Table 7 Number of cancers detected in the screening program that were positive/negative by screening FDG-PET and by one or more of the combined screening tests

Disease	A	B	C	D	E	F	Total detected	Major combined screening tests
Thyroid cancer	46	24	24	13	94*	59	107	Neck ultrasonography
Colon/rectum cancer	50	24	18	10	92*	60	102	FOBT
Lung cancer	42	14	7	16	63	58	79	Chest CT
Breast cancer	19	5	12	3	36*	22	39*** (35)	Breast ultrasonography
Prostate cancer	18	0	3	26	21	44**	47	PSA
Gastric cancer	6	2	0	22	8	28**	30	Gastroscopy
Malignant lymphoma	5	7	6	1	18*	6	19	CT
Renal cancer	5	2	0	6	7	11	13	CT, Ultrasonography
Esophagus cancer	5	0	3	0	8	5	8	Gastroscopy
Uterine cancer	5	1	1	1	7	6	8	Pelvic MRI
Ovarian cancer	6	0	0	1	6	7	7	Pelvic MRI
Pancreas cancer	6	0	0	1	6	7	7	Abdominal CT
Head and neck cancer	0	6	0	0	6*	0	6	Neck CT
Others	22	3	2	5	27	27	32	
Total	235	88	76	105	399*	340	504 (500)	

A positive by PET and positive by one or more of the combined screening tests, *B* positive by PET and negative by any of the combined screening tests, *C* positive by PET and no combined screening tests performed, *D* negative by PET and positive by one or more of the combined screening tests, *E* positive by PET, regardless of the combined screening tests, *F* positive by one or more of the combined screening tests, regardless of PET

* $P < 0.001$, in comparison to "Positive by one or more of the combined screening tests, regardless of PET"

** $P < 0.001$, in comparison to "positive by PET, regardless of the combined screening tests"

*** Double breast cancer was detected in four subjects

Table 8 Detection of thyroid cancer by screening FDG-PET and by each of the combined screening tests

Modality	Relative sensitivity* (%)	Positive predictive value (%)	Number of detected cancers**	Number of subjects with results***
FDG-PET	87.9	32.9	107	400
Neck ultrasonography	92.9 (76.8)	21.5	56	262
Neck CT	57.4 (72.3)	20.6	47	245
Tumor marker (CEA)	5.1 (85.9)	30.8	78	319

* Rate of test-positive subjects over the total subjects in whom thyroid cancer was detected in the screening program and who underwent the corresponding test. Numbers in parentheses represent the rate of PET-positive subjects and the corresponding total subjects

** Of the subjects who underwent the corresponding test

*** Number of thorough examination results obtained for the subjects who underwent the corresponding test and who were positive for thyroid cancer by screening FDG-PET and/or by one or more of the combined screening tests if any

cases of benign disease were found and 13 cases were strictly followed up. Thyroid cancers were most frequently found in women, in the age groups of 50–59 years and 60–69 years. The detection rates with FDG-PET and combined screening tests are shown in Table 8. FDG-PET showed a relative sensitivity of 87.9% (86.9%) and positive predictive value of 32.9% (33.6%). Excluding the case of PET/negative and CT/positive findings with screening tests performed by PET/CT are shown in parentheses. PET showed a relative sensitivity of 80.6% (54 of 67 cases) and a positive predictive value of 28.9% (54 of 187 cases), PET/CT showed a relative sensitivity of 100.0% (40 of 40 cases) and a positive predictive value of 40.4% (40 of 99 cases). PET/CT had a better detection rate, sensitivity, and positive predictive value than dedicated PET ($P < 0.01$). When excluding PET/negative and CT/positive findings with screening tests performed by PET/CT, PET/CT showed a relative sensitivity of 97.5% and positive predictive value of 43.4%, both of which were higher as compared with dedicated PET ($P < 0.01$).

Thyroid ultrasonography performed in 262 cases showed a relative sensitivity of 92.9% and positive predictive value of 21.5%. Head and neck CT performed in 245 cases showed a relative sensitivity of 57.4% and positive predictive value of 20.6%. Serum carcinoembryonic antigen (CEA) measured in 319 cases showed a relative sensitivity of 5.1% and positive predictive value of 30.8%. Otolaryngologic examination and head and neck magnetic resonance imaging (MRI) were excluded from the

analysis because of infrequent use. The final diagnosis of cancer was confirmed by surgical procedures (63 cases) and biopsy (37 cases). The location of the detected cancers was the right lobe (50 cases), left lobe (43 cases), and isthmus (5 cases). The pathological classification of the detected cancers was papillary carcinoma (87 cases) and follicular carcinoma (6 cases). The relative sensitivity of FDG-PET for clinical staging was 60.0% (12 of 20 cases) for Stage I, 92.3% (12 of 13 cases) for Stage II, and 100.0% (2 o-f 2 cases) for Stage III, whereas no Stage IV cases were detected. Stage I and II cases were positive on PET in 72.7 % (24 of 33 cases). In lesions with a largest diameter of less than 14mm, PET was positive for cancer in 26 of 37 cases, whereas in those more than 15mm PET was positive for cancer in all 20 cases. FDG-PET negative thyroid cancers were most frequently papillary carcinomas under clinical stage II with a largest diameter of 3–13mm. Typical benign thyroid diseases showing FDG-PET positivity were adenomatous goiter (102 cases), chronic thyroiditis (54 cases), and follicular adenoma (16 cases).

Colon/rectal cancer

A total of 481 subjects (289 men, 192 women) were suspected of having colon/rectal cancer. 102 cases (68 men, 34 women) of colon/rectal cancers and 220 cases of benign disease were found, of which 13 cases were strictly followed up. Colon/rectal cancers were most frequently found in the age groups of 50–59 years and 60–69 years. No cases of PET/negative and CT/positive findings with screening tests performed by PET/CT were encountered. The detection rates with FDG-PET and combined screening test were shown in Table 9. FDG-PET showed a relative sensitivity of 90.2% and positive predictive value of 22.6%. There were no significant differences in the relative sensitivity or positive predictive value between PET and PET/CT. Abdominal ultrasonography performed in 294 cases showed a relative sensitivity of 3.9% and positive predictive value of 66.7%. Abdominal and pelvic CT performed in 250 cases showed a relative sensitivity of 17.8% and positive predictive value of 50.0%. Abdominal and pelvic MRI performed in 225 cases showed a relative sensitivity of 30.0% and positive predictive value of 56.3%. Serum CEA measured in 383 cases showed a relative sensitivity of 11.4% and positive predictive value of 32.1%. Fecal occult blood test (FOBT) performed twice in 312 cases showed a relative sensitivity of 68.1% and positive predictive value of 28.0%. The final diagnosis of cancer was confirmed by surgical procedures (47 cases) and colonoscopy biopsy and endometric mucosal resection (47 cases). The location of the detected cancers was the sigmoid colon in 37 cases, rectum in 30 cases, ascending colon in 19 cases, and descending colon, transverse colon, and cecum in 4 cases each. The pathological classification of the detected cancers was adenocarcinoma in 66 cases. The relative sensitivity of FDG-PET for clinical staging was 85.7% (12 of 14 cases) in Stage 0, 76.9% (10 of 13 cases) in Stage I, 100.0% (8 of 8 cases) in Stage II, 100.0% (1 case) in Stage IIIa, and 100.0% (1 case) in Stage IIIb, with no Stage IV cases found. Stage I and II cases were positive on PET in 88.6% (31 of 35 cases). The relative sensitivity of FDG-PET for macroscopic invasion depth was 91.7% in M (cancer invades only mucosa: 11 of 12 cases), 75.0% in SM (cancer invades submucosa: 3 of 4 cases), 100.0% in MP (cancer invades muscularis propuria: 1 case), 100.0% in SS (cancer invades through muscularis propria: 6 of 6 cases), 100.0% in SE (cancer invades through subserosa but not to any neighboring organs or tissues: 1 case), 100.0% in Si (cancer directly invades other organs or structures: 1 case). The relative sensitivity of FDG-PET for microscopic invasion depth was 88.0% in m (cancer invades only mucosa: 22 of 25 cases), 100.0% in

Table 9 Detection of colon/rectum cancer by screening FDG-PET and by each of the combined screening tests

Modality	Relative sensitivity* (%)	Positive predictive value (%)	Number of detected cancer**	Number of subjects with results***
FDG-PET	90.2	22.6	102	481
Abdominal ultrasonography	3.9 (76.5)	66.7	51	294
Abdominal CT	17.8 (91.1)	50.0	45	250
Abdominal MRI	30.0 (80.0)	56.3	30	225
Tumor marker (CEA)	11.4 (67.1)	32.1	79	383
FOBT (two times screening)	68.1 (85.5)	28.0	69	312

*Rate of test-positive subjects over the total subjects in whom colon/rectum cancer was detected in the screening program and who underwent the corresponding test. Numbers in the parentheses represent the rate of PET-positive subjects and the corresponding total subjects

**Of the subjects who underwent the corresponding test

***Number of thorough examination results obtained for the subjects who underwent the corresponding test and who were positive for colon/rectum cancer by screening FDG-PET and/or by one or more of the combined screening tests if any

Table 10 Detection of lung cancer by screening FDG-PET and by each of the combined screening tests

Modality	Relative sensitivity* (%)	Positive predictive value (%)	Number of detected cancers**	Number of subjects with results***
FDG-PET	79.7	35.4	79	225
Chest X-ray	50.0 (66.7)	37.5	6	35
Chest CT	91.2 (52.9)	33.0	34	99
Tumor marker (CEA)	32.3 (78.5)	72.4	65	167
Tumor marker (SCC)	7.0 (72.1)	75.0	43	126

*Rate of test-positive subjects over the total subjects in whom lung cancer was detected in the screening program and who underwent the corresponding test. Numbers in the parentheses represent the rate of PET-positive subjects over the corresponding total subjects
**Of the subjects who underwent the corresponding test
***Number of thorough examination results obtained for the subjects who underwent the corresponding test and who were positive for lung cancer by screening FDG-PET and/or by one or more of the combined screening tests if any

sm (cancer invades submucosa: all 15 cases), 100.0% in mp (cancer invades muscularis propria: 1 case), 100.0% in ss (cancer invades through muscularis propria: all 12 cases), 100.0% in se (cancer invades through subserosa but not to any neighboring organs or tissues: 2 of 2 cases), 100.0% in si (cancer directly invades other organs or stuctures: 2 of 2 cases). The relative sensitivity of FDG-PET for its shape was 91.6% of Type 0 (11 of 12 cases), 100.0% of Type 1 (all 15 cases), 90.5% of Type 2 (19 of 21 cases), 100.0% of Type 3 (all 5 cases), with no cases of Type 4 or 5 found. The relative sensitivity of FDG-PET for pathological differentiation type was 97.5% of G1 (39 of 40 cases) and 100.0% of G2 (all 14 cases), with no G3 type found. Lesions with a largest diameter of less than 40 mm were PET positive in 35 of 41 cases, whereas those measuring more than 41 mm were PET positive in all 6 cases. FDG-PET negative colon/rectum cancers were most frequently adenocarcinomas, under clinical Stage I, to M of macroscopic invasion depth, to m of microscopic invasion depth, in G1 type of cell differentiation, with a largest diameter of 5–40 mm. Typical benign colon/rectum diseases showing FDG-PET positivity were adenoma (57 cases), polyposis (28 cases), polyp (28 cases), diverticulum (14 cases), and inflammation (10 cases).

Lung cancer

A total of 225 subjects (143 men, 82 women) were suspected of having lung cancer. Seventy-nine cases (50 men, 29 women) of lung cancer and 88 cases of benign disease were found, and 32 cases were strictly followed up. Lung cancers were most frequently found in men, in the age group of 60–69 years. The detection rates with FDG-PET and combined screening test are shown in Table 10. FDG-PET showed a relative sensitivity of 79.7% (69.6%) and positive predictive value of 35.4% (35.0%). Excluding the case of PET/negative and CT/positive findings with screening test performed by PET/CT are shown in parentheses. PET showed a relative sensitivity of 59.0% (23 of 39 cases) and positive predictive value of 25.0 % (23 of 92 cases), whereas PET/CT showed a relative sensitivity of 100.0% (all 40 cases) and positive predictive value of 47.1% (40 of 85 cases). PET/CT had a better detection rate, sensitivity, and positive predictive value than dedicated PET ($P < 0.01$). In the case of excluding PET/negative and CT/positive findings with screening tests performed by PET/CT, PET/CT showed a relative sensitivity of 80.0% and positive predictive value of 49.2%, which are higher than those of dedicated PET ($P < 0.01$). Chest X-ray performed in 35 cases showed a relative sensitivity of 50.0% and positive predictive value of 37.5%. Chest CT performed in 99 cases showed a relative sensitivity of 91.2% and positive predictive value of 33.0%. Serum CEA measured in 167 cases showed a relative sensitivity of 32.3% and positive predictive value of 72.4%. Positive sputum cytology was not noted in any case. The final diagnosis of cancer was confirmed by surgical procedures (54 cases), biopsy (13 cases), and cytology (5 cases). The location of detected cancers was in the right lung in 42 cases (upper lobe 22, middle lobe 6, and lower lobe 13) and left lung in 31 cases (upper lobe 18, lower lobe 13). The pathology of the detected cancers was adenocarcinoma in 46 cases, squamous cell carcinoma in 9 cases, and small cell cancer in 4 cases. The relative sensitivity of FDG-PET for clinical staging was 62.5% (20 of 32 cases) in Stage IA, 100.0% (1 case) in Stage IB, 0.0% (1 case) in Stage IIA, 100.0% (2 of 2 cases) in Stage IIB, 100.0% (2 of 2 cases) in Stage IIIA, 100.0% (2 of 2 cases) in Stage IIIB, and 100.0% (2 of 2 cases) in Stage IV.

Stage I and II cases were positive on PET in 65.7% (23 of 35 cases). Excluding the case of PET/negative and CT/positive findings with screening tests performed by PET/CT was 14 of 35 cases. In lesions with a largest diameter of less than 30 mm, 17 of 32 cases (11 of 32 cases) were PET positive. In lesions with a largest diameter of more than 30 mm, 4 of 7 cases (4 of 7 cases) were PET positive,

Table 11 Detection of breast cancer by screening FDG-PET and by each of the combined screening tests

Modality	Relative sensitivity* (%)	Positive predictive value (%)	Number of detected cancers**	Number of subjects with results***
FDG-PET	92.3	43.4	39	127
Inspection and palpation	25.0 (75.0)	66.7	8	44
Mammography	44.4 (77.8)	57.1	9	45
Breast ultrasonography	83.3 (91.7)	18.5	12	64
Chest CT	68.4 (89.5)	38.2	19	87

*Rate of test-positive subjects over the total subjects in whom breast cancer was detected in the screening program and who underwent the corresponding test. Numbers in the parentheses represent the rate of PET-positive subjects over the corresponding total subjects
**Of the subjects who underwent the corresponding test
***Number of thorough examination results obtained for the subjects who underwent the corresponding test and who were positive for breast cancer by screening FDG-PET and/or by one or more of the combined screening tests if any

with the case of PET/negative and CT/positive findings with screening tests performed by PET/CT shown in parentheses. GGO was found in 31 cases, in 22 of which cancer was finally diagnosed. Of 22 cancers diagnosed as a result of further examinations, there were 5 PET positive cases (1 case) in 8 pure GGO type lung cancers, 5 cases (4 cases) in 7 mixed GGO type lung cancers, and all 5 cases (5 cases) in solid nodule type lung cancers, whereas in 2 cases information regarding the type was not provided. All 9 cases of unproven cancer underwent strict follow-up. FDG-PET negative lung cancers were most frequently found in adenocarcinoma with GGO type, under clinical Stage I, with a largest diameter of 5–40 mm. Sputum cytology was excluded from the analysis because it was rarely reported. Typical benign lung diseases showing FDG-PET positivity were inflammation (24 cases), inflammatory scar (11 cases), nontuberculous lesions (6 cases), and sarcoidosis (6 cases).

Breast cancer

A total of 123 subjects (127 breasts) were suspected of having breast cancer. Thirty-five cases (39 breasts) of breast cancers and 57 cases of benign disease were found, whereas 3 cases were strictly followed up. Breast cancers were most frequently found in the age group of 40–69 years. The detection rates with FDG-PET and combined screening tests are shown in Table 11. FDG-PET showed a relative sensitivity of 92.3% (87.2%) and a positive predictive value of 43.4% (42.0%). Excluded cases with PET/negative and CT/positive findings with screening tests performed by PET/CT are shown in parentheses. There were no significant differences in the relative sensitivity or positive predictive value between PET and PET/CT, or between PET and the excluded cases of PET/negative and CT/positive findings with screening tests performed by PET/CT. Mammography performed in 45 cases showed a relative sensitivity of 44.4% and positive predictive value of 57.1%. Breast ultrasonography performed in 64 cases showed a relative sensitivity of 83.3% and positive predictive value of 18.5%. Chest CT performed in 87 cases showed a relative sensitivity of 68.4% and positive predictive value of 38.2%. The final diagnosis of cancer was confirmed by surgical procedures (28 cases) and biopsy (10 cases). The location of the detected cancer showed no laterality, but cancers were most frequently found in C area, which is defined as the upper outer quadrant of the breast in the guidelines for mammography of Japan. The pathological classification of detected cancers was invasive carcinoma in 18 cases (papillotubular carcinoma 12 cases, scirrhous carcinoma 5 cases, and solid-tubular carcinoma 3 cases) and 6 cases of non-invasive carcinoma (including 5 cases of noninvasive ductal carcinoma). The relative sensitivity of FDG-PET for clinical staging was 66.7% (2 of 3 cases) in Stage 0, 90.0% (9 of 10 cases) in Stage I, 100.0% (4 of 4 cases) in Stage II A, 100.0% (2 of 2 cases) in Stage IIB, and 100.0% (1 of 1 case) in Stage IIIA, with no Stage IIIB, IIIC, or IV cases found. Stage I and II cases were positive on PET in 94.7% (18 of 19 cases). FDG-PET negative breast cancers were clinical Stage I or less, and comprised similar numbers of invasive type and non-invasive type. The most common benign breast disease that was FDG-PET positive was mastopathy (13 cases).

Gastric cancer

Ninety-eight subjects (59 men, 39 women) were suspected of having gastric cancer. Thirty cases (25 men, 5 women) of gastric cancers and 65 cases of benign disease were found. Gastric cancers were most frequently found in the age groups of 40–49 years, 50–59 years and 60–69 years. FDG-PET showed a relative sensitivity of 26.6% and positive predictive value of 15.5%. Three of 13 cancers were found by PET, and 6 of 17 cancers were found by PET/CT. Twenty-two of 30 gastric cancers were detected by gastric endoscopy, and 2 cases of gastric

Table 12 Cancer detection by screening FDG-PET in the 14 qualified major PET centers with ≥300 subjects screened and with thorough examination results obtained for ≥50% of those referred for further evaluation

Disease	Relative sensitivity* (%)	Positive predictive value (%)	Number of detected cancers**	Number of Subjects with results***
Thyroid cancer	77.8	24.3	45	216
Colon/rectum cancer	80.0	16.8	31	219
Lung cancer	71.0	24.2	31	118
Breast cancer	80.0	33.3	15	58
Others	62.5	16.8	63	401
Total	71.9	20.4	185	1012

*Rate of PET-positive subjects over the total subjects in whom each cancer was detected in the screening program
**Of the subjects who underwent the corresponding test
***Number of thorough examination results obtained for the subjects who underwent the corresponding test and who were positive for each cancer by screening FDG-PET and/or by one or more of the combined screening tests, if any

cancer were detected by only PET positive findings (without combined screening test or with negative findings in combined screening tests), and 6 cases by positive findings on PET and tumor markers such as CEA and pepsinogen. The final diagnosis of cancer was confirmed by biopsy (17 cases) and surgical procedures (13 cases). The most common pathological classification of the detected cancers was adenocarcinoma in 11 cases. Eight cases of PET negative Stage I and 1 case of Stage III were found. The most common benign diseases that were FDG-PET positive were gastritis (29 cases) and polyps (9 cases).

Prostate cancer

A total of 100 subjects were suspected of having prostate cancer. Forty-seven cases of prostate cancers and 33 cases of benign disease were found and 11 cases were strictly followed up. Prostate cancers were most frequently found in the age groups of 60–69 years and 70–79 years. FDG-PET showed a relative sensitivity of 44.7% and positive predictive value of 58.3%. Five of 16 cancers were found by PET, and 16 of 31 cancers by PET/CT. Abdominal and pelvic MRI performed in 49 cases showed a relative sensitivity of 66.7% and positive predictive value of 53.3%. Prostatic specific antigen (PSA) measured in 86 cases showed a relative sensitivity of 100.0% and positive predictive value of 52.5%. The final diagnosis of cancer was confirmed by biopsy (30 cases) and surgical procedures (7 cases). The most common pathological classification of detected cancers was adenocarcinoma in 19 cases. Six cases of Stage II (2 cases PET positive), 1 case of Stage (1 case PET positive) and 2 cases of Stage IV (1 case PET positive) were found. The most common benign diseases that were FDG-PET positive were prostatitis (5 cases) and prostatic hypertrophy (4 cases).

Results of screening tests performed in facilities performing over 300 screening tests per fiscal year and obtaining clear results in over 50% of cases referred for further examinations

Of the 38 facilities from which replies regarding the results of further examinations were obtained, 14 facilities that performed over 300 screening tests per fiscal year were evaluated and obtained clear results in over 50% of cases referred for further examinations, which are associated with little deviation and high reliability. In the 14 facilities, 16406 cases of cancer screening were performed in a year, and 1430 cases of positive findings suggesting possible cancer amounting to 8.7% of the total screening tests were found, and results of 1012 cases referred for further examinations accounting for 70.8% of the total screening tests were obtained. One-hundred and eighty-five cases of cancer amounting to 1.13% of the total screening tests were detected, and comprised 0.81% (0.79%) PET positive cases and 0.32% PET negative cases. The relative sensitivity of detected cancer was 71.9% (69.7%) and the positive predictive value was 20.4% (20.5%). Excluded PET/negative and CT/positive cases with screening tests performed by PET/CT are shown in the parentheses. The rate of detected cancers obtained by further examinations was 18.3%. Assuming the cancer detection rate of the unclear results to be the same as that of the obtained results, the cancer detection rate was surmised to be 1.59% in FDG-PET cancer screening with further examinations for all subjects with suspected possible cancer. The results of various screening tests for the most frequently found cancers are listed in Table 12.

Discussion

In this survey, with the cooperation of many PET facilities performing FDG-PET cancer screening, we were able to clarify the performance profile of FDG-PET and PET/CT for cancer screening on the basis of the guidelines published by The Japanese Society of Nuclear Medicine and The Clinical PET Promotion Committee. Reports on FDG-PET cancer screening in individual or a few facilities have been published, but no large-scale surveys such as this have ever been undertaken in Japan, making the present results highly significant. Although the numbers of facilities performing FDG-PET cancer screening are increasing, the effectiveness of FDG-PET for cancer screening has not been proved. We must accordingly clarify the conditions and results of FDG-PET cancer screening and evaluate its effectiveness as soon as possible. This survey focused particularly on the results of cases of suspected possible cancer, and so the results of all such cases were required. It was not easy for each facility to find out where further examinations were performed or to obtain the results. Some subjects did not undergo further examinations, which might be one reason for the difficulty of this survey. Results were finally obtained from one half of cases with possible cancer, as a result of which the "positive predictive value" and "detection rate" could be obtained by analyzing the true positive and false positive cases, and the approximate relative "sensitivity" comparing FDG-PET with the combined screening tests was obtained. To determine the exact "sensitivity," it would be necessary to survey for cancer in all subjects with negative FDG-PET cancer screening test findings, although such a survey was not required in "The Guidelines of FDG-PET Cancer Screening" and would be virtually impossible to implement in all negative subjects. To prove the effectiveness of FDG-PET cancer screening in a strict sense, determination of the "detection rate" and "sensitivity" alone would not be adequate, and it would be necessary to survey the death rate and survival periods of subjects undergoing and not undergoing FDG-PET cancer screening under careful follow-up. It is necessary to prove the effectiveness of cancer screening, regardless of whether FDG-PET cancer screening is performed, to conduct a detailed survey for several years, although this is difficult in practice. It seems possible to prove the effectiveness of FDG-PET cancer screening by continuing this survey while revising the guidelines.

In this survey, all facilities used a largely uniform method for FDG-PET (including PET/CT) screening tests. The wide variability in the rate of subjects with suspected possible cancer on the basis of PET positive findings among the facilities (1.7%–24.6%) suggested that the criteria of diagnosis, both for FDG-PET imaging features and the results of combined screening tests, differed in each facility and according to individual radiologists. Fixed combined screening tests differed in each facility and the subject population differed as well. Because these factors affect the rate of suspected possible cancer, sensitivity, and detection rate, it would be necessary for evaluating the effectiveness of FDG-PET (including PET/CT) cancer screening to define the criteria of diagnosis and recommendations for further examinations as well as to analyze the well-evaluated combined screening tests under exactly investigated and standardized conditions if possible. The selection of the most appropriate combined tests to make cancer screening more effective is problematic. Five-hundred cases of cancer, amounting to 1.14% of the total FDG-PET cancer screening tests from which the results of further examinations were obtained, were detected. Several facilities have already reported their cancer detection rates with FDG-PET cancer screening, for example, 2.31% in Atsuchi Memorial Clinic PET Center (PET positive; 1.78%, PET negative; 0.53%, total number of performed FDG-PET cancer screenings; 7480 subjects, between June 2002 and March 2006) [8], 1.78% in Nishidai Clinic Diagnostic Imaging Center (PET positive; 1.20%, PET negative; 0.58%, total number of performed FDG-PET cancer screenings; 16 922 subjects, between October 2000 and March 2006), 3.16% in HIMEDIC Imaging Center at Lake Yamanaka (PET positive; 1.51%, PET negative; 1.66%, total number of performed FDG-PET cancer screenings; 9357 subjects, between October 1994 and June 2005) [9]). These data are based on the number of subjects undergoing FDG-PET cancer screening, and should not be compared directly with the data obtained from our survey because of the inclusion of some persons who underwent FDG-PET screening tests several times within several years. Detection rates with FDG-PET cancer screening within a single fiscal year have been reported to be 1.60% in Atsuchi Memorial Clinic PET Center between April 2005 and March 2006 [8], 1.57% of first screening subjects examined in HIMEDIC Imaging Center at Lake Yamanaka [9], which were comparable with the data in our survey. The cancer detection rate of 1.14% (PET positive; 0.90%, PET negative; 0.24%) obtained in this survey is a little lower than those in these previous reports. This is attributed to the fact that the final results were obtained from only 46% of the subjects with suggested possible cancer, and many cancers were possibly present in these subjects but without any clear result. The present survey focused on 14 facilities from which a fairly high rate of results was obtained, although it contained a slightly high rate of FDG-PET cancer screening repeaters, with cancer

of detected cancer by each clinical stage made no sense because of the small numbers of cases falling into each stage, whereas the relative sensitivity of PET for thyroid cancer, breast cancer and lung cancer, tended to be somewhat low in the less-advanced clinical stages, but to reach almost 100% with more advanced clinical stages. The relative sensitivity of PET for colon/rectal cancer, even in the case of cancer in adenoma with Stage 0 was high at 86%, possibly because the PET findings indicated not a cancer itself but rather an adenoma in a pre-cancerous state. Another reason was that accumulation on PET in the colon/rectum region, where physiological accumulation of FDG is commonly noted, indicated not a cancer itself but a physiological accumulation of FDG-PET, and as a result the detection rate of colon/rectum cancer did not depend on form, invasion depth, or cell differentiation of cancer. This is suggested by the result of the low positive predictive value in the case of colon/rectum cancer, compared with the high positive predictive value of cancers in lung and breast, where little physiological accumulation of FDG occurs. Gastric cancer had a low relative sensitivity of detection by PET and was most frequently detected by gastric endoscopy. The sensitivity of detecting advanced gastric cancer by FDG-PET has been reported to be 60%–90% [18–20]. Although the sensitivity of detecting gastric cancer with PET was very low in this survey, it is supposed that early stage cancers accounted for the majority of detected gastric cancers. Prostate cancer also had a low relative sensitivity of detection by PET, and further examination was mostly suggested in the presence of a high PSA level. Gastric endoscopy and PSA will contribute, respectively, to the detection of gastric cancer (especially in early stage cancer) and prostate cancer, which has a low sensitivity with FDG-PET, indicating that especially PSA is an advisable combined screening test for FDG-PET cancer screening test because it is easy to measure and of low invasiveness. If it is difficult to perform gastric endoscopy as a combined screening test, the recommendation of having another gastric examination should be made to the subject after explaining the fact that early stage gastric cancer is less detectable by FDG-PET.

Of the detected cancers in this survey, the number of detected cancers by FDG-PET was significantly larger than that by combined screening tests. However, the cancer screening test focused on in this survey was FDG-PET, and fixed combined screening tests were suggested to be selected to supplement FDG-PET, which would result in highlighting the advantages of FDG-PET. On the other hand, in the case of cancers that were frequently detected by FDG-PET, they were sometimes detected because of positive findings by combined screening tests despite negative findings by FDG-PET, which indicates the importance of applying combined screening tests to FDG-PET. In a subsequent survey, it will be necessary to investigate the variable screening tests best used in conjunction with FDG-PET.

PET/negative and CT/positive status with screening test performed by PET/CT made up 11% of all PET positive cases, and 5 of 6 cases of renal cancer were detected by PET/CT with such PET/negative and CT/positive findings. Although 8 of 40 cases of lung cancer were detected by CT integrated in PET/CT, the other cases of lung cancer were detected by PET positivity. In this survey, PET/CT had a higher sensitivity, positive predictive value and rate of subjects with suspected possible cancer than PET alone. When comparing PET with PET/CT, however, differences in diagnostic criteria in each facility or according to individual radiologists, fixed combined screening tests and rate of obtained results in further examinations would introduce bias. Furthermore, the PET integrated in recently available PET/CT scanners is likely to be more up-to-date and to show higher performance than PET scanners themselves, and so we must carefully analyze these conditions when making such comparisons.

The positive predictive value of screening test performed by PET/CT scanners was higher than that by PET scanners, first because many cases would have been regarded as not requiring any further examination because of the documentation on CT images of physiological accumulation from the FDG positive area. Second, the differences in the detection rate and sensitivity between PET/CT and PET were dependent on the presence of many PET/negative and CT/positive cases (8 of 40 cases of lung cancer, 5 of 6 cases of renal cancer), whereas some other kinds of cancer showed a higher detection rate (lung cancer) or sensitivity (thyroid cancer, lung cancer) with PET/CT than with PET even if excluding PET/negative and CT/positive cases. A major reason was that the PET findings were often regarded as negative and explainable as physiological accumulation or slight accumulation while seeming like possible cancer by PET and CT imaging totally. And last, PET/CT facilitates accurate confirmation of a lesion's shape adjusted to the PET findings because PET/CT enables both PET and CT imaging with little change of scanning time or place (position of subject), so that PET/CT showed greater accuracy than PET and CT. For this reason, the rate of suggested possible cancer was higher with PET/CT (excluding PET/negative and CT/positive cases) than with PET. PET/CT is probably superior to PET for cancer screening as well as for follow-up examinations of cancer patients, and PET/CT will be more effective

detected in 18.3% of the subjects obtaining a final result. If cancer was detected at the same rate in the subjects who did not obtain a final result and all the subjects were to undergo further examinations, it is assumed that cancer would be detected in 1.59% of the subjects with suspected possible cancer. The PET positive rate (relative sensitivity) in detected cancer was 79.0%, which is slightly higher than that in the previously published reports [8,9]. Although we were able to clarify the condition and results of FDG-PET cancer screening rather than evaluate its effectiveness, because this detection rate was to a large extent dependent on the combined screening tests performed, this survey was considered to provide promising data useful in proving the effectiveness of FDG-PET cancer screening. The positive predictive value with cancer screening, which is the rate of proved cancer in subjects suggesting possible cancer, is important. False positive findings cause unnecessary anxiety for subjects and require considerable cost and time for further examinations. In this survey, the positive predictive value was 29.0% in subjects with PET positive findings, and 26.5% in subjects with suggested possible cancer by screening program. The positive predictive value was higher with PET/CT than with PET (24.5% versus 37.3%; 36.9% in excluding the case of PET/negative and CT/positive findings with screening test performed by PET/CT), which indicated that PET/CT was more useful than PET from the aspect of identifying physiological accumulation of FDG on CT images. Fourteen percent of PET positive cases were considered not to require further examination with the result of excluded cancer with combined screening, although these cases were not proved to be true negatives, which indicated that false positive cases would be decreased by selecting suitable combined screening tests. The positive predictive value that depended on the criteria of the PET examination and combined screening tests differed greatly in individual facilities, and so a reevaluation would be necessary after standardizing combined screening tests for FDG-PET cancer screening. Thyroid cancer, colon/rectum cancer, lung cancer, and breast cancer were frequently found in PET positive cases, as has been already reported. These four kinds of cancer, malignant lymphoma and esophagus cancer had a high relative sensitivity of being detected with PET, whereas gastric cancer, renal cancer, and prostate cancer had a low relative sensitivity, as also previously reported [8,9]. The relative sensitivities of FDG-PET for detecting thyroid cancer, colon/rectum cancer, and breast cancer were very high, at about 90% each. The sensitivity of thyroid ultrasonography for detecting thyroid cancer was higher still than that of PET, but this did not indicate the uselessness of PET because it was performed in not so many facilities. There is some doubt that the early detection of thyroid cancer makes a contribution to prolonging the survival time, because the progression of thyroid cancer is generally very slow. The sensitivity of CT, MRI and CEA for detecting colon/rectum cancer was low and the sensitivity of FOBT was up to 67%, which indicated a high sensitivity of PET for detecting colon/rectum cancer. The sensitivity of PET for detecting colon/rectum cancer was supposed to be lower than that of colonoscopy and barium enema, but these screening tests are onerous for subjects and less often performed in every facility, which indicated that PET was useful as an easy screening test for colon/rectum cancer. The positive predictive value was 28%, which was higher than that ever hitherto reported [10–12], and the main reason was that PET/negative with FOBT/positive cases were not considered as suggesting possible cancer in many facilities. The sensitivity of detecting breast cancer was as high with PET as with ultrasonography. The sensitivity of mammography for detecting breast cancer was low at 44% (4 of 9 cases were positive), which is an unreliable number because of the less frequent use in facilities performing FDG-PET cancer screening. The detection rate of breast cancer with mammography was higher than that previously reported [13, 14], the reason being that mammography was less often performed and its detection had a possibility of being influenced by PET detection. Although mammography has the highest sensitivity of any breast cancer screening test, it is expected to be influenced by the diagnostic experience, diagnostic circumstances, conditions of filming and condition of the breast itself (the sensitivity of detecting breast cancer is decreased in dense breasts) [15].

The sensitivity of detecting lung cancer was slightly lower than that of the other three cancers mentioned earlier. It is supposed that many early stage cancers were found by combined CT, because chest CT has a generally very high sensitivity for detecting lung cancer, especially in the early stage [16, 17].

The image of CT that is integrated in PET/CT is usually obtained under free breath, low exposure dose of X-ray and thick reconstruction interval, which results in low sensitivity of detecting cancer in the early stage. Seven cases of early lung cancer with pure GGO type were found by PET/CT with PET/negative and CT/positive findings. It is necessary to conduct further investigation for evaluating the effective of CT integrated in PET/CT for detecting early stage lung cancer, together with the details of the filming condition and necessity of conducting immediate further examinations such as biopsy and of providing some immediate treatment. The clinical stage of each detected cancer was investigated in this survey. Determination of the relative sensitivity

than PET even if the CT integrated in PET/CT uses a low radiation dose. In this survey, PET centers performing FDG-PET cancer screening were shown to already possess many more PET/CT scanners than PET scanners despite the fact that PET/CT scanners are only about to be approved for use in Japan. The number of cancer screening procedures performed by PET/CT is expected to greatly increase [21], and thus it is surmised that cases of suspected possible cancer by PET/negative but CT/positive status, in which cancer can be excluded by identifying the shape of the lesion, and thereby rendering further examinations unnecessary will similarly increase.

The effect of radiation exposure has to be considered more carefully for PET cancer screening tests targeting healthy subjects than patients. The radiation dosage received from FDG was estimated to be 0.019 mSv/MBq [22] according to which the average radiation dosage from an average injected dosage of FDG in this survey was estimated as 4.1 mSv. There has been concern that the radiation dosage to which patients are exposed will be increased by the CT integrated in PET/CT, but the average mAs value was kept low (44.8 mAs) in facilities using a consistent mAs value as well as in facilities using a variable mAs value, namely 78.6 mAs during chest scanning and 88.7 mAs during abdominal scanning. The mAs value fixed in CT scanning differed according to machine and filming conditions, and moreover detailed information was withheld by all companies, interfering with attempts to estimate the radiation dosage received. When supposing that FDG-PET screening test was performed with the PET/CT machine "Aquiduo 16" manufactured by Toshiba (Toshiba Medical Systems, Tokyo, Japan), the effective radiation dosage was estimated from the mAs value mentioned earlier as about 5.7 mSv (using a consistent mAs value to CT scanning), 10.2 mSv (using a variable mAs value for CT scanning of the chest part) and 11.5 mSv (using a variable mAs value to CT scanning for the abdominal part). Supposing that this estimated effective radiation dose was not that different from estimates of other PET/CT scanners, the received radiation dosage would be estimated as 4.1 mSv for FDG-PET screening tests performed with PET machines, 9.8 mSv (using a consistent mAs value) and 14.3–15.6 mSv (using a variable mAs value to CT scanning) with FDG-PET screening tests performed with PET/CT machines. The estimated life shortening of a 60-year-old adult caused by a radiation dosage on the basis of these data mentioned earlier with the method of Iinuma of the National Institute of Radiological Sciences was 0.18 days in the case of men and 0.19 days for women whose FDG-PET screening test was performed with a PET scanner, 0.44 days (using a consistent mAs value to CT scanning) and 0.65–0.70 days (using a variable mAs value to CT scanning) for men, 0.56 days (using a consistent mAs value to CT scanning) and 0.81–0.89 days (using a variable mAs value to CT scanning) for women whose FDG-PET screening test was performed with a PET/CT scanner [22–24]. Estimated lifetime cancer mortality risk from full-body CT examination in a 45-year-old adult, using a radiation dosage of 11.6 mSv for men and 13.5 mSv for women, was reported to be around 0.08% for a single examination and 1.9% for annual examinations until the age of 74 years [25], which should be compared with our future data.

Nine cases of cancer were detected in subjects in their 20s and 30s who underwent FDG-PET cancer screening. Although in youth not only cancer development but also the genetic effect of radiation exposure should be considered, the International Commission on Radiological Protection (ICRP) recommendations appear to place less weight on the genetic effect than cancer development, and the new soon-to-be published ICRP recommendations appear to give even less significance to it. In this survey, there were quite a few cancers found by CT integrated in the PET/CT scanner such as renal cancer and lung cancer, and provided that an explanation was provided about the advantages of undergoing PET/CT and the disadvantages of radiation exposure, there was no problem at the level of the individual, whereas at the group level it will be necessary to undertake further detailed investigations as to whether early cancer detection leads to life prolongation considering the fact that the number of FDG-PET screening tests performed with PET/CT is expected to increase and to prepare for the next publication of "The Guidelines of FDG-PET/CT."

In "The Guidelines of FDG-PET Cancer Screening," the number of FDG-PET cancer screenings performed and detailed information of screened cancers are supposed to be reported regularly by every facility performing FDG-PET cancer screening, although it is onerous to provide this information, and with this in mind subsequent questionnaires will be improved to achieve greater simplification and accuracy. The questionnaire is now being improved by being adaptable to database management. It would be ideal for exact analysis to obtain detailed information about all subjects with suspected possible cancer by screening test, but it was onerous for the facilities to supply this. The questionnaire was supposed to be returned within 3 months after the term of the survey, but 6 months would be preferable for subsequent questionnaires to obtain detailed information about subjects with suspected possible cancer, because at least 6 months would be needed to obtain the results of further examinations.

Conclusions

A total of 50 558 healthy subjects underwent FDG-PET (including PET/CT) scanning with or without other tests for cancer screening in 46 PET centers during the fiscal year of 2005 in Japan. On analyzing 43 996 cases from 38 PET centers from which detailed information was obtained, 500 cases of cancers (1.14%) were found, of which 0.90% were PET positive and 0.24% were PET negative, resulting in the relative sensitivity of PET being 79.0%. PET/CT had a better detection rate, sensitivity, and positive predictive value than dedicated PET ($P < 0.01$).

We were able to clarify the performance profile of FDG-PET and PET/CT for cancer screening on the basis of a Japanese nationwide survey. The number of facilities possessing PET is increasing steadily, highlighting the necessity of evaluating the usefulness of "FDG-PET cancer screening" as soon as possible by undertaking long-term investigations of large series of subjects.

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Long-term follow-up study of a population-based 1996–1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography

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Summary Early diagnosis and treatment are important for improvement of the low survival rate of patients with lung cancer. The objective of this study was to evaluate the long-term survival rate of patients identified to have lung cancer by our population-based baseline and annual repeat low-radiation dose computed tomography (low-dose CT) screenings, conducted in 1996–1998. A total of 13,037 CT scans were obtained from 5480 subjects (2969 men, 2511 women) aged 40–74 years at the initial CT screening. Lung cancer was detected in 63 subjects (57 were detected by CT scans and underwent surgery; 1 was detected by sputum cytology and

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underwent surgery; 3 rejected treatment; and 2 were interval cases that developed symptoms prior to the next annual repeat CT screening). Follow-up study included review of medical records. Death certificates were examined to check for any deceased interval case among participants. Postoperative follow-up of the 50 survived patients ranged from 70 to 117 (median, 101) months. Eight patients died during follow-up (6 due to lung cancer from 20 to 67 months after surgery and 2 deaths unrelated to lung cancer, each 7 and 60 months following surgery). Three patients who rejected treatment died 14 months to 6 years after positive screening CT scans, and the 2 interval cases died at each 17 and 30 months, respectively, following negative screening CT scans. Survival was analysed in 59 patients with lung cancer detected by low-dose CT screening (excluding two patients; one was detected by sputum cytology and the other had mass lesion already noted on the chest radiograph of the previous year). The 10-year survival calculated by the Kaplan–Meier method was 83.1% (95% CI: 0.735–0.927) for death from all causes and 86.2% (95% CI: 0.773–0.951) for death from lung cancer. The survival rate was excellent for never-smokers, patients with BAC and adenocarcinoma/mixed types with non-solid CT density pattern, associated with Noguchi's type A or B and pathologic stage IA. A poorer prognosis was noted in smokers with adenocarcinomas/mixed types, associated with part-solid or solid CT density pattern and Noguchi's type C or D. All patients with non-solid tumours measuring 6–13.5 mm at presentation are alive, patients with part-solid tumours, measuring 17 mm or more, or solid tumours, measuring 13 mm or more at presentation were associated with increased risk of lung cancer-related morbidity or mortality.
The estimated rate of possible over-diagnosis was 13% in total and we failed to cure 17% of patients encountered in the programme. Low-dose CT screening substantially improves the 10-year survival for lung cancer with minimal use of invasive treatment procedures.

1. Introduction

The cure rate of patients with lung cancer is low; nearly 174,000 new cases of lung cancer and 162,000 deaths from it (93% of the diagnosed cases) are expected in the United States in 2006 [1]. This reflects the advanced stage of the disease when first detected and treated. This dismal low cure rate of lung cancer has remained low for a long time. The cure rate has not improved also under the well organized traditional chest radiography screening for lung cancer in Japan, mainly due to the poor performance of such screening in detecting lung cancer at an early stage [2–4]. The use of low-dose computed tomography (CT) in screening for lung cancer is promising in resolving this problem, by allowing a better detection of small, low-density nodules, and could potentially lead to an excellent cure rate for the disease [5]. We conducted a population-based annual screening trial for lung cancer using a mobile low-dose spiral CT scanner from 1996 to 1998 and have reported its usefulness in detecting and treating small lung cancers [6,7]. In the present study, we report the results of a long-term follow-up study of all 63 consecutive patients involved in the programme, including 58 patients with lung cancer identified in the programme and subsequently treated by surgery, three patients who had lung cancer identified in the programme but did not receive treatment and two interval patients who were negative in the programme but developed symptoms prior to the next annual repeat CT. We summarized the outcome of the patients and the clinicopathological features by examining the medical records of those who survived without any lung cancer-related disorders, failure cases who died of lung cancer or survived lung cancer with a related morbidity and the interval cases.

2. Subjects and methods

2.1. Background

Since 1987, annual chest screening had been performed in Japan for every individual aged more than 40 years by chest miniature fluoro-photography, as well as sputum cytology for smokers, based on the Health and Medical Services Law for the Aged. We conducted a population-based mobile low-dose CT screening programme for lung cancer in 1996–1998 among the residents of the 29 municipalities of Nagano Prefecture, a rural area in Japan [6,7]. Most of the participants in our programme had previously undergone a population-based standard annual chest screening test.

2.2. Subjects

The subjects of the present study were described previously [8]. Briefly, this study is based on a total of 13,037 CT scans from 5480 participants (2969 men, 2511 women) who were 40–74 years old at the initial CT screening in 1996, including 2969 (54.2%) men and 2511 (45.8%) women. There were 2047 (37.4%) smokers, 393 (7.2%) ex-smokers (who have stopped smoking for more than 5 years) and 3040 (55.4%) non-smokers (who have smoked fewer than 100 cigarettes during their lifetime): the 2969 men included 1927 (64.9%) smokers, 383 (12.9%) ex-smokers and 659 (22.2%) non-smokers, and the 2511 women included 120 (2.2%) smokers, 10 (0.2%) ex-smokers and 2381 (43.4%) non-smokers. All participants gave informed consent for the screening.

2.3. CT imaging

Low-dose CT scan of the thorax was taken in a mobile CT unit (model CT-W950SR; Hitachi Medical, Tokyo, Japan); the technical scan parameters were 120 kV, 50-mA tube current in 1996 and 25-mA in 1997 and 1998, 10-mm collimation, 2-s tube rotation, and 10 mm/s table speed. Immediate work-up examinations were recommended for participants who had suspicious lesions (possible or probable lung cancer). For participants who had a nodule/nodules smaller than 3 mm, they were placed on a 3-month-delayed work-up examinations to check any interval increase in size. The work-up examinations were conducted at Shinshu University Hospital, Matsumoto, Japan, and were mainly based on high-resolution CT (HRCT) examinations (Hi Speed Advantage CT, GE Medical Systems, WI) without intravenous contrast injection; the scan parameters were 120 kV, 200-mA tube current, 1-mm collimation, 1-s tube rotation, and 1 mm/s table speed.

2.4. Image reading

Interpretation of CT images was based on commonly used imaging features, namely morphological characteristics and interval growth tendency. Benign lesions represented round nodules with smooth, well-defined margins, non-round nodules with angular configuration, presence of benign calcification within the nodule and stability of tumour size. Malignant lesions had irregular, lobulated, shaggy or poorly defined margins, margins with spiculation or pleural tail, interval increase in size or density or interval change of internal structures of the lesion on a series of follow-up HRCT images [9–11].

2.5. Assessment of tumour growth

Tumour growth was determined by comparing the current HRCT images with the corresponding previous ones, displayed side-by-side on a high-resolution cathode-ray tube (CRT) monitor. HRCT images were evaluated at the level of largest tumour diameter. Interval tumour growth was determined by comparing the spatial relationships with neighbouring structures, i.e., the distance between the tumour margin and the neighbouring pulmonary vessels and bronchi. The maximum transverse tumour diameter was measured on the CRT monitor and an increase by 2-mm (which corresponded to 5 pixels on HRCT images, i.e., 1 pixel = 0.4 mm) or more during the follow-up period denoted tumour growth. A clinically important tumour growth represented interval increase in tumour density on the HRCT images of 30 HU or more (tumour density represented the average CT value for the region of interest, defined on the CRT monitor by manual tracing using a light pen just along the interior edge of the tumour). Tumour growth was also considered when a change was observed in the internal density pattern, i.e., the appearance of a part-solid pattern in a non-solid nodule or enlargement of a dense central zone in a part-solid nodule. When possible, we calculated also the tumour volume doubling time (TVDT) using the formula of Schwartz [12], to quantitate the growth rate of the lesion, in addition to the comparative analysis on a series of follow-up CT images.

2.6. Diagnostic work-up

To supplement non-contrast HRCT examinations, we performed contrast enhanced dynamic CT scans initially and contrast enhanced dynamic magnetic resonance imaging (MRI) studies later in our work-up examinations. These were expected to provide additional information related to the lesion vascularity and help characterize the nodular lesions in terms of malignancy [13–15]. Positron emission tomography (PET) was not made available during our programme for the purpose of making differential diagnosis of lung nodules.

2.7. Intervention and surgery

When the suspicious lesion was identifiable on X-ray TV fluoroscopy or our pulmonologists considered it could be approachable, even if it was not identifiable, fibreoptic bronchoscopic lung biopsy under TV fluoroscopy guidance was performed, combined with transbronchial needle aspiration, forceps biopsy, brushing and washing prior to thoracotomy. CT fluoroscopy for the use of this purpose was not made available during our programme.

For the patients with a strongly suspicious lung cancer based mainly on HRCT findings, we recommended thoracotomy, with lobectomy or other minor procedures (wedge resection or segmentectomy), or video-assisted thoracic surgery (VATS). When the diagnosis of malignancy was confirmed intra-operatively using frozen sections, extended resection of the lung and lymph nodes was performed immediately. For the patients with a transbronchial lung biopsy (TBLB)-based diagnosis of lung cancer, we recommended thoracotomy. Patient with histopathological diagnosis of small cell lung cancer (SCLC) received adjuvant chemotherapy postoperatively. The period between first suspicion of lung cancer based on the CT screening and surgery ranged from 1 to 48 months (median 4.3 months).

When work-up examinations for patients with suspicious non-cancerous lesions were performed at community/local hospitals, the referring physicians were requested to send copies of the results of examinations and treatments to the Matsumoto Research Centre, the coordinating centre of our CT screening programme.

2.8. Histopathological diagnosis and staging

The histopathological diagnosis was re-classified in 54 patients (58 lesions) based on the updated WHO 2004 classification [16] (by T.H., a pathologist with a subspecialty interest in pulmonary diseases). Lesions were diagnosed in 53 of these patients by screening CT scans (including 4 patients each with two lesions in the same lung or both lungs) and in one patient by sputum cytology. All 54 patients underwent surgery at Shinshu University hospital or its allied hospitals. The pathology was not revised in three patients who underwent surgery at other hospitals and histopatho-

logical materials were not available for the present study. Stage classification was based on the International System for Staging Lung Cancer 1997 [17].

2.9. Outcome determination

We summarized the outcome of all 63 patients with lung cancer encountered in our CT screening programme by reviewing the medical records. The date of CT screening examination, date of operation, and date of outcome (date of death or of the last follow-up when the subject was confirmed to be alive) were determined. The outcome of patients was examined according to the smoking status, histopathology, tumour size, CT density pattern (non-solid, part-solid and solid), pathological stage and Noguchi's classification. In calculating post-surgical survival, zero time represented the date of operation. Censoring was conducted on either the date of death, relocation, or the end of the follow-up period. Death certificates were examined from May 1, 1996 to December 31, 2005, in all 29 municipalities to check for any interval case (i.e., death from lung cancer of a CT screening-negative case) among all 5480 participants who were enrolled in 1996 and screened by initial CT scans with or without annual repeat CT scans. We examined the death certificate, because this was the only officially available information in Japan on the inhabitant's death and we presumed this would provide us information on nearly all deceased cases due to lung cancer, since a notice of death of the inhabitant was strictly controlled by the municipality office and people's removal was uncommon at this rural mountain area where we had conducted the CT screening programme. The investigation was approved by the Ethics Committee of the Osaka Medical Centre for Cancer and Cardiovascular Diseases and the Ethics Committee of the Azumi General hospital.

2.10. Statistical analysis and survival rates

Survival was calculated using the Kaplan–Meier method on the basis of death due to all causes and due to lung cancer. Survival curves were compared by log rank test and the modified Wilcoxon test. All analyses were completed using the PHREG Procedure, available in SAS (Version, 6.07) package [18].

3. Results

Among the 43 patients who received TBLB, 25 had lung cancer and 15 of these were positive (with cytological or histopathological diagnosis of lung cancer) at TBLB. The other 18 patients were found to have non-cancerous lesions; i.e., negative results at TBLB. However, two of the 18 patients (one with focal fibrosis and one with inflammatory pseudotumour1) subsequently underwent surgery due to an increase in nodule size in one patient and increase in density and change in interval structure/pattern in another patient, on the repeat HRCT scans. Thus, the calculated overall accuracy of X-ray TV fluoroscopy guided TBLB for 43 patients was 77%, sensitivity for patients with lung cancer of 60%, specificity for patients with non-cancerous lesions of 100%, with a positive predictive value of 64% and a negative predictive value of 100%.

Another 14 patients were considered to have highly suspicious lung cancer by the HRCT work-up examinations. They subsequently underwent surgery but the histopathological examination of the surgical specimens indicated that the lesion was not malignant; specifically, 10 lesions were diagnosed as atypical adenomatous hyperplasia (AAH), 2 as focal fibrosis, 1 as organizing pneumonia and 1 as granuloma ($n=1$).

The final analysis indicated that our screening programme identified 63 patients with lung cancer based on screening 5480 individuals. For these 63, 58 patients (including one patient who had a cytology detected-CT negative central cancer) underwent surgery between August 1996 and June 2000, 3 rejected treatment, and the remaining 2 were interval cases (developed symptoms and showed chest radiograph abnormalities prior to the next annual repeat CT screening).

The 57 patients who were identified by CT scans in the programme and subsequently underwent surgery, ranged in age from 46 to 75 years (median: 66, mean: 65.1) at the time of surgery; they comprised 24 (42%) women and 33 (58%) men (Tables 1A–1C). All female patients were never-smokers. Three (5.3%) male patients were never-smokers, one (1.7%) was ex-smoker and 29 (50.9%) were smokers. The final diagnosis in the 57 patients was bronchioloalveolar carcinoma (BAC) in 21 patients (22 lesions, 37%) (Table 1A), adenocarcinoma with mixed subtypes in 24 patients (27 lesions, 42%) (Table 1B), non-BAC-adenocarcinoma in 10 (18%) (Table 1C, which included squamous cell carcinoma in 6 (11%), small cell carcinoma in 3 (5%) and large cell carcinoma in 1 (2%)) and well-differentiated adenocarcinoma in 2 (4%). The latter two were diagnosed in 1997 based on the WHO classification prior to 2004, both (a man and woman) never-smoked, had stage IA lesion and remain alive at present 8 years and 5 months after surgery.

The postoperative pathological stage based on the International System 1997 [17] for 53 (93%) patients with a solitary lesion was Stage IA in 46 (80.7%), IB in 2 (3.5%), IIA in 2 (3.5%), IIB in 1 (1.8%), and IIIA in 2 (3.5%). The pathological stage for the 4 patients (7.0%) who each had two pulmonary lesions, was Stage IA in 2 (3.5%) (two separate lesions <30 mm in size in the contralateral lobes, of synchronous origin [19]), Stage IB in 1 (1.8%) (two lesions in the contralateral lobes, of synchronous origin, one larger and another smaller than 3 cm), and Stage IV in 1 (1.8%) (one lesion directly invaded the right upper chest wall (T3), and the other was smaller than 30 mm in the right basal lung (M1), accompanied by ipsilateral mediastinal nodal involvement (N2)).

With regard to outcome, 21 patients with BAC (14 non-smokers and 7 smokers at study entry) are still alive at the time of writing of this report (Table 1A). With regard to features of the nodules identified on the original HRCT images taken at the first work-up examination: 13 showed non-solid-, 7 part-solid- and 1 solid CT density pattern, the tumour size ranged from 6 to 18 mm (median; 9 mm), the TVDT ranged from 168 to 1421 days (median 729 days) [12]; Noguchi's classification was type A (localized bronchioloalveolar carcinoma) in 13, type B (localized bronchioloalveolar carcinoma with foci of collapse of alveolar

Table 1A Clinico-pathologic features and outcome of 21 patients with BAC

Case no.	Age (years)	Sex	Smoking history (pack-years)	CT pattern	Size on CT detection	Noguchi' class	Pathological stage	Survival
1	67	F	0	Non-solid	7.0	A	IA	Alive
2	69	F	0	Non-solid	7.0	B	IA	Alive
3	59	F	0	Non-solid	8.0	A	IA	Alive
4	68	F	0	Non-solid	12.0	A	IA	Alive
5	58	F	0	Non-solid	13.0	B	IA	Alive
6	62	F	0	Non-solid	13.5	A	IA	Alive
7	62	F	0	Part-solid	6.0	A	IA	Alive
8	64	F	0	Part-solid	9.0	A	IA	Alive
9	64	F	0	Part-solid	10.0	A	IA	Alive
10	70	F	0	Part-solid	17.0	B	IA	Alive
11	66	F	0	Part-solid	18.0	B	IA	Alive
12	60	F	0	Solid	12.0	B	IA	Alive
13	61	M	0	Non-solid	6.0	A	IA	Alive
14	65	M	80	Non-solid	6.0	A	IA	Alive
15	55	M	30	Non-solid	7.0	A	IA	Alive
16	73	M	50	Non-solid	7.5	A	IA	Alive
17	64	M	0	Non-solid	8.0	A	IA	Alive
18	62	M	0	Non-solid	9.0	A	IA	Alive
19	72	M	25	Non-solid	10.0	C	IA	Alive
20	68	M	30	Part-solid	9.0	B	IA	Alive
21	61	M	27	Part-solid	10.0	B	IA	Alive

structure) in 7, and type C (localized bronchioloalveolar carcinoma with foci of active fibroblastic proliferation) in 1; and pathological stage was IA in all 21 lesions.

Of the 24 patients (Table 1B) with adenocarcinoma: 17 (70.8%) are alive free of lung cancer-related disorders, 1 (4.2%) is alive with lung cancer-related disorder, 5 (20.8%) died of lung cancer (they had tumours $\geq$13 mm on the first HRCT scans) and 1 (4.2%) died of disorder unrelated to lung cancer. This group consisted of 11 women who were all non-smokers and are alive (including one with lung cancer-related morbidity), and 13 men who were smokers, with 5 deaths from lung cancer and one death not related to lung cancer. With regard to features of the nodules identified on the original HRCT images taken at the first work-up examination: the tumour size ranged from 6 to 45 mm (median; 14.5 mm); the CT density patterns were non-solid in 1, part-solid in 12 and solid in 11; TVDT ranged from 60 to 1158 days (median 302 days); Noguchi's classification was type A in 1, type B in 2, type C in 18, type D (poorly differentiated adenocarcinoma) in 1 and unknown in 2; and the pathological stage was IA in 18, IB in 2, IIA in 1, IIB in 1, IIIA in 1 and IV in 1.

Of the 10 patients with histopathological diagnosis other than BAC or adenocarcinoma (Table 1C), 8 (80%) are still alive while the remaining 2 died; one (10%), with tumour which measured 16.5 mm, due to lung cancer and the other (10%) due to pneumonia. Nine of 10 patients were smokers and one was ex-smoker; tumour size ranged from 8 to 31 mm (median; 17 mm); the CT density pattern was solid in all lesions, TVDT ranged from 52 to 346 days (median 66.5 days); and pathological stage was IA in 7, IB in 1, IIA in 1 and IIIA in 1. Nine of 10 patients with CT screening–-detected solid non-BAC adenocarcinoma were cured by surgery, including all three cases of SCLC who received adjuvant chemotherapy after surgery [8]. One patient with large cell carcinoma, whose tumour measured 28 mm also received chemotherapy postoperatively but discontinued it shortly after due to intolerance, is still alive.

Among the 57 patients, 22 had solid nodules (1 BAC, 12 adenocarcinoma and 10 non-BAC-non-adenocarcinoma) and 15 (68.2%) of these are alive, while 5 (22.7%) died of lung cancer (4 with adenocarcinoma and 1 with squamous cell carcinoma) and 2 (9.1%) died of disorders unrelated to lung cancer.

There was no failure case from all 21 patients with BAC and from all 14 patients with non-solid tumours which were smaller than 14 mm. There was no failure case from all 10 patients with part-solid lesions smaller than 17 mm and from all 7 patients with solid nodules smaller than 13 mm.

Table 2A shows summary of the seven treatment failure cases ($n=7$), six deaths from lung cancer ($n=6$) and one lung cancer-related morbidity ($n=1$), with the pertinent data in Tables 1B and 1C. They included 3 patients detected in the initial and 4 patients detected in the repeat annual-CT screening; all six male patients, were smokers and the remaining one female patient was non-smoker; most of them had a more advanced pathological stage than IA; 6 of all 7 patients had adenocarcinoma with mixed subtypes (Noguchi's classification of type C or D) and the remaining one had squamous cell carcinoma.

The interval between CT screening and surgery and its influence on survival varied depending on the cases; prolongation was mostly caused by patient's delay to visit the hospital to receive work-up examinations, patient's hesitation to undergo surgery or the referring physician's hesitation to recommend surgery due to difficulty in establishing diagnosis of lung cancer. In this regard, even 1-month delay appeared to degrade the outcome of a patient who

Table 1B Clinico-pathologic features and outcome of 24 patients with adenocarcinoma, mixed types

Case no.	Age (years)	Sex	Smoking history (pack-years)	CT pattern	Size on CT detection	Noguchi's class	Pathological stage	Survival
22	70	F	0	Non-solid	6.0	A	IA	Alive
23	73	F	0	Part-solid	9.0	B	IA	Alive
24	62	F	0	Part-solid	8.0	C	IA	Alive
25	68	F	0	Part-solid	11.0	C	IA	Alive
26	69	F	0	Part-solid	11.0	C	IA	Alive
27	74	F	0	Part-solid	17.0	C	IA	Alive[a]
28	55	F	0	Part-solid	17.0	C	IA	Alive
29	48	F	0	Part-solid	17.0	C	IA	Alive
30	71	F	0	Part-solid	19.0	C	IA	Alive
31	65	F	0	Solid	12.0	C	IA	Alive
32	46	F	0	Solid	14.5	C	IA	Alive
33	59	M	60	Part-solid	18.0	B	IA	Alive
34	52	M	60	Part-solid	16.0	C	IIA (T1N1M0)	Alive
35	73	M	30	Part-solid	18.0	C	IA	Died of lung cancer
36	68	M	30	Part-solid	17.0		IA	Alive
37	57	M	35	Solid	10.5	C	IA	Alive
38	73	M	30	Solid	12.0	C	IA	Died of renal cancer
39	61	M	40	Solid	12.0	C	IV (T3N2M1)	Alive
40	59	M	15	Solid	14.0	C	IB (T2N0M0)	Died of lung cancer
41	62	M	30	Solid	14.5	C	IA	Alive
42	72	M	40	Solid	15.0	C	IIB (T3N0M0)	Died of lung cancer
43	62	M	25	Solid	19.0	C	IA	Alive
44	55	M	38	Solid	13.0	D	IIIA (T1N2M0)	Died of lung cancer
45	68	M	46	Solid	45.0		IB (T2N0M0)	Died of lung cancer

[a]Alive with disease.

had a rapidly growing carcinoma, as was shown in a 56-year-old patient (Case 4, Table 2A) who had a lung tumour with a solid-density pattern, TVDT of 104 days, measuring 17 mm at presentation, developed hilar and mediastinal nodal enlargement during his hesitation to undergo surgery. In addition, delay in making diagnosis could also be considered to have degraded the outcome of a never-smoker female (Case 7, Table 2A), who had lung cancer with TVDT

Table 1C Clinico-pathologic features and outcome of 10 patients with non-adenocarcinomas

Case no.	Age (years)	Sex	Smoking history (pack-years)	CT pattern	Size on CT detection	Histology	Pathological stage	Survival
48	72	M	0	Solid	18.0	SCC	IA	Alive
49	67	M	72	Solid	8.0	SCC	IIA (T1N1M0)	Alive
50	47	M	27	Solid	11.0	SCC	IA	Alive
51	65	M	47	Solid	16.5	SCC	IA	Died of lung cancer
52	73	M	50	Solid	17.0	SCC	IA	Alive
53	72	M	48	Solid	31.0	SCC	IIIA (T2N2M0)	Died of pneumonia
54	74	M	25	Solid	12.0	SCLC	IA	Alive
55	66	M	15	Solid	17.0	SCLC	IA	Alive
56	71	M	28	Solid	19.5	SCLC	IA	Alive
57	73	M	30	Solid	27.5	Large cell carcinoma	IB (T2N0M0)	Alive

Table 2A Treatment failure cases

Case	Age/sex	Prior CT screen	Tumour size on initial HRCT (mm)	CT density pattern	Pathological stage/Noguchi's type	Histology	TVDT*	Interval between screening and surgery (months)	Interval between surgery and death (years, months)
1	59/M	–	14	Solid	IB/Type C	Ad	131	3	3, 9
2	73/M	–	18 (Lt), 15 (Rt)	Part-solid	IA/Type C	Ad	1158 (Lt)	18	2, 7
3	68/M		45 (Lt), 20 (Rt)	Solid	IB/Type ?	Ad		4	4, 11
4	56/M	Normal: 96	17	Solid	IIIA/Type D	Ad	104	2	4, 8
5	73/M	Normal: 96	15	Solid	IIIB/Type C	Ad	72	2	1, 8
6	67/M	Emphysema (96–97)	16	Solid	IIIB	Sq	52	1	5, 7
7	74/F	Non-cancerous (misclassified)	15	Part-solid	IA/Type C	Ad	370	18	9, 2 (alive, with mediastinal nodal involvement)

Ad: Adenocarcinoma with mixed subtypes, Sq: Squamous cell carcinoma, TVDT*: tumour volume doubling time (days).

of 370 days, which had been classified as suspicious inflammatory nodule at the initial CT, but classified next year as probable lung cancer at the repeat annual CT.

Three lung cancer-related deaths were due to rejection of treatment and 2 similar deaths were due to interval occurrence of lung cancer (Table 2B). Among the former group of 3 patients, one never-smoker female had a fairly large mass on the initial CT scans, which had been identified on a chest radiograph taken in the previous year, refused treatment, but soon developed bone metastasis; another never-smoker female had a part-solid lesion, 16 mm in size in the right upper lung on the initial CT scans, did not receive treatment but developed superior vena cava syndrome 64 months after the initial CT screening (Fig. 1); and the third was a male smoker with a diagnosis of SCLC, established by TBLB, but refused treatment [8]. Both of the two interval cases were male smokers. One developed cough and chest radiograph abnormality, 4 months after a negative repeat CT screening [8]. Another patient presented with dry cough 10 months after a negative initial CT screening (with CT diagnosis of emphysema) and chest radiograph demonstrated disseminated nodular lesions in both lungs.

Survival was analysed for 59 patients with lung cancer detected by low-dose CT screening (excluded 2 patients; one was diagnosed with lung cancer by sputum cytology, not by CT scans, and the other who had a mass lesion, already noted on the chest radiograph of the previous year and rejected treatment). The 5-year survival was 89.8% (95% CI: 0.821–0.975) for death from all causes and 91.5% (95% CI: 0.837–0.993) for death from lung cancer. The 10-year survival was 83.1% (95% CI: 0.735–0.927) for death from all causes and 86.2% (95% CI: 0.773–0.951) for death from lung cancer. Analysis of survival for 57 patients (excluding the two patients who rejected treatment) showed the 5-year survival was 91.2% (95% CI: 0.839–0.986) for death from all causes and 93% (95% CI: 0.839–0.986) for death from lung cancer. The 10-year survival was 86.0% (95% CI: 0.769–0.950) for death from all causes and 87.7% (95% CI: 0.791–0.962) for death from lung cancer.

The survival rates for patients with BAC, pathological stage IA and non-smokers were excellent. For example, the 10-year survival rate was 100% (95% CI: 1.0–1.0) for BAC cases for death from all causes and from lung cancer, while the rate was 76.9% (95% CI: 0.607–0.931) for adenocarcinoma with mixed subtypes for death from all causes and from lung cancer, and that for non-BAC-adenocarcinoma was 66.7% (95% CI: 0.400–0.934) for death from all causes and 80% (95% CI: 0.552–1.000) from lung cancer. The latter included all three patients with small cell carcinoma who were detected by CT screening, treated by surgery and adjuvant chemotherapy and who remain alive [8].

With regard to survival according to pathological stage, there was significant difference in survival due to lung cancer between stage I and stage II–IV (log rank test: $p = 0.0668$, Wilcoxon test: $p = 0.0646$), with a much better survival for patients with early stage lung cancer than advanced disease. Specifically, the pathologic stage was I in 51 patients and II–IV in 6. The 10-year survival of the former group was 88.5% (95% CI: 0.798–0.971) for death from all causes and 90.3% (95% CI: 0.822–0.984) for death from lung cancer. In contrast, the 10-year survival rate of the latter group was

Table 2B Failure cases (3 refusals of treatment and 2 interval cases)

Case	Age/sex	Prior CT screen	Tumour size at presentation	Histology	Treatment	Cause of death	Interval between detection and death (years, months)
1	63/F	–	43		Refused	Bone metastasis	1, 2
2	72/F	–	16	Adenocarcinoma	Refused	SVC syndrome	6, 0
3	70/M	Non-ca (misclassified)	20 (13 mm in prior year)	SCLC	Refused	Died, unrelated to lung cancer	2, 0
4	61/M	Normal	21	SCLC	Partial resection, chemo-therapy	Died	1, 6
5	66/M	Emphysema	25, with multiple smaller nodules	Poorly diff adenoCa	Refused	Died, bone and brain metastases	0, 7.5

non-ca: non-cancerous, poorly diff: poorly differentiated, mets: metastases.

only 50.0% (95% CI: 0.10–0.90) for death both from all causes and lung cancer.

4. Discussion and summary

We have followed-up all 59 patients with mostly small lung cancer detected by our low-dose CT screening programme, conducted from 1996 to 1998, for 70–117 (median, 101) months after surgery to the end of July 2006. The survival analyses showed excellent prognosis with a 10-year survival of 83.1% for death from all causes and 86.2% for death from lung cancer. The survival was particularly excellent for never-smokers with BAC, adenocarcinoma with mixed types of non-solid CT density pattern associated with Noguchi's type A or B. A poorer prognosis was noted for smokers with adenocarcinomas of mixed types, showing part-solid or solid CT density pattern and Noguchi's type C or D (we had no E or F cases in the programme). Interestingly, patients with squamous cell carcinomas, SCLCs and large cell carcinoma also had a fairly excellent prognosis. The period between surgery and death for smokers ranged from 20 to 67 months (median, 51 months), therefore nearly 5 years appeared to be a sufficient duration to evaluate the mortality among smokers [20,21]. We should note here that our screening programme comprised many non-smokers among participants who most frequently developed BAC or well-differentiated adenocarcinoma leading to an improved survival rate of the patients [22–24]. A Japanese study on the 267 surgically treated patients has shown 5-year survival rate at 55% for the non-smoker (versus 45% for current smoker) [25]. Care should be taken in comparing our results with those from other programmes intended for smokers.

In 1995, the detection rate of lung cancer in the standard mass screening in Japan was 0.05% of total participants (data reported by the Japanese Research Committee of Studies on Evaluation of Effectiveness of Cancer Screening in 1998, Japanese publication). Specifically, in the rural area of Nagano, Japan, the estimated 1998 annual mortality rate due to lung cancer was 37.3 per 100,000 population. However, we detected and treated many patients with small lung cancer in our initial in 1996 and repeat annual-CT screenings in 1997–1998. The detection rate was approximately nine times higher than that in the standard mass screening in Japan. Because we had a considerable number of missed cases (by detection or interpretation error due to our unfamiliarity with the CT findings of lung cancer at an early phase of the programme, particularly at the initial screening [26]), we examined the corrected number of patients, who had recognizable evidence of abnormality which was retrospectively identified on the CT images of the previous year, in addition to the actual (observed) number of patients detected in the programme. The former represents the number of patients that would have been identified had our initial and the first year annual repeat CT scans been interpreted by experienced observers. We actually detected 23 patients at the initial CT screening, 24 at the first annual- and 9 at the second annual-repeat CT scans; but the corrected numbers of the patients were 38, 13 and 5, respectively.

TVDT has been used to define tumour growth rate; TVDT of less than 400 days has been a rough standard for the

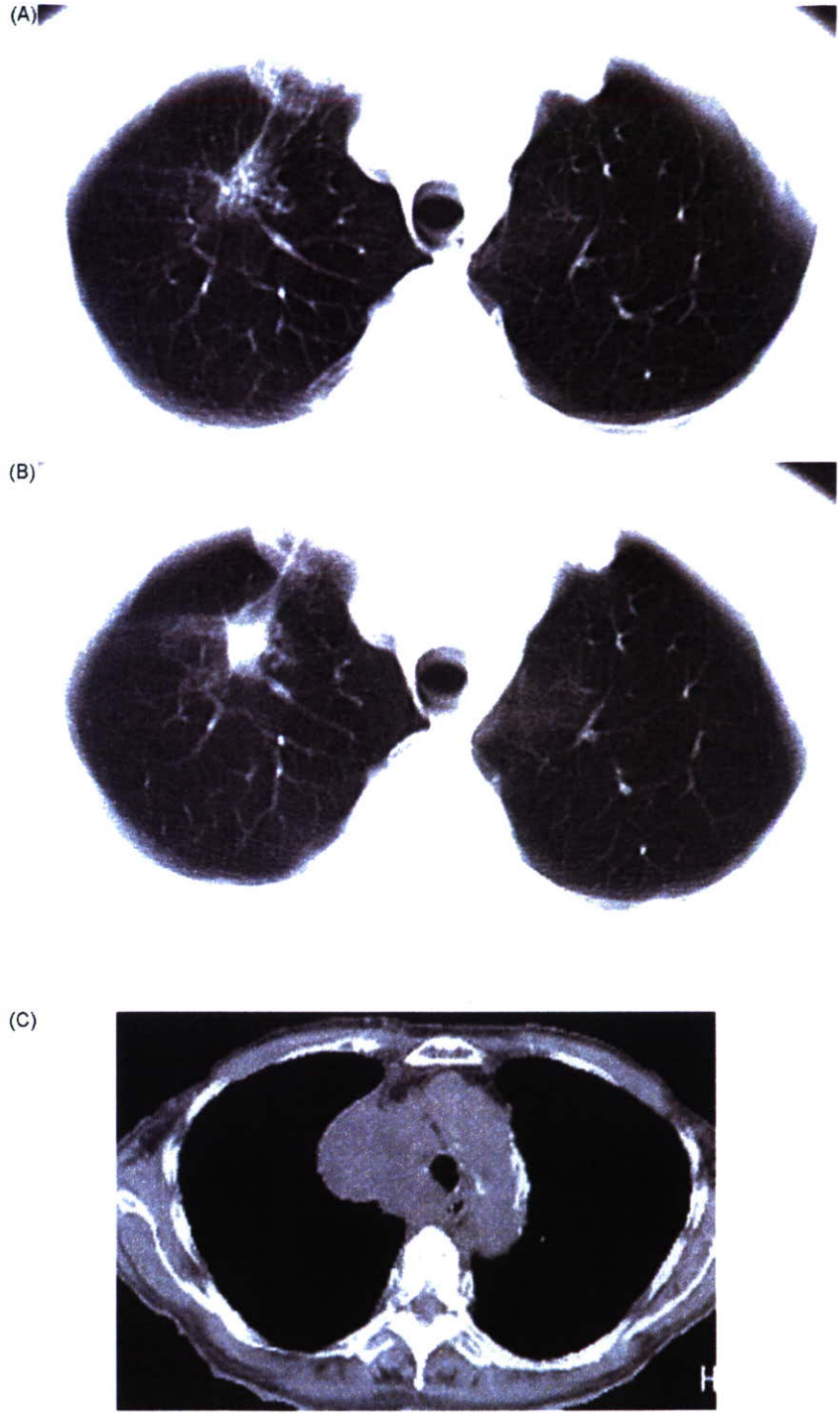

Fig. 1 A 72-year-old woman with untreated partly solid lesion that advanced after 5 years to a huge invasive solid mass, causing superior vena cava syndrome. (A) Screening low-dose CT scan obtained in June 1996 shows an irregularly shaped partly solid lesion in the right upper lung, which was classified as probable lung cancer. (B) Repeat CT images in June 1998 (no repeat CT in 1997) shows the lesion to have increased in size and again reported as highly suspicious lung cancer. (C) Conventional CT taken in October 2001 due to suspected SVC syndrome showed a huge soft-tissue density mass invading the mediastinum.

aggressive lung cancers, although possibility of a wider range of doubling time at a slowly growing side associated with well-differentiated adenocarcinoma has been indicated, particularly with CT-screening detected small pulmonary nodules [27,28]. In our programme, many cases with BAC or well-differentiated adenocarcinoma were involved at the initial CT screening (34 patients among 5480 participants), mostly non-smokers (22 patients among 3040 non-smokers).

The average TVDT for non-smokers was 607 days (nearly twice as long as that for smokers; which was on average 292 days) and this appears to have caused a length-time bias [12] leading to a great discrepancy between the detection rate by CT screening and mortality rate.

We cannot estimate the extent of over-diagnosis (i.e., a cancer that was treated, but never would have led to death of the patient) [29] and influence of lead-time, length-time and over-diagnosis issues on survival rate of the patients based on the medical information of our real patients. Therefore, we provide the results of our study to estimate the age of the patient at the time that the lesions would have grown to 30 mm, based on the tumour size at presentation and the calculated TVDT, together with the expected time of patient's death by adding 2 years to it (Table 3), since it is reported that patients with lung cancer of 30 mm or larger in size, when untreated, would die of lung cancer in 2 years in average [30]. TVDT was calculated for

Table 3 Estimated age of patient's death calculated by tumour volume doubling time related to CT pattern, histology and smoking status

Case	Sex	Age	Expected age of death	CT pattern	Histology	Smoking status	Size	TVDT
1	F	46	49	Solid	Adeno-M	Never	14.5	230.9
2	M	47	53	Solid	SCC	Smoker	11	346.1
3	F	48	56	Part-solid	Adeno-M	Never	17 (12 × 21)	661.4
4	M	52	57	Part-solid	Adeno-M	Smoker	16	285.8
5	F	51	59	Part-solid	Well Ad	Never	12	526
6 d	M	55	59	Solid	Adeno-M	Smoker	17	103.7
7	F	55	62	Part-solid	Adeno-M	Never	17	381.1
8 d	M	59	62	Solid	Adeno-M	Smoker	14	130.9
9	M	57	62	Solid	Adeno-M	Smoker	10.5	269.1
10	M	59	65	Part-solid	Adeno-M	Smoker	18	570.8
11 d	M	61	66	Solid	Adeno-M	Smoker	10.5 (12?)	60.3
12	M	55	67	Non-solid	BAC	Smoker	12	787
13	F	58	67	Non-solid	BAC	Never	13	632.7
14	M	62	67	Solid	Adeno-M	Smoker	19	609.8
15	M	61	67	Part-solid	BAC	Smoker	10	168.2
16	F	62	68	Part-solid	Adeno-M	Never	8	155.3
17	M	62	68	Solid	Adeno-M	Smoker	14.5	198.2
18 d	M	65	69	Solid	SCC	Smoker	16.5	51.6
19	M	66	69	Solid	SCLC	Smoker	17	54.1
20	M	67	71	Solid	SCC	Smoker	8	66.2
21	F	64	72	Part-solid	BAC	Never	10	477.9
22	F	64	73	Part-solid	BAC (M)	Never	9	311.4
23	F	68	74	Part-solid	Adeno-M	Never	10.5	284
24 (d)	M	71	74	Solid	SCLC	Smoker	12	132.2
25	M	73	75	Solid	Large cell carcinoma	Smoker	27.5	67
26	F	62	76	Non-solid	BAC	Never	13.5	1206
27	M	68	76	Part-solid	Adeno-M	Smoker	17	755.3
28	M	73	76	Solid	Adeno-M	Smoker	12	131.3
29 (d)	M	72	76	Solid	Adeno-M	Smoker	15	72.2
30	M	73	76	Solid	SCC	Smoker	17	73.3
31	M	74	76	Solid	SCLC	Smoker	12	60.4
32	M	71	76	Solid	SCLC	Smoker	19.5	141.7
33	M	68	76	Part-solid	BAC	Smoker	9	492.9
34	F	62	77	Part-solid	BAC	Never	6	570.5
35	F	70	79	Non-solid	Adeno-M	Never	6	318.4
36 S	F	74	79	Part-solid	Adeno-M	Never	17	369.8
37	M	62	80	Non-solid	BAC	Never	9	1386
38	F	73	81	Part-solid	Adeno-M	Never	9	451.5
39	F	69	81	Part-solid	Adeno-M	Never	11	852
40	M	61	82	Non-solid	BAC	Never	6	813.5
41 d	M	73	82	Part-solid	Adeno-M	Smoker	18	1158
42	F	67	83	Non-solid	BAC	Never	7	728.9
43	M	65	83	Non-solid	BAC	Smoker	6	881.3
44	M	67	88	Non-solid	Well Ad	Smoker	13	1733
45	F	68	89	Non-solid	BAC	Never	12	1421

d: died of lung cancer, (d): died of unrelated disorder, S: survived with lung cancer.