Jpn. J. Cancer Res. **91**, 1–8, January 2000

Reproducibility of Diagnosis and Its Influence on the Distribution of Lung Cancer by Histologic Type in Osaka, Japan

Seiichiro Yamamoto,[1,6] Tomotaka Sobue,[1] Naohito Yamaguchi,[1] Satoru Yamamoto,[2] Masanori Kikui,[3] Yoko Kusunoki,[4] Akira Oshima[4] and Aya Hanai[5]

[1]Cancer Information and Epidemiology Division, National Cancer Center Research Institute, 5-1-1 Tsukiji, Chuo-ku, Tokyo104-0007, [2]Department of Pathology, National Kinki Chuo Hospital, 1180 Nagasone-cho, Sakai, Osaka 591-8025, [3]Pathology Department, Osaka Prefectural Habikino Hospital, 3-7-1 Habikino, Habikino, Osaka 583-8588, [4]Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases and [5]Japanese Association of Cancer Registries, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511

The histologic types of lung cancer cases diagnosed in 1979–1980 (n=799) and 1987 (n=587) were independently reviewed by two pathologists in order to investigate the reproducibility of the diagnosis of the histologic type when the WHO classification (1981) was used. The specimens from 354 surgical cases and biopsy or cytology specimens from 1032 non-surgical cases were reviewed. The inter-observer agreement was 87.9% (κ=0.79) for surgical cases and 81.4% (κ=0.72) for non-surgical cases. When compared to the original diagnosis, the agreement was 86.8% (κ=0.78) for surgical and 86.4% (κ=0.79) for non-surgical cases in 1979–1980 and the agreement was 92.8% (κ=0.87) for surgical and 89.1% (κ=0.83) for non-surgical cases in 1987. By histologic type, no difference in the agreement was observed except for large cell carcinoma. The distribution of histologic types after the review differed only slightly (less than 6%) from the original distribution. This suggests that in Osaka, Japan, the diagnosis based on the WHO classification (1981) had only a limited influence on the distribution of histologic types, and is not a major reason for the changing trends in lung cancer incidence by histologic type.

Key words: Reproducibility of diagnosis — WHO classification — Lung cancer — Histologic type — Incidence trend

The recent changes in the incidence of lung cancer by histologic type reported in different countries consistently show a relative increase in adenocarcinoma compared to squamous cell carcinoma in both males and females, especially for the younger age group.[1–7] Among white males in the United States, a decrease in the incidence of squamous cell carcinoma was first noticed in 1981. The incidences of small cell and large cell carcinoma began to decline in 1986 and that of adenocarcinoma started to drop in 1991.[6] It has been postulated that the time lag for the decrease in squamous cell carcinoma and adenocarcinoma can be explained by the change from high-tar non-filtered cigarettes to low-tar filtered cigarettes[8–11] and the different influence of smoking cessation.[12–14]

In Japan, where the incidence of lung cancer is relatively low and the proportion of adenocarcinoma is relatively high compared to the United States and European countries, a relative increase in adenocarcinoma was also observed. According to data from the Osaka Cancer Registry, the cumulative risk (age 0 to 74) of lung cancer in both males and females increased 1.4 fold for adenocarcinoma and 1.6 fold for small cell carcinoma in the period from 1974 to 1993, while the cumulative risk of squamous cell carcinoma in the same period remained almost constant.[15]

Campobasso *et al.*[16] showed that changes in the distribution of histologic types might be artificial and due to the change in diagnostic criteria for histologic types in the WHO classification revised in 1981 (the 1981 WHO classification).[17] Based on a pathological review of 722 surgical cases, they reported that the change in diagnostic criteria between the WHO classification published in 1967 (the 1967 WHO classification)[18] and the 1981 WHO classifications alone resulted in a substantial change in the histologic distribution, including an 11% decrease in squamous cell carcinoma and a 15% increase in adenocarcinoma. This magnitude of change in the histologic distribution, if it exists in Osaka, Japan, would partly explain the relative increase in adenocarcinoma.

In order to estimate the magnitude of the influence of diagnosis based on the 1981 WHO classification on the histologic distribution we conducted a pathological review of cases in two major hospitals in the area covered by the Osaka Cancer Registry. First, we investigated the inter-observer reproducibility of the diagnosis of histologic type

[6] To whom correspondence should be addressed.
E-mail: siyamamo@ncc.go.jp

based on the 1981 WHO classification. Next, the reproducibility between the original and the review diagnosis was investigated. Then, based on the review diagnosis, we estimated the corrected trends for the incidence of lung cancer by histologic type, recently reported using the data from the Osaka Cancer Registry.[15)]

SUBJECTS AND METHODS

All the lung cancer patients diagnosed in 1979–1980 and in 1987 at the Osaka Prefectural Habikino Hospital and Kinki Chuo National Hospital were ascertained by two pathologists (M. K. and S. Y.) in the hospitals. There were 887 ascertained cases in 1979–1980 and there were 643 cases in 1987. Of these, there were 1435 cases with original diagnoses of one of the four major lung cancer types: squamous cell carcinoma (36.6%), adenocarcinoma (45.7%), small cell carcinoma (13.5%), and large cell carcinoma (4.2%). Forty-nine cases for which the quality of histology or cytology specimens was not good enough for review were excluded from the study by the pathologists, leaving 1386 cases, of which 354 had been surgically resected and 1032 had not. There were 799 cases from 1979–1980 and 587 from 1987.

For the review, the most definitive slide, on which the final diagnosis had been based before treatment, was selected for each non-surgical case by the pathologists. When a biopsy specimen was not available, a cytology specimen from the primary lesion was used. A specimen from other sites such as lymph nodes, pleura or sputum was used when a specimen from the primary lesion was not available. For the surgical cases, one resected specimen which was the most appropriate for the diagnosis was selected from the available specimens by the pathologists. As a result, 354 resected specimens and 1032 biopsy, cytology, or other specimens (henceforth referred to as biopsy/cytology specimens) were used for review. Of the biopsy/cytology specimens, 698 were biopsy specimens, 204 were cytology specimens, and 130 were obtained from other than the primary site. Slides stained with hematoxylin and eosin were used for the review, since immunostaining was not used routinely before 1987. The original diagnoses followed the classification of the Japan Lung Cancer Society published in 1978 (the 1978 JLCS classification).[19)]

The cases were reviewed in the following way. First, the two pathologists reviewed all the cases from the two hospitals independently, without knowledge of the original diagnoses. Then, the same two pathologists independently reviewed the cases for whom conflicting diagnoses were made in the first review, in attempts to obtain consensus diagnoses without knowledge of the original diagnoses or the results of the first review. The first and the second reviews were based on the 1981 WHO classification and results were classified into the four aforementioned histologic types or 'others' (including combined types). Since consensus diagnoses were not obtained even after the second review for 6.5% of surgical cases and 9.2% of non-surgical cases, two review diagnoses by two pathologists were treated as the final review diagnoses for each case. That is, for those cases, for whom consensus diagnoses were not obtained by the first review, two second review results by two pathologists were treated as the final review diagnoses. For those cases, for whom consensus diagnoses were obtained by the first review, two first review results by two pathologists were treated as the final review diagnoses. As a result, 2772 final review diagnoses were obtained for 1386 cases.

To examine inter-observer reproducibility, the overall agreement between the first diagnoses of the two pathologists was evaluated in terms of proportion of agreement and the κ coefficient. The partial κ coefficients were also calculated for each histologic type. Next, the reproducibility between the original diagnosis and the final review diagnosis based on the 1981 WHO classification was investigated. The overall agreement between the original diagnoses and the final review diagnoses was also evaluated in terms of the proportion of agreement and the κ coefficient. The proportion of concordant diagnoses was also calculated for each histologic type, defined as the number of concordant diagnoses for the type divided by the number of original diagnoses for the type.

The percent changes of the histologic type distribution were calculated as the differences between the proportions of the histologic types in the final review diagnoses and those in the original diagnoses. Next, the corrected incidence rates were estimated by applying the results to the lung cancer incidence rate of each histologic type for 1974–1993, which was calculated based on the data from the Osaka Cancer Registry.[15)] The correction of incidence rate of each histologic type for the periods 1974–1993; 1974–1977, 1978–1981, 1982–1985, 1986–1989, and 1990–1993 was done by using the following method. First, a set of correction coefficients was estimated, by which the incidence rate of each histologic type based on the original diagnoses was converted into five incidence rates (for the four major histologic types and 'others') based on the final review diagnoses. Then, the incidence rate of each histologic type based on the final review diagnoses was estimated by summing up incidence rates converted from the original diagnoses. The correction coefficients were the weighted averages of the proportions of concordant diagnoses for the surgical cases and those for the non-surgical cases. To correct the incidences for the periods from 1974–1977 and 1978–1981, the results for the 1979–1980 cases were used. For the later periods, the results for the 1987 cases were used. Since the proportions of surgical and non-surgical cases in the Osaka Can-

cer Registry were almost constant during the study period,[20] average proportions during the periods (0.235 for surgical and 0.765 for non-surgical cases) were used as the weights for all the periods.

RESULTS

The distribution of lung cancer histologic types based on the original diagnoses is shown in Table I. For the sur-

Table I. Distribution of Lung Cancer Histologic Types Based on the Original Diagnosis for the Reviewed Subjects

Year	Subjects	Type of specimen	Total	Squamous cell carcinoma (%)	Adeno-carcinoma (%)	Small cell carcinoma (%)	Large cell carcinoma (%)
1979–80	Surgical	Resected	205	99 (48.3)	84 (41.0)	10 (4.9)	12 (5.9)
	Non-surgical	Biopsy/cytology	594	188 (31.6)	283 (47.6)	101 (17.0)	22 (3.7)
	Total		799	287 (35.9)	367 (45.9)	111 (13.9)	34 (4.3)
1987	Surgical	Resected	149	59 (39.6)	77 (51.7)	2 (1.3)	11 (7.4)
	Non-surgical	Biopsy/cytology	438	160 (36.5)	191 (43.6)	73 (16.7)	14 (3.2)
	Total		587	219 (37.3)	268 (45.7)	75 (12.8)	25 (4.3)
Total	Surgical	Resected	354	158 (44.6)	161 (45.5)	12 (3.4)	23 (6.5)
	Non-surgical	Biopsy/cytology	1032	348 (33.7)	474 (45.9)	174 (16.9)	36 (3.5)
	Total		1386	506 (36.5)	635 (45.8)	186 (13.4)	59 (4.3)

Table II. Inter-observer Agreement for Histologic Type of Lung Cancer Based on the First Review

		Diagnosis for the surgical subjects by the second pathologist							κ
		Squamous cell carcinoma	Adeno-carcinoma	Small cell carcinoma	Large cell carcinoma	Others	Total	(%)	
Diagnosis for the non-surgical subjects by the first pathologist	Squamous cell carcinoma	143	5	2	6	1	157	44.4	0.86
	Adeno-carcinoma	3	157	1	7	2	170	48.0	0.86
	Small cell carcinoma	2	0	2	0	1	5	1.4	0.35
	Large cell carcinoma	3	4	0	9	0	16	4.5	0.45
	Others	2	3	1	0	0	6	1.7	—
	Total	153	169	6	22	4	354	100.0	0.79
	(%)	43.2	47.7	1.7	6.2	1.1	100.0		

		Diagnosis for the non-surgical subjects by the second pathologist							κ
		Squamous cell carcinoma	Adeno-carcinoma	Small cell carcinoma	Large cell carcinoma	Others	Total	(%)	
Diagnosis for the non-surgical subjects by the first pathologist	Squamous cell carcinoma	312	50	16	16	1	395	38.3	0.77
	Adeno-carcinoma	23	379	30	25	4	461	44.7	0.72
	Small cell carcinoma	0	2	131	1	2	136	13.2	0.79
	Large cell carcinoma	2	8	2	16	0	28	2.7	0.35
	Others	3	2	5	0	2	12	1.2	—
	Total	340	441	184	58	9	1032	100.0	0.72
	(%)	32.9	42.7	17.8	5.6	0.9	100.0		

gical cases, the most predominant histologic type in 1979–1980 was squamous cell carcinoma followed by adenocarcinoma, while in 1987 it was adenocarcinoma followed by squamous cell carcinoma. The proportion of small cell carcinoma was very small due to therapeutic indications. For non-surgical cases, the most predominant histologic type in both 1979–1980 and 1987 was adenocarcinoma, followed by squamous and small cell carcinoma.

The inter-observer agreement for the first review is shown in Table II. The diagnoses were concordant for 311 out of 354 surgical cases (87.9%), and the κ coefficient was 0.79 (95% confidence interval [CI]: 0.73–0.84). Overall, high reproducibility between the pathologists was observed. The partial κ coefficients were very high for squamous cell carcinoma (0.86) and adenocarcinoma (0.86), while they were not so high for small cell carcinoma (0.35) and large cell carcinoma (0.45). The two pathologists concurred on the histologic type for 840 out of 1032 non-surgical cases (81.4%). The κ coefficient was 0.72 (95%CI: 0.68–0.75). Overall, high reproducibility between the pathologists was also observed for the non-surgical cases, although it was lower than for the surgical cases. The partial κ coefficients were very high for squamous cell carcinoma (0.77), adenocarcinoma (0.72), and

Table III. Comparison of the Original versus the Review Diagnoses for the Surgical Subjects

	Review diagnosis							Proportion of concordant diagnoses (%)
	Squamous cell carcinoma	Adeno-carcinoma	Small cell carcinoma	Large cell carcinoma	Others	Total	(%)	
Original diagnosis in 1979–80								
Squamous cell carcinoma	181	12	0	5	0	198	48.3	91.4
Adeno-carcinoma	2	155	0	10	1	168	41.0	92.3
Small cell carcinoma	3	4	11	1	1	20	4.9	55.0
Large cell carcinoma	0	13	0	9	2	24	5.9	37.5
Total	186	184	11	25	4	410	100.0	86.8
(%)	45.4	44.9	2.7	6.1	1.0	100.0		
Original diagnosis in 1987								
Squamous cell carcinoma	114	0	1	2	1	118	39.6	96.6
Adeno-carcinoma	0	151	1	2	0	154	51.7	98.1
Small cell carcinoma	0	0	4	0	0	4	1.3	100.0
Large cell carcinoma	2	12	0	7	1	22	7.4	31.8
Total	116	163	6	11	2	298	100.0	92.6
(%)	38.9	54.7	2.0	3.7	0.7	100.0		

Table IV. Comparison of the Original versus the Review Diagnoses for the Non-surgical Subjects

	Review diagnosis							Proportion of concordant diagnoses (%)
	Squamous cell carcinoma	Adeno-carcinoma	Small cell carcinoma	Large cell carcinoma	Others	Total	(%)	
Original diagnosis in 1979–80								
Squamous cell carcinoma	353	17	2	1	3	376	31.6	93.9
Adeno-carcinoma	60	484	3	13	6	566	47.6	85.5
Small cell carcinoma	18	13	167	0	4	202	17.0	82.7
Large cell carcinoma	8	14	0	22	0	44	3.7	50.0
Total	439	528	172	36	13	1188	100.0	86.4
(%)	37.0	44.4	14.5	3.0	1.1	100.0		
Original diagnosis in 1987								
Squamous cell carcinoma	293	23	0	2	2	320	36.5	91.6
Adeno-carcinoma	18	353	5	4	2	382	43.6	92.4
Small cell carcinoma	12	7	125	0	2	146	16.7	85.6
Large cell carcinoma	4	14	0	10	0	28	3.2	35.7
Total	327	397	130	16	6	876	100.0	89.1
(%)	37.3	45.3	14.8	1.8	0.7	100.0		

Table V. Summary of Pathologic Review Studies of Lung Cancer by Histologic Type

Author (country, year)	Institution	Subjects: Types of specimen	Subjects: Study period	Number	% change after pathologic review: Agreement (%)	Squamous cell carcinoma	Adenocarcinoma	Small cell carcinoma	Large cell carcinoma	Others
Present study	2 hospitals in Osaka	All (resection: 25.7%)		1598	(86.5)	3.2	−1.4	−2.4	−0.4	1.1
		Resection	1979–80	410	(86.8)	−2.9	3.9	−2.2	0.2	1.0
		Biopsy/cytology		1188	(86.4)	5.4	−3.2	−2.5	−0.7	1.1
		All (resection: 25.4%)		1174	(90.0)	0.4	2.0	−1.2	−2.0	0.7
		Resection	1987	298	(92.1)	−0.7	3.0	0.7	−3.7	0.7
		Biopsy/cytology		876	(89.1)	0.8	1.7	−1.9	−1.4	0.7
Butler (USA, 1987)	New Mexico Cancer Registry	Autopsy: 1.5%[a)] Resection: 92.4% Cytology: 6.1%	1970–72	307	(52.1)	−7.2	7.2	6.5	12.7	−19.2
			1980–82	418	(65.2)	−5.5	−0.7	1.9	1.9	2.4
Campobasso (Italy, 1993)	Turin University Hospital	Resection: 100%	1954–74	722	(69.8)	−11.0	15.0	1.0	−8.0	3.0

a) Percentages are calculated for 1970–72 and 1980–82 combined.

small cell carcinoma (0.79), while they were not so high for large cell carcinoma (0.35).

The reproducibility of the diagnoses was evaluated by comparing the original diagnoses based on JLCS classification with the final review diagnoses based on the 1981 WHO classification, as shown in Tables III and IV. For the surgical cases originally diagnosed in 1979–1980, 356 (86.8%) of the 410 reviewed were diagnosed as the same histologic types as the original (Table III). The κ coefficient was 0.78 (95%CI: 0.73–0.83). The proportions of concordant diagnoses were high for adenocarcinoma (92.3%) and squamous cell carcinoma (91.4%), while they were low for small cell carcinoma (55.0%) and large cell carcinoma (37.5%). For the surgical cases originally diagnosed in 1987, the proportion of agreement (92.6%) and the κ coefficient (0.87, 95%CI: 0.82–0.92) were higher than those of cases diagnosed in 1979–1980. Of 1188 non-surgical cases originally diagnosed in 1979–1980, 1026 (86.4%) were diagnosed as the same histologic types as the original (Table IV) and the κ coefficient was 0.79 (0.76–0.82), showing comparably high reproducibility to that for the surgical cases. The proportion of concordant diagnoses were highest for squamous cell carcinoma (93.9%), followed by adenocarcinoma (85.5%), small cell carcinoma (82.7%), and large cell carcinoma (50.0%). For non-surgical cases originally diagnosed in 1987, the proportion of agreement (89.1%) and the κ coefficient (0.83, 95%CI: 0.80–0.86) were both higher than those diagnosed in 1979–1980.

The percentage changes of the histologic type distribution after the final review are summarized in the first row of Table V. For the 1979–1980 cases, adenocarcinoma increased and squamous cell and small cell carcinoma decreased for the surgical cases, while squamous cell carcinoma increased and adenocarcinoma and small cell carcinoma decreased for the non-surgical cases. Overall, this resulted in a 3.2% increase in squamous cell carcinoma and 1.4% and 2.4% decreases in adenocarcinoma and small cell carcinoma, respectively. The percentage change was smaller in 1987 than in 1979–1980, although a small increase in adenocarcinoma and a small decrease in large cell carcinoma were observed. The corrected trends of lung cancer incidence by histologic types are shown in Fig. 1. Although less striking, the trend toward a decrease in squamous cell carcinoma and increases in adenocarcinoma and small cell carcinoma was observed even after the correction.

DISCUSSION

The reproducibility of diagnoses according to the 1981 WHO classification of lung cancer among pathologists was investigated. High overall agreement was observed. For each histologic type, excellent inter-observer agreement was found for squamous cell carcinoma and adenocarcinoma, and good agreement for small cell carcinoma, but good agreement was not obtained for large cell carcinoma. The agreement was higher for surgical cases, but was still reasonably high for non-surgical cases. This is consistent with the results of previous studies,[16, 21)] so it seems likely that the reproducibility of diagnosis based on the 1981 WHO classification among the study pathologists can be generalized to other pathologists.

The reproducibility was lower in 1979–1980 compared to 1987 (not shown). The main reason is thought to be the different quality of the specimens. There were proportion-

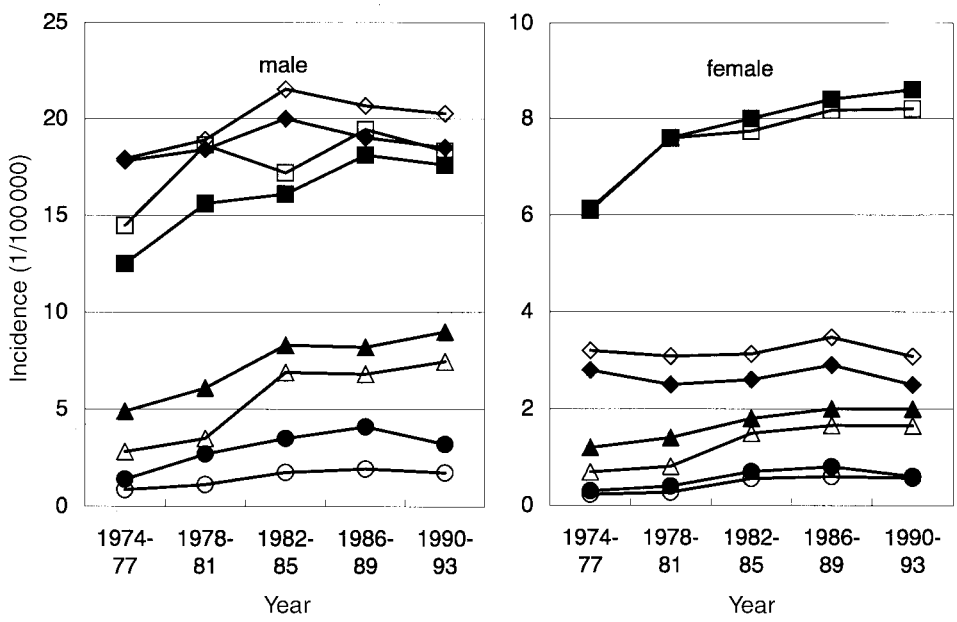

Fig. 1. Trends of lung cancer incidence by histologic types uncorrected and corrected for the review following the WHO classification (1981). Symbols are as follows: squamous cell carcinoma (uncorrected) (◆), squamous cell carcinoma (corrected) (◇), adenocarcinoma (uncorrected) (■), adenocarcinoma (corrected) (□), small cell carcinoma (uncorrected) (▲), small cell carcinoma (corrected) (△), large cell carcinoma (uncorrected) (●), large cell carcinoma (corrected) (○).

ally more biopsy specimens for the 1987 cases (82.0%) compared to the 1979–1980 cases (57.1%), while there were fewer 'other' specimens for the 1987 cases (8.0% versus 16.0%). The quality and condition of the slides from 1987 were also better than that from 1979–1980. Another possible reason is the year of issue of the 1978 JLCS classification, which is rather similar to the 1981 WHO classification (explained later). Japanese pathologists were believed to be more familiar with the classification in 1987 than in 1979–1980, therefore diagnoses based on it should have been more stable. The reasons for disagreement are not specific to the study pathologists. This also suggests that the high reproducibility can be generalized to other pathologists.

However, even after the second review, some conflicting diagnoses still remained. There are several reasons for this. The main reason is the poor quality of some of the slides, especially from the cytology specimens. Our results were based on a single slide; in clinical settings, where the diagnoses were based on multiple slides, the reproducibility among pathologists should be higher. There existed some cases with conflicting diagnoses due to differences in the way the pathologists interpreted the 1981 WHO classification, but this occurred only rarely. All these considerations support the idea that high reproducibility of diagnosis based on the 1981 WHO classification can be expected among pathologists other than the study pathologists.

We found that the original and the review diagnoses were highly reproducible. This is not consistent with other studies (Table V).[16, 22] The overall tendency seen in other studies was a substantial decrease in squamous cell carcinoma and a substantial increase in adenocarcinoma. This may have arisen from differences in the classification criteria used for the original diagnoses. While the original diagnoses in other studies followed the 1967 WHO classification, the original diagnoses in our study followed the 1978 JLCS classification. The classification of the JLCS differs from the 1967 WHO classification and is rather similar to the 1981 WHO classification. A notable difference between the JLCS and the 1981 WHO classifications is in the definition of a variant of adenocarcinoma. In the 1981 WHO classification, a solid carcinoma with mucous formation is classified as an adenocarcinoma, while it is classified as a large cell carcinoma with mucin in the 1978 JLCS classification. This would explain some of the decrease in large cell carcinoma in our review. Another possible reason for the difference from other studies was the difference in the subjects, since our study includes a higher proportion of non-surgical cases than other studies. Table V shows that the results are more similar to the results of other studies for surgical cases than for non-surgical cases. A review of the preoperative biopsy/cytology specimens for the surgical cases indicated that their review results were more similar to those based on the resected specimens than those based on biopsy/cytology specimens

from the non-surgical cases (not shown). This suggests that the difference between the surgical and the non-surgical cases resulted from a difference in the characteristics of the subjects and not from the difference in the type of specimen. Therefore, the high reproducibility of the original and the review diagnoses shown in this study, even if it is inconsistent with other reports, is not surprising. This consideration, together with the high reproducibility between the study pathologists, suggests that the reviewed diagnoses are valid. This assures the validity of the correction coefficients.

However, this study had some methodological limitations in applying the review results to estimate the corrected trends. First, the study subjects may not be representative cases registered in the Osaka Cancer Registry. The subjects were not randomly sampled, but were all patients seen in the two major hospitals in Osaka. They consisted of 25.3% (1979–1980) and 23.0% (1987) of the cases registered in the Osaka Cancer Registry. The Osaka Cancer Registry has been operating since 1962, and covers the approximately 8 000 000 residents of Osaka, Japan. In the male study subjects, the proportion of each histologic type was 43% for squamous cell carcinoma, 38% for adenocarcinoma, 15% for small cell carcinoma, and 5% for large cell carcinoma. This is similar to the corresponding figures in the Osaka Cancer Registry of 39%, 36%, 16%, and 7%, respectively.[15] A similar relationship was observed for the female subjects. In terms of the distribution of histologic types, the study subjects were considered representative, although this does not necessarily assure the applicability of the results.

A second problem is the representativeness of the study period. Our subjects were sampled from patients seen before (1979–1980) and after (1987) the publication of the 1981 WHO classification, and the results were applied to the histologic type incidence trends between 1974 and 1993. While we applied the results from 1979–1980 to the incidence in 1974–1981 and those from 1987 to 1982–1993, the corrected trends were similar to those when we applied the results from 1979–1980 to 1974–1985 and those from 1987 to 1986–1993 (not shown). Furthermore, since higher reproducibility of diagnosis is expected after 1987, the corrected trends would be more similar to the observed trends if we estimated the corrected trends based on the review results after 1987.

Fig.1 shows that, to cancel out the increasing trend of adenocarcinoma, it is necessary to increase the number of reviewed diagnoses as adenocarcinoma in 1974–1977 much more than in the study results. Since the study subjects consisted of 1/4 of the cases registered in the Osaka Cancer Registry, the hypothetical review results for the rest of the cases by the two study pathologists would have to be consistently very different from the study results to cancel out the trends. This seems unlikely. Thus, even if the validity of the corrected incidence is limited, the validity of the increasing trend of adenocarcinoma seems assured.

In conclusion, our study showed that the diagnoses based on the 1981 WHO classification were highly reproducible among pathologists and in good agreement with the original diagnoses based on the 1978 JLCS classification, and that the influence of the classification on the trends in the incidence of histologic types in Japan is limited. Increasing incidence of adenocarcinoma was confirmed even after the review according to the 1981 WHO classification. Possible reasons for this increase should be investigated.

ACKNOWLEDGMENTS

This study was supported by a Grant-in-Aid from the Ministry of Health and Welfare of Japan for a Comprehensive 10-Year Strategy for Cancer Control.

(Received August 25, 1999/Revised October 9, 1999/Accepted October 18, 1999)

REFERENCES

1) Kung, I. T. M., So, K. F. and Lam, T. H. Lung cancer in Hong Kong Chinese: mortality and histological types, 1973–1982. *Br. J. Cancer*, **50**, 381–388 (1984).
2) Choi, J.-H., Chung, H. C., Yoo, N. C., Lee, H. R., Lee, K. H., Choi, W., Lim, H. Y., Koh, E. H., Kim, J.-H., Roh, J. K., Kim, S. K., Lee, W. Y. and Kim, B. S. Changing trends in histologic types of lung cancer during the last decade (1981–1990) in Korea: a hospital-based study. *Lung Cancer*, **10**, 287–296 (1994).
3) Janssen-Heijnen, M. L. G., Nab, H. W., van Reek, J., van der Heijden, L. H., Schipper, R. and Coebergh, J. W. W. Striking changes in smoking behaviour and lung cancer incidence by histological type in southeast Netherlands, 1960–1991. *Eur. J. Cancer*, **31A**, 949–952 (1995).
4) Russo, A., Crosignani, P., Franceschi, S. and Berrino, F. Changes in lung cancer histological types in the Varese cancer registry, Italy 1976–1992. *Eur. J. Cancer*, **33**, 1643–1647 (1997).
5) Thun, M. J., Lally, C. A., Flannery, J. T., Calle, E. E., Flanders, W. D. and Health, C. W., Jr. Cigarette smoking and changes in the histopathology of lung cancer. *J. Natl. Cancer Inst.*, **89**, 1580–1586 (1997).
6) Travis, W. D., Lubin, J., Ries, L. and Devesa, S. United States lung carcinoma incidence trends. Declining for most histologic types among males, increasing among females. *Cancer*, **77**, 2464–2470 (1997).

7) Cha, Q., Chen, Y.-Z. and Du, Y.-X. The trends in histological types of lung cancer during 1980–1988, Guangzhou, China. *Lung Cancer*, **17**, 219–230 (1997).
8) Hoffmann, D., Rivenson, A., Murphy, S. E., Chung, F.-L., Amin, S. and Hecht, S. S. Cigarette smoking and adenocarcinoma of the lung: the relevance of nicotine-derived N-nitrosamines. *J. Smoking-related Dis.*, **4**, 165–189 (1993).
9) Wynder, E. L. and Muscat, J. E. The changing epidemiology of smoking and lung cancer histology. *Environ. Health Perspect.*, **103** (Suppl. 8), 143–148 (1995).
10) Charloux, A., Quoix, E., Wolkove, N., Small, D., Pauli, G. and Kreisman, H. The increasing incidence of lung adenocarcinoma: reality or artifact? A review of the epidemiology of lung adenocarcinoma. *Int. J. Epidemiol.*, **26**, 14–23 (1997).
11) Stellman, S. D., Muscat, J. E., Thompson, S., Hoffmann, D. and Wynder, E. L. Risk of squamous cell carcinoma and adenocarcinoma of the lung in relation to lifetime filter cigarette smoking. *Cancer*, **80**, 382–388 (1997).
12) Lubin, J. H. and Blot, W. J. Assessment of lung cancer risk factors by histologic category. *J. Natl. Cancer Inst.*, **73**, 383–389 (1984).
13) Higgins, I. T. and Wynder, E. L. Reduction in risk of lung cancer among ex-smokers with particular reference to histologic type. *Cancer*, **62**, 2397–2401 (1988).
14) Sobue, T., Suzuki, T., Fujimoto, I., Matsuda, M., Doi, O., Mori, T., Furuse, K., Fukuoka, M., Yasumitsu, T., Kuwahara, O., Ichitani, M., Taki, T., Kuwabara, M., Nakahara, K., Endo, S., Sawamura, K., Kurata, M. and Hattori, S. Lung cancer risk among exsmokers. *Jpn. J. Cancer Res.*, **82**, 273–279 (1991).
15) Sobue, T., Ajiki, W., Tsukuma, H., Oshima, A., Hanai, A. and Fujimoto, I. Trends of lung cancer incidence by histologic type: a population-based study in Osaka, Japan. *Jpn. J. Cancer Res.*, **90**, 6–15 (1999).
16) Campobasso, O., Andrion, A., Ribotta, M. and Ronco, G. The value of the 1981 WHO histological classification in inter-observer reproducibility and changing pattern of lung cancer. *Int. J. Cancer*, **53**, 205–208 (1993).
17) World Health Organization. "Histological Typing of Lung Tumours. International Histological Classification of Tumours," 2nd Ed. (1981). WHO, Geneva.
18) World Health Organization. "Histological Typing of Lung Tumours. International Histological Classification of Tumours," 1st Ed. (1967). WHO, Geneva.
19) The Japan Lung Cancer Society. "General Rule for Clinical and Pathological Record of Lung Cancer," 1st Ed. (1978). Kanehara Co., Tokyo.
20) Osaka Cancer Registry. "Cancer Incidence and Mortality in Osaka 1963–1989" (1993). Osaka Foundation for Prevention of Cancer and Circulatory Diseases, Osaka.
21) Hanai, A., Whittaker, J. S., Tateishi, R., Sobin, L. H., Benn, R. T. and Muir, C. S. Concordance of histological classification of lung cancer with special reference to adenocarcinoma in Osaka, Japan, and the North-West region of England. *Int. J. Cancer*, **39**, 6–9 (1987).
22) Butler, C., Samet, J. M., Humble, C. G. and Sweeney, E. S. Histopathology of lung cancer in New Mexico, 1970–72 and 1980–81. *J. Natl. Cancer Inst.*, **78**, 85–90 (1987).