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Cytological and histological correlation of primary lung cancer: a preliminary study of 106 cases with resectable tumors.

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Abstract

In order to increase the accuracy of diagnosis in lung cancer, analysis concerning cytological and histological correlation was attempted. The present study consists of 106 patients, who were seen during the past approximately five years and underwent radical surgery to remove tumors completely; mere biopsy specimens were excluded. These patients were 63 years old on the average, 78 males and 28 females, 29 cases of the hilar type (H) and 77 of the peripheral type (P), and 27 and 76 cases of the clinical stage I in H and P, respectively. Histologically, there were 53 adenocarcinomas (Ad), 38 squamous cell carcinomas (Sq), 4 adenosquamous cell carcinomas (Ad + Sq), 5 large cell carcinomas (LCC), and 6 small cell carcinomas (SCC); among them, 3 Ad and 21 Sq in H, and 50 Ad and 17 Sq in P. The overall positive percentages were 65.5 (H) and 26.0 (P) by combination of spontaneous, aerosol-induced and Saccomanno's methods, against 96.6 (H) and 72.8 (P) with inclusion of brushing method. 94.8% of Sq in H and 66.7% of Ad and 70.6% of Sq in P were positive by the brushing. A comparative study of these four methods, performed at least once on the same patient, also confirmed the superiority of brushing. Cyto- and histological agreement was 21/21 (100%) for Sq in H, whereas 30/34 (88.2%) for Ad and 13/15 (86.7%) for Sq in P. In conclusion, cyto- and histological findings in H and P corresponded well, and as far as cytology of peripheral type is concerned, a combined method, especially with brushing, is strongly recommended.

KEYWORDS: primary lung cancer, cytology, histology

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CYTOLOGICAL AND HISTOLOGICAL CORRELATION OF PRIMARY LUNG CANCER: A PRELIMINARY STUDY OF 106 CASES WITH RESECTABLE TUMORS

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Abstract. In order to increase the accuracy of diagnosis in lung cancer, analysis concerning cytological and histological correlation was attempted. The present study consists of 106 patients, who were seen during the past approximately five years and underwent radical surgery to remove tumors completely; mere biopsy specimens were excluded. These patients were 63 years old on the average, 78 males and 28 females, 29 cases of the hilar type (H) and 77 of the peripheral type (P), and 27 and 76 cases of the clinical stage I in H and P, respectively. Histologically, there were 53 adenocarcinomas (Ad), 38 squamous cell carcinomas (Sq), 4 adenosquamous cell carcinomas (Ad + Sq), 5 large cell carcinomas (LCC), and 6 small cell carcinomas (SCC); among them, 3 Ad and 21 Sq in H, and 50 Ad and 17 Sq in P. The overall positive percentages were 65.5 (H) and 26.0 (P) by combination of spontaneous, aerosol-induced and Saccomanno's methods, against 96.6 (H) and 72.8 (P) with inclusion of brushing method. 94.8 % of Sq in H and 66.7 % of Ad and 70.6 % of Sq in P were positive by the brushing. A comparative study of these four methods, performed at least once on the same patient, also confirmed the superiority of brushing. Cyto- and histological agreement was 21/21 (100 %) for Sq in H, whereas 30/34 (88.2 %) for Ad and 13/15 (86.7 %) for Sq in P. In conclusion, cyto- and histological findings in H and P corresponded well, and as far as cytology of peripheral type is concerned, a combined method, especially with brushing, is strongly recommended.

Key words: primary lung cancer, cytology, histology.

The recent increase in lung cancer among the Japanese population, especially in relation to cigarette-smoking (1), has made the need for detection of the lung cancer using the simplest diagnostic procedures, such as chest x-ray examination and exfoliative cytology, urgent. Accurate cancer cell typing is essential for selecting the appropriate therapies, such as surgical procedure or anti-cancer chemotherapeutic regimen, and also for predicting patients' prognosis. For this purpose, a great effort has been made by many investigators (2-6). We present a preliminary study consisting of a total of 106 cases whose tumors were

completely resectable.

PATIENTS AND METHODS

Patients. A total of 106 cases with lung cancer, who were admitted to the 1st and 2nd Clinics of Department of Surgery, Okayama University Hospital, during the period from January 1977 to March 1982, consisted of the present study. Prior to surgery, cytological procedures as mentioned below were performed on these cases.

Methods for cytology. These included four methods: i) spontaneous sputa (Spont), ii) aerosol-induced sputa (Airsol) (7), iii) Saccomanno's method (Saccomanno) (8), and iv) brushing method (Brush) (9).

Histological subclassification. This was based on the "General rule for clinical and pathological record of lung cancer", published by the Japan Lung Cancer Society (10).

RESULTS

Clinical information and originating site of tumors. A total of 106 cases consisted of 29 hilar types (H) and 77 peripheral types (P) (Table 1). Male patients dominated in both types, *i.e.*, 28 and 50 cases, respectively, and the average age was 63 years.

Histological subtyping. Histologically, there were 53 cases with adenocarcinoma (Ad), 38 squamous cell carcinoma (Sq), 4 adenosquamous cell carcinoma (Ad + Sq), 5 large cell carcinoma (LCC) and 6 small cell carcinoma (SCC) (Table 2). Among them, there were 3 Ad and 21 Sq in H, and 50 Ad and 17 Sq in P.

Positivity according to clinical staging and methodology. Twenty-seven out of 29

TABLE 1. CLINICAL INFORMATION AND ORIGINATING SITE OF TUMORS

Site of origin	No. of cases	No. of cases by sex		Age (yrs)	Average age (yrs)
		M	F		
Hilar type	29	28	1	37-77	64
Peripheral type	77	50	27	33-81	61

TABLE 2. HISTOLOGICAL SUBTYPING OF 106 CASES

Histology	Hilar	Peripheral	Total
Adenocarcinoma (Ad)	3	50	53
Squamous cell carcinoma (Sq)	21	17	38
Adenosquamous cell carcinoma (Ad + Sq)	0	4	4
Large cell carcinoma (LCC)	3	2	5
Small cell carcinoma (SCC)	2	4	6
Total	29	77	106

TABLE 3-A. POSITIVITY ACCORDING TO CLINICAL STAGING AND METHODOLOGY

<i>Hilar Type</i>												
Clinical stage	Spont			Airsol			Saccomanno			Brush		
	No.	(+)	%	No.	(+)	%	No.	(+)	%	No.	(+)	%
0	1	1		1	1		1	1		1	1	
I	22	6	27.3	20	13	65.0	22	13	59.0	25	22	88.0
III	1	1		1	1		1	1		N.D.		
<i>Peripheral Type</i>												
Clinical stage	Spont			Airsol			Saccomanno			Brush		
	No.	(+)	%	No.	(+)	%	No.	(+)	%	No.	(+)	%
I	42	9	21.4	41	5	12.2	43	13	30.2	74	51	68.9
III	1	0		1	0		1	0		N.D.		

TABLE 3-B. POSITIVITY ACCORDING TO METHODOLOGY (SUM UP OF 3-A)

	Spont			Airsol			Saccomanno			Brush	
	No.	(+)	%	No.	(+)	%	No.	(+)	%	No.	(+)
Hilar	24	8	33.3	22	15	68.2	24	15	62.5	26	23
Peripheral	43	9	21.0	42	5	11.9	44	13	29.5	74	51

TABLE 3-C. POSITIVITY ACCORDING TO METHODOLOGY (SUM UP OF 3-B)

	Excluding brushing		Including brushing	
	(+) No.	%	(+) No.	%
Hilar	19	65.5	28	96.6
Peripheral	20	26.0	56	72.8

cases with H and 76 of 77 cases with P were in the clinical stage I, *i.e.*, T1 or T2, NoMo (Table 3). The overall positive percentage was 65.5 (H) and 26.0 (P) by a combination of spontaneous, aerosol-induced and Saccomanno's methods, against 96.6 (H) and 72.8 (P) with inclusion of brushing method. This implied that H can be detected within a range of 62 to 68 % by either Saccomanno's or aerosol-induced method, whereas P needs brushing otherwise cannot obtain satisfactory positivity.

Positivity according to originating site of tumors and frequency of repeating sputum collections. Apart from aerosol-induced and Saccomanno's methods, we have been most concerned with the frequency of repeating sampling of spontaneous sputum (Table 4). For unknown reasons, 11 patients in H submitted spontane-

TABLE 4. POSITIVITY ACCORDING TO ORIGINATING SITE OF TUMORS
AND FREQUENCY OF REPEATING SPUTUM COLLECTIONS

<i>Hilar Type</i>									
Frequency of repetition	Spont			Airsol			Saccomanno		
	No.	(+)	%	No.	(+)	%	No.	(+)	%
1	11	0		15	10	66.7	19	12	63.2
2	5	4	80.0	6	4	66.7	3	1	33.3
3	5	3	60.0	1	1		2	2	
4	1	0							
5	1	1							
6	1	0							
Averaged frequency (times)	2.0			1.2			1.0		

<i>Peripheral Type</i>									
Frequency of repetition	Spont			Airsol			Saccomanno		
	No.	(+)	%	No.	(+)	%	No.	(+)	%
1	23	5	21.8	33	5	15.1	35	11	31.4
2	7	1	14.3	9	0		8	2	20.0
3	3	1	33.3				1	0	
4	1	0							
6	5	1	20.0						
8	3	1	33.3						
9	1	0							
Averaged frequency (times)	2.1			1.2			1.2		

ous sputum only once, but none of them proved to be positive. On the other hand, five patients each produced sputum twice and three times, and out of these, four and three cases were positive, respectively. This indicated that H needs repeated cytology of spontaneous sputum, at least, three times.

Positivity according to histological subclassification and methodology. 94.8 % of Sq in H, and 66.7 % of Ad and 70.6 % of Sq in P were positive by brushing (Table 5-A). A comparative study of these four methods was attempted in the same individual and performed at least once (Table 5-B). H yielded approximately 69 % of positivity by either aerosol-induced or Saccomanno's method, whereas brushing was necessary for P to reach the same level of positivity as H.

Agreement of cytology with histological subclassification. "False-negative" cases were found most frequently among Ad of P, *i.e.*, 16 of 50 cases examined (Table 6). On the other hand, Sq of H and Sq and Ad of P showed a high percentage of

TABLE 5-A. POSITIVITY ACCORDING TO HISTOLOGICAL SUBCLASSIFICATION AND METHODOLOGY
Hilar Type

	Spont			Airsol			Saccomanno			Brush		
	No.	(+)	%	No.	(+)	%	No.	(+)	%	No.	(+)	%
Ad	3	2		3	3		3	2		2	1	
Sq	17	6	35.3	17	10	58.8	18	12	66.7	19	18	94.8
LCC	2	0		1	1		2	0		3	2	
SCC	2	0		1	1		1	1		2	2	
Total	24	8	33.3	22	15	68.2	24	15	62.5	26	23	88.5

Peripheral Type

	Spont			Airsol			Saccomanno			Brush		
	No.	(+)	%	No.	(+)	%	No.	(+)	%	No.	(+)	%
Ad	25	3	12.0	29	0		28	5	17.9	48	32	66.7
Sq	11	4	36.4	9	5	55.5	10	7	70.0	17	12	70.6
Ad+Sq	2	0		3	0		3	0		3	2	
LCC	2	2					1	1		2	2	
SCC	3	0		1	0		2	0		4	3	
Total	43	9	21.0	42	5	12.0	44	13	29.5	74	51	68.9

TABLE 5-B. POSITIVITY OF THE PATIENTS TO WHOM ALL FOUR METHODS WERE COMBINED
Hilar Type (16 of 29 patients)

	No. of cases	Spont		Airsol		Saccomanno		Brush	
		(+)	%	(+)	%	(+)	%	(+)	%
Ad	2	1		2		1		1	
Sq	13	5	38.5	8	61.6	9	69.2	12	92.3
SCC	1	0		1		1		1	
Total	16	6	39.5	11	68.8	11	68.8	14	87.5

Peripheral Type (25 of 77 patients)

	No. of cases	Spont		Airsol		Saccomanno		Brush	
		(+)	%	(+)	%	(+)	%	(+)	%
Ad	17	1	5.9	0		4	23.5	13	76.5
Sq	7	3	42.9	4	57.1	5	71.4	4	57.1
SCC	1	0		0		0		1	
Total	25	4	16.0	4	16.0	9	36.0	18	72.0

TABLE 6. AGREEMENT OF CYTOLOGY WITH HISTOLOGICAL SUBCLASSIFICATION

No. of cases	Histological subclassification									
	Hilar type					Peripheral type				
	Ad 3	Sq 21	Ad+Sq 0	LCC 3	SCC 2	Ad 50	Sq 17	Ad+Sq 4	LCC 2	SCC 4
Cytology										
Ad	1	-	-	-	-	30	1	-	-	1
Sq	2	21	-	1	-	2	13	2	1	1
Ad+Sq	-	-	-	-	-	-	-	-	-	-
LCC	-	-	-	1	-	1	-	-	1	-
SCC	-	-	-	-	1	-	-	-	-	-
Undetermined	-	-	-	-	1	1	1	-	-	1
Total	3	21	-	2	2	34	15	2	2	3
% of good agreement	33.3	100				88.2	86.7			
No. of false-negative cases	0	0	0	1	0	16	2	2	0	1

TABLE 7. POSITIVITY OF PERIPHERAL TYPE ACCORDING TO TUMOR SIZE

Tumor size (cm)	No. of cases	Spont			Airsol			Saccomanno			Brush		
		No.	(+)	%	No.	(+)	%	No.	(+)	%	No.	(+)	%
< 3	44	24	1	4.2	26	1	3.8	25	3	12.0	42	25	59.5
> 3	33	19	8	42.1	16	4	25.0	19	10	52.6	32	26	81.3

TABLE 8-A. RELATIONSHIP BETWEEN FREQUENCY OF LYMPH NODAL METASTASIS, TUMOR SITE AND HISTOLOGICAL SUBCLASSIFICATION

	Hilar type					Peripheral type				
	Ad	Sq	Ad+Sq	LCC	SCC	Ad	Sq	Ad+Sq	LCC	SCC
No. of cases	3	21	0	3	2	50	17	4	2	4
No. of cases with metastasis	1	1	0	1	1	17	8	1	1	1
%	33.3	4.8		33.3		34.0	47.1	25.0		25.0

TABLE 8-B. RELATIONSHIP BETWEEN FREQUENCY OF NODAL METASTASIS AND HISTOLOGY (SUM UP OF 8-A)

	Ad	Sq	Ad+Sq	LCC	SCC
No. of cases	53	38	4	5	6
No. of cases with metastasis	18	9	0	2	2
%	34.0	24.0		40.0	33.3

agreement, *i.e.*, 21/21 (100 %) of Sq in H *vs.* 30/34 (88.2 %) of Ad and 13/15 (86.7 %) of Sq in P.

Positivity of the peripheral type according to tumor size. A comparative study of tumors of P smaller than or equal to 3 cm with those larger than 3 cm in diameter was made (Table 7). Brushing method in tumors larger than 3 cm in diameter was 81.3 % positive against 59.5 % in tumors less than 3 cm. This obviously showed that a tumor size larger than 3 cm will yield a high percentage of positivity.

Relationship between frequency of lymph nodal metastasis, tumor site and histological subclassification. A single nodal metastasis was taken as positive in the present series, out of varied numbers of the regional lymph nodes submitted to our laboratory (Table 8). As far as Ad and Sq were concerned, there was no significant difference in frequency of nodal metastasis; more cases with radically resected specimens are needed in future to draw more definite conclusions.

DISCUSSION

The present study consists only of the patients who underwent radical surgery with complete removal of their tumors; biopsied materials, such as endoscopic bronchial, transcutaneous pulmonary needle, mediastinal, scalene nodal or other lymph nodal, were excluded. The biopsied specimens obviously represent a merely limited area of a given tumor. Therefore, as Reid and Carr (3) stated, "diagnosis based on a biopsy specimen was rather inaccurate in predicting the structure of the main mass". This is especially the case when two or more structural patterns, *e.g.*, adeno and squamous, are present in the tumor. Through reviewing whole transverse sections of tumors, we had the impression that the majority of tumors has quite varied histologies. This is not surprising. In fact, as early as in 1957, Strauss and Weller (11) proposed a pattern of tumor differentiation in the form of Y; a continuous gradient from undifferentiated small round cell tumors, represented by the base of the stem, to squamous carcinoma and adenocarcinoma as represented by the arms. At the bifurcation lay those in the undifferentiated pleomorphic group. More recent study by Trump, Wilson and Harris (12) proposed a concept of tumor initiation, promotion and progression in the bronchial epithelium; mucous cells and/or basal cells will be initiated followed by promotion by intrinsic or extrinsic factor(s) to manifest basal cell hyperplasia, epidermoid metaplasia, dysplasia and carcinoma *in situ*. This will subsequently progress to invasive carcinoma, such as epidermoid or mixed epidermoid and adenocarcinoma. The variegated histology thus reflects the difficulty in interpreting cancer cell typing by cytology in our daily clinical practice. So that, it would be better to keep the presence of heterogeneous structural patterns in mind; indeed, according to Trump *et al.* (12) the frequency of combined epidermoid and adenocarcinoma can be close to 50 %, although they stated that this percent based on 150 tumors does not reflect the

incidence of these tumors.

To our knowledge, out of a large number of previous reports concerning pulmonary cytology, little work has been based solely on radically resected specimens; the majority of work has included biopsied specimens. At the same time, we must point out the usefulness or limitation of cytology depending on whether tumors are located near the hilum or peripherally. Our study (Tables 3 and 5) so far indicates that the hilar type can be detected up to 60 to 70 % using either aerosol-induced or Saccomanno's method. On the other hand, the peripheral type will need brushing to enhance diagnostic accuracy by cytology; other methods do not yield satisfactory positivity. The brushing is certainly a physical burden to patients, and also requires some experience and technical skill of clinicians. Yet, this procedure can be worthwhile to be attempted in the present situation, particularly in the peripheral type, as compared to bronchial washing which may be of very little value in lung cancer diagnosis (13).

We are currently increasing the number of cases with radically resected tumors, preferably up to one and a half or twice of the present cases, in order to draw more definite conclusions. In this way, we may get closer to the cytological diagnostic level of certain cancers, *e.g.*, cervical, in near future; this is solely based on how to detect the early, *i.e.*, non-invasive, lesion in the lung cancer.

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