoma less than 2 cm in diameter. (A) Type A carcinoma is localized bronchioloalveolar carcinoma. (B) Type B carcinoma is localized bronchioloalveolar carcinoma with collapse of alveolar structure. (C) Type C carcinoma is localized bronchioloalveolar carcinoma with a focus of fibroblastic proliferation. (D) Type D carcinoma is solid adenocarcinoma with mucin production. (E) Type E carcinoma is tubular or acinar adenocarcinoma. (F) Type F carcinoma is true papillary carcinoma.
• **Prognosis**

• This histologic classification (Noguchi's classification) is well correlated with patient prognosis and CT findings.

• **Type A and B tumors** have an extremely favorable prognosis, and patients have a 5-year survival rate 100%.

• **Type C tumors** are similar to type A and B and show replacement growth of alveolar lining cells but the 5-year survival rate is 75%. Compared to replacement-type adenocarcinomas.

• **type D, E, and F tumors** have a poor prognosis and the 5-year survival rate of patients with type D tumors is 50%.

• type A and B adenocarcinomas with an extremely favorable prognosis are candidates for limited surgery such as wedge resection or segmentectomy, or careful observation alone.
• **VARIANTS OF ADENOCARCINOMA.**

• The variants include five subtypes.

• Well-differentiated fetal adenocarcinoma (WDFA) or PET is rare. The average age of incidence is in the fifth decade. Grossly, the tumor is non encapsulated but well defined, and it is not related to visible bronchi.

• Histologically, the tumor grows expansively, and is composed of irregular tubular structures consisting of columnar epithelial cells with irregularly dispersed oval nuclei and clear cytoplasm, which are continuous with morular structures composed of polygonal cells with scant cytoplasm. The nuclei in morulae are often optically clear or they resemble ground glass, and they are rich in biotin, whereas cytoplasm in some morular cells is argyrophilic, often containing chromogranin A, synaptophysin, and N-CAM. The stroma is fibrous with no cellular atypia. The prognosis is much better than that of biphasic blastoma.
• The difference is the absence of morular structures, even though the glandular structures with clear cytoplasm resemble those seen in pulmonary blastoma and WDFA. This subtype is now classified as clear-cell adenocarcinoma in the revised classification.

• Mucinous adenocarcinoma, mucinous cystadenocarcinoma, and signet ring adenocarcinoma resemble the tumors of the same name in the gastrointestinal tract. Signet ring carcinoma is a special form of bronchial gland-type adenocarcinoma. Adenocarcinomas with spindle cell or giant-cell components (or both) are categorized as pleomorphic carcinoma under carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements.
Pulmonary endodermal tumor resembling fetal lung (well-differentiated fetal adenocarcinoma, WDFA). Columnar epithelial cells forming irregular tubules are continuous with morulae consisting of polygonal cells with occasional clear nuclei.
Histology of clear-cell adenocarcinoma. Tall columnar cells with clear cytoplasm are arranged in a papillary fashion. Nuclei are apically situated. Similar papillotubular structures are also seen in pulmonary blastoma and in well-differentiated fetal adenocarcinoma (WDFA).
• **Small-Cell Carcinoma**

  - Small-cell carcinoma of the lung has attracted considerable attention because of its complex pathobiologic characteristics and high degree of malignancy in spite of its high sensitivity to antitumor agents and radiation.

  - Pathologically, this neoplasm was originally classified as mediastinal sarcoma. In 1926, Barnard became the first to classify it as bronchogenic carcinoma. However, after 1968, electron microscopic analysis of this tumor favored a neuroendocrine nature with regard to histogenesis and function. Since the 1980s, however, the concept of a bronchial epithelial neoplasm of endodermal stem cell origin with some neuroendocrine characteristics.
• MORPHOLOGIC VARIATION.

• Gross features.

• This tumor arises not only in the major bronchi but also in the peripheral portion of the lung. Tumors arising in a major bronchus may spread subepithelially along its long axis. Replacement of the bronchial epithelium, which is often present in squamous cell carcinoma, is hardly ever seen in small-cell carcinoma.

• Therefore, the lining of the bronchus is nodular, instead of the fusion and disruption of the folds that are apparent in squamous cell carcinoma. In the more advanced stage, nodular growth involving the lung parenchyma is seen.

• Tumors arising in the periphery of the lung show solid nodular growth with a fairly well-defined border and a fleshy, medullary cut surface. Central fibrosis with anthracosis may occur. Early mediastinal lymph node involvement is a well-known phenomenon that may be extremely extensive and that is, on rare occasions, associated with an undetectable primary focus.
• Microscopic features.
• Small-cell carcinoma is characterized by the diffuse growth of small cells with the following features:
  • (a) hyperchromatic, finely granular nuclei;
  • (b) inconspicuous nucleoli;
  • (c) a thin nuclear membrane;
  • (d) scant, faintly stained, and, at times, very finely granular cytoplasm; and
  • (e) ill-defined cell borders.
• The stroma is delicate, vascular, and scant, with rare lymphocytic infiltration. Mitotic figures and individual cell necrosis are frequently seen.
• Occasionally, the tumor cells form rosettes, trabeculae, and nests of various sizes with a peripheral radial arrangement of the cells. Foci of epithelial differentiation, such as squamous cell and glandular differentiation, may be seen, and these are more evident on immunostaining for cytokeratin and secretory components.

• The typical small cell described earlier was termed an oat cell, and, if the cell size was somewhat increased, it was called the intermediate cell type. The latter frequently forms cell nests. Both subtypes are grouped together as small-cell carcinoma in the third WHO edition.

• If squamous, glandular, or “large” cells are readily seen, the neoplasm is designated combined small cell carcinoma.
• **Immunohistochemical findings.**
• IHC most frequently used are neural cell adhesion molecule (N-CAM) (CD56), chromogranin A, and synaptophosphin.
• These markers can also be found in typical and atypical carcinoids, large-cell neuroendocrine carcinoma, and, rarely, in adenocarcinoma.
• Besides these antigens, the tumor cells often stain positively with either polyclonal or monoclonal antibodies to enzymes, such as aromatic L-amino acid decarboxylase (AADC; L-Dopa decarboxylase), neuron-specific (or γ) enolase (NSE), and creatine kinase BB (CK-BB, brain form); to peptide hormones, such as gastrin-releasing peptide (GRP or bombesin), calcitonin, and various pituitary and brain-gut peptide hormones; and to other antigenic substances such as Leu-7.
• SMALL-CELL CARCINOMA VERSUS ATYPICAL CARCINOID.
• Some typical small-cell carcinomas resemble carcinoid tumor histologically because they are composed of solid nests and trabeculae of small, round to polygonal cells with round, finely stippled nuclei and a small amount of finely granular eosinophilic cytoplasm. Rosettes may frequently be seen, mitotic figures are easily found, and the stroma is scant and vascular. Distinction between the two is often difficult.
• Therefore, if areas more suggestive of small-cell carcinoma are apparent (i.e., they have an increased degree of nuclear atypism, frequent mitotic figures [more than 20 per 10 high-power fields], and extensive areas of necrosis), diagnosing this as small-cell carcinoma is safe.
• Spindling of the nuclei does not necessarily indicate small-cell carcinoma because spindle cell carcinoid may be found in the periphery of the lung.
• **Large-Cell Carcinoma**
  - The histologic diagnosis of large-cell carcinoma is made after the exclusion of squamous cell carcinoma, small-cell carcinoma, adenocarcinoma, and other lung cancers of specific type. The male-to-female ratio in affected cases is 4 or 5:1, which lies between the ratios of squamous cell carcinoma and adenocarcinoma.

• **GROSS FEATURES.**
  - Large-cell carcinoma arises more frequently in the periphery of the lung, and it may invade thoracic wall if it is untreated.
  - Typical undifferentiated large-cell carcinoma forms a spherical tumor with well-defined borders, and it has a bulging, fleshy, homogeneous, rather sarcomatous cut surface.
  - Anthracotic pigments are not seen because of compressive growth. However, some large-cell carcinomas resemble poorly differentiated adenocarcinoma or squamous cell carcinoma grossly.
HISTOLOGIC FEATURES.

Most large-cell carcinomas are composed of solid nests of polygonal cells with vesicular nuclei, prominent nucleoli, moderately abundant cytoplasm, well-defined cell borders, and rather scant fibrovascular stroma.

Carcinomas with frequent mucin-producing cells are classified as adenocarcinoma according to the WHO criteria, but those with occasional or a few mucin-producing cells are placed in the large-cell category.

Large-cell carcinomas are either cytocohesive or incohesive. In the latter case, marked infiltration of inflammatory cells, which consist of both lymphoid cells and polymorphonuclear leukocytes, is present.
The WHO has defined five histological variants of large-cell carcinoma: large-cell neuroendocrine carcinoma (LCNEC); basaloid carcinoma; lymphoepithelioma-like carcinoma; clear-cell carcinoma; and large-cell carcinoma with a rhabdoid phenotype. Variants other than LCNEC are rare.

Basaloid carcinoma is similar to basaloid squamous cell carcinoma but lacks squamous cell characteristics.

Lymphoepithelioma-like carcinoma is histologically similar to epipharyngeal lymphoepithelioma, and has the Epstein-Barr virus genome by in situ hybridization.

Large-cell carcinoma with the rhabdoid phenotype is made up of large cells containing eosinophilic globular cytoplasmic inclusions, which are vimentin-positive. Rhabdoid cells may also be present in poorly differentiated adenocarcinomas. Giant-cell carcinoma, which was a variant of large-cell carcinoma in the second edition of the WHO classification, is now classified in the category of carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements.
**Large-Cell Neuroendocrine Carcinoma**

- The revised WHO classification of lung and pleural tumors recommended inclusion of large-cell neuroendocrine carcinoma (LCNEC) in the category of large-cell carcinoma.
- LCNEC is defined as a large-cell carcinoma showing histologic features such as organoid nesting, trabeculae, and rosette-like and palisading patterns that suggest neuroendocrine differentiation and in which the latter can be confirmed by IHC or electron microscopy.
- The tumor cells are generally large with moderate to abundant cytoplasm, vesicular to finely granular nuclei, and, often, prominent nucleoli.
- In distinguishing large-cell neuroendocrine carcinoma from atypical carcinoid, in addition to histology, the mitotic count is useful, with 2 to 10 mitotic figures per 10 high-power fields in atypical carcinoids and a larger number in LCNEC.
Neuronal cell adhesion molecule N-CAM (CD56) • immune marker positive
Various terms proposed for non-small-cell lung cancers with neuroendocrine properties are encountered occasionally, including neuroendocrine carcinoma of intermediate cell type, non-small-cell carcinoma with neuroendocrine features, and large-cell neuroendocrine carcinoma. The marker substances used for determination of neuroendocrine properties. The WHO has recommended that CD56, chromogranin A, and synaptophysin be used to confirm the diagnosis of LCNEC immunohistochemically.

Neuroendocrine (NE) tumors of the lung include four histological subtypes: LCNEC, typical carcinoid, atypical carcinoid, and small-cell carcinoma. However, Asamura et al. examined 366 NE tumors in Japanese patients clinicopathologically, and reported that the 5-year survival rate was 96.2% for those with typical carcinoid, 77.8% for atypical carcinoid, 40.3% for LCNEC, and 35.7% for small-cell carcinoma. LCNEC and small-cell carcinoma are the two most highly malignant NE tumors and show no significant difference in prognosis.
• **Adenosquamous Carcinoma**

• Adenosquamous carcinoma, a mixture of adenocarcinoma and squamous cell carcinoma, comprises about 3.5% of surgically resected lung cancers. It arises both in the hilar region (major bronchi) and in the periphery of the lung. Theoretically, the following four types exist:

• (a) Collision of adenocarcinoma and squamous cell carcinoma, in which the gross features and serial chest radiographs, if available, may be of great help.

• (b) Adenocarcinoma showing squamous metaplasia in areas.

• (c) Tumors composed of bipotential cells showing glandular cell differentiation in some areas and squamous cell differentiation in others.

• (d) Mucoepidermoid tumor with marked cell atypia or of a less differentiated form.
In our series, about 90% of cases were peripheral in origin. The histology of lymph node metastasis cannot always be predicted from the histology of the primary focus. However, the adenocarcinomatous component tends to metastasize more frequently, unless the squamous cell carcinoma component is predominant in the primary tumor.

Analyses of 56 cases of surgically resected adenosquamous carcinomas revealed that the outcome was significantly poorer than that of adenocarcinomas and squamous cell carcinomas, particularly in stages I and II, and that the amount of the adenocarcinoma component did not affect the survival rate.
• Histology of spindle cell squamous carcinoma (pleomorphic carcinoma). (A) The tumor is composed of spindle-shaped to polygonal cells displaying diffuse sarcomatous growth in which osteoclast-like giant cells are scattered. (B) In small areas, tumor cells are arranged in solid nests with a slight tendency toward keratinization.
• Carcinoma with Pleomorphic, Sarcomatoid, and Sarcomatous Elements

• This new category, in the revised WHO classification, consists of a group of poorly differentiated non-small-cell carcinomas that contain a component of sarcoma or sarcoma-like elements. These tumors include
  • (a) carcinoma with spindle and/or giant cells.
  • (b) carcinosarcoma.
  • (c) pulmonary blastoma.
• Carcinomas with spindle and/or giant cells consist of three subtypes—in other words, any of the subtypes of non-small-cell carcinoma containing spindle cells and/or giant cells and carcinoma consisting only of spindle cells and giant cells.
• **GIANT-CELL CARCINOMA.**

  Giant-cell carcinoma contains mononucleated or multinucleated giant cells, is often cytoincohesive, and is occasionally associated with features of adenocarcinoma, which should be diagnosed as pleomorphic adenocarcinoma with giant cells, in some areas. Leukocytosis resulting from the colony-stimulating factor produced by the tumor may also occur in giant-cell carcinoma, as it does in some large-cell carcinomas.

  Giant-cell carcinoma is often more resistant to treatment compared with large-cell carcinoma. This difference may be explained by the difference in the degree of organelle development, which is generally rather poor in large-cell carcinoma but which may be well developed in giant-cell carcinoma.

  A metastatic site occasionally seen in cases of giant-cell carcinoma is the small intestine.
Giant-cell carcinoma. Polygonal cells with marked pleomorphism, occasionally possessing multiple nuclei, are growing cytoincohesively, admixed with many lymphoid cells. The giant tumor cells display cannibalism.
CARCINOSARCOMA AND PULMONARY BLASTOMA.

Carcinosarcoma is defined as a tumor composed of carcinoma and sarcoma. The sarcomatous component in many so-called carcinosarcomas consists of spindle-shaped cells and resembles fibrosarcoma.

Pulmonary blastoma, This tumor, which is defined by Spencer, resembles fetal lung and is composed of tubular structures simulating tubules in the pseudoglandular stage and immature mesenchymal components, which may differentiate toward striated muscle, smooth muscle, cartilage, or a combination of these. The tubules are composed of cuboidal to columnar cells with clear cytoplasm and hyperchromatic nuclei, which may be located near the apical portion of the cells.

Grossly, this is a nodular tumor occurring in the periphery of the lung and sometimes projecting into the bronchial lumen.

Pleuropulmonary blastoma, which is seen in children younger than 10 years, is a cystic or solid sarcoma. The cysts are lined by metaplastic epithelium, and they produce a pseudobiphasic pattern. The tumor shows features of chondrosarcoma, leiomyosarcoma, rhabdomyosarcoma, liposarcoma, undifferentiated sarcoma.
• **Carcinoid Tumors**

Carcinoid tumors are considered tumors of low-grade malignancy. They constitute about 1% to 2% of all lung tumors. Carcinoid tumors often arise in persons who are younger than is usual for lung cancers, and the male-to-female ratio is about 1:1. The tumor is considered to arise from Kulchitsky cells, which belong to the diffuse endocrine system.

Most of these tumors arise in the main to segmental bronchi, but tumors of peripheral origin are occasionally seen.

Grossly, the tumor is polypoid and endobronchial in the major bronchi, bicameral or iceberg-shaped in the intermediate-sized bronchi, and solid and nodular in the periphery of the lung. The tumor is well defined, with a smooth, sometimes lobulated or granular, ivory to pink, glistening cut surface. Necrotic foci are rarely seen.
• **Histologically**, it is made up of nests, trabeculae, and mosaic patterns of medium-sized polygonal cells with oval to spheric, rather uniform, finely granular nuclei, and lightly eosinophilic granular to clear cytoplasm. Rosettes and small acinar structures with or without mucin may be present. Mitotic figures are rare. Peripherally situated tumors may be composed of spindle-shaped cells. The stroma is vascular and scant, and amyloid deposits with bone formation may be seen.

• The argentaffin reaction is often negative.

• Antigenic substances found in small-cell carcinoma, such as enzymes, amine and peptide hormones, and chromogranin A, are also present in carcinoid tumors, with the IHC reaction being more intense and diffuse in comparison with small-cell carcinoma.

• Pancreatic polypeptide has so far been demonstrated in some carcinoid tumors but not in small-cell carcinoma.

• The following two other antigenic substances were found in bronchial carcinoid tumor: N-CAM (CD56), which has been detected in all cases examined so far, and S-100 protein, which is present in the sustentacular cells situated at the border of cell nests in approximately 40% of cases.

• BCL-2 protein, which is expressed in most small-cell carcinomas, is expressed infrequently in carcinoid tumor.
• Bronchial Gland Carcinomas

• Adenocarcinoma differentiating toward the bronchial gland. In this section, special tumors resembling salivary gland tumors are covered, including adenoid cystic carcinoma, mucoepidermoid carcinoma, and malignant mixed tumors. These tumors are rare and, histologically, are identical to tumors of the same name in the salivary gland.

• Adenoid cystic carcinoma arises in the trachea and main bronchi. The following two types are found on the basis of gross features:
  • One is nodular, projecting into the tracheobronchial lumen in a polypoid fashion.
  • The other shows diffuse subepithelial growth along the long axis of the bronchus. This tumor grows infiltratively beyond the grossly recognizable tumor border. Therefore, confirmation of complete removal by frozen section is required. Lymph node and distant organ metastases are seen in 15% to 35% of cases. If the tumor is removed completely, the chance of cure is high. Because tumor growth is slow, patients with this disease may survive for years.
  • Acinar (or tubular) adenocarcinoma with a cribriform pattern should not be diagnosed as adenoid cystic carcinoma.
Muonepidermoid carcinoma is another rare tumor; it is seen in young persons, and it shows no sex predilection. It arises in the main to segmental bronchi and shows endobronchial polypoid growth. The prognosis is excellent after complete tumor removal of low-grade histology. However, mucoepidermoid carcinoma with a high grade of malignancy has been reported.

- Acinic cell tumor of the bronchus, which is also a low-grade malignant bronchial gland tumor, is extremely rare.
- Other rare bronchial gland tumors (carcinomas) include epithelial-myoepithelial tumor (carcinoma) (adenomyoepithelioma) and myoepithelial carcinoma.
- Carcinoma in pleomorphic adenoma has not been reported, but a case of malignant mixed tumor showing a mixture of adenosquamous carcinoma, chondrosarcomatous areas, and myxomatous areas was reported.
- IHC and electron microscopy are helpful for the differential diagnosis. The prognosis is worse in adenoid cystic carcinoma, followed by carcinoid tumor and mucoepidermoid tumor, although it is much better than in adenocarcinoma and squamous cell carcinoma.
• **MISCELLANEOUS TUMORS AND TUMOR-LIKE LESIONS**

- Mesothelioma, localized fibrous tumor, malignant lymphoma including MALToma, and soft tissue sarcoma One of the soft tissue sarcomas, intravascular sclerosing bronchioloalveolar tumor. malignant angioendothelioma or epithelioid hemangioendothelioma or sarcoma
- Primary malignant melanoma of the lung
- Multiple meningotheiolioid nodule (arachnoid nodule), which was previously called chemodectoma or paraganglioma.
- Benign clear-cell (sugar) tumor of the lung. Recently, this tumor has come to be considered to present a family of tumors showing perivascular epithelioid cell differentiation (PEComas) which includes angiomyolipoma, lymphangiolemyomatosis, clear-cell “sugar” tumor of the lung.
- Others: Sclerosing Hemangioma, Inflammatory Pseudotumor, Tumorlet, Hamartoma

• **METASTATIC TUMORS OF THE LUNG**
Thankyo For Your Listening