では、末梢発生の扁平上皮癌は漸増の後、減少傾向がみられた一方で、肺門部発生の扁平上皮癌の年間発生数には大きな変動は見られなかった。このことから、肺門部発生の扁平上皮癌の診療機会の減少は、肺腺癌の増加に伴う相対的な比率の低下であって、絶対数の減少によるものではない可能性が示唆された。

E. 結論

肺門部早期扁平上皮癌の全国調査に向けた検討を開始した。宮城県における肺癌検診発見扁平上皮癌例の発生部位の推移に関する検討から肺門部発生の扁平上皮癌の年間発生数には大きな変動は見られなかった。

F. 健康危険情報

特になし

G. 研究発表

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H. 知的財産権の出願・登録状況

1. 特許取得

なし

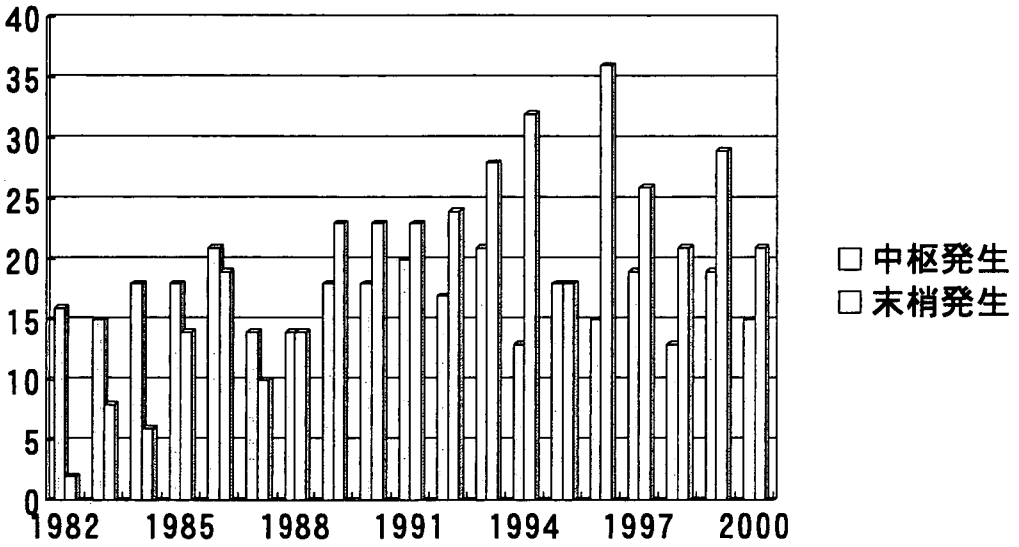
2. 実用新案登録

なし

3. その他

なし

図１　検診発見男性扁平上皮癌例の発生部位の年度別推移



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LUNG CANCER

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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KEYWORDS
Lung cancer;
Screening;
Computed tomography (CT);
Chest

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 ≥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

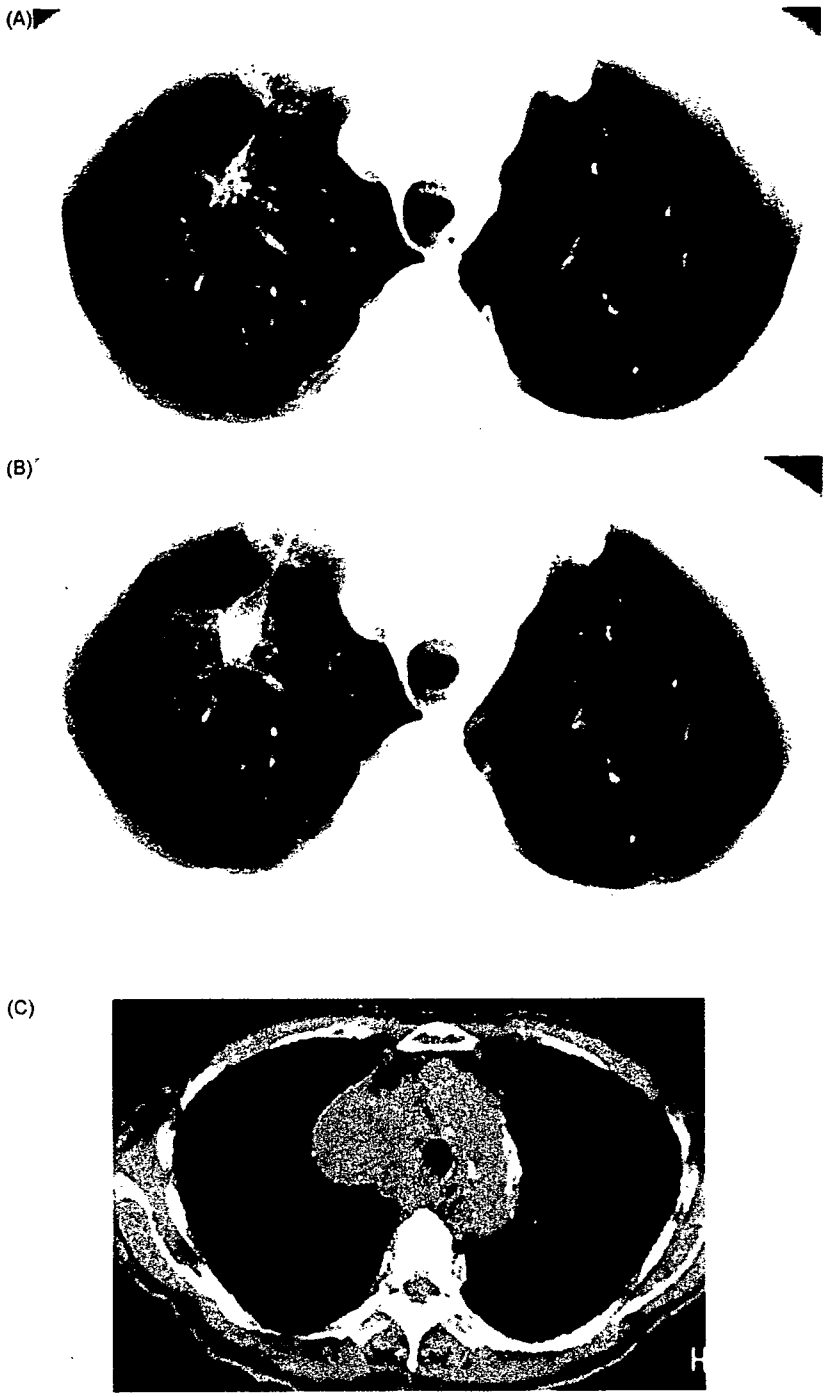

Fig. 1 A 72-year-old woman with untreated partly solid lesion that advanced after 5 years to a huge invasive solid mass, causing superior vena cava syndrome. (A) Screening low-dose CT scan obtained in June 1996 shows an irregularly shaped partly solid lesion in the right upper lung, which was classified 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.

all 45 consecutive patients for whom follow-up CT examinations were available. These cases included 10 patients with non-solid lesions, 17 patients with part-solid lesions, and 18 patients with solid lesions. The median TVDT (mean, range) was 847 days (991, 318–1733 days), 478 days (488, 155–1158 days), and 117 days (157, 52–610 days) for non-solid, part-solid and solid tumours, respectively [12]. The calculated median age (mean, range) at the time that the lesions would have grown to 30 mm was 74 years (73.8, 57–86 years), 71 years (69.7, 54–80 years), and 66 years (65, 47–74 years), respectively, and the expected median age to die for those patients was 76 years, 73 years, and 68 years, respectively. When we compared the expected death time thus obtained with the average life span of people in Japan (which in 2006 was 78.64 years for males and 85.59 years for females) and presumed those patients who had a higher expected age to die due to lung cancer than people's average life span as possible cases of over-diagnosis, our population-based low-dose CT screening programme might be considered to include approximately 13.3% (6 of 45 cases) of possible over-diagnosis in total, with 17.9% for male patients and 5.9% for female patients, and 40% for non-solid lesions. Because the above calculations were based on the assumption that the tumour growth rate remains constant (though in reality lung cancers might progress with accelerated growth rate or increase their aggressiveness with increase in tumour size, possibly having a "critical mass size" to alter biologic behaviour), the number of possible over-diagnosis cases would become even smaller [31]. We had observed increase of tumour aggressiveness during the course of tumour progression in one patient, who had a part-solid density lesion but was untreated for unknown reason for nearly 5 years, when a fatal progression was noted, associated with transformation of the lesion to a denser solid invasive mass (Fig. 1).

In our programme, all 10 patients with non-solid tumours measuring 6–13.5 mm at presentation, were pathological stage IA and are alive. Therefore, the CT feature that could be otherwise considered as a high risk for death related to non-solid tumour, such as upper limit of tumour size or distortion of internal structures, could not be clarified. With regard to BAC, however, we need further studies giving consideration not only to tumour size but also tendency of this histologic type to exhibit multifocal involvement by diffuse aerogenous metastatic spread leading to a degraded prognosis [32,33]. Next, part-solid-tumours measuring $\geq$17 mm or solid-density tumours, measuring $\geq$13 mm at presentation were associated with increased risk of lung cancer-related morbidity or mortality and early treatment of these types of lung cancer appears appropriate for excellent prognosis.

A low-dose CT screening includes the advantage of early detection and treatment to save life and disadvantage of cost and risks (due to low-dose radiation exposure). Therefore, the cost-effectiveness and benefits-risks considerations are important in planning a population-based screening. In order to plan an effective CT screening for lung cancer, it is important to define subjects suited to undergo CT screening, although this may vary depending on the features of the target population to be screened. In our programme, lung cancers were detected in patients over 45 years of age, and more tumours were seen in patients over 55 years of age. Lung cancers were detected in 24 women, 33 men, 28 non-smokers, one ex-smoker and 28 smokers. This means that lung cancers were identified not only in smokers but also in non-smokers. These data suggest that it would be inappropriate to exclude non-smokers from any such screening programme. However, many of the lung cancers detected in non-smokers were highly differentiated adenocarcinomas, which tended to progress slowly, as have been reported recently [22–24,32,33]. Considered together, it is essential also to determine the most appropriate screening interval to ensure precision and efficiency in CT screening. Patients with tumours measuring $\leq$15 mm are reported to have a better outcome than those with larger tumours [31,34]. Even a more impressive better disease-free survival was noted in patients with tumours measuring $\leq$10 mm [29]. Mediastinal lymph node metastasis was not encountered in patients with squamous cell carcinoma $\leq$20 mm, adenocarcinoma $\leq$10 mm, adenocarcinoma of Noguchi's classification type A or B and small cell carcinoma $\leq$10 mm [35]. These studies indicate that a high survival rate would be expected for patients with tumours $\leq$15 mm in diameter. Therefore, lung cancer surgery should ideally be performed before the tumour size exceeds 15 mm (from our study not exceeding 13 mm in the case of solid-CT pattern) or BAC is still types A to B, before it progresses and transforms to type C.

This fact should be considered in determining appropriate screening intervals of the repeat screening. Based on our study on TVDT, we postulate that annual repeat CT screening would be appropriate to permit lung cancers measuring $\leq$15 mm to be detected in most cases. However, for non-smokers in whom lung cancer grows slowly, the interval of repeat CT screening could be longer to detect most of the lung caner at a size smaller than 15 mm; it could be longer than this, when a larger number of subjects are studied and we could clarify the upper limit of tumour size permitting curable surgical treatment.

On the other hand, even for lung cancers that grow at a rapid rate (e.g., TVDT 50 days) in smokers, annual repeat CT screening could detect most lung cancers measuring $\leq$15 mm; TVDT was longer than 50 days in all of the 45 patients in whom TVDT was calculated (Table 3). However, we had 4 failure cases (n=4) among the total 33 repeat CT screening detected and surgery undertaken cases (n=33) (Table 2A) and, in addition, two interval cases (n=2) which were presumed to have had very short TVDT (Table 2B). This indicates that our CT screening programme failed to cure 6 of 35 (17%) patients. Table 2A shows the TVDT data for 6 of the 7 failure cases. The TVDT of 2 (with a solid-density CT pattern) of 4 cases detected by repeat screening was 72 and 52 (i.e., pathological stage of IIIB and IIIB). These findings emphasize the aggressiveness of tumours with solid density pattern and the short TVDT, and that tumours measuring larger than 10 mm at presentation should be excised surgically immediately, although it is conceivable that patients with tumours larger than 13–15 mm might need other forms of therapy in addition to surgery. For an exceptionally rapidly growing lung cancer (e.g., TVDT 30 days) as was seen in our programme, or the interval case, as we found, we need appropriate modifications to the protocol, such as biannual-CT screening. Specific risk factors need to be clarified in those subjects for whom biannual examination would be recommended. There is a real need to accumulate more information to quantify the benefits asso-

ciated with various screening intervals, considering the wide range of tumour growth rate and biology and curability of small lung cancers.

4.1. Conclusion

Our population-based CT screening for lung cancer found many patients with BAC, adenocarcinoma with mixed types of non-solid CT density pattern mostly in non-smokers. The survival rates of these patients were excellent. A poorer prognosis was noted in smokers harbouring adenocarcinomas with mixed types, showing part-solid or solid CT density pattern. Patients with non-adenocarcinoma had a fairly excellent prognosis. Our findings suggest that low-dose CT screening of selected populations can lead to early detection and successful treatment of lung malignancy, with a significant improvement in 10-year survival rates.

Conflict of interest

None declared.

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