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15) 平成18年度 厚生労働省がん研究助成金「がん検診の適切な方法とその評価法の確立に関する研究」班：有効性評価に基づく肺がん検診ガイドライン，2006.

Reprinted from
Jpn J Clin Oncol 2008;38(8)534–539
doi:10.1093/jjco/hyn072

Trends in Lung Cancer Incidence by Histological Type in Osaka, Japan

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Trends in Lung Cancer Incidence by Histological Type in Osaka, Japan

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Received March 11, 2008; accepted July 13, 2008; published online August 9, 2008

Background: In Japan, an increase in age-adjusted incidence rates of lung adenocarcinoma (ADC) and a decrease in lung squamous cell carcinoma (SQCC) have been reported.
Methods: The number of lung cancer incidence, age-adjusted rates, and age-specific rates by birth-cohort according to histological type were examined using the data from Osaka Cancer Registry.
Results: The numbers of lung cancer incidence among men and women have increased, particularly in ADC. The age-adjusted incidence rates of ADC among men and women have continuously increased, while those of SQCC and small cell carcinoma (SMCC) turned to decrease since 1990s. A trough of lung cancer incidence rates was observed among men in 1935–39 birth-cohorts. The declining trend appeared in 1955–59 birth-cohorts. Lung cancer incidence rates among women have increased since 1895–99 birth-cohorts, but those rates leveled off or decreased in 1950s birth-cohorts. Trends of ADC by birth-cohort were almost the same as those of all histological types. The SQCC among men peaked in 1915–19 birth-cohorts, and decreased in the subsequent birth-cohorts. The SMCC among men peaked in 1920s birth-cohorts, and decreased or leveled off in the subsequent birth-cohorts.
Conclusions: Lung cancer incidence rates by birth-cohorts were almost parallel to the smoking prevalence. However, those for ADC among young women in 1950s birth-cohorts were not parallel to the smoking prevalence, which requires careful monitoring to confirm such findings.

Key words: lung cancer – incidence – histological type – birth-cohort

BACKGROUND

Lung cancer is the leading cause of cancer deaths in Japan, with 45 927 men and 17 307 women dying from lung cancer in 2006. To date, increase in the incidence rates of lung adenocarcinoma (ADC) and decrease in the incidence rates of squamous cell carcinoma (SQCC) and small cell carcinoma (SMCC) have been reported in Japan (1,2). The same trend has been reported in Western countries also (3–5). Some previous studies reported that there was a trough of lung cancer incidence or mortality in Japanese male 1935–39 birth-cohorts because of the limited cigarette supply just after World War II (6–10). Soda et al. (7) reported the birth-cohort analysis by histological type using Nagasaki Cancer Registry in 2000. However, this study was based on the small number of registered lung cancer cases and excluded the cases without histological diagnoses.

In the present study, we updated the recent trends in lung cancer incidence by histological type and tried to clarify their characteristics by birth-cohort, using the data from Osaka Cancer Registry (OCR) with the large number of lung cancer incidence.

MATERIALS AND METHODS

OCR, which started in 1962, is the population-based cancer registry covering Osaka prefecture (population: 8.8 million, 2005 census). Using OCR data on lung cancer incidence

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(International Classification of Diseases 10th revision C33–C34) diagnosed between 1975 and 2003, we calculated the number of lung cancer incidence per year, age-adjusted rates and age-specific rates by birth-cohort according to histological type.

Histological types were categorized into three major types: ADC (ICD-O: 8140, 8141, 8200, 8211, 8250, 8251, 8260, 8310, 8323, 8440, 8470, 8480, 8481 and 8490), SQCC (ICD-O: 8050, 8052 and 8070–8076), SMCC (ICD-O: 8041–8045) and the others.

Incident years are divided into 5-year periods: 1975–78, 1979–83, 1989–93, 1994–98 and 1999–2003. Birth years were also divided into 5-year periods. The population data by age group in Osaka prefecture were obtained from the data of Population Census. For age-standardization, the Japanese model population in 1985 was used.

The data from OCR included the cases without specific histological diagnosis: a maximum of 60.4% in 1975–78 and a minimum of 31.4% in 1994–98. Based on the assumption that distributions of histological types in the same sex and age group were the same between those with and without a specific histological type, we compensated for the proportion of cases without a specific histological type. The detailed procedure was followed to the previous study (1); first, the sex-, age (5-year)- and incident year (or birth-cohort)-specific numbers of incidence were calculated for all histological types including the cases without histological diagnosis. Second, the sex-, age (10-year)- and incident year (or birth-cohort)-specific proportion of each histological type among the cases with histological diagnosis were calculated for three major histological types. Finally, the sex-, age (5-year)-, incident year (or birth-cohort)-specific number of incidence were multiplied by the corresponding sex-, age- and incident year (or birth-cohort)-specific proportion to approximate the number of incidence by histological type.

RESULTS

Table 1 shows the trends in the number of lung cancer incidence per year according to histological type. Lung cancer incidence per year for all histological types among men and women increased consistently; from 1086 in 1975–78 to 3487 in 1999–2003 among men and from 395 in 1975–78 to 1482 in 1999–2003 among women. As for histological type, the number of ADC incidence has increased remarkably among men and women. The shift in main histological type among men occurred in the 1990s.

Table 2 shows the trends in the age-adjusted rates according to the histological type. The age-adjusted rates for all histological types peaked in 1994–98 and recently leveled off among men, while those consistently increased among women. The rates for ADC consistently increased among men and women. In contrast, the rates for SQCC and SMCC peaked in 1989–93 among men, and decreased subsequently. Those rates for SQCC and SMCC peaked in 1984–88 and 1989–93, respectively, among women, and decreased subsequently.

Fig. 1 shows the trends in the age-specific lung cancer incidence rates with 95% confidence interval by birth-cohort for all histological types. Among men, there was a trough in rates for all age groups in 1935–39 birth-cohorts, which was consistent with the previous findings (7,10). In the subsequent birth-cohorts, the rates increased for all age groups, but the declining tendency appeared in 1955–59 birth-cohorts. Among women, the trough in rates in 1935–39 birth-cohorts was not confirmed. The rates for aged $\geq$50 years increased gradually, while it seemed that the rates for aged $<$50 years turned to decrease or level off after 1950–54 birth-cohorts: however, these trends were unstable because of the wide confidence intervals due to the small number of incidence.

Table 1. Trends in the number of lung cancer incidence per year according to histological type

Histological type	Incident year					
	1975–78	1979–83	1984–88	1989–93	1994–98	1999–2003
Men						
Adenocarcinoma (%)	372 (34.2)	510 (35.7)	696 (35.5)	853 (35.8)	1191 (40.2)	1497 (42.9)
Squamous cell carcinoma (%)	474 (43.6)	582 (40.8)	760 (38.8)	921 (38.6)	1086 (36.6)	1208 (34.7)
Small cell carcinoma (%)	142 (13.0)	203 (14.2)	315 (16.1)	410 (17.2)	483 (16.3)	543 (15.6)
Others (%)	99 (9.1)	132 (9.3)	189 (9.7)	200 (8.4)	204 (6.9)	239 (6.8)
All histological types (%)	1086 (100)	1428 (100)	1961 (100)	2383 (100)	2964 (100)	3487 (100)
Women						
Adenocarcinoma (%)	242 (61.2)	328 (60.2)	453 (58.7)	579 (60.3)	792 (64.8)	996 (67.2)
Squamous cell carcinoma (%)	86 (21.9)	106 (19.5)	163 (21.2)	184 (19.2)	218 (17.9)	241 (16.3)
Small cell carcinoma (%)	32 (8.0)	73 (13.3)	97 (12.5)	132 (13.7)	152 (12.5)	178 (12.0)
Others (%)	35 (8.9)	38 (6.9)	59 (7.6)	65 (6.8)	60 (4.9)	66 (4.4)
All histological types (%)	395 (100)	545 (100)	772 (100)	961 (100)	1223 (100)	1482 (100)

Table 2. Trends in age-adjusted lung cancer incidence rates per 100 000 person-years according to histological type

Histological type	Incident year					
	1975–78	1979–83	1984–88	1989–93	1994–98	1999–2003
Men						
Adenocarcinoma	15.5	18.9	21.7	22.3	26.0	27.2
Squamous cell carcinoma	20.4	22.2	25.0	25.6	24.8	22.3
Small cell carcinoma	6.0	7.6	10.1	11.1	10.8	10.0
All histological types	46.2	53.7	62.9	64.7	66.5	64.3
Women						
Adenocarcinoma	7.9	9.2	10.5	11.3	13.1	13.8
Squamous cell carcinoma	2.8	3.0	3.8	3.5	3.4	3.1
Small cell carcinoma	1.0	2.0	2.3	2.5	2.4	2.3
All histological types	12.9	15.2	17.9	18.6	19.9	20.2

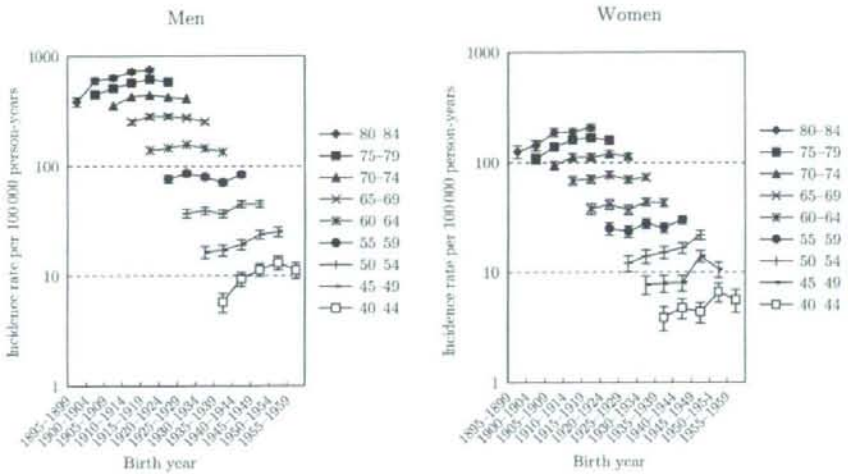

Figure 1. Trends in age-group-specific lung cancer incidence rates with 95% confidence interval by birth-cohort for all histological types.

Figs 2–4 show the trends in the age-specific incidence rates with 95% confidence interval by birth-cohort for ADC, SQCC and SMCC, respectively. The rates for ADC among men increased gradually for all age groups, but the declining tendency appeared in 1955–59 birth-cohorts. Furthermore, it seemed that there was a slight trough in rates in 1935–39 birth-cohorts, as well as findings in all histological types. The trends in ADC among women were almost similar with those in all histological types. The rates for SQCC among men peaked in 1910–14 birth-cohorts and decreased in the subsequent birth-cohorts. The trough in rates during 1935–39 birth-cohorts was not clear for SQCC among men. Trends in the rates for SQCC among women aged ≥65 years were similar with those among men. The trends in aged <65 years were, however, unclear because of the wide confidence interval. The rates for SMCC among men peaked around 1920s birth-cohorts and turned to slightly decrease or level off in the subsequent birth-cohorts. The rates for SMCC among women were unclear because of the wide confidence interval.

DISCUSSION

In the present study, we reported the population-based trends in lung cancer incidence including birth-cohort analyses according to histological type using OCR. The number of lung cancer incidence per year increased continuously because of the population aging. The main histological type of lung cancer switched from SQCC to ADC among men in

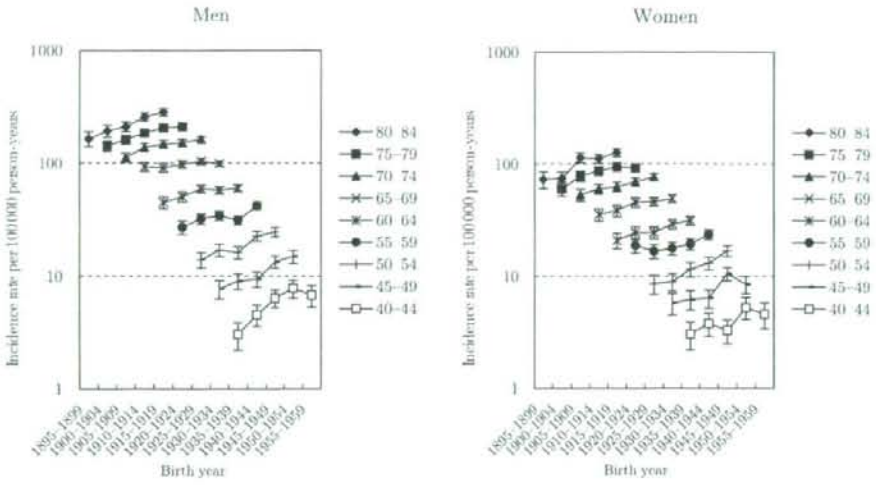

Figure 2. Trends in age-group-specific incidence rates with 95% confidence interval by birth-cohort for adenocarcinoma.

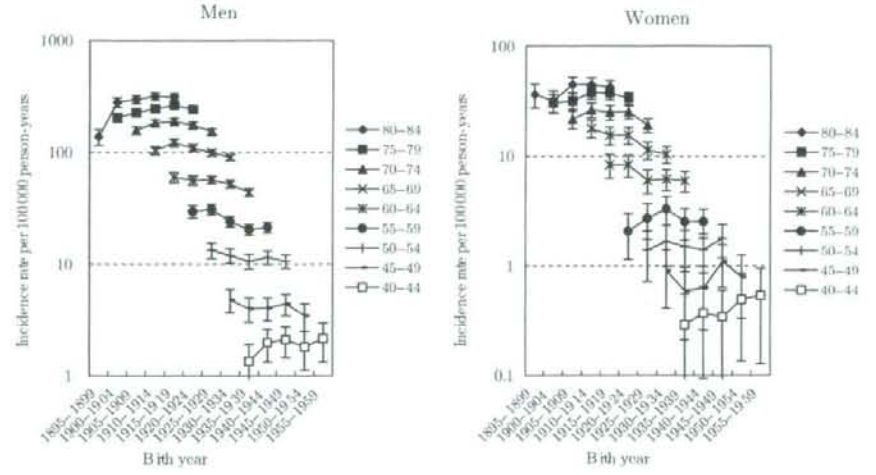

Figure 3. Trends in age-group-specific incidence rates with 95% confidence interval by birth-cohort for squamous cell carcinoma.

1990s. The declining trends for SQCC and SMCC continued in the updated present study.

Smoking prevalence by birth-cohort among Japanese men was reported to have two peaks: around the 1925 birth-cohort and around the 1950 birth-cohort (11). In addition, there was a trough of smoking prevalence in 1930–40 birth-cohorts because of the limited cigarette supply just after World War II (11). In general, the trends in lung cancer incidence or mortality by birth-cohort were parallel to the trends in the smoking prevalence. Our results were consistent with the findings from previous studies, showing that lung cancer mortality and incidence rates among men in 1935–39 birth-cohorts were lower than the subsequent birth-cohorts (6–10). Since the smoking prevalence among Japanese men was declining after 1950s birth-cohorts, the appearance of declining trends of lung cancer incidence among men in 1955–59 birth-cohorts was an expected result.

Classically, smoking behavior was considered to be more strongly associated with SQCC than with ADC. However, SQCC incidence rates by birth-cohort among men were not

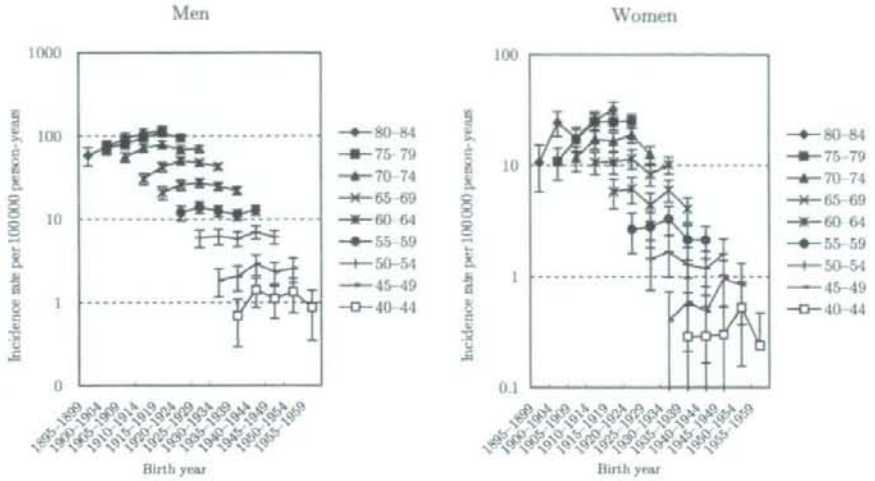

Figure 4. Trends in age-group-specific incidence rates with 95% confidence interval by birth-cohort for small cell carcinoma.

parallel to the smoking prevalence by birth-cohort. SQCC incidence rates among men after 1940–44 birth-cohorts leveled off, whereas the smoking prevalence among men after 1940–44 birth-cohorts increased. One reason would be the switching from non-filtered cigarettes to filtered cigarettes. Filtered cigarettes were considered to be associated with peripheral ADC because of the deep inhalation (3,12,13). According to the information from Japan Tobacco Inc., the switching from non-filtered cigarettes to filtered cigarettes occurred in the 1960s in Japan (14). The shift from SQCC to ADC among men in 1990s observed in the present study might have been the result of this shift in cigarette types.

The smoking prevalence by birth-cohort among women is continuously increasing after 1930s birth-cohorts (11). However, lung cancer incidence among women in 1950s birth-cohorts, particularly for ADC, seemed to be leveling off or decreasing. Marugame et al. (15) also reported the trends in lung cancer mortality by birth-cohort using the National Vital Statistics. In that study, lung cancer mortality trends appeared to be decreasing for female birth-cohorts born after 1960. Although our results were unstable because of the wide confidence intervals, those were not contradictory to this previous study. There is no clear explanation for these findings among younger Japanese women. There would be some factors other than active smoking for lung cancer incidence among them.

The present study has some limitations. First, there may be some missing cases in the OCR. The proportion of death certificate only for lung cancer in OCR was 19.3% in 1998–2002 (16). Therefore, lung cancer incidence may be under-estimated as a whole. Secondly, the trends by histological type among young women were unstable because of the small number of incidence; the number of lung cancer incidence among women aged <50 years per year was ~80 cases in 2003. Finally, the data from OCR included many lung cancer cases without specific histological diagnoses. We had to use assumption in order to calculate the number of incidence according to histological type. The proportions of lung cancer cases without histological diagnoses for aged <80 years decreased between 1975–78 and 1999–2003; from 49.7 to 16.4% among aged 40–49 years, from 47.4 to 17.6% among aged 50–59 years, from 55.9 to 22.7% among aged 60–69 years and from 70.8 to 31.6% among aged 70–79 years, respectively. However, those for aged ≥80 years were still high: from 78.9 to 64.1%. Therefore, we require carefulness to interpret the findings, particularly for elderly.

In conclusion, we reported recent trends in lung cancer incidence according to histological type. The increase in ADC incidence and the decrease in SQCC and SMCC incidence were confirmed. The trends in lung cancer incidence among young women in 1950s birth-cohorts, particularly for ADC, were not parallel to the smoking prevalence. We need careful monitoring of the trends in lung cancer incidence, particularly for ADC among young women.

Acknowledgements

We would like to thank Dr Akira Oshima, Cancer Patients Information Service, Osaka Medical Center for Cancer and Cardiovascular Disease, and Professor Hiroyasu Iso, Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine for their valuable comments. We also thank the staff at the Osaka Cancer Registry for data collection.

Funding

Funding to pay the Open Access publication charges for this article was provided by 'The Third-Term Comprehensive 10-Year Strategy for Cancer Control', Ministry of Health, Labour and Welfare, Japan.

Conflict of interest statement

None declared.

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British Journal of Cancer (2008) 98, 1602 – 1607

www.bjcancer.com

Clinical Studies

Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography

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Lung cancer screening programmes using chest X-ray and sputum cytology are routinely performed in Japan; however, the efficacy is insufficient. Screening using low-dose computed tomography (CT) is a more effective approach and has the potential to detect the disease more accurately. A total of 7183 low-dose CT screening tests for 4689 participants and 36 085 chest X-ray screening tests for 13 381 participants were conducted between August 1998 and May 2002. Sensitivity and specificity of lung cancer screening were calculated by both the detection method and the incidence method by linkage of the screening database and the Cancer Registry database. The preclinical detectable phase was assumed to be 1 year. Sensitivity and specificity by the detection method were 88.9 and 92.6% for low-dose CT and 78.3 and 97.0% for chest X-ray, respectively. Sensitivity of low-dose CT by the incidence method was 79.5%, whereas that of chest X-ray was 86.5%. Lung cancer screening using low-dose CT resulted in higher sensitivity and lower specificity than traditional screening according to the detection method. However, sensitivity by the incidence method was not as high as this. These findings demonstrate the potential for overdiagnosis in CT screening-detected cases.
British Journal of Cancer (2008) **98,** 1602 – 1607. doi:10.1038/sj.bjc.6604351 www.bjcancer.com
Published online 6 May 2008

Keywords: sensitivity; specificity; lung cancer; screening

Lung cancer is the leading cause of cancer death in Japan, with 45 927 men and 17 307 women dying from lung cancer in 2006. Since 1987, lung cancer screening programme using chest X-ray and sputum cytology for all residents aged 40 years of age and older regardless of smoking status has been conducted by the Ministry of Health and Welfare. Unfortunately, the efficacy of lung cancer screening using chest X-ray and sputum cytology is insufficient (Fontana *et al*, 1986; Marcus *et al*, 2000a, 2006b; Sagawa *et al*, 2003a). Therefore, a more effective approach is required to decrease lung cancer deaths.

Annual lung cancer screening using low-dose computed tomography (CT) has been performed as an opportunistic screening method since the early 1990s in Japan. Several study groups introduced low-dose CT for population-based screening in clinical trials. These previous studies reported a high detection rate, an ability to detect small tumours and a high survival rate in detected cases (Henschke *et al*, 2001, 2006; Sone *et al*, 2001; Nawa *et al*, 2002; Sobue *et al*, 2002a; Swensen *et al*, 2002; Diederich *et al*, 2004; Jett, 2005; Libby *et al*, 2006). Some studies referred to interval cancer cases of lung cancer screening using low-dose CT, and one study referred to the sensitivity of screening (Sone *et al*, 2001; Diederich *et al*, 2004). However, screening databases are yet to be linked to a cancer registry, which is essential for accurate evaluation of screening, including the confirmation of all interval cancer cases. To date, no study has been conducted on sensitivity and specificity of annual lung cancer screening using low-dose CT and cancer registry data. Therefore, the present study was conducted to evaluate sensitivity and specificity of annual lung cancer screening using low-dose CT and data from screening and local cancer registry databases.

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Received 24 September 2007; revised 18 February 2008; accepted 26 March 2008; published online 6 May 2008

MATERIALS AND METHODS

Study setting

Since 1998, annual population-based lung cancer screening using low-dose CT has been conducted at five municipalities in Osaka prefecture: A (city), B (city), C (town), D (town) and E (town). All residents aged 40 years of age and older were recruited by mail using a letter from the public health division of each municipality regardless of smoking status. Subjects recruited to the lung cancer screening programme underwent either miniature chest X-ray or low-dose chest CT.

As a principle, heavy smokers were recommended to undergo low-dose CT screening. In addition, the persons who want to undergo low-dose CT screening also underwent low-dose CT screening. Others underwent chest X-ray screening.

A high-risk group for lung cancer, smokers with over a 20 pack index or who had haemosputum, was examined by 3-day pooled sputum cytology.

Low-dose CT or chest X-ray images were reviewed and classified by two trained physicians to determine the need for further clinical examination. Sputum cytology was also performed by a certified cytopathologist to determine the need for further clinical examination.

Those diagnosed with the need for further clinical examination were regarded as screen-positive. These individuals were asked to undergo further diagnostic evaluation at Osaka Medical Center for Cancer and Cardiovascular Disease. All individuals with positive chest X-ray screening were asked to undergo chest CT as a further examination.

Data collection

All subjects were individuals who had undergone either low-dose CT or chest X-ray screening tests between August 1998 and May 2002. The following participants were excluded from the analyses: (1) participants who had a past history of lung cancer, (2) participants who were suspected of having lung cancer by a previous screening or other medical examination and had received medical treatment and (3) participants who were suspected of having lung cancer at the previous screening or by other medical examination, but had refused further examinations.

Participants were divided into two groups: (a) low-dose CT group and (b) chest X-ray group. The low-dose CT group consisted of persons who had undergone low-dose CT at least one time during the study period, whereas the chest X-ray group consisted of persons who had undergone only chest X-ray. The low-dose CT group included those who had undergone both CT screening and chest X-ray screening within the study period. For these cases, screenings using chest X-ray were ignored to evaluate low-dose CT screening.

All data were entered into the screening database that was linked to the Osaka Cancer Registry (OCR) database with data reflecting incidence cases through December 2003. The indices used to collate the two databases were name, sex, address and date of birth. Information about lung cancer cases was extracted from hospital medical records or the OCR file.

We assumed that the preclinical detectable phase was 1 year for interval cancer cases. For death certificate-only cases, the date of 3 months before death was regarded as the date of diagnosis. Using these parameters, all lung cancer cases diagnosed within 1 year after a negative screen were regarded as interval lung cancers. Screen-detected cases were considered as true-positive cases regardless of the time between the date of screening and the date of diagnosis.

Statistical analyses

The sensitivity of screening was calculated by both the detection method and the incidence method. Although the detection method is simple and widely used, sensitivity estimated by detection method is affected by length and overdiagnosis biases (Day, 1985). The incidence method is not affected by length or overdiagnosis bias and is often used for breast cancer screening or colorectal cancer screening (Fletcher *et al*, 1993; Zappa *et al*, 2001).

Detection method

Sensitivity and specificity were calculated by the detection method using the following formulae.

		True disease state	
		+	−
Screening test	+	a	b
	−	c	d

$$\text{Sensitivity} = a/(a+c)$$

$$\text{Specificity} = d/(b+d)$$

Sensitivity and specificity calculated by the detection method were stratified by smoking status, histological type and screening rank. The screening rank was classified as the initial and repeated screenings, regardless of the number of years since the initial screening.

Incidence method

In addition, we calculated sensitivity by the incidence method using the following approximate formula (Day, 1985; Zappa *et al*, 2001):

$$\text{Sensitivity} = 1 - [I(t)/I]$$

Where $I(t)$ = the observed number of interval cancer cases during time t and I = the expected number of cases in the absence of screening.

We calculated the number of expected lung cancer cases in the absence of screening based on the following data. Age-specific lung cancer incidence rates provided from the OCR in 2001 were 16.3, 61.6, 180.9, 477.3 and 770.2 (per 100 000 person-years) for men, and 6.3, 25.9, 53.4, 116.7 and 241.3 for women, for age groups 40–49, 50–59, 60–69, 70–79 and ⩾80, respectively. Lung cancer incidence rates in the OCR were weighted by smoking status. According to the previous large-scale cohort study in Japan, the lung cancer incidence rates among ex-smokers and current smokers were assumed to be 2.2 times and 4.5 times of that of nonsmokers, respectively, among men, and 3.7 times and 4.2 times, respectively, among women (Sobue *et al*, 2002b). According to an official report from Osaka prefecture in 2003, the proportions of current smokers, ex-smokers and nonsmokers were 40, 30 and 30% among men, and 11, 7 and 82% among women, respectively (Department of public health, Osaka Prefecuture, 2006).

We assumed that smoking status proportions were the same across all age groups, so the expected incidence rate according to sex and smoking status was modified using the following formulae:

$$\text{Expected incidence rate among male nonsmokers} = \text{Incidence rate in OCR}/(4.5\times0.40 + 2.2\times0.30 + 1\times0.30)$$

$$\text{Expected incidence rate among female nonsmokers} = \text{Incidence rate in OCR}/(4.2\times0.11 + 3.7\times0.07 + 1\times0.82)$$

The expected incidence rates for ex-smokers and current smokers were assumed to be 2.2 times and 4.5 times of that of nonsmokers, respectively, among men, and 3.7 times and 4.2 times, respectively, among women.

The differences in sensitivity and specificity among the stratified variables were tested by χ^2 test. All statistical analyses were performed using SAS software, version 8.01 (SAS Institute Inc., Cary, NC, USA).

Ethical approval

The protocol for the present study was approved by the Ethics Committee of Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan. Informed consent for participation in the clinical trial, including CT screening, was obtained from all individuals.

RESULTS

From August 1998 to May 2002, a total of 7190 low-dose CT screening tests and a total of 36 085 chest X-ray screening tests were performed. Seven screening participants were excluded from analysis because they did not meet the eligibility criteria. Participants were ineligible for the following reasons: two participants were under follow-up care, one was suspected of having lung cancer but refused further examination and four had a history of lung cancer. A total of 7183 low-dose CT screening tests for 4689 participants (2765 men and 1924 women) and 36 085 chest

X-ray screening tests for 13 381 participants (4180 men and 9201 women) enrolled in the study.

Table 1 shows the number of screening tests by sex, age group, smoking status and rank of screening tests. Most of the participants who underwent low-dose CT screening were male current smokers or ex-smokers. Sputum cytology was additionally performed for 3539 screening tests for the low-dose CT group and 5417 screening tests for the chest X-ray group.

Table 1 Number of screening tests performed by age group, smoking status and rank: (a) low-dose CT group and (b) chest X-ray group: Osaka, 1998–2002

	Male	Female	Total
(a) Low-dose CT group			
Age (years)			
40–49	700	490	1190
50–59	1147	1132	2279
60–69	1885	886	2771
70–79	690	194	884
80–	43	16	59
Smoking status			
Nonsmoker	362	2048	2410
Ex-smoker	1012	113	1125
Current smoker	3091	557	3648
Rank			
Initial	2765	1924	4689
Repeated	1700	794	2494
Total	4465	2718	7183
(b) Chest X-ray group			
Age (years)			
40–49	1258	4862	6120
50–59	1679	8632	10311
60–69	4163	7910	12073
70–79	2695	3670	6365
80–	573	643	1216
Smoking status			
Nonsmoker	2807	23 790	26 597
Ex-smoker	4328	740	5068
Current smoker	3233	1187	4420
Rank			
Initial	4180	9201	13 381
Repeated	6188	16 516	22 704
Total	10 368	25 717	36 085

CT = computed tomography.

Forty cases in the low-dose CT group and 29 cases in the chest X-ray group were detected by the screening. Five interval cases in the low-dose CT group and eight interval cases in the chest X-ray group were confirmed by linkage to OCR (Table 2). All of the interval cancer cases for both the low-dose CT group and the chest X-ray group were smokers. As for the low-dose CT group, all of them were nonadenocarcinoma. Two cases, one in the low-dose CT group and one in the chest X-ray group, were detected by sputum cytology on negative radiological screen.

Table 3 shows sensitivity and specificity by the detection method according to histological type, smoking status and rank of screening. As a result, sensitivity and specificity (95% confidence interval) of screening were 88.9% (79.7–98.1%) and 92.6% (92.0–93.2%) for the low-dose CT group, and 78.3% (65.1–91.6%) and 97.0% (96.9–97.2%) for the chest X-ray group, respectively. Specificity of chest X-ray screening was significantly higher than that of low-dose CT screening ($P<0.001$). The difference in sensitivity by the detection method was not significant.

As for histological type, sensitivity for adenocarcinoma was significantly higher than that for nonadenocarcinoma (low-dose CT: 100 *vs* 61.5%; $P<0.001$, and chest X-ray: 95.8 and 50.0%; $P<0.001$); however, the histological type of three interval cases in the chest X-ray group was unknown. As for screening rank, specificity for the repeated screenings was significantly higher than that for the initial screenings (low-dose CT: 95.7 *vs* 91.0%; $P<0.001$, and chest X-ray: 97.7 *vs* 95.9%; $P<0.001$). As for sex, specificity for men was significantly lower than that for women (low-dose CT: 92.1 *vs* 93.5%; $P<0.05$, and chest X-ray: 95.7 *vs* 97.6%; $P<0.001$). Sensitivity of chest X-ray screening for women was significantly higher than that for men (100 *vs* 68.2%; $P<0.05$). As for smoking status, sensitivity of both low-dose CT and chest X-ray for nonsmokers was 100%.

Table 4 shows sensitivity estimated by the incidence method. Until the end of December 2003, a total of 14 434 person-years (total for men: 9173 person-years; total for women: 5512 person-years) for the low-dose CT group and a total of 59 725 person-years (total for men: 17 962 person-years; total for women: 41 763 person-years) for the chest X-ray group had been followed up for. The mean follow-up terms were 3.1 person-years and 4.5 person-years, respectively. The number of expected lung cancer cases was calculated to be 24.4 persons for the low-dose CT group and 59.3 persons for the chest X-ray group. As a result, sensitivity

Table 2 Interval cancer cases of screening: (a) low-dose CT group and (b) chest X-ray group

	Sex	Age (years)	Pack index	Smoking status	Histological type	Location	Rank	Clinical stage
(a) Low-dose CT group								
1	F	71	48	Current	Squamous	Unknown	Initial	III
2	M	60	43	Current	Large cell	Peripheral	Initial	III
3	M	72	48	Current	Small cell	Unknown	Repeated	IV
4	M	72	45	Current	Squamous	Unknown	Repeated	I
5[a]	F	59	29	Ex	Squamous	Central	Initial	I
(b) Chest X-ray group								
1	M	68	48	Current	Squamous	Unknown	Repeated	III
2	M	83	61	Current	Small cell	Unknown	Repeated	Unknown
3	M	72	21	Ex	Adeno	Unknown	Repeated	I
4	M	69	25	Current	Undifferentiated	Unknown	Initial	III
5	M	60	50	Current	Unknown	Unknown	Initial	Unknown
6[a]	M	63	68	Ex	Squamous	Central	Repeated	I
7	M	59	80	Current	Unknown	Unknown	Repeated	Unknown
8	M	85	15	Ex	Unknown	Unknown	Repeated	Unknown

CT = computed tomography. [a]Detected by sputum cytology.

Table 3 Sensitivity and specificity by the detection method according to histological type, smoking status and rank of screening: (a) low-dose CT group and (b) chest X-ray group

	No. of screenings	Screen-detected cases	Interval cases	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
(a) Low-dose CT group					
Sex					
Men	4465	29	3	90.6 (80.5–100)	92.1 (91.3–92.9)
Women	2718	11	2	84.6 (65.0–100)	93.5 (92.6–94.4)
Smoking status					
Nonsmoker	2410	13	0	100	93.5 (92.5–94.4)
Ex-smoker	1125	6	1	85.7 (59.8–100)	91.5 (89.9–93.1)
Current smoker	3648	21	4	84.0 (69.6–98.4)	92.4 (91.6–93.3)
Histological type					
Adenocarcinoma	—	32	0	100	—
Nonadenocarcinoma	—	8	5	61.5 (35.1–88.0)	—
Rank					
Initial	4688	32	3	91.4 (82.2–100)	91.0 (90.2–91.8)
Repeated	2494	8	2	80.0 (55.2–100)	95.7 (94.9–96.5)
Total	7183	40	5	88.9 (79.7–98.1)	92.6 (92.0–93.2)
(b) Chest X-ray group					
Sex					
Men	10368	15	8	65.2 (45.8–84.7)	95.7 (95.3–96.1)
Women	25717	14	0	100	97.6 (97.3–97.8)
Smoking status					
Nonsmoker	26597	13	0	100	97.4 (97.3–97.7)
Ex-smoker	5068	4	3	57.1 (20.5–93.8)	95.9 (95.3–96.4)
Current smoker	4420	12	5	70.6 (48.9–92.2)	95.7 (95.1–96.3)
Histological type					
Adenocarcinoma	—	23	1	95.8 (87.8–100)	—
Nonadenocarcinoma	—	6	4	50.0 (21.7–78.3)	—
Unknown	—	0	3	—	—
Rank					
Initial	13381	13	2	86.7 (69.5–100)	95.9 (95.5–96.2)
Repeated	22704	16	6	76.2 (58.0–94.4)	97.7 (97.5–97.9)
Total	36085	29	8	78.3 (65.1–91.6)	97.0 (96.9–97.2)

CI = confidence interval; CT = computed tomography.

(95% confidence interval) estimated by the incidence method was 79.5% (63.5–95.5%) and 86.5% (77.8–95.2%), respectively. The difference in sensitivity by the incidence method was not statistically significant.

Discussion

The present study is the first report on sensitivity and specificity of annual lung cancer screening using low-dose CT and data from a local Cancer Registry. Sensitivity and specificity of low-dose CT screening according to the detection method were 88.9 and 92.6%. The sensitivity estimated by the incidence method resulted in a value of 79.5%. On the other hand, sensitivity and specificity of chest X-ray in the same time frame by the detection method were 78.3 and 97.0%, respectively. Furthermore, sensitivity of chest X-ray screening by the incidence method was 86.5%.

In previous studies conducted in the1980s, sensitivity and specificity of annual lung cancer screening using chest X-ray and sputum cytology were also evaluated by the detection method. In those studies, sensitivity and specificity for usual screening were 63.6–88.0% and 94.7–99.6%, respectively (Sobue *et al*, 1991c; Soda *et al*, 1993; Sagawa *et al*, 1994b; Tsukada *et al*, 2002). The use of low-dose CT screening resulted in a higher sensitivity and lower specificity than usual screening. The reported high sensitivity in participants undergoing low-dose CT screening is the result of improvement in the detection of small tumours. The lower specificity value indicates the difficulty of diagnosing nodules detected by screening.

Several points must be considered when the present study results are compared with previous results. Since 1980s, lung cancer incidence by histological type has undergone a change over time. With a large decline in the smoking rate among men, the proportion of squamous cell carcinoma or small cell carcinoma has decreased, whereas the proportion of adenocarcinoma has increased (Yoshimi *et al*, 2003). The current environment may be more advantageous for lung cancer screening because adenocarcinoma occurring in the peripheral lung has a longer doubling time than squamous cell carcinoma (Arai *et al*, 1994). In addition, as most low-dose CT screening-detected lung cancer lesions are too small to detect by chest X-ray and have a longer preclinical phase, simple comparison of low-dose CT screening with chest X-ray screening is difficult.

We used the detection method and stratified analyses by screening rank and histological type. As for screening rank, specificity of both low-dose CT and chest X-ray for the repeated

Table 4 Sensitivity of screening by the incidence method: (a) low-dose CT group and (b) chest X-ray group

	Person-years	Expected incidence	Screen-detected cases	Interval cases	Sensitivity (%) (95% CI)
(a) Low-dose CT group					
Sex					
Men	9173	21.8	29	3	86.2 (71.8–100)
Women	5512	2.5	11	2	20.0 (0–69.6)
Smoking status					
Nonsmokers	4878	1.7	13	0	100
Ex-smokers	2388	4.2	6	1	76.2 (35.5–100)
Current smokers	7419	18.6	21	4	78.5 (59.8–97.2)
Total	14 685	24.4	40	5	79.5 (63.5–95.5)
(b) Chest X-ray group					
Sex					
Men	17 962	42.1	15	8	81.0 (69.1–92.8)
Women	41 763	17.2	14	0	100
Smoking status					
Nonsmokers	42 976	17.4	13	0	100
Ex-smokers	8452	19.2	4	3	84.3 (68.1–100)
Current smokers	8297	22.8	12	5	78.1 (61.1–95.1)
Total	59 725	59.3	29	8	86.5 (77.8–95.2)

CI = confidence interval; CT = computed tomography.

screenings was significantly higher than that of the initial screenings. The high specificity associated with repeated screenings is due to the fact that the review of previous images facilitates ruling out benign nodules. Sensitivity of low-dose CT and chest X-ray for the repeated screenings was lower than that of the initial screenings; however, the difference was not statistically significant. Sensitivity for the initial screenings was affected by length bias and overestimation because lung cancers with long preclinical detectable phases were more prevalent. Regarding histological type, adenocarcinoma sensitivity estimated by the detection method was significantly higher than that for nonadenocarcinoma for both low-dose CT and chest X-ray. In the previous study, sensitivity of chest X-ray was 86.4% for adenocarcinoma and 44.2% for nonadenocarcinoma (Sobue *et al*, 1991c). Both low-dose CT screening and chest X-ray screening have a high sensitivity for the detection of adenocarcinoma. In contrast, sensitivity estimated by the detection method for nonadenocarcinoma remained low. As for smoking status, both low-dose CT and chest X-ray had superior performance for nonsmokers.

Although the detection method is simple and widely used, it is affected by overdiagnosis or length bias because cancers with long preclinical detectable phases are included in the denominator. In the 1980s, lung cancer was considered to be an aggressive and rapid-growing cancer; however, it has been reported that low-dose CT screening-detected lung cancer has a long doubling time and good prognosis (Sone *et al*, 2001; Nawa *et al*, 2002; Sobue *et al*, 2002a; Swensen *et al*, 2002; Henschke *et al*, 2006; Libby *et al*, 2006). The incidence method, which is not affected by overdiagnosis bias and length bias, is preferred for the correct evaluation of low-dose CT screening. Screening for breast cancers or colorectal cancers, with long doubling times, has been evaluated using the incidence method whereas lung cancer screening has been evaluated using the detection method only (Fletcher *et al*, 1993; Zappa *et al*, 2001).

In this study, we calculated expected lung cancer incidence to be 24.4 persons for the low-dose CT group and 59.3 persons for the chest X-ray group according to age-specific lung cancer incidence rate in the OCR, smoking status in Osaka prefecture and the relative risk of lung cancer incidence associated with smoking according to a large-scale cohort study in Japan. Unexpectedly, the sensitivity of low-dose CT screening estimated by the incidence method (79.5%) was lower than that of chest X-ray screening (86.5%); however, the difference was not statistically significant. There are several possible explanations for this contradiction. First, the mean follow-up term of the low-dose CT group (3.1 person-years) was shorter than that of the chest X-ray group (4.5 person-years). Furthermore, the mean pack index of current smokers among the low-dose CT group (42 for men and 23 for women) was somewhat higher than that of the chest X-ray group (38 for men and 16 for women). Therefore, expected lung cancer incidence for the low-dose CT group might be underestimated. Second, four screen-detected cases among the chest X-ray group were checked with lesions other than cancer. These lung cancer cases were incidentally detected by the subsequent chest CT as a further examination on positive tests; all of them were adenocarcinoma. When these cases were regarded as interval cases, sensitivity (95% confidence interval) of chest X-ray screening by the incidence method resulted in 79.7% (69.5–90.0%). Considering these points, sensitivity of low-dose CT screening according to the incidence method with 3–5 person-years of follow-up period would be almost equal to that of chest X-ray screening. These findings suggest that the efficacy of low-dose CT screening might be limited to rapid-growing lung cancer with a short preclinical detectable phase ($<=1$ year). Since low-dose CT screening-detected lung cancer is slow growing, further research with a longer follow-up period is required.

A total of 40 lung cancer cases were detected by low-dose CT screening, suggesting the possibility of overdiagnosis by low-dose CT screening. In particular, low-dose CT screening detected 13 lung cancer cases in nonsmokers whereas expected incidence in nonsmokers was only 1.7 persons. All of these cases were peripheral adenocarcinoma. In contrast, expected lung cancer incidence for the chest X-ray group was higher than the number of screen-detected cases. This fact might suggest that there is little possibility of overdiagnosis by chest X-ray screening.

Of the five interval cancer cases in the low-dose CT group, four cases were squamous cell carcinoma or small cell carcinoma, which are strongly associated with smoking (Sobue *et al*, 1991d; Shimizu *et al*, 1994; Stellman *et al*, 2001). Three cases had remarkable emphysaema. These interval cancer cases associated with smoking indicate the limitation of low-dose CT screening for

nonadenocarcinoma among smokers. In other words, the high sensitivity of low-dose CT screening identified using the detection method is due to the detection of adenocarcinoma with a long preclinical detectable phase.

This study has some limitations. First, many nodules were detected by low-dose CT screening, but subsequent pathological examinations were not performed. In this study, small pure ground-glass opacity nodules (< 10 mm) were carefully observed, and no invasive treatment was performed. In these cases, lung cancer was highly suspected, but a lung cancer diagnosis was not made and the cases were not registered in the OCR. Given the presence of such cases, the sensitivity according to the detection method might be underestimated. Second, to compare usual screening with low-dose CT screening, the preclinical detectable phase was assumed to be 1 year. We need to assess a longer preclinical detectable phase, because most of the low-dose CT screening-detected lung cancer cases were slow growing. Third, the sample size was relatively small for proper evaluation, particularly for stratified analyses.

In summary, the present findings suggest that lung cancer screening using low-dose CT has a higher sensitivity and a lower specificity than usual lung cancer screening by chest X-ray, when using the detection method analysis. However, sensitivity estimated by the incidence method was not as high as that estimated by detection method. As all interval cancer cases were associated with smoking, low-dose CT screening showed limited efficacy for nonadenocarcinoma in smokers. Furthermore, these findings demonstrate the potential for overdiagnosis in low-dose CT screening-detected cases.

ACKNOWLEDGEMENTS

This study was supported by a grant-in-aid from the Ministry of Health, Labor and Welfare of Japan for a Third term Comprehensive Control Research for Cancer (Grant no. 19141901). We would like to thank the staff of the Division of Epidemiology and the Osaka Cancer Registry, Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Disease.

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Treatment strategy for patients with small peripheral lung lesion(s): intermediate-term results of prospective study☆

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Received 1 June 2008; received in revised form 19 July 2008; accepted 21 July 2008; Available online 28 August 2008

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European Journal of Cardio-thoracic Surgery 34 (2008) 1068–1074

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Received 1 June 2008; received in revised form 19 July 2008; accepted 21 July 2008; Available online 28 August 2008

Abstract

Background: This prospective study was undertaken to establish a novel management algorithm using new indicators to decide the type of lung resection for small peripheral lung lesions. **Methods:** Inclusion criteria were: (1) ≤20 mm peripheral lung lesion(s) and (2) absence of significant lymph node swelling on preoperative CT. Along with the conventional criteria, the percentage of ground-glass opacity (GGO) (≥50% as GGO type and <50% as solid type) on high-resolution CT scan was employed. In accordance with such indicators, a wide wedge resection (WWR), segmentectomy or lobectomy was planned for individual patients. The primary endpoint was to estimate the effectiveness of limited resection in patients with lung cancer by analyzing their locally disease-free survival rates at 5 and 10 years. **Results:** Of 179 patients enrolled between 1997 and 2002, 90 were male and 89 female. They were divided into 77 GGO types and 102 solid types. During surgery, conversions from limited resections to standard operations were performed on six patients to avoid the risk of local-regional recurrence. Finally, WWR was performed on 73 patients, segmentectomy on 26 and lobectomy on 80, respectively. There were 138 lung cancers and 41 non-cancers. Of 138 cancer patients, 114 patients are alive and 24 died. There were no local-regional recurrences among the 58 cancer patients who underwent limited resection. **Conclusions:** This intermediate-term outcome suggests that the selection of the type for lung resection using this management algorithm for small peripheral lung lesions was effective for preventing both local-regional recurrences and the excessive resection of normal lung tissue.

Keywords: Lung cancer; Ground-glass opacity; Peripheral lung lesion; Bronchioloalveolar carcinoma; Limited resection

1. Introduction

In the last decade, the development of mass screening using low-dose spiral (helical) computed tomographic (CT) scan (low-dose CT) or increased opportunities to take chest CT scans during disease follow-up have enabled the discovery of very small or very fine hazy lesions in the lung field. Most such lesions are invisible on plain chest X-ray film. After detecting lesion sites using low-dose or conventional CT, further examinations by high-resolution (thin section) CT (HRCT) are usually conducted in order to establish radiological diagnoses. As the next step, it depends on the result of informed consent to each patient whether a CT-guided-transbronchial [1] or percutaneous biopsy [2] is employed for diagnosis, a thoracotomy with or without video-assisted thoracic surgery (VATS) is employed for diagnosis and treatment, or diligent follow-up is continued.

Solitary ground-glass opacity (GGO) lesions that cannot be detected by plain chest X-ray film or early generation CT scan have been highlighted as a new entity in the last decade. If the lesion does not decrease in size or does not disappear during further follow-up for 3–6 months, it is strongly suspected to be lung cancer. Non-invasive bronchioloalveolar carcinoma (BAC) is represented as pure GGO lesions on HRCT [3]. However, it is difficult to establish a definitive histo(cyto)diagnosis for small lesions measuring 10 mm or less in diameter.

Previous reports on intentional limited resections never enrolled such small peripheral lung lesions as study candidates [4,5]. However, in the future, a dramatic increase of such lesions is likely in accordance with rapid progress in the development of diagnostic technologies.

Therefore, the establishment of a systematic management algorithm for small peripheral lung lesions, from detection of the lesions to treatment, is important. Thus, we

☆ This work was supported in part by a Grant-in Aid for Cancer Research (17-6) from the Ministry of Health, Labor and Welfare, Japan.
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1010-7940/$ – see front matter
doi:10.1016/j.ejcts.2008.07.044

have carried out this prospective study concerning diagnoses and treatment strategies for patients with such small peripheral lung lesions. The intermediate-term results of this study are presented here.

2. Patients and methods

2.1. Study design

This study, a prospective trial done in one center (Osaka Medical Center for Cancer and Cardiovascular Diseases), was designed to deliver a high-quality service to patients with small peripheral lung lesions. This is an essential requirement to inform patients of the different approaches available and select the most appropriate surgical treatment. Since the study began in 1997, written informed consent was obtained from each patient. Data for this study were retrieved from our hospital database whose use for research was approved by the ethical review board of the Osaka Medical Center for Cancer and Cardiovascular Diseases on March 7, 2008 (Approval No.: 0803095086).

2.2. Patients

One hundred and seventy-nine patients with proven or suspected lung cancers were enrolled in this study.

All patients eligible for the trial who presented over the 5-year recruitment period (between October 1997 and September 2002) were offered entry into the study. Inclusion criteria for the trial were: (1) peripheral lung lesion(s) 20 mm or less in diameter on preoperative HRCT and (2) absence of hilar or mediastinal lymph node swellings greater than 10 mm in diameter on preoperative contrast-enhanced CT (clinically N0). Exclusion criteria were: (1) poor cardio-pulmonary or other organ dysfunction that would make the patient intolerable to standard surgical procedures such as lobectomy with systematic lymph node dissection (compromised cases); and (2) coexistence of active malignant lesions in any other organs.

2.3. Preoperative selection criteria for the type of lung resection

Lesions were classified into three groups: 10 mm or less, 11–15 mm, and 16–20 mm, according to the maximal diameter on HRCT. Three expert radiologists measured the percentage of GGO area at the maximal slice of the lesions on HRCT, and participants were divided into those with ≥50% GGO area as GGO type or <50% GGO area as solid type [6]. Pure GGO was defined as a complete hazy shadow, with preservation of the bronchial and vascular margins in the lesion on HRCT. Lesion location and lesion number were also taken into consideration in deciding the type of lung resection. At the time informed consent was obtained from patients with very small lesions measuring less than 10 mm in diameter or pure GGO, diligent observation was also available as one of the selection arms. When the lesion increased in size and/or density on HRCT during observation, it would be recruited as a candidate for resection (Fig. 1).

In accordance with these selection criteria, wide wedge resection (WWR), segmentectomy, or lobectomy with or without systematic lymph node dissection, were planned for individual patients. We designated the method of wedge resection with safe margin macroscopically greater than the lesion diameter as WWR.

2.4. Intraoperative process for the final decision on the type of resection

Fig. 1 shows the algorithms for deciding the type of surgery. First, we consider lesion size and GGO area when deciding the type of lung resection. However, lesion location, number and intraoperative factors are also important. For the GGO type less than 20 mm in diameter, we basically planned limited resection. For the solid type, less than 15 mm in diameter, we basically planned limited resection.

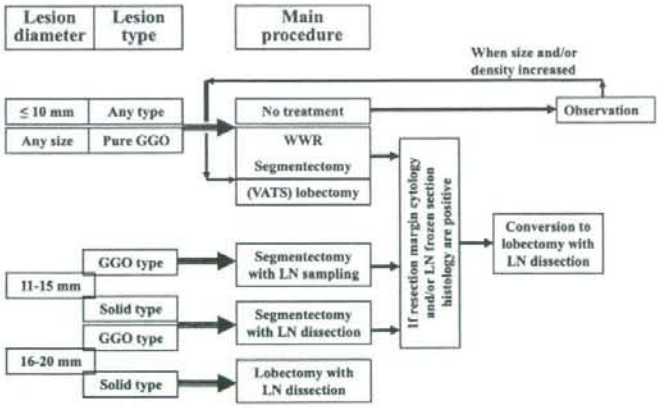

Fig. 1. Algorithms for deciding the type of resection. The main procedure also depends on the number and/or the location of lesion(s) beside the size and ground-glass opacity (GGO) pattern. If cytology of the resection margin and/or lymph node (LN) frozen section histology are positive, the procedure is converted to lobectomy with LN dissection as a final procedure. VATS: video-assisted thoracic surgery; WWR: wide angle resection.

If a definitive histo(cyto)diagnosis of lung cancer was obtained, we started the planned resection. For limited resection cases, if positive findings were obtained from the intraoperative histodiagnosis of lymph nodes using frozen sections, or the lavage cytology of the resection margin [7], we converted the procedure immediately from a limited resection to a lobectomy with systematic lymph node dissection. Of course, if we judged that the resection margin was macroscopically insufficient, we also converted the procedure from a limited resection to a lobectomy. Basically, we do not try to perform additional resection, even for WWR.

If preoperative histological or cytological diagnoses could not be made, we usually performed needle aspiration cytology on lesions through the thoracotomy wound. However, some specimens were too small to confirm the cytology. If cytological diagnosis was difficult, we performed WWR with a curative intent. Then, lavage cytology of the resection margin was employed as previously described [7]. In brief, when limited resection was performed with a stapler alone, all fired cartridges were washed in 200 ml of saline solution. When the lesion was excised with the aid of a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser or electric scissors alone, the resected specimen was similarly washed without flooding of the pleural surface. When lesions were resected by a combination of methods, both the fired cartridges and the resected specimen were washed. After centrifugation, the sediment was immediately fixed with Saccomano solution and then smeared on a glass slide by the cytospin method. After final refixation with ethanol and diethyl ether, the sediment was stained by means of the Papanicolaou method.

When it was predicted that the lesion would be too small to detect at the time of VATS or thoracotomy, CT-guided marking with indocyanine green (ICG) dye was performed immediately before surgery. VATS was employed for superficial lesions; while an Nd:YAG laser was employed for WWR or segmentectomy for deep-seated lesions to secure the safe margin [8].

2.5. Statistical analysis

The primary endpoint was the analysis of the locally disease-free survival rate at 5 and 10 years in lung cancer patients with limited resections. The secondary endpoint was the comparison of 5- and 10-year survival rates between patients with limited resections and lobectomies. We performed survival analysis with StatView J 5.0 (SAS Institute, Cary, North Carolina), and survival curves were calculated by the Kaplan–Meier method [9].

We estimated the sample size for this trial from the result of our previous retrospective study on intentional limited resection in highly selected T1N0 NSCLC patients. In our previous study, the recurrence at the resection margin occurred in only one of 46 patients (2.2%) and mediastinal recurrence was reported in 3 patients (6.5%) [5]. Based on these experiences, we estimated that 50 patients enrolled in the limited resection arm would be needed in this study.

Table 1
Patient characteristics

No. of patients	179
Gender	
Male	90
Female	89
Median age (range)	60 (34–82) years
Average lesion diameter (range)	13.7 (5–20) mm
Tumor number	
Solitary	159
Multiple	20
Preoperative diagnosis	
Proven	61
Suspected	118
Preoperative CT-guided marking	
Done	35
Not done	144
VATS	
Employed	40
Not employed	139
Median follow-up of 155 surviving patients	92 months

VATS: video-assisted thoracic surgery.

3. Results

Between October 1997 and September 2002, 179 patients were enrolled. Of those, 90 were male and 89 were female. The median age was 60 years old. Of those, 159 had solitary lesions and 20 had multiple lesions. The average maximal diameter on HRCT was 13.7 mm, with a range from 5 mm to 20 mm (Table 1). The lesions were divided into 77 GGO types and 102 solid types. Of the 77 GGO types, 30 were pure GGO. There were no surgery-related deaths in this series. Sixty-one of 179 patients were preoperatively proven to have lung cancer. However, 118 patients did not have any preoperative histological or cytological diagnosis. Preoperative CT-guided marking was employed for 35 patients with GGO lesions and intact pleura on HRCT. VATS procedure was employed for 40 patients. The median follow-up time of surviving patients was 92 months (Table 1).

The conversion from limited surgery to a standard procedure was performed in six patients. These consisted of three patients with lymph node metastases on frozen section histology; two with macroscopically insufficient margins, and one with a lavage cytology positive margin (Table 2).

Finally, adenocarcinoma was proven in 128 patients, non-adenocarcinoma in 10, AAH in 2, lymphoproliferative disorders (LPD) in 4, and benign lesion in 35. Of the 128 lung adenocarcinomas, 68 were GGO types including 22 pure GGO, and 60 solid types. All of the 10 non-adenocarcinomas,

Table 2
The reason for converting from limited resection to lobectomy in lung cancer patients

Reasons	No. of patients
Lymph node metastasis	3
Lavage cytology of the resection margin (+)	1
Macroscopically insufficient margin	2
Total	6

Table 3
Relationship between HRCT findings and histological findings

	GGO type		Solid type	Total
	Pure GGO	GGO > 50%	GGO < 50%	
Lung cancer				
Adenocarcinoma	22	46	60	128
Non-adenocarcinoma[a]	0	0	10	10
AAH	1	1	0	2
Lymphoproliferative disorder	4	0	0	4
Benign lesions				
Tumor	0	1	10	11
Inflammation	2	0	22	24
Total	29	48	102	179

[a] There were four of each squamous cell carcinoma and small cell lung cancer, and one of each carcinosarcoma and pleomorphic carcinoma; GGO: ground-glass opacity; AAH: atypical adenomatous hyperplasia.

Table 4
Histology and final surgical procedure

	Limited resection		Lobectomy	Total
	WWR	Segmentectomy		
Lung cancer				
Adenocarcinoma	33	25	70	128
Non-adenocarcinoma	0	0	10	10
AAH	1	1	0	2
Lymphoproliferative disorder	4	0	0	4
Benign lesions				
Tumor	11	0	0	11
Inflammation	24	0	0	24
Total	73	26	80	179

which consisted of 4 squamous cell carcinomas, 4 small cell carcinomas, one carcinosarcoma and one pleomorphic carcinoma were solid types. Two atypical adenomatous hyperplasia (AAH) cases were GGO types, one of which was a pure GGO type. These two AAH cases had been diagnosed as BAC at frozen section histology and corrected to AAH in the final report. All of the four LPDs were pure GGO types. All but three of the 35 benign lesions (benign tumors or inflammations) belonged to the solid type (Table 3). All patients with benign lesions are alive and uneventful. Of 24 inflammations, 11 were tubercular nodules, 10 nonspecific inflammatory nodules and one of each cryptococcosis, mycobacterium avium complex (MAC) infection and sarcoidosis.

Table 4 shows the final surgical procedures employed for lesions with different histologies. WWRs were performed on 33 patients with adenocarcinomas and all but one non-cancer patient, including one AAH, 4 LPDs, 11 benign tumors and 24 inflammations. Segmentectomies were employed for 25 patients with adenocarcinomas and one with AAH. Lobectomies were employed for 70 patients with adenocarcinomas. Lobectomies were also employed for all 10 patients with non-adenocarcinomas. VATS was employed in 29 of 73 WWRs, 5 of 26 segmentectomies and 6 of 80 lobectomies.

Fig. 2 shows the distributions of 138 cancer patients treated at each of the major steps according to our study protocol. As a result of following our comprehensive judgment of the HRCT, tumor size, number and location, the surgical procedure employed was shifted from a WWR to lobectomy. However, lobectomy was also employed for deep-seated smaller lesions, the multiple smaller lesions found in one lobe or lesion(s) originated from the middle lobe. As a result, lobectomy was deemed to be necessary in three cases where GGO type was 10 mm or less in diameter. For one patient this decision was based on the existence of multiple BACs in the right upper lobe, for another it was based on histological diagnosis showing endometriosis in an adjacent segment of the same right lower lobe, and finally it was deemed necessary in another patient because the tumor was located in the deep parenchyma of the middle lobe.

Of 138 cancer patients, 24 patients died. Of those, 16 died from disease-related causes and 8 from unrelated causes. Recurrences have been observed in 22 of 138 cancer patients. There were no local-regional recurrences among 58 patients with limited resection (Table 5). One of the 33 patients with WWRs demonstrated distant metastasis in a different lobe of the lung. This recurrence might not have been avoidable, even if lobectomy had been performed as the standard

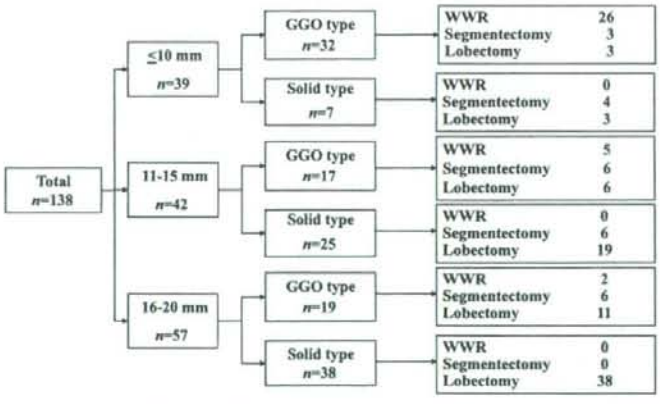

Fig. 2. The number of cancer patients treated at each of the major steps of the study. GGO: ground-glass opacity. WWR: wide angle resection

Table 5
Surgical outcomes in 138 patients with lung cancer

Procedure type	First relapse site	
	Local-regional	Distant
WWR (n = 33)	0	1*
Segmentectomy (n = 25)	0	0
Lobectomy (n = 80)	7	14

* Pulmonary metastases to different lobe; WWR: wide wedge resection.

operation. Of 80 patients undergoing lobectomy, 21 had recurrences (Table 5). Of those, 7 demonstrated local-regional recurrences: 5 ipsilateral carcinomatous pleuritis, 1 at the resection margin of the chest wall and 1 at the regional lymph node. The median follow-up times of surviving patients in the limited resection and lobectomy groups were 91 and 98 months, respectively.

Fig. 3 shows the comparison of relapse-free survival curves (a) and overall survival curves (b) between lung cancer patients with limited resection and with lobectomy. There were no operative deaths. Both 5- and 10-year relapse-free survival rates were 98.3% in the limited resection group, and 73.8% in the lobectomy group (Fig. 3a). The difference was significant (p = 0.0001). Overall survival rates at 5 and 10 years were 96.6% and 94.7% in the limited resection group, and 80.0% and 71.4% in the lobectomy group, respectively (Fig. 3b). This difference was also significant (p = 0.0014). All 18 patients with pathologically advanced lesions more than stage IA were included in the lobectomy group. There were no local recurrences but one distant metastasis in a different lobe was detected among the 58 patients undergoing limited resection. Of 21 patients with recurrences after lobectomy, 5 died more than 5 years postoperatively and 3 are alive with disease more than 5 years after surgery.

4. Discussion

In a large collaborative study, the International Early Lung Cancer Action Program (IELCAP) Investigators [10] screened 31,567 asymptomatic persons at risk for lung cancer using low-dose CT (1993–2005). Of those participants, 484 received a diagnosis of lung cancer and 412 (85%) had clinical stage I lung cancer. The 10-year lung-cancer-specific survival rate among the 302 participants, who underwent resection regardless of the type of surgery, was 92%. They also reported that all 8 untreated stage I patients died within 5 years after diagnosis. However, the surgical procedure employed for 78% of the participants was lobectomy, although the median tumor diameter was 13 mm at baseline and 9 mm on annual CT. It may depend on the minority of the patients with bronchioloalveolar subtype (5%).

We reported previously that a novel classification based on the semiquantitative analysis of BAC component areas in small peripheral lung adenocarcinomas 20 mm or less in diameter reflects both clinicopathological and prognostic characteristics [11]. In order to better apply this data preoperatively, we conducted a study to clarify the prognostic value of GGOs found in small lung adenocarcinomas measuring 20 mm or less in diameter on HRCT scanning. There was good correlation between histological BAC and GGO area on HRCT scanning in patients with small adenocarcinomas measuring 20 mm or less in diameter, and there were no relapses among patients with GGO greater than 50% on the CT slice showing the maximal cross section of the lesion. This novel classification based on the semiquantitative analysis of GGO area on HRCT should become a useful independent preoperative indicator when deciding the surgical procedures [6].

Thus, as an indicator at the time of deciding surgical procedures in this prospective study, we employed the GGO area (<50% or >50%) on HRCT taken immediately before surgery. Pure GGO is a good candidate for WWR without lymph node dissection because of the extremely low risk of lymphatic invasion. Besides BACs or AAHs, LPDs, such as lymphoid interstitial pneumonitis (LIP) or early stage pulmonary marginal zone lymphoma of mucosa associated lymphoid tissue (MALT), are also detected as pure GGO on HRCT.

The final decision on conversion to lobectomy in each patient scheduled for limited resection was done according to the results of not only conventional intraoperative histologies or cytologies of the lesions or lymph nodes, but also intraoperative lavage cytologies of the resection margins [8]. This technique was developed in our department, and is routinely employed in patients undergoing limited resection, if lavage cytology of the chest cavity immediately after thoracotomy was negative. Previously, we reported that 21 of 199 patients (10.5%) showed cytologically positive results on the surgical margin during the attempted procedure [7]. Needless to say, the percentage was higher in compromised limited resection for patients with poor cardio-pulmonary or other organ function. Of note in this prospective study, only one of 58 cancer patients (1.7%) undergoing planned limited

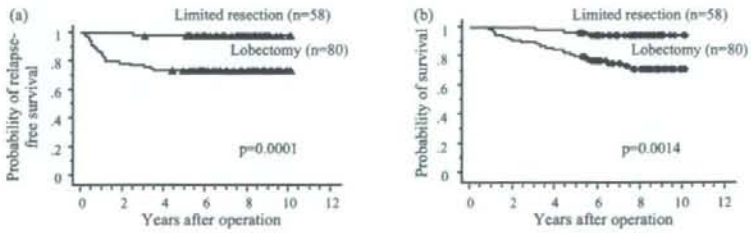

Fig. 3. Intermediate-term results of lung cancer patients. Limited resection (segmentectomy or wide wedge resection) vs lobectomy. (a) Relapse-free survival (p = 0.0001); (b) overall survival (p = 0.0014).