Review Article

PULMONARY CYTOLOGY: CURRENT STATUS OF CYTOLOGIC TYPING OF RESPIRATORY TRACT TUMORS

PULMONARY CYTOLOGY

REVIEW ARTICLE

Pulmonary Cytology

Current Status of Cytologic Typing of Respiratory Tract Tumors

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PREVIOUS ATTEMPTS to classify lung cancer have resulted in conflicting viewpoints on its etiology, diagnosis, treatment, and prognosis.[1] This situation is not surprising, because in a random survey of 57 studies pertaining to human lung cancer, 13 different systems of histologic classification were used.[2] These classifications characterized the tumors largely according to growth pattern and cell size and shape. Basing classification on such features easily leads to confusion, because the majority of tumors reveal two or more structural patterns on histologic examination of multiple paraffin blocks.[3] Therefore, with such systems, tumors that show similar features at the cellular level are placed in different categories, and comparison of data becomes exceedingly complex.

Interobserver variability has been demonstrated in the classification of tumor type from tissue sections, especially for poorly differentiated and undifferentiated carcinomas. Between two separate panels of pathologists, disagreements in typing were observed in 40% or 53% of the poorly differentiated epidermoid carcinomas, 42% or 58% of the poorly differentiated adenocarcinomas, and 23% or 90% of the large cell carcinomas.[4,5] In addition, individual pathologists from one panel demonstrated intraobserver variability by making different diagnoses between the first and second readings of the same slide in a range of 2% for the most consistent reader to 20% for the least consistent.[5]

World Health Organization Classification

In order to provide for a more accurate and more defined morphologic classification, 19 pathologists from 17 countries collaborated to produce the WHO manual "Histological Typing of Lung Tumors."[1] Since 1967, over 120 epidemiologic, clinical, and pathologic studies have referred to, or based data on, the WHO lung tumor classification of 1967.[6] The classification resulted in 13 types, most of which have several subtypes. The purpose of the WHO classification was to define a sufficient number of tumor categories, according to objective criteria, so that only a minimum of tumors remained unclassified.

The majority of lung tumors can be classified within the first six groups of the WHO classification (Table 1). Typing is based largely upon descriptive light-microscopic, cytologic, and histologic criteria, with little consideration given to patterns of differentiation at the cellular level. For example, Group II, small cell anaplastic carcinomas, are subtyped into fusiform, polygonal, lymphocytelike ("oat cell") and others, according to the shape of the cells. However, the various subtypes of tumors within Group II show different features of differentiation at the cellular level.[7] Some

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Table 1—WHO Classification (1967)

I. Epidermoid carcinomas
II. Small cell anaplastic carcinomas
1. Fusiform cell carcinomas
2. Polygonal cell carcinomas
3. Lymphocytelike ("oat cell") carcinomas
4. Others
III. Adenocarcinomas
1. Bronchogenic adenocarcinomas
2. Bronchiolo-alveolar carcinomas
IV. Large cell carcinomas
1. Solid tumors with mucinlike substances
2. Solid tumors without mucinlike substances
3. Giant cell carcinomas
4. "Clear" cell carcinomas
V. Combined epidermoid and adenocarcinomas
VI. Carcinoid tumors

show features characteristic of mucous and/or basal cells, whereas cells of both oat cell carcinomas and carcinoid tumors (Group VI) contain presumptive endocrine granules and may share a common histogenesis.[8-17] Carcinoid tumors are considered low-malignancy forms, whereas oat cell carcinomas are highly malignant.

Group IV, large cell carcinomas, are divided into the following subtypes: solid tumors with mucinlike substances, solid tumors without mucinlike substances, giant cell carcinomas, and clear cell carcinomas. These represent a collection of dissimilar tumors. Cells constituting solid tumors with mucinlike substances may be highly differentiated for secretion (adenocarcinoma), whereas many clear cell tumors are composed of cells filled with glycogen, showing very poor specialization features. Recently, the WHO classification of lung tumors was updated, and proposed changes have been published.[18] The most significant change appears to be that solid carcinomas with mucinlike substances, diagnosed as large cell carcinomas in the 1967 schema, will now be classified as a subtype of adenocarcinomas.

The Importance of Pulmonary Cytology

Cytology has become a reliable tool for the detection of pulmonary carcinoma cells in spontaneous cough and induced sputa, bronchial washings, bronchial brushings, fine needle aspiration biopsies, and pleural and pericardial effusions.

Many studies have provided statistics on the percentage of positive cytologic detection (percent yield) of malignant cells in bronchial secretions, some of which report the percentage of detection by specific cell type.[19-21] Irrespective of tumor type, the overall percentage of positive preoperative cytologic detection of malignant lung tumors is about 80%,[21-24] with some studies demonstrating greater positive diagnoses of 92%,[25] 94%,[21] and 98%.[26]

Sputum cytology has detected radiographically undemonstrable primary lung neoplasms;[27-36] and, in one study, pulmonary cytology yielded the only microscopic diagnoses prior to major surgery in 32% of cases.[37]

Matching Correlation Between Cytologic and Histologic Diagnoses in Man

Since the first comparison between exfoliated cells and tissue sections was performed for clinical diagnoses of uterine cancer,[38] many such correlations have evaluated matching cytologic and histologic diagnoses for pulmonary neoplasia.[3,21,24,26,39-52] In these studies the histologic diagnosis was accepted as the "true" tumor type.

In general, pulmonary cytology has been very successful in the diagnosis of moderately to well differentiated epidermoid carcinomas and moderately to well differentiated adenocarcinomas. For example, Lange and Høeg[44] diagnosed 93% (43/46) of well differentiated epidermoid carcinomas and 100% (19/19) of adenocarcinomas by exfoliative cytology in agreement with histologic evaluations. Similarly, Kanhouwa and Matthews[47] matched 100% (50/50) of moderately to well differentiated epidermoid carcinomas and 100% (14/14) of moderately to well differentiated adenocarcinomas by cytologic and histologic evaluation (Table 2).

However, much confusion and controversy persists in the cytologic classification of poorly differentiated epidermoid carcinomas, poorly differentiated adenocarcinomas, and the so-called undifferentiated carcinomas, such as large cell carcinomas (including giant cell carcinomas and clear cell carcinomas) and oat cell carcinomas. One reason is the lack of rigid cytologic criteria used for the various tumor types. For instance, Johnston and Frable[21] considered oat cell carcinoma to be a separate entity, whereas Koss,[23] Naib,[53] and Frost[54,55] considered oat cell carcinomas to be poorly differentiated epidermoid carcinomas. Koss[23] classified large cell carcinomas as poorly differentiated epidermoid carcinomas, whereas Frost[55,56] stated that the cells of adenocarcinomas were basically a large cell undifferentiated type. Although Naib[53] categorized giant cell carcinomas as types of epidermoid carcinomas, Koss[23] and Johnston and Frable[21] classified the basic cellular patterns of most giant cell carcinomas as variants of adenocarcinoma. Furthermore, Takahashi[57] stated that clear cell carcinoma, a subtype of large cell carcinoma according to the WHO classifica-

Table 2—Comparison of Cytologic and Histologic Typing of Human Lung Tumors (Courtesy of Kanhouwa and Matthews,[47] Copyright 1976, International Academy of Cytology)

Histologic diagnosis	No. cases	Cytologic diagnosis	No. correct*	No. discrepancies	% correct*
Well and moderately differentiated epidermoid carcinoma	50	Epidermoid	50		100
Well and moderately differentiated adenocarcinoma	14	Adenocarcinoma	14		100
Small cell carcinoma	19	Small cell carcinoma	17		90
		Epidermoid		2	
Large cell anaplastic carcinoma	6	Large cell anaplastic	5		83.3
		Adenocarcinoma		1	
Poorly differentiated adenocarcinoma	16	Large cell anaplastic		13	0
		Epidermoid		3	
Poorly differentiated epidermoid carcinoma	6	Adenocarcinoma		1	0
		Large cell anaplastic		5	

* Correct = matching correlations between cytologic and histologic diagnoses.

tion,[1] was indistinguishable from poorly differentiated epidermoid carcinoma or poorly differentiated adenocarcinoma.

Therefore, it is hardly surprising that previous studies, using light-microscopic criteria based upon growth patterns and cell size and shape, have provided relatively poor matching accuracy of pulmonary cytology versus histology for various forms of poorly differentiated carcinomas. For example, 16 tumors, diagnosed histologically as poorly differentiated adenocarcinomas, shed single cells which were typed as poorly differentiated epidermoid carcinomas using sputum cytology.[26] Similarly, 29% (20/68) of adenocarcinomas, diagnosed as such by histology, were interpreted cytologically as epidermoid carcinomas by examination of sputa that sometimes revealed single cells.[24]

No matching diagnoses were made by Kanhouwa and Matthews[47] on six cases of poorly differentiated epidermoid carcinomas and 16 cases of poorly differentiated adenocarcinomas, as diagnosed histologically (Table 2). Instead, 18 of these tumors were classified cytologically as large cell anaplastic carcinomas. Evidently, the criteria for cytologic diagnosis of epidermoid carcinomas and adenocarcinomas,[56,58,59] used by Kanhouwa and Matthews,[47] were very narrow; so the large cell carcinoma group increased in size.

The comparison of cytologic and histologic typing of human lung tumors between two institutions provided similar results.[21] The criteria for cytologic diagnosis of large cell carcinomas used by Johnston at Duke University (Table 3) were evidently broad and demonstrated lower numbers of matching correlations for epidermoid carcinomas and adenocarcinomas than the more narrow criteria employed by Frable at the Medical College of Virginia (Table 4). Future epidemiologic or clinical studies using histologic and/or cytologic typing between these two institutions would probably result in the classification of similar tumor types being placed in completely different categories.

Table 3—Comparison of Cytologic and Histologic Typing of Human Lung Tumors: Duke University Results (Courtesy of Johnston and Frable,[21] Copyright 1976, American Association of Pathologists)

	Cytologic diagnosis					
Histologic diagnosis	Squamous cell carcinoma	Large cell undifferentiated carcinoma	Small cell undifferentiated carcinoma	Adenocarcinoma	Mucoepidermoid carcinoma	% correlation
Squamous cell carcinoma	86	23	0	4	2	75
Large cell undifferentiated carcinoma	5	24	0	4	2	69
Small cell undifferentiated carcinoma	0	1	28	1	0	93
Adenocarcinoma	0	7	0	35	0	83
Mucoepidermoid carcinoma	0	1	0	0	3	75

Table 4—Comparison of Cytologic and Histologic Typing of Human Lung Tumors: Medical College of Virginia Results (Courtesy of Johnston and Frable,[21] Copyright 1976, American Association of Pathologists)

	Cytologic diagnosis					
Histologic diagnosis	Squamous cell carcinoma	Large cell undifferentiated carcinoma	Small cell undifferentiated carcinoma	Adenocarcinoma	Mucoepidermoid carcinoma	% correlation
Squamous cell carcinoma	171	2	3	7	1	93
Large cell undifferentiated carcinoma	5	10	6	3	0	42
Small cell undifferentiated carcinoma	1	1	48	4	0	86
Adenocarcinoma	4	0	0	32	1	86
Mucoepidermoid carcinoma	5	1	0	5	0	0

Matching Correlation Between Cytologic and Histologic Diagnoses in Hamsters

In recent years the Syrian golden hamster has been demonstrated to be a good experimental model for human lung cancer. This animal has a low incidence of spontaneous respiratory tract tumors and offers great resistance to pulmonary infection.[60] The baseline data of normal hamster tracheobronchial and human bronchial epithelium show many similarities.[61,62] With the use of both ultrastructural and histochemical techniques, respiratory tract carcinomas in the hamster, induced by benzo(a)pyrene–ferric oxide (BP-Fe_2O_3), resembled those seen in humans.[7,63] Using the light-microscopic criteria of the WHO classification, tracheobronchial carcinomas resembling human bronchogenic epidermoid carcinomas, adenocarcinomas, large cell carcinomas, and combined epidermoid and adenocarcinomas were induced in the hamster by intratracheal instillation of BP-Fe_2O_3.[60,64,65]

Matching accuracy of cytology versus histology for various hamster tumor types was quite similar to that of previously described human studies (Table 5).[65] Specifically, matching correlations occurred in 95% (18/19) of epidermoid carcinomas and 93% (13/14) of adenocarcinomas. However, cytologic and histologic diagnoses agreed in only 42% (5/12) of large cell anaplastic carcinomas.

Recognition of Cytoplasmic Differentiation Features in Cytologic Specimens

The majority of classifications of human and hamster respiratory tract tumors utilize light-microscopic descriptions based largely on cellular growth pattern, size, and shape, with little reference to differentiation at the cellular level. However, a recent histogenetic classification of respiratory tract carcinomas utilized specific features of cytoplasmic differentiation as observed in ultrastructural and histologic sections[7,63] and in cytologic preparations[66] to differentiate and subtype the tumors. This approach demonstrated that various tumors, previously typed in different categories according to conventional criteria, actually share common characteristics at the cell level and thus may be typed in similar groups according to cytoplasmic features of functional differentiation.

In order to classify lung carcinomas according to features of their cytoplasmic differentiation, it is important to consider which epithelial cell types are potentially capable of hyperplastic, metaplastic, dysplastic, and neoplastic changes.[7] It appears that only five cell types, that is, basal cells, mucous cells, endocrine cells, Clara cells, and possibly Type II alveolar cells can give rise to pulmonary carcinomas in man and hamster.[7,63] Most respiratory tract carcinomas possess morphologic features of epidermoid differentiation (keratinization) and/or adeno differentiation (secretion) and were thus subdivided into epidermoid carcinomas, combined epidermoid and adenocarcinomas, and adenocarcinomas using a histogenetic classification.[7,63]

Specific morphologic features of cytoplasmic differentiation can provide for the differential diagnosis of various tumor types, including poorly differentiated epidermoid carcinomas and poorly differentiated adenocarcinomas. On ultrastructural examination, tonofilament bundles represent epidermoid differentiation[7,67-69] whereas secretory granules,[7,67] extracellular and/or intracellular alveoli, and/or a well-developed Golgi apparatus and endoplasmic reticulum correspond to adeno features,[7] which can be used as criteria to provide for accurate diagnoses. These features, which can be discerned by light microscopy in Papanicolaou-stained cytologic preparations,[66] have often been misinterpreted or even ignored by cytologists in their diagnoses of various lung tumor types.

The transparency afforded by the Papanicolaou procedure, which uses two counterstains in solutions

Table 5—Comparison of Cytologic and Histologic Typing of Hamster Lung Tumors (Courtesy of Schreiber et al,[65] Copyright 1974, Cancer Research, Inc.)

Histologic type (WHO Classification in parentheses)	Number of animals	Cytologic type			Sensitivity† (% correct)
		Epidermoid carcinoma	Adeno-carcinoma	Anaplastic carcinoma	
Epidermoid carcinoma (I)	19	18		1	18/19 (95)
Adenocarcinoma (III 1a, 1b)	14		13	1	13/14 (93)
Combined epidermoid-adenocarcinoma (V)	4	4*	4*		
Large cell anaplastic carcinoma (IV 2, 3, 4)	12	6	1	5	5/12 (42)

* Diagnosis of both tumor types was made in these animals.
† Sensitivity = matching correlations between cytologic and histologic diagnoses.

of high alcoholic content, offers greater capability of detecting differentiation features at the cellular level in cytologic preparations of lung tumors, as compared with routine histologic stains such as hematoxylin and eosin, applied to tumors in paraffin sections. Thus, the cytoplasmic features of epidermoid differentiation are recognized by a glassy appearance (hyalinization) and/or dense concentric rings or their fragments, corresponding to tonofilament bundles, with Papanicolaou stain.[66] Adeno characteristics include a foamy appearance in the cytoplasm, which corresponds to secretory granules and a well-developed Golgi apparatus, whereas cytoplasmic basophilia represents well-developed endoplasmic reticulum.[66] Extracellular alveoli are sometimes observed between overlapping cells of tight to loose clusters. These are a characteristic of carcinomas that possess a well-differentiated adeno component and retain gross glandular organization.[66] The overlapping cells are joined at their luminal surfaces by well-developed junctional complexes providing for the presence of the extracellular alveoli. Also, with the use of the Papanicolaou stain, clear vacuoles can sometimes be seen within the cells. These correspond to intracellular alveoli that may be observed in overlapping cells of tight to loose clusters (when gross glandular organization is maintained) as well as in single cells, exfoliated from tumors in which gross glandular organization is lost.[66] Since tumors that lack gross glandular organization do not possess well-developed junctional complexes, they appear solid in histologic sections but often possess other well-differentiated adeno features at the cellular level.[66]

Previously, these cytoplasmic features of epidermoid and adeno differentiation have not been understood, thereby leading to discrepancies in matching correlations between cytologic and histologic diagnoses. Approximately 50% of human and hamster respiratory tract tumors exhibit both epidermoid and adeno differentiation features, to varying degrees, at the cellular level.[7,63,70] Therefore, large numbers of cells from these combined tumors exhibit mixtures of both epidermoid and adeno cytologic features in Papanicolaou preparations.

Poorly Differentiated Epidermoid and/or Adenocarcinomas

The concept of combined tumors is generally not appreciated and has led to confusion. For example, vacuolated cells shed from tumors classified histologically as poorly differentiated epidermoid carcinomas were typed cytologically with the use of conventional criteria as poorly differentiated adenocarcinomas.[3,40,43] In contrast, eosinophilic cells exfoliated from tumors diagnosed histologically as adenocarcinomas were suggestive of degenerative changes and consequently were classified by conventional cytology as poorly differentiated epidermoid carcinomas.[3,23,71] However, these tumors probably exhibited features of both epidermoid and adeno differentiation. Many adenocarcinomas, diagnosed as such by conventional cytologic criteria,[55,56] actually possess tonofilament bundles of prekeratin, recognizable as rings in Papanicolaou-stained preparations.[66] Similarly, many single cells, with or without hyalinization, shed from tumors diagnosed as epidermoid carcinomas by conventional cytologic criteria,[55,59] possess intracellular alveoli, which are often thought to represent degenerative vacuoles by those using conventional cytology. However, these structures were found to be filled with mucosubstances[66] and therefore represent true secretory vacuoles, indicative of adeno differentiation in tumors in which gross glandular organization is either maintained or lost.[66,70] The distinct borders of the intracellular alveoli were similar in various cytologic preparations, regardless of whether the specimen had been prepared fresh (eg, imprint smears, sputa, and bronchial brushings) or prepared by prefixation, ie, fixed in Saccomanno's fluid in the operating room (eg, bronchial washings).[66] These tumors are classified his-

togenetically as combined epidermoid and adenocarcinomas, in which the adeno component predominates over the epidermoid component.[66,70]

Large Cell Anaplastic Carcinomas and Giant Cell Carcinomas

Large cell anaplastic carcinomas[54,55] and giant cell carcinomas,[21,53] diagnosed as such by conventional cytologic criteria, clearly demonstrated specific cytoplasmic features of dual differentiation according to the histogenetic cytologic criteria.[66,70] Both epidermoid and adeno features can be seen in many of these tumors, often in the same cell. The large number of combined tumors seen cytologically is to be expected, because approximately 50% of respiratory tract tumors present varying degrees of both epidermoid and adeno differentiation features at the cellular level.[7,63,70]

Obviously the epidermoid and/or adeno features discernible in cytologic preparations of large cell and giant cell tumors reflect the patterns of differentiation seen at the ultrastructural level. Recently, epidermoid and adeno features of differentiation at the cell level were revealed in large cell carcinomas, ie, solid tumors with or without mucinlike substances (WHO Groups IV 1,2), often in the same tumor cell.[7] Similarly, giant cell carcinomas, diagnosed cytologically by conventional criteria,[21,53] demonstrated both epidermoid and adeno differentiation features with the use of electron microscopy.[72] Ultrastructurally, the epidermoid and adeno characteristics of these subtypes were the same as described above.

The concept of dual differentiation in large cell and giant cell carcinomas is generally poorly recognized. Previous cytologic studies[3,21,49] using conventional criteria have described either epidermoid or adeno characteristics in large cell tumors (diagnosed as such on paraffin sections). Both epidermoid and adeno features were never described in the same large cell carcinoma, let alone in the same tumor cell.[3,21,49] In one study,[49] 11 of 14 (79%) large cell carcinomas (diagnosed histologically on paraffin sections) were classified after cytologic examination as either poorly differentiated epidermoid carcinomas or poorly differentiated adenocarcinomas.

As in these cytologic studies, several electron-microscopic studies of large cell and giant cell carcinomas did not recognize the dual differentiation of epidermoid and adeno cytoplasmic features in any one tumor.[69,73-80] These studies indicated that large cell and giant cell carcinomas are similar to either poorly differentiated epidermoid carcinomas or poorly differentiated adenocarcinomas. For example, four reports of large cell carcinomas demonstrated epidermoid features of bundles of tonofilaments (tonofibrils),[73,75,79,80] whereas other investigators described large cell carcinomas presenting with adeno features of intra- and/or intercellular alveoli (lumens) and/or mucous granules.[69,76,80] Similarly, several electron-microscopic studies of giant cell carcinomas have noted features of either epidermoid differentiation[78] or adeno differentiation,[74,77] but dual differentiation was never described.

The specific epidermoid and/or adeno characteristics of poorly differentiated, large cell, and giant cell tumors, which are impossible to detect with the use of H&E-stained tissue sections, can be discerned by light-microscopic cytology with the Papanicolaou method.[70] Therefore, Papanicolaou-stained imprint smears of surgical biopsy specimens of lung tumors promise to provide more accurate typing than either H&E-stained frozen or paraffin sections.

Reliability of Revised Cytologic Criteria Based Upon Features of Cytoplasmic Differentiation

The histogenetic cytologic classification is based on objective cytoplasmic features of functional differentiation,[66] whereas conventional cytologic classifications rely largely on subjective criteria pertaining to cell size, shape, and growth pattern.[21,23,53-56,59] Using the revised cytologic criteria, the most common type of respiratory tract tumor is the combined epidermoid and adenocarcinoma, which possesses characteristics of mucous and/or basal cells.[66,70]

This large number of combined tumors is not surprising in light of studies on the histogenesis of epidermoid metaplasia and carcinoma *in situ* in human and hamster respiratory epithelium.[81,82] The data have shown that epidermoid metaplasia and carcinoma *in situ* may have arisen from changes in mucus-secreting cells. The combined epidermoid and adenocarcinomas probably originated from malignantly transformed metaplastic mucous cells and/or from malignantly transformed basal cells that demonstrated mucous cell characteristics. These two cell types can demonstrate both epidermoid and adeno functional differentiation within a single cell. Utilizing ultrastructural and histochemical techniques, Klein-Szanto et al[83,84] have recently confirmed the presence of both tonofilament bundles (epidermoid differentiation) and various secretory characteristics (adeno differentiation) in metaplastic and dysplastic epithelial cells, carcinoma *in situ*, and microinvasive carcinomas of the rat trachea.

Utilizing the revised cytologic criteria,[66] the differentiation features of combined epidermoid and adenocarcinomas are easily recognizable with the Papa-

Table 6—Reliability of Histogenetic Cytologic Criteria Applied to 86 Resected Human Lung Tumors (Hess et al,[70] Copyright 1980, International Academy of Cytology)

	Cytologic diagnosis (imprint smears)												
Histogenetic histologic diagnosis (including TEM)	Moderately to well differentiated epidermoid carcinoma	Poorly differentiated epidermoid carcinoma	CEAC/A	CEAC/B	CEAC/CI	CEAC/CII	CEAC/D	Adenocarcinoma I	Adenocarcinoma II	Carcinoid	Oat cell	% correlation	
Moderately to well differentiated epidermoid carcinoma	13											(16/17)	94
Poorly differentiated epidermoid carcinoma	2	1	1										
CEAC/A			3									(3/3)	100
CEAC/B	5			6	1							(6/12)	50
CEAC/CI					11	6		1				(27/28)	96
CEAC/CII					5	5							
CEAC/D					1		3	1	1			(3/6)	50
Adenocarcinoma I					2			5	1			(8/13)	62
Adenocarcinoma II					2		1	1	1				
Carcinoid										1		(1/1)	100
Oat cell											4	(4/4)	100
Atypical endocrine							2					(0/2)	0

CEAC = combined epidermoid and adenocarcinoma. A = epidermoid component, well-differentiated; adeno component, well-differentiated. B = epidermoid component, well-differentiated; adeno component, poorly differentiated. C = epidermoid component, poorly differentiated; adeno component, well-differentiated. D = epidermoid component, poorly differentiated; adeno component, poorly differentiated. I = gross glandular organization maintained. II = gross glandular organization lost. TEM = transmission electron microscopy.

Table 7—Reliability of Conventional Cytologic Criteria Applied to 86 Resected Human Lung Tumors (Hess et al,[70] Copyright 1980, International Academy of Cytology)

	Cytologic diagnosis (imprint smears)													
			Small cell anaplastic carcinoma					Large cell undifferentiated carcinoma						
Conventional histologic diagnosis (WHO)	Moderately differentiated to well differentiated epidermoid carcinoma	Poorly differentiated epidermoid carcinoma	Fusiform cell	Polygonal cell	Oat-cell	Moderately differentiated to well differentiated adenocarcinoma	Poorly differentiated adenocarcinoma	Solid-mucin	Solid-no mucin	Giant cell	Clear cell	Combined epidermoid adenocarcinoma	Carcinoid	% correlation
Moderately to well differentiated epidermoid carcinoma	23	2					2	1	1					(25/30) 83
Poorly differentiated epidermoid carcinoma									1					
Small cell anaplastic carcinoma														
Fusiform cell														—
Polygonal cell	1													(0/1) 0
Oat cell				1	3									(3/4) 75
Bronchogenic adenocarcinoma														
Moderately to well differentiated						3	6	5	2	2				(13/29) 45
Poorly differentiated		1		1			4	1	4					
Bronchioloalveolar carcinoma														—
Large cell carcinoma														
Solid-mucin	2	2				1	1	2	1	2				(2/11) 18
Solid-no mucin	1	1					3	3						(0/8) 0
Giant cell														—
Clear cell		2												(0/2) 0
Combined epidermoid adenocarcinoma														—
Carcinoid tumor					1									(0/1) 0

WHO = World Health Organization.

nicolaou stain[85] and can be observed in well-preserved cells of imprint smears, obtained from surgically resected tumors, as well as in exfoliated cells from preoperative specimens such as sputa and bronchial washings, that have undergone various degrees of autolysis.[70] However, combined tumors are diagnosed in different categories as either epidermoid carcinomas, adenocarcinomas, or large cell carcinomas, with the use of conventional cytologic criteria.[70]

The revised cytologic criteria have been demonstrated to be more reliable and accurate in matching the histologic diagnosis, as compared with conventional cytologic criteria.[70] A greater number of matching correlations was obtained for histogenetic cytodiagnoses versus histogenetic histologic evaluations than were achieved for conventional cytodiagnoses versus WHO histologic evaluations (Tables 6 and 7).[70] Relatively high matching reliability for combined epidermoid and adenocarcinomas occurred when the revised cytologic criteria were used (Table 6, large box). Different degrees of both epidermoid and adeno differentiation of most of the combined tumors were recognized in the cytologic preparations.

Although the accuracy of the revised cytologic criteria for adenocarcinomas was low (62%) (Table 6), these cytodiagnoses were actually more accurate than the histogenetic histologic diagnoses.[70] Several of these tumors revealed epidermoid characteristics, with the use of the Papanicolaou stain.[66,70] Consequently, they were classified cytologically as combined epidermoid and adenocarcinomas with a poorly differentiated epidermoid component. The epidermoid features were not detectable with the use of H&E-stained paraffin sections.

The apparent high number (83%) (Table 7) of matching correlations between conventional cytodiagnoses and WHO histologic diagnoses for epidermoid carcinomas is false, because many of these tumors were actually combined epidermoid and adenocarcinomas, diagnosed as such with the new criteria on the basis of specific cytoplasmic features of functional differentiation revealed by light and electron microscopic examination.[70]

The revised cytologic criteria were derived from a three-year study consisting of consecutive cases of lung cancer patients at four hospitals and consecutive cases of respiratory tract tumors of hamsters from two 1-year studies.[66] Although the number of cases in some categories is small (Tables 6 and 7),[70] these studies provided an adequate number of cases to demonstrate convincingly that similar reliability and reproducibility of various tumor types were revealed for varied types of respiratory tract cytologic specimens, such as imprint smears of human and hamster resected tumors, hamster tracheal washings, and preoperative human specimens of sputa, bronchial washings, and bronchial brushings.

The new cytologic data clarify poorly differentiated epidermoid carcinomas and poorly differentiated adenocarcinomas as well as eliminate vague categories such as large cell carcinomas.[70] It is hoped that the revised diagnostic criteria will be recognized, understood, and used by cytopathologists, so that comparison of results between various institutions will be more accurate and perhaps more meaningful.

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