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Lung cancer screening CT: From a radiological point of view

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1. Epidemiology

Lung cancer is the most common cancer in the world and the leading cause of cancer deaths in industrialized countries. According to the most recent global cancer statistics in 1990, 1.04 million new cases of lung cancers were diagnosed (12.8% incidence of the world total new cancer cases) and 921,000 cases were died of lung cancer (17.8% mortality of the world total cancer deaths) [1]. The incidence of this disease is greater in men (37.5 per 100,000) than in women (10.8 per 100,000). Lung cancer is the most common and the leading cause of cancer death in men, while this disease is the fifth most common cancer and the second most common cause of cancer death after breast cancer. In 2003, 171,900 new cases (12.9% of all new cancer cases) and 157,200 deaths (28.4% of all cancer deaths) are estimated in the United States alone; lung cancer will rank second in terms of incidence and will rank first in terms of mortality [2].

Many risk factors of lung cancer are known and hypothesized. Of these, tobacco smoke is by far the most important etiologic agent of lung cancer, accounting for over 85% of the risk of this neoplasm [3]. Smokers have about a 20-fold increase in lung cancer risk compared to never-smokers [4]. The risk of lung cancer increases with the duration of smoking and the number of cigarette smoked. There is no evidence of a threshold level of exposure. The likelihood of developing lung cancer decreases among individuals who quit smoking. However, the risk of lung cancer for former smokers remains high for more than 40 years since quitting smoking. Passive smoking (environmental tobacco smoke) is also causative of lung cancer and is estimated to be responsible for about 17% of lung cancers among never-smokers [5].

Tobacco smoking increases the risk of all four major histologic types of lung cancer (squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma) [4]. Although the most intimately associated histologic types are squamous cell carcinoma and small cell carcinoma, adenocarcinoma is also related to tobacco smoking [6-8]. However, the association of smoking with bronchioloalveolar carcinoma (BAC) is somewhat controversial and at most weak [9, 10]. Other risk factors of lung cancer include radiation exposure, industrial or organic substances (arsenic, radon, nickel, chromium, and asbestos), certain lung diseases (idiopathic pulmonary fibrosis and chronic obstructive lung diseases), and dietary, genetic, and immunologic factors [4, 11, 12]. However, these etiologies account for only a minor fraction of deaths of lung cancer.

Thus, because the majority of lung cancer can be attributable to tobacco use, smoking cessation should be the first and foremost issue in reducing the death of lung cancer.

2. Changing patterns of histologic types of lung cancer

The World Health Organization (WHO) classification in 1999 is widely used for the histologic classification of lung cancer [13]. The first five categories account for approximately 90% of all lung carcinomas and include squamous cell carcinoma (30% of cases), adenocarcinoma (30.7%), small cell carcinoma (18.2%), large cell carcinoma (9.4%), and adenosquamous carcinoma (1.5%) [14]. Recently, a notable shift has occurred in the incidence rates of histologic subtypes of lung cancer. After steady increase in incidence since 1973, adenocarcinoma has replaced squamous cell carcinoma as the most frequent histologic subtype of lung cancer in the last two decades. This overall increase in adenocarcinoma is largely due to a dramatic increase in BAC, which can develop often in never-smoked young females [9, 15]. The incidence of BAC is reported to have risen from less than 5% to 24% of all lung cancers during the recent 35 years or from 9.3% to 20.3% during the recent 10 years.

3. Radiologic appearance of lung neoplasms

The aim of screening CT of the lung is to detect early lung cancer. Since early endobronchial cancer in the central bronchi is difficult to identify with this technique, targeted tumors of screening CT are tumors in the peripheral lung parenchyma [16, 17]. CT is much more sensitive than chest X-ray (CXR) in detecting small lung nodules, especially those of ground-glass opacity (GGO) because of its excellent spatial and density resolution [18, 19]. Single-detector helical CT can delineate as small as a 3-mm

nodule [20]. Therefore, since the advent of CT for clinical use in early 1980s, many small GGO nodules that must have been missed with CXR have been discovered.

GGO is defined as a hazy increase in the lung opacity on high-resolution CT (HRCT) without association with obscuration of underlying vessels, whereas a solid portion is defined as an area of increased homogeneous lung opacity that obscures underlying vessels [21]. When GGO is seen in BAC, GGO areas represent areas of a growth pattern of tumor cells replacing alveolar lining cells pathologically, which is termed lepidic growth [22]. Recently, intensive efforts have been made to clarify the evolution of replacement-type neoplasms in the lung from a viewpoint of the morphologic, immunologic, and genetic approaches [23-25]. It is beneficial to review the incidence of peripheral occurrence and CT appearance of each tumor category and to gain an insight into the progression of lung neoplasms having a replacement growth pattern for the understanding of lung screening CT and for managing the lesions detected at screening CT.

3.1. Adenocarcinoma

Adenocarcinoma arises from bronchiolar or alveolar epithelium and is the most common subtype of lung carcinoma in the peripheral lung parenchyma (49%-92% of cases) [15, 26, 27]. Invasive adenocarcinoma demonstrates a lobulated solid mass associated usually with coarse spiculation (93%) and pleural tag (69%), and sometimes with bubblelike areas of low attenuation (31%) and air bronchogram (3%) [28].

BAC, a subtype of adenocarcinoma originates from Clara cell or pneumocyte II or goblet cell [10]. According to the most recent version of the WHO classification that used a more strict histopathologic criterion than the former one, the tumor is required to have a purely lepidic growth pattern without invasive growth [13]. In CXR era, the radiologic appearance was described as a single nodule or multiple nodules or consolidation in the peripheral lung parenchyma [10]. After the introduction of CT in the clinical use, bubblelike areas of low attenuation that reflect small patent air-containing bronchi within the nodule were described characteristic to BAC [29]. Afterward, another authors reported that a small GGO nodule in the peripheral lung might be an early sign of BAC on thin-section CT [30]. Recently, many articles of thin-section CT features correlating with pathologic findings and prognosis in small BAC have been published [22, 31, 32].

3.2. Squamous cell carcinoma

Squamous cell carcinoma generally arises in a segmental or lobar bronchus and therefore, is typically centrally located [26]. This tumor is first recognized as a mucosal plaque that grows into a polypoid lesion and subsequently incurs distal atelectasis and obstructive pneumonitis in most cases. However, 22% to 43% of the tumors originate in the smaller bronchi and appear as a peripheral lesion [15, 27, 33]. Peripheral squamous cell carcinoma appears as a spiculated (85%) and lobulated (96%) solid mass associated often with pleural tag (62%) and extensive necrosis (61%) [28, 34]. Sometimes vascular convergence (11%) and cavitation (29%) are seen.

3.3. Small cell carcinoma

Small cell carcinoma is typically located in the lobar and mainstem bronchi. This carcinoma spreads in the submucosa and subsequently forms a mass that obliterate

underlying airways and vessels. The tumor develops a peripheral mass in 4%-37% of cases and shows an expansive growth [15, 27, 35]. Peripheral small cell carcinoma appears as a homogeneous solid mass associated often with lobulation (72%) and coarse spiculation (44%), and sometimes with pleural tag (17%) [28, 36]. Macroscopic necrosis is rarely seen.

3.4. Large cell carcinoma

Large cell carcinoma is a poorly differentiated tumor that does not have the typical appearance of small cell carcinoma and that has no evidence of either squamous or glandular differentiation pathologically. This tumor is found as a bulky peripheral mass in 53%-68% of cases [15, 27, 37]. Peripheral large cell carcinoma appears as a lobulated solid mass associated often with coarse spiculation (67%) and sometimes with pleural tag (22%) and necrosis (11%) [28].

3.5. Adenosquamous carcinoma

Adenosquamous carcinoma arises in the peripheral lung in 83%-96% of cases and is radiologically indistinguishable from other non-small cell carcinomas [38-40]. About half of cases develop tumor in previously injured lungs such as scar, pneumoconiosis, radiation fibrosis, and interstitial fibrosis. Sometimes cavitation (13%) is seen in tumor [39].

4. Stepwise progression of replacement-type lung neoplasms

A typical adenomatous hyperplasia (AAH) is defined as preinvasive neoplasm of the lung according to the WHO classification [13]. This neoplasm shows a replacement growth of the alveolar lining cells with atypical cuboidal or low columnar cells and has been incidentally found in cancer-bearing lungs, especially in those with adenocarcinoma (Table 1) [41-43]. Although most lesions are less than 3 mm in diameter, larger lesions up to 32 mm have been reported [44]. Lesions of AAH demonstrate a GGO nodule on thin-section CT [22]. Researchers have found that certain populations of AAH cells share morphologic, biologic, and genetic properties with BAC cells and therefore, advocated a possible progression from AAH to BAC [23-25, 45].

In 1995, Noguchi et al. [46] proposed a new classification of small adenocarcinoma of the lung (2 cm or smaller) and correlated their classification with prognosis (Table 1). This classification is widely accepted in Japan, because the classification correlates well with prognosis. Patients with type A or B tumor showed no lymph node metastasis and had an excellent prognosis with a 5-year survival rate of 100%. On the other hand, patients with type C (adenocarcinoma with a replacement growth pattern) showed a high incidence (28%) of lymph node metastasis and had a poorer prognosis with a 5-year survival rate of 75%. Type A and type B tumors correspond to BAC and type C tumors are compatible with adenocarcinoma with mixed subtypes in the WHO classification.

As a result of morphologic and prognostic analysis, Noguchi et al. regarded types A and B as localized BAC and type C as an advanced form of types A and B tumors. Thus, the concept of stepwise progression of lung neoplasms having a replacement growth pattern from AAH through type A to type B and then to type C adenocarcinoma has been proposed. Invisibility of AAH and early BACs of GGO on CXR has made a longitudinal study of these tumors difficult for a long time. However, a recent article of

Table 1. Pathologic Definitions of Atypical Adenomatous Hyperplasia and small Adenocarcinomas of the Lung.

Neoplasm	Definition
Atypical adenomatous hyperplasia ⁴⁷	Uniform proliferation of atypical cuboidal to low-columnar cells along the alveolar septa
Adenocarcinoma (2 cm or smaller) ⁴⁶	
Type A	Localized bronchioloalveolar carcinoma
Type B	Localized bronchioloalveolar carcinoma with foci of collapse of alveolar structure
Type C	Localized bronchioloalveolar carcinoma with foci of active fibroblastic proliferation
Type D	Poorly differentiated adenocarcinoma
Type E	Tubular adenocarcinoma
Type F	Papillary adenocarcinoma with compressive and destructive growth

transverse and longitudinal CT analysis in replacement-type lung neoplasms has demonstrated supportive radiologic evidence for the evolution of the tumors [22]. Transverse CT studies in the series revealed that lesion size, percentages of GGO areas of lesion, and incidence of CT findings due to tissue contraction significantly increased according to the progression of histology (from AAH through type A to type B and then to type C). Longitudinal CT analysis in the same article also described that lesions were first recognized as a GGO nodule (56% of 48 lesions) with subsequent increase in size (75%), then solid portions appeared in the nodule (17%), and finally solid portions increased (23%) with occasional augmentation of tissue contraction (6%). The solid portions represented areas of collapsed alveolar structure or fibroblastic proliferation in pathologic studies.

Thus, it seems little doubt that a certain proportion of AAH lesions progress to BAC and then to invasive adenocarcinoma. Types D-F tumors are separated entities and belong to invasive adenocarcinoma both pathologically and radiologically [31, 46]. Some AAH lesions are reported to regress spontaneously [47]. Equivalent or even better prognosis of patients with lung cancer associated with AAH compared with those not associated with AAH is reported in the literature [48, 49]. Therefore, how often AAH evolves into invasive cancer and how often spontaneous regression of AAH occurs remain to be investigated.

5. Overviews of lung cancer screening trials using CXR

5.1. Biases

Mortality, survival, fatality, stage distribution, and resectability are used to determine the effectiveness of screening programs [50, 51]. Mortality means the ratio of the number of deaths from cancer to the total number of persons screened and is expressed as deaths per 1,000 persons screened per year. Survival is defined as the ratio of the number of individuals alive following diagnosis of cancer to the number of individuals with cancer detected. Fatality is a counterpart of survival, since fatality is one minus survival.

There are four major biases (selection bias, lead-time bias, length-bias, and overdiagnosis bias) that influence the measurement of outcome of participants in screening programs. Selection bias is caused by the fact that individuals who choose to participate in screening programs are different from those who do not [50, 51].

Lead-time bias results from the fact that the time of diagnosis is moved forward by screening, therefore, even if the time of death is not altered, the observed survival will be longer in a case detected by screening than it otherwise would have been.

The growth rate of tumors is variable and therefore, tumors have a variable length of time in a preclinical, screen detectable phase. Slowly growing tumors have a longer preclinical phase (the length of time between onset of disease and the first appearance of signs or symptoms) and are more likely to be detected by screening procedures when they are asymptomatic than more rapidly growing tumors. Consequently, a higher proportion of indolent tumors is found in the screened group, which will produce apparently improved survival. This event is termed length-time bias.

Overdiagnosis bias is seen when the lead time (the length of time between disease detection and the first appearance of signs or symptoms) is indefinitely long and therefore, occurs with the detection of a subclinical disease that would not have developed symptoms before the individual die of other causes. This bias produces apparent increases in the number of cases of cancer and in survival in screened group but does not influence mortality.

The measurement of outcome based on survival, fatality, stage distribution, or resectability is not appropriate and can be misleading, because the measurement is susceptible to lead-time bias, length-bias, and overdiagnosis bias. On the other hand, mortality is considered to be least subject to lead-time bias, length-bias, and overdiagnosis bias. Selection bias can be eliminated by randomized trials, because random assignment can create screen and control populations that have an equal risk of dying from the disease. Thus, it is believed that mortality obtained through a randomized controlled trial is the best method for evaluating the effectiveness of screening.

5.2. Prior randomized controlled trials

In the 1970s, four large randomized controlled trials were conducted to evaluate the effectiveness of the screening methods for detecting early lung cancer [52-55]. Of these, three trials that were carried out in the United States and the other one was done in Czechoslovakia. The studies at the John Hopkins Medical Institutions and the Memorial Sloan-Kettering Cancer Center were designed to evaluate the additional effectiveness of sputum cytology by comparing lung cancer mortality between the study population offered annual CXR plus sputum cytologic examinations at 4-month intervals and the control group offered annual CXR alone [53, 54].

The Mayo Clinic trial compared offering CXR and sputum cytology every 4 months to offering advice that the two tests should be obtained once a year [52]. As a consequence, this trial compared only the effectiveness between intensive screening and less intensive screening, rather than no screening procedure at all. A similar design was used in the Czechoslovakian trial [55]. The study group had CXR and sputum cytology every 6 months for 3 years, whereas the control group had a single screen at the end of the 3-year study. However, none of the four randomized controlled trials demonstrated a reduction in lung cancer mortality by means of screening.

5.3. Results and criticisms of the Mayo Clinic trial

The results in the Czechoslovakian trial mirrored those in the Mayo Clinic trial [55, 56]. So, I would like to give an overview of the Mayo Clinic trial, because the results contain educational issues and have been extensively discussed until now.

In this trial, the study group consisted of 4,618 individuals who were screened for an average of 6 years and then observed for an additional 3 years, whereas the control group consisted of 4,593 individuals who were followed, on average, for 9 years [52]. In the study, lung cancer was identified in 206 cases in the screened group, which were significantly greater than 160 cases detected in the control group. Stage distribution (48% versus 32% for the rate of stage I or II), resectability (46% versus 32%), and the 5-year survival rate (33% versus 15%) were significantly better in the screened group. However, no significant difference in lung cancer mortality was seen between the two groups (3.2 and 3.0 per 1,000 person-years for the screen and control group, respectively). The considerably more cancers detected in the screen group and the discrepancy between better survival and lack of mortality advantages have been a major source of controversy until now [50, 57-59]. The criticism included no screening study group to determine the true efficacy of CXR, short follow-up periods, small sample size, contamination problem, and failure of randomization assignment.

In response to the criticisms, Marcus and his colleagues [60] extended the follow-up periods of the participants of the Mayo Clinic trial to a median follow-up of 20.5 years and reevaluated the mortality. However, the results were still the same and no significant difference ($P = 0.09$) in lung cancer mortality (4.4 and 3.9 per 1,000 person-years for the screen and control group, respectively) was demonstrated between the two groups. The authors concluded that the discrepancy was mainly due to overdiagnosis bias in the screening. In other words, the screen group included more cancers that were clinically irrelevant.

5.4. Recent case-control studies

Regardless of the worldwide trends, annual lung cancer screening using CXR with or without sputum cytology has been widely performed as a public health policy in Japan since 1987. Based on the experience, many researchers conducted case-control studies in several prefectures in Japan. A case-control study is one method to evaluate the efficacy of screening [61]. In this study, controls are randomly selected from the same district who are matched to case subjects on variables that are related to the risk of cancer or the opportunity to be screened, such as gender, age, or smoking habits. The study uses an odds ratio (relative risk) for the assessment, representing the rate of dying from lung cancer in screened individuals divided by the rate in control individuals. Recently the results have been available in English literature and the authors suggested that screening using CXR with or without sputum cytology might reduce lung cancer mortality by 40%-60% [62-64]. However, the conclusion of mortality benefit should be interpreted carefully, because selection bias is inevitably involved in case-control studies [61].

6. Rationale of CT screening for lung cancer

Since the failure in demonstrable reduction in lung cancer mortality in four major randomized controlled trials, no screening tests such as CXR or sputum cytology have

been recommended for the detection of early lung cancer. Symptoms are usually a late sign for lung cancer and mostly indicate advanced disease. Patients with stage I or II are usually treatable with surgery alone. However, over 90% of patients with lung cancer are symptomatic at the time of diagnosis and only 22% of patients are found to have stage I or II [65, 66]. The 5-year survival rate for all stages of lung cancer is only 15% in the most recent cancer statistics and the improvement in this survival rate for the recent three decades is only 3% [1].

The prognosis of patients with lung cancer is intimately related to the stage of the disease at the time of diagnosis (Table 2). The 5- year survival rate for patients with stage IA disease is most favorable and reported to be as high as 67% or 74% [66, 67]. However, the survival rate sharply drops to 1% or 11% for patients with stage IV disease. Thus, detection of lung cancer at early stages followed by appropriate therapy has a high possibility to increase the proportion of cases of early stages (a downward stage shift) and the proportion of curable disease with resultant improvement in survival. However, for mortality benefit, it is crucial to demonstrate that advantages in cancer stage distribution, proportion of patients who have curative treatment, and the survival rate are not attributable to overdiagnosis.

Table 2. 5-year survival rates by tumor stages

Stage	TNM Classification (pathologic stage)	5-year Survival (%)	
		Mountain et al. ⁶⁷	Naruke et al. ⁶⁶
IA	T1 N0 M0	67	74
IB	T2 N0 M0	57	53
IIA	T1 N1 M0	55	52
IIB	T2 N1 M0	39	45
	T3 N0 M0	38	43
IIIA	T3 N1 M0	25	37
	T1-3 N2 M0	23	19
IIIB	T4 N0-2 M0	7	12
	Any TN3 M0	3	3
IV	Any T Any N M1	1	11

6.1. Tumor size versus prognosis in T1 disease

Although several studies have demonstrated that the prognosis of patients with stage IA disease (T1 N0 M0) is better than that of patients with stage IB disease (T2 N0 M0), there is controversy regarding the relation between tumor size and prognosis of patients with stage IA non-small cell lung cancer. Since the majority of lung cancer detected with screening CT belong to T1 category with being mostly less than 2 cm, it is vital for CT screening programs to determine if there are any thresholds of tumor size that represent an prognostic determinant [16, 17].

Patz et al. [68] described in a series of 510 patients with stage IA non-small cell lung cancer that there was no significant relationship between tumor size and survival on

the basis of Cox proportional hazards modeling, of which results were supported by several other authors [69-73]. However, removal of N factor from their analysis made the results all the more clinically less useful, because lymph node metastasis is a well-known strong prognostic factor [66, 67]. Several investigators described that even in patients with tumors 3 cm or less, lymph node metastasis was pathologically verified in 17%-56% and that incidence of nodal metastasis in this tumor category significantly increased as the increase in tumor size and that nodal metastasis was a significant prognostic factor [70, 71, 74, 75]. In another study, all of 28 patients with localized BAC of 2 cm or less and with no lymph node metastasis survived 5 years [46].

On the other hand, other researchers described the results contradictory to the conclusion of Patz et al. [74, 76-78]. Koike et al. [74] reported in a study of 496 patients with clinical stage IA non-small cell lung cancer that the 5-year survival rate (80%) of the group with tumor size of 2 cm or less was significantly better than that (69%) of the group with tumor size of 2.1 to 3 cm. Since lymph node status is often difficult to know before surgery, the studies in such patient populations in which multivariate analysis is applied to determine an independent prognostic factor is clinically more useful.

6.2. Prognosis of small peripheral lung carcinoma

6.2.1. Adenocarcinoma

There are some articles of excellent prognosis of patients with small peripheral adenocarcinoma [46, 75]. Takizawa et al. [75] described in a series of small adenocarcinoma (1.1 cm to 2.0 cm) that the 5-year survival rate was as high as 91% for patients without lymph node metastasis. These excellent prognostic advantages in small adenocarcinoma are attractive for CT screening scheme. However, differentiation between AAH and type A adenocarcinoma is difficult with CT [22]. This is also true for pathologic diagnosis. According to the pathologic literature, although low grade (less atypical) AAH can be easily distinguished from BAC, high grade (more atypical) AAH is almost indistinguishable from BAC [25, 47]. Since the incidence of BAC is rapidly increasing in recent years and this tumor has much opportunity to be detected by screening CT because of its long preclinical phase, difficulties in discrimination between AAH and BAC will be a cause of overdiagnosis for screening CT [9, 15].

In a study of 1105 autopsies, 111 undiagnosed or misdiagnosed malignancies were found and lung cancer was the most common primary site (33% of 111 cases) [79]. According to the standard autopsy protocols, the major bronchi were cut into two halves through the hilum and sections were made at approximately 1.5-cm intervals [80]. If such techniques are used, the majority of small nodules that were detected with helical CT can be easily missed in autopsy examinations. Actually, Dammas et al. [80] reported in a series of CT-autopsy correlative study that 32% of small lung nodules detected at CT were not described on the autopsy report. Thus, overdiagnosis due to very slow-growing BAC can be a problem with screening CT also.

6.2.2. Squamous cell carcinoma

There are several studies of favorable prognosis of patients with small peripheral squamous cell carcinoma. Asamura et al. [70] reported that incidence of lymph node metastasis is quite low (6%) in patients with this neoplasm of 2 cm or less and that the 5-year survival rate reached as high as 96% for patients with stage IA disease. Ishida et al.

[81] described the similar 5-year survival rate (88%) for patients with peripheral squamous cell carcinoma less than 2 cm without lymph node metastasis.

6.2.3. Large cell carcinoma

Prognosis of patients with large cell carcinoma is poor and the 5-year survival rate ranges from 1%-20% [82-85]. The majority of tumors were found at advanced stages because of its aggressiveness and its rapid growth rate. In the literature, the proportion of stage I disease accounted only for 10-13% of all cases. However, several studies indicated that patients with an early stage had significantly better prognosis than those with advanced stages [84-86].

6.2.4. Small cell carcinoma

The traditional categories of limited disease and extensive disease have been used for classification of small cell carcinoma. Limited disease is defined as carcinoma confined to a single radiation port (one hemithorax with or without contralateral mediastinal or supraclavicular lymphadenopathy), which corresponds to stages I to IIIA disease of TNM classification [66]. Extensive disease is defined as carcinoma extending beyond a single radiation port, which corresponds to stages IIIB to IV disease of TNM subset. The primary treatment procedures for this tumor are radiotherapy and systemic chemotherapy, because the disease is disseminated in the majority of cases at the time of diagnosis [87].

However, some researchers described in the series of surgically resected cases of small cell carcinoma that significantly prolonged survival periods were obtained in cases with stage I disease compared to cases of more advanced stages and suggested that surgical resection might be offered for cases of a limited-stage (T1-2 N0 M0 tumors) [88, 89]. If screening CT enables a downward stage shift of this tumor, the more precise staging using TNM system will be clinically useful for selecting patients who are candidates for surgical treatment.

Prognosis for patients with small cell carcinoma is dismal with a median survival of 6-10 months and only 1.8% survived 5 years [87, 90]. There are some studies regarding prognosis of patients with peripheral small cell carcinoma of the lung [91, 92]. Gephardt et al. [91] described in the study of 17 cases with peripheral small cell carcinoma that all tumors were resectable with a better median survival of 1.7 years. Quoix et al. [92] reported that the median survival (24 months) of patients with peripheral small cell carcinoma was significantly longer than that (11 months) of patients with limited disease and concluded that this improved prognosis in patients with peripheral small cell carcinoma might be due to small tumor volume or to difference in fundamental biologic behavior.

Spontaneous regression is extremely rare for invasive adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and small cell carcinoma [93]. Almost all patients with lung cancer who had had no surgical resection eventually died of lung cancer within five years after diagnosis [94-96]. Therefore, there is little room for overdiagnosis for invasive lung carcinomas. Thus, detection of invasive lung carcinomas at early stages will be advantageous for mortality reduction of CT screening.

7. Results of prior lung cancer screening CT

Until now, six major trials of lung cancer screening using low-dose helical CT have been published [16, 17, 97-103]. The results in each study and the total number of the six studies are summarized in Table 3. Statistical comparisons of the total number between the baseline CT and annual repeat CT are shown in Table 4. Of the six trials, four were conducted in high-risk population and the other two included high-risk and non-high-risk groups. Single detector helical CT was used in five trials and multidetector helical CT was used for the other one. All of the prior studies were nonrandomized trials. So, we must interpret the results with caution, because such kind of trials is susceptible to various biases as mentioned before.

Table 3. Study Results of Low-dose CT Screening for Lung Cancer.

Institute	National Cancer Center Hospital, Japan ^{16,112}	Shinshu University Japan ^{17,113}	Cornell University United States ^{18,114}	Mayo Clinic United States ¹⁹	Munster University Germany ¹¹¹	Hitachi Health Care Center, Japan ¹¹⁰	Total
Type of helical CT	Single detector	Single detector	Single detector	Multidetector	Single detector	Single detector	---
Parameter (kVp/mA/thickness/pitch)	120/50/10 mm/2	120/25 or 50/10 mm/2	140/40/10 mm/2	120/40/5 mm/1.5	120/50/5 mm/2	120/50/10 mm/2	---
Eligible age (years)	≥40	≥40	≥60	≥50	≥40	≥50	---
Smoking history (pack-years)	>20	46% smokers	≥10	≥20	≥20	62% smokers	---
BASELINE SCREENING							
Screened No.	1,611	5,483	1,000	1,520	817	7,956	18,387
Positive results, No. (%)	186 (11.5)	279 (5.1)	233 (23)	782 (51)	409 (50)	541 (6.8)	2,430 (13)
Detected cancer, No. (%)	13 (0.81)	22 (0.40)	27 (2.70)	21 (1.38)	12 (1.47)	37 (0.47)	132 (0.72)
Rate of benign nodule (%)	93%	92%	88%	97%	97%	93%	95%
Biopsy No.	22	29	31	32*	14	51	179
Benign lesion, No. (%)	8 (36)	7 (24)	4 (13)	7 (22)*	3 (21)	15 (29)	44 (25)
AAH, No.	0	2	0	0	0	5	7
Histology of cancer, No. (%)							
BAC	0	12 (55)	4 (15)	4 (19)	0	13 (35)	33 (25)
Adenocarcinoma	10 (77)	7 (32)	18 (67)	11 (52)	6 (50)	22 (59)	74 (56)
Squamous cell carcinoma	3 (23)	3 (14)	1 (4)	3 (14)	5 (42)	0	15 (11)
Large cell carcinoma	0	0	0	1 (5)	0	1 (2)	2 (2)
Small cell carcinoma	0	0	0	2 (10)	1 (8)	0	3 (2)
Others	0	0	4 (15)	0	0	1 (2)	5 (4)
Stage I disease, No. (%)	10 (77)	20 (91)	23 (85)	13 (62)	7 (58)	33 (80)	106 (80)
Size of cancer (mean, range)	20 mm	15 mm (6-47)	ND	18 mm (7-55)	25 mm (12-60)	17 mm (7-26)	18 mm (6-60)
≤1 cm, No. (%)	0	5 (23)	15 (56)	4 (19)	0	6 (16)	30 (23)
1.1-2 cm, No. (%)	8 (62)	15 (68)	8 (30)	13 (62)	4 (33)	24 (65)	72 (55)
>2 cm, No. (%)	5 (38)	2 (9)	4 (15)	4 (19)	8 (67)	7 (19)	30 (23)
CXR negative cancer, No. (%)	8 (62)	13 (59)	20 (74)	ND	ND	ND	71 (70)
5-year survival rate	76%	ND	ND	ND	ND	ND	76%

Table 3 Continued

ANNUAL REPEAT SCREENING							
Screened No.	7,891	8,303	1,184	1,464	ND	5,568	24,410
Positive results, No. (%)	770 (9.8)	309 (3.7)	30 (2.5)	375 (26)	ND	148 (2.7)	1,632 (6.7)
Detected cancer, No. (%)	19 (0.24)	37 (0.45)	7 (0.59)	2 (0.14)	ND	4 (0.07)	69 (0.28)
Rate of benign nodule	98%	88%	77%	100%	ND	97%	96%
Biopsy No.	49	34	9	32*	ND	51	175
Benign lesion, No. (%)	27 (55)	9 (26)	1 (11)	7 (22)*	ND	15 (29)	59 (34)
AAH, No.	0	7	0	0	ND	0	7
Histology of cancer, No. (%)							
BAC	0	16 (43)	0	0	ND	0	16 (23)
Adenocarcinoma	14 (74)	16 (43)	5 (71)	0	ND	4	39 (57)
Squamous cell carcinoma	4 (21)	2 (5)	0	2 (100)	ND	0	8 (12)
Large cell carcinoma	0	0	0	0	ND	0	0
Small cell carcinoma	1 (5)	3 (8)	1 (14)	0	ND	0	5 (7)
Others	0	0	1 (14)	0	ND	0	1 (1)
Stage I disease, No. (%)	15 (79)	32 (86)	5 (71)	0	ND	4 (100)	56 (81)
Size of cancer (mean, range)	15 mm	12 mm (4-35)	8 mm (5-25)	22 mm (8-36)	ND	ND	13 mm (4-36)
≤ 1 cm, No. (%)	5 (26)	15 (41)	4 (57)	1 (50)	ND	ND	25 (38)
1.1-2 cm, No. (%)	12 (63)	21 (57)	2 (29)	0	ND	ND	35 (54)
> 2 cm, No. (%)	2 (11)	1 (3)	1 (14)	1 (50)	ND	ND	5 (8)
Symptom-detected cancer, No.	4	1	2	2	ND	ND	9
Squamous cell carcinoma	4	1	1	1	ND	ND	7
Small cell carcinoma	0	0	1	1	ND	ND	2
5-year survival rate	65%	ND	ND	ND	ND	ND	65%

ND, not described; * total number of baseline and annual repeat CT.

7.1. Detection rate, size, and stage of lung cancer

Detected cancers at baseline CT ranged from 0.4% to 2.7% (mean, 0.72%) of screened individuals. This means 720 lung cancers (range, 400-2,700) per 100,000 persons were discovered with this technique, on an average. In a series of Shinshu University, baseline CT identified 7.2 times as many cancers (350 per 100,000 persons) than the annual incidence of lung cancer (48 per 100,000 persons) [97]. As expected, the number of detected cancers was significantly larger ($P < 0.001$) at baseline CT (mean, 0.72%, range, 0.40-2.70%) than at annual repeat CT (mean, 0.28%, range, 0.07-0.59%) (Table 4). The detection rate by helical CT was 2.4 to 3.8 times higher (mean, 2.9 times) than CXR.

The diameter of all cancers detected at baseline CT of the six trials was 6-60 mm (mean, 18 mm): 1 cm or smaller in 23% (range, 0-56%); 1.1-2 cm in 55% (range, 30%-68%); more than 2 cm in 23% (range, 9%-67%). Thus, tumors of 2 cm or less accounted for 78% of all cancers on baseline CT. The mean diameter of tumors identified on annual repeat CT decreased to 13mm (range, 4-36 mm). The proportion of tumors of 2 cm or less was significantly smaller ($P = 0.01$) in annual repeat CT than in baseline CT. The proportion of stage I disease at baseline CT (mean, 80%) was not significantly

Table 4. Comparison of Total Cases between Baseline CT and Annual Repeat CT.

	Baseline CT	Annual Repeat CT	<i>P</i>
Screened No.	18,387	24,410	---
Positive results, No. (%)	2,430 (13)	1,632 (6.7)	< 0.001
Detected benign nodules, No. (%)	2,298 (95)	1,563 (96)	NS
Detected cancer, No. (%)	132 (0.72)	69 (0.28)	< 0.001
Biopsy, No. (%)	179 (7.4)	124 (7.6)	NS
False positive, No. (%)	44 (25)	44 (35)	NS
Histology of cancer, No. (%)			
BAC	33 (25)	16 (23)	NS
Adenocarcinoma	74 (56)	39 (57)	NS
Squamous cell carcinoma	15 (11)	8 (12)	NS
Large cell carcinoma	2 (2)	0	NS
Small cell carcinoma	3 (2)	5 (7)	NS
Others	5 (4)	1 (1)	NS
Stage I disease, No. (%)	106 (80)	56 (81)	NS
Size of cancer (mean, mm)	18	13	---
≤1 cm, No. (%)	30 (23)	25 (38)	0.047
1.1-2 cm, No. (%)	72 (55)	35 (54)	NS
>2 cm, No. (%)	30 (23)	5 (8)	0.006
5-year survival rate (%)	76	65	NS

Data from 16, 17, and 97-103. NS, statistically not significant.

different from that at annual repeat CT (mean, 81%). However, among stage I tumors, repeat CT discovered a significantly greater proportion of smaller tumors than baseline CT. The proportion of stage I disease at both baseline (80%) and annual repeat CT (81%) was considerably greater than that (38% or 31%) reported in the prior randomized controlled trials using CXR or that (29%) in the symptom-based lung cancer [52, 55, 67].

7.2. Histology distribution of lung cancer

The proportion (81%) of BAC plus adenocarcinoma in baseline CT was significantly larger than that (34%-40%) reported in prior case-control studies using CXR or that (30%) in Mayo Clinic trial or that (31%) in the symptom-based lung cancer [14, 52, 62-64]. This tendency in screening CT was conspicuous in the studies that were performed on non-high-risk population [97, 98, 100]. Some type C adenocarcinomas and BAC grow very slowly and have a long preclinical phase [104, 105]. This preclinical detectable phase must be longer for helical CT than for CXR. The majority of BAC lesions less than 2 cm are invisible on CXR and therefore, these tumors must have been overlooked in the prior screening trials with CXR [19, 106]. Thus, helical CT is much more susceptible to lead-time bias and length-bias than CXR.

Among the total cancer cases detected at six trials, no significant difference in distribution of histology of lung cancer was seen between baseline CT and annual repeat

CT. However, when we examined the studies individually, a less proportion of slowly growing tumors (BAC) and a larger proportion of rapidly growing tumors in annual repeat CT were seen in three of the six trials [17, 100, 103]. In the series of Shinshu University, the proportion of BAC was high both in baseline and repeat CT [97, 98]. However, the researchers described that they had had little knowledge about the appearance of BAC on CT at the reading of baseline CT and admitted that they had overlooked many small BAC with GGO at baseline CT [107]. Thus, the authors must have paid special attention to GGO nodules at annual repeat CT reading and resultantly changed criteria of positive results enabled discovery of as many BACs at annual repeat CT as at baseline CT.

7.3. Rate of noncalcified nodules and biopsy

Noncalcified nodules were detected in 13% (range, 5.1-51%) of all participants at baseline CT and this rate was significantly ($P < 0.001$) reduced to 6.7% (range, 2.5-26%) at annual repeat CT. Comparison of annual repeat CT with prior CT contributed to the reduction of positive diagnoses at annual repeat CT. However, the vast majority of the indeterminate nodules discovered at both baseline (95%) and annual repeat CT (96%) proved to be benign lesions. Interestingly, Nawa et al. [100] reported that the prevalence of noncalcified nodules was not related to smoking history at any age. Biopsy was performed in 7.4% of all cases of positive diagnosis at baseline CT and 7.6% of all cases of positive diagnosis at annual repeat CT with no statistically significant difference between the two. Diagnosis of benign lesions was obtained in 25% of biopsy cases for baseline CT and in 34% of biopsy cases for repeat CT. In two studies, several AAH lesions were surgically resected because these lesions mimicked BAC on CT scans [97, 98, 100]. In retrospect, among all participants, approximately 9% underwent unnecessary additional CT and 0.24% had unnecessary biopsy procedures.

7.4. Survival

Survival data are available in one article [102]. The 5-year survival rate in this report was 76% at baseline CT and 65% at annual repeat CT. These survival figures were considerably higher than those (40% or 33%) reported in the prior randomized controlled trials using CXR [52, 55]. Since the majority of slowly growing tumors will be detected at baseline CT theoretically, a smaller proportion of adenocarcinoma will be discovered at repeat CT. Therefore, the effectiveness of screening CT will be reflected more exactly in repeat CT, because annual repeat CT is less subject to the biases. Unfortunately, such events did not occur in their studies and the high proportion of adenocarcinoma (77%) in baseline CT remained almost the same in repeat CT (74%). If a 5-mm lung cancer with a volume doubling time (VDT) of 567 days (a mean value of BAC) is discovered at helical CT in an individual at age of 60, this individual will be 72 years of age when the lung cancer grows into 3 cm, much time for the individual to die of other diseases [105].

Screening helical CT enabled a downward stage shift of lung cancer and marked survival advantages. Simultaneously, this procedure allowed a very high detection rate of lung cancer and a high proportion of adenocarcinomas, which suggests that the survival must have been overestimated due to overdiagnosis [50]. Mortality of CT depends largely on that what proportion of indolent tumors will actually cause death and

what proportion of these tumors will be clinically irrelevant lesions. Thus, we must wait for the results of the randomized controlled trials to draw a final conclusion regarding mortality advantages of helical CT.

8. Evaluation of solitary pulmonary nodules detected at screening CT

Randomized controlled trials using low-dose helical CT are now in planning or in progress in several countries such as the United States, Italy, France, the Netherlands, or so forth [108, 109]. In the United States, National Cancer Institute started this trial in September 2000 that was designed to compare the effectiveness of helical CT and CXR for screening for lung cancer. Eligible criteria were men and women, ages 55 to 74, who had smoked at least 30 pack-years. Half were allocated helical CT and the other half were allocated CXR. However, this study will take approximately 14 years from the started year to complete.

Recently, whole-body screening using multidetector helical CT has been introduced for purposes of detection of lung cancer, colon cancer, or coronary calcium detection in the United States despite no scientific evidence to justify such screening [110-112]. Although the charge for this screening method is not covered by medical insurance, the number of self-referred patients who seek whole-body CT is now increasing. Circumstances are almost the same in Japan. The number of centers that offer helical CT of the chest for screening for lung cancer and the number of self-referred individuals who undergo this technique as part of general health checkups or as screening for lung cancer has been increasing in recent years in Japan. The decision about taking screening CT is a matter of individual choice. Thus, it seems that the number of individuals who seek screening CT of the lung will increase and radiologists will have more chance to read screening helical CT scans of the lung.

The high incidence rate of false-positive diagnosis in lung screening CT incurs unnecessary monitoring and unnecessary invasive diagnostic procedures. These problems burden the participants with additional costs, anxiety, or even morbidity. Therefore, how effectively diagnose and manage the solitary pulmonary nodules (SPNs) detected at screening CT with less invasive techniques, without impairing the cure rate of patients with lung cancer is an important issue.

8.1. Radiologic techniques

A SPN is radiologically defined as an intraparenchymal lung lesion measuring less than 3 cm in diameter and is not associated with atelectasis or adenopathy [113]. To make a timely and accurate diagnosis of an etiology of a SPN can lead to a potential for cancer cure. The diagnostic evaluation of a SPN largely consists of noninvasive radiologic procedures and invasive procedures by sampling of tissue or cells. Radiologic procedures include CXR, noncontrast CT, contrast-enhanced CT, magnetic resonance imaging with gadopentate dimeglumine, and positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG). On the other hand, invasive procedures comprise CT-guided transthoracic needle biopsy, transbronchial biopsy, and surgical biopsy (thoracoscopic and open lung biopsy).

Numerous small SPNs (1 cm or smaller in diameter) invisible on CXR have been discovered by screening CT for lung cancer. In one series, all of the SPNs ($n = 1,157$) detected by helical CT were 2 cm or smaller and 92% were less than 8 mm [103]. Therefore, how to manage the small SPNs has become a critical issue for lung cancer screening programs using helical CT. Although there are many articles describing a potential for discrimination between benign and malignant SPNs, all of them were based on the findings on CXR or CT scans obtained with older CT techniques and based on the findings of much larger SPNs that were detected on CXR or incidentally discovered by CT [28, 114-116]. As a result, the traditional radiologic criteria can not be applied to small SPNs discovered by screening CT. Therefore, new radiologic criteria for diagnosis of small SPNs are required.

As a promising noninvasive procedure, contrast-enhanced CT and PET with FDG have been used for differentiating benign from malignant pulmonary nodules. Although accuracy of 93% was attained with contrast-enhanced CT, all nodules less than 1 cm were excluded from the diagnostic statistics because of technically inadequate CT examinations [117]. Similarly, high accuracy (94%) was reported for PET [118]. However, all nodules assessed in their series were 1 cm or larger because of limited scanner resolution (7-8 mm). In addition, PET with FDG produces a false-negative diagnosis for BAC lesions because this tumor shows a low FDG uptake [119]. Furthermore, PET is available only in limited academic centers and more expensive than other imaging modalities. Thus, HRCT is currently the most prevalent modality and is used as the first noninvasive examination for evaluation of indeterminate SPNs detected at screening CT.

8.2. HRCT

HRCT is obtained by reconstructing the targeted areas of thin-section CT scans (parameters: 1-1.5 mm collimation; 120-140 kVp; 140-240 mA; a matrix size, 512 X 512) with a high-spatial frequency algorithm, using a small field of view. A pixel size of 0.3 mm-0.5 mm can be obtained with these parameters, depending on the field of view used [120].

The presence of benign patterns of calcification on CXR or CT is a reliable radiologic sign for benign SPNs [121]. Benign patterns of calcification refer to dense central, laminated, diffuse, or popcorn calcification. Although calcification in lung cancer is sometimes (6%) detected at CT, the type of calcification is amorphous, punctate, or reticular [122]. As to identification of calcification, HRCT is more accurate than conventional CT, which is more accurate than CXR [123-125]. If calcification is not apparent at visual inspection, quantitative CT densitometry is useful [125]. A nodule can be diagnosed as having calcification when pixels with CT values of 200 HU or more are identified within the nodule on CT scans [121].

If HRCT failed to demonstrate benign calcification, they are treated as indeterminate SPNs, which require further analyses of various HRCT findings such as size, margins, contour, location, density, or internal characteristics of the SPNs. Although there are several approaches such as logistic modeling, Bayes theorem, or neural network analysis for prediction of malignancy on the basis of radiologic features and clinical data, all these methods only predict the likelihood of a given SPN [115, 116, 126]. Radiologic signs that are specific to benignity or malignancy will be clinically useful, even though their sensitivity might not be high.

Takashima et al. [105] evaluated HRCT features on the initial diagnostic CT in 80 indeterminate SPNs (mean size, 12 mm) detected at population-based lung screening CT and suggested quite different criteria from traditional criteria for prediction of the etiology of the SPNs [114, 115]. These authors described that lesion size, the amount of GGO areas of nodule, and presence or absence of air bronchogram, concave margins, and polygonal shape were significant factors to determine malignancy. In their study, an optimal threshold of lesion size was as small as 1.1 cm. Henschke et al. [127] also described in a series of indeterminate SPNs detected at lung screening CT in a high-risk group that the GGO components in nodule were a preferable sign to malignancy. According to Bayes theorem, lesion size more than 2 cm and spiculated margins showed a high likelihood of malignancy [115]. However, other parameters such as GGO, concave margins, or polygonal shape were not included as a useful radiologic feature in the theorem.

Takashima et al. [128] extended the analysis to small indeterminate SPNs (1 cm or smaller) detected at population-based lung screening CT to search specific HRCT features to benign lesions. In their study, the prevalence of polygonal shape, peripheral subpleural lesion, a predominantly solid lesion and three-dimensional (3D) ratios were significantly greater in benign lesions than in malignancies. The researchers also reported that among all combinations of HRCT findings specific to benignity, a combined criterion of a predominantly solid lesion and peripheral subpleural lesion or polygonal shape or a 3D ratio of greater than 1.78 attained the highest sensitivity (60%). The authors concluded that their CT criterion at the first diagnostic HRCT may obviate unnecessary additional CT scans and invasive diagnostic procedures in about 60% of cases with small benign SPNs.

8.3. Volume doubling times

Growth rate measurement in indeterminate SPNs can afford some valuable information on managing and diagnosing these nodules [129, 130]. Growth rates of nodules can be evaluated by calculating their VDTs by comparing size of nodules on a set of CXRs or CT scans. Several authors described that time delay in surgical treatment up to median of 82 days did not affect prognosis of patients with lung cancer and they justified the observation strategy of the indeterminate SPNs [131, 132]. Thus, if its gain outweighs the risk, radiological follow-up is generally taken for SPNs that are still indeterminate on the first diagnostic CT to determine their growth rates.

According to the early literature, all SPNs for which VDTs were 7 days or less or 490 days or more were benign, while that VDTs of primary lung cancers ranged from 30 days to 490 days [129, 130]. However, the VDTs of lesions were calculated using serial CXRs in all the studies. In a recent series of lung cancers detected at screening CT in which VDTs were estimated on CT scans, the VDTs of lung cancers ranged from 52 days to 1733 days with a mean value of 452 days (Table 5) [133]. In their study, lung cancers were classified in three types (pure GGO nodule, nodule of GGO plus solid components [mixed GGO], and pure solid nodule) on the basis of HRCT appearance. The researchers found that the VDTs of pure GGO nodules (mean, 813 days) were significantly longer than those (457 days) of mixed GGO nodules, which were significantly longer than those of pure solid nodules (149 days).

Table 5. Volume doubling times of lung neoplasms and their growth in size for 3, 6, and 12 months.

High-resolution CT Appearance and Histology	Doubling Time (mean, range [days])	Increment in 5-mm Nodule (mean, range [mm])			Increment in 10-mm Nodule (mean, range [mm])		
		3 months	6 months	1 year	3 months	6 months	1 year
Pure GGO nodules							
AAH ¹⁰⁵	630 (136-1071)	0.2 (0.1-0.8)	0.3 (0.2-1.8)	0.7 (0.4-4.5)	0.3 (0.2-1.6)	0.7 (0.4-3.5)	1.5 (0.8-9)
Type A adenocarcinoma ¹³³	755 (311-1421)	0.1 (0.1-0.3)	0.3 (0.2-0.7)	0.6 (0.3-1.5)	0.3 (0.2-0.8)	0.6 (0.3-1.4)	1.2 (0.6-3)
Mixed GGO nodules							
Type B adenocarcinoma ¹³³	562 (168-893)	0.2 (0.1-0.6)	0.4 (0.2-1.4)	0.8 (0.5-3.5)	0.4 (0.2-1.3)	0.8 (0.5-2.8)	1.6 (1-6.5)
Type C adenocarcinoma ¹³³	489 (155-1158)	0.2 (0.1-0.7)	0.4 (0.2-1.4)	0.9 (0.4-3.5)	0.4 (0.2-1.4)	0.9 (0.4-3)	2 (0.8-7)
Pure solid nodules							
Type C adenocarcinoma ¹³³	213 (60-610)	0.5 (0.2-2)	1.2 (0.4-5)	1.3 (0.7-15)	1 (0.4-4)	2 (0.7-10)	5 (1.5-32)
Type D adenocarcinoma ¹³³	73, 104	1.5, 1.1	6, 2.5	11, 6	3.5, 2.2	8, 5	22, 13
Squamous cell carcinoma ¹³³	129 (52-346)	0.9 (0.3-2.5)	1.9 (0.6-6)	4.5 (1.4-18)	2.8 (0.6-5)	4 (1.3-12)	9 (3-40)
Small cell carcinoma ¹³³	97 (54-142)	1.2 (0.8-2.5)	2.5 (0.8-6)	7 (4-18)	2.4 (1.6-5)	5.5 (3.5-12)	14 (8-40)
Large cell carcinoma ¹³⁴	79	1.5	3.5	9.0	3	7	19

Pure GGO nodules having the longest VDTs consisted of types A and B tumors, mixed GGO nodules having intermediate VDTs included types B and C tumors, and pure solid nodules having the shortest VDTs comprised types C and D tumors, squamous cell carcinoma, and small cell carcinoma (Figs. 1-3) [133]. Furthermore, all nodules with pure GGO and mixed GGO were invisible on CXR. Another study suggested that as at HRCT appearance, AAH was still indistinguishable from type A tumors with growth rate analysis because of considerable overlap in VDTs between these two categories [105].

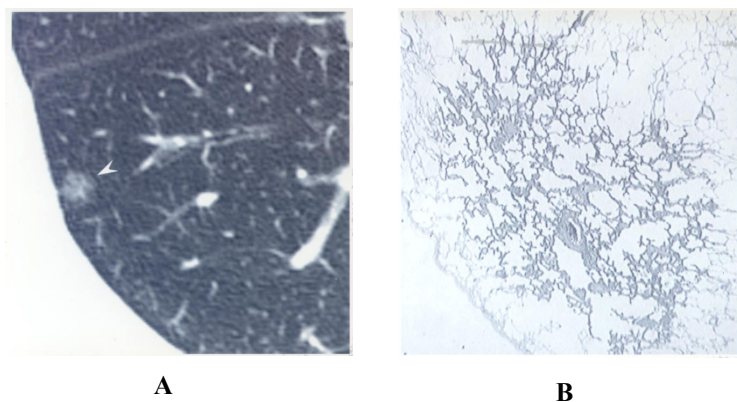


Figure 1. Type A adenocarcinoma in a 71-year-old woman. **A**, HRCT scan shows a 6-mm GGO nodule (arrowhead). **B**, Photomicrograph shows growth of tumor cells replacing alveolar lining cells without alveolar collapse. (H and E, $\times 12.5$).

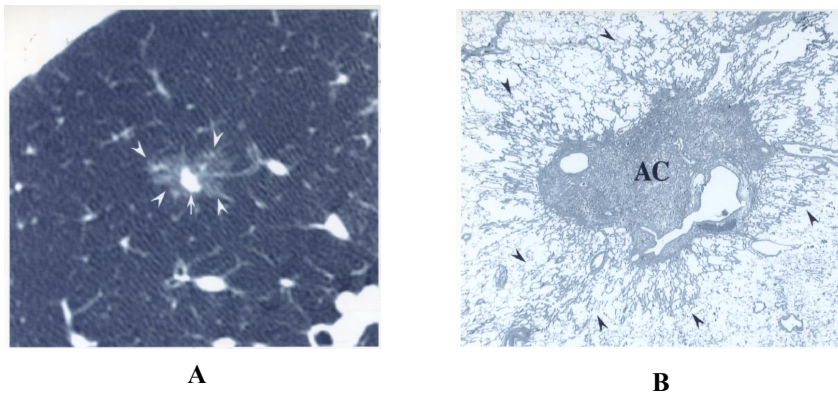


Figure 2. Type B adenocarcinoma in a 69-year-old woman. A, HRCT scan shows a 15-mm mixed GGO nodule that consists of GGO (arrowheads) and solid areas (arrow). B, Photomicrograph shows that solid areas correspond to foci of alveolar collapse (AC) and that GGO areas represent replacement growth pattern of tumor (arrowheads). (H and E, $\times 12.5$).

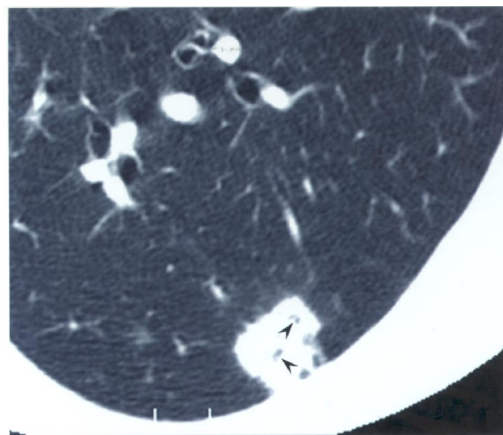


Figure 3. Type C adenocarcinoma in a 69-year-old woman. HRCT scan shows a 13-mm solid nodule with small cavities (arrowheads).

These studies indicate that the early literature lacks information about DTs in slowly growing cancers such as types A and B, and some type C tumors that are invisible on CXR and that very rapidly growing cancers may have been escaped from the screening CT programs. Based on the cancer histology, the longest mean VDT was seen in type A tumors (755 days), followed by type B tumors (562 days), type C tumors (373 days), squamous cell carcinoma (129 days), small cell carcinoma (97 days), and type D tumors (89 days). These values were generally compatible with those measured on CXRs [104, 130, 134].

8.4. Role of the first follow-up CT

Takashima et al. [105] addressed the role of the first follow-up HRCT taken 42-120 days (mean, 93 days) after the initial HRCT for prediction of benignity or malignancy in indeterminate SPNs detected at screening CT. In their study, growth of lesion was identified in 56% of 36 malignant lesions and the other malignant lesions remained the same size, while that among 44 benign lesions, regression was seen in 27%, lesion growth in 5%, and no change in size in 68%. The information on the growth of lesion improved the sensitivity of initial HRCT alone for prediction of both benignity and malignancy by 22%. Yankelevitz et al. [135] suggested that a single repeat HRCT scan obtained 30 days after the first HRCT scan was enough to depict lesion growth in most malignant tumors as small as 5 mm. However, most tumors in their study had short VDTs less than 100 days.

Detection of lesion growth on two-dimensional (2D) CT images depends on the resolution of CT, the initial size and the VDT of lesion, and the period of time between a set of CT scans [105, 136]. Therefore, all these parameters should be taken into consideration to determine the optimal intervals between the follow-up CT scans. With the current CT technology, changes in lesion size as small as 0.3-mm can be appreciated with HRCT images [120, 135]. Correlation between VDTs and the degrees of lesion growth for a given period of time in each tumor histology is summarized in Table 5. For a pure GGO or a mixed GGO nodule, follow-up CT obtained 6 months after the initial CT may be enough if the nodule is 5 mm or larger and a 3-month interval is appropriate if the nodule is 10 mm or larger to detect lesion growth. On the other hand, a 3-month interval is appropriate for a pure solid nodule of 5 mm or larger.

9. Biopsy procedures of peripheral nodules

9.1. Bronchoscopy

Flexible fiberoptic bronchoscopy (FFB) is best suited for tissue diagnosis in centrally located lung lesions. The overall diagnostic yield of this procedure is about 70% for central lesions and over 90% for lesions that are visible on bronchoscopy [137]. However, fluoroscopic assistance is required for peripheral lung lesions and therefore, small peripheral lesions that are invisible under fluoroscopy are not candidates for biopsy through FFB. Diagnostic yield of this technique is proportional to the size of lesion [137-139]. In addition, when a bronchus entering the proximal portion of the lesion at CT (positive bronchus sign) is absent, the yield is low [140]. Thus, the yield of FFB decreases to 30%-54% for peripheral lesions less than 2 cm in diameter and therefore, this procedure is not indicated for biopsy of peripheral lung lesions discovered at screening CT [137-139].

9.2. Percutaneous biopsy

Percutaneous transthoracic needle aspiration (PTNA) via fluoroscopic or CT guidance is widely used for peripheral lung lesions. CT guidance is preferable, because this technique allows avoidance of bullae, fissures, and vessels and permits sampling in viable portions of lesion. Recently, CT fluoroscopy with use of helical CT has been applied to the biopsy of peripheral lung lesions. This technique offers real-time visualization of lesions during biopsy and therefore, enabled biopsy of smaller lesions

and lesions in technically difficult areas with a single puncture during a single breath-hold in the majority (75%-90%) of cases [141-144]. Diagnostic yield of this procedure is comparable to that of conventional CT-guided PTNA. Thus, CT fluoroscopy has potential to improve overall success rates and will replace conventional CT assistance for PTNA of small lung nodules.

PTNA offers sensitivity of 90%-99% and specificity of 96%-100% for diagnosis of lung cancer [145-147]. Cutting core biopsy provides no advantage over aspiration biopsy in diagnosis of lung carcinoma [148, 149]. However, cutting biopsy can increase the diagnostic accuracy of specific diagnosis of benign lesions and histologic typing of malignant lymphoma. There are conflicting results with respect to the relation of diagnostic accuracy to size of lesion. Some investigators described that the accuracy of CT-guided PTNA is significantly less for pulmonary nodules 1.5 cm or smaller than for larger nodules, while other authors reported that lesion size did not influence the diagnostic accuracy of PTNA [146, 150-152].

9.3. Surgical biopsy

Several investigators recommend excisional surgical biopsy as the initial investigation of choice for indeterminate SPNs detected at screening CT for the following reasons: (1) the vast majority of screen detected SPNs were 2 cm or less and the incidence of nondiagnostic samplings in nodules of this size category is high, ranging from 16% to 23% [146,152]; (2) malignant lesions are ultimately found in 20-30% of patients with nondiagnostic samplings in PTNA and 29% of patients with nonspecific benign diagnoses in PTNA [153, 154]. In my opinion, PTNA can be used for diagnosis of solid nodules; however, GGO nodules should be surgically removed to determine histopathologic diagnosis for the following reasons: (1) accuracy of PTNA is high but the targeted lesions in the literature have been solid lesions; (2) differentiation between severe AAH and BAC is difficult even by pathologic examinations [25, 47]; (3) discrimination between BAC and invasive adenocarcinoma is possible only on the basis of histopathologic studies [46, 155].

Video-assisted thoracic surgery (VATS) allows visualization of the entire hemithorax and lung and permits sampling of pulmonary, pleural, and mediastinal lesions through a small incision with minimal pain and morbidity. Therefore, VATS should be used as the primary surgical procedure for the diagnosis of peripheral lung lesions. Reported accuracy of VATS for peripheral lung lesions is as high as up to 100% [156, 157]. In some instances, however, it may be required to place marking devices or marking materials into or adjacent to the nodule under CT guidance before surgery for identification of the nodule at surgery [158-160].

9.4. Is biopsy necessary for pure GGO nodules?

GGO nodule is one of the common findings detected at screening CT of the lung. This CT feature is nonspecific and represents benign and malignant conditions such as edema, hemorrhage, inflammatory diseases, focal fibrosis, AAH, BAC (types A and B tumors), or type C tumors [22, 161]. When a GGO nodule persists and shows no decrease in size, the likelihood of a replacement-type lung neoplasm is high. However, differentiation between focal fibrosis, AAH, BAC, and type C tumor is often difficult even with repeat HRCT scans [98, 100, 162]. Focal fibrosis and AAH were the main

benign entities that were surgically resected among the nodules detected at screening CT [98, 100]. To date, there are no articles with regard to PTNA results in small GGO nodules. Although several authors described the role of PTNA for the diagnosis of BAC, all these investigators described difficulties in differentiation between BAC, adenocarcinoma with BAC components, and reactive bronchial cells [155, 163].

Controversy exists regarding whether lung biopsy should be done for a persistent GGO nodule [162]. Noguchi et al. described that no patients with type A or B tumor died of the disease [46]. Other researchers confirmed the favorable prognosis in these tumor categories and any contradictory results have not been reported until now [32, 164]. Type C tumors are heterogeneous with respect to prognosis and HRCT appearance. However, Takashima et al. [165] reported in a series of 52 patients with type C adenocarcinoma that no patients with a pure GGO pattern died of the disease. Thus, follow-up HRCT scans may be enough for a pure GGO nodule. Surgical removal should be considered only when the nodules have developed solid components within them at repeat HRCT scans. Flow chart of evaluation of indeterminate SPNs detected at screening CT is summarized in figure 4.

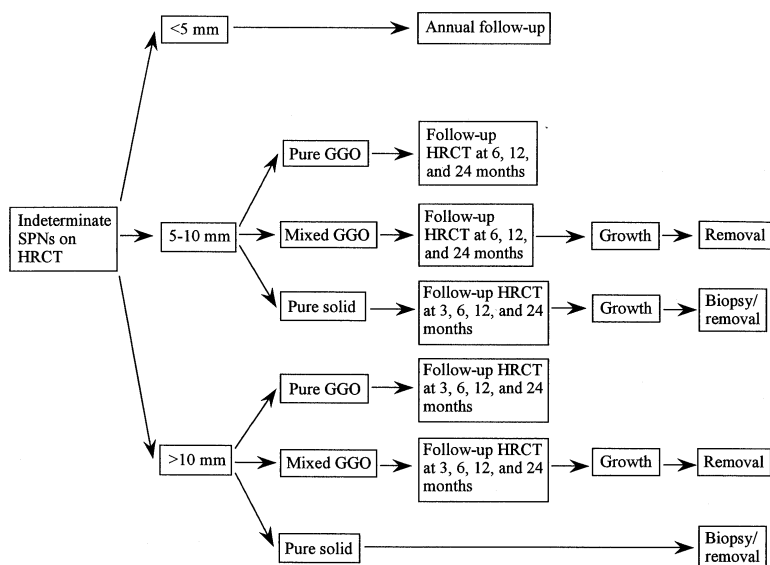


Figure 4. Flow chart of evaluation of SPNs detected at low-dose lung screening CT.

10. Computer-aided diagnosis

Multidetector helical CT (MDCT) enabled scanning of the entire lungs several times faster than conventional single detector helical CT with a thinner collimation [166, 167]. MDCT offers the simultaneous evaluation of high resolution and standard imaging protocols from one data acquisition during a single breath-hold and also provides 3D analyses. This imaging procedure will be the standard technique for screening for lung cancer. With the use of MDCT, benign lesions with benign calcification will be

correctly diagnosed at the initial screening test; however, the number of indeterminate small nodules may increase due to its better spatial resolution. MDCT requires much more time for reading than single detector helical CT, because MDCT provides enormous data. Thus, computer-aided diagnosis (CAD) systems have the potential of reducing the burden and saving the time of radiologists in the following manners: (1) automatic detection of pulmonary nodules; (2) qualitative assessment such as by neural network [126]; (3) quantitative assessment (growth rate and GGO portions). However, these systems are only in a preliminary stage and therefore, there are no commercially available CAD systems currently.

10.1. Detection of pulmonary nodules

There are several articles in respect to automatic detection of lung nodules with CAD systems [168-171]. Sensitivity for detection of nodules ranged from 38% to 94% (mean, 75%) with false-positive results per CT study of 1.3-28.3 (mean, 11.8). The causes for false-negative diagnosis of CAD depended on the image segmentation algorithm used in each CAD system. Missed nodules with CAD were adjacent to the vessel or the pleural surface or embedded in regions of diffuse pathologic features or GGO nodules. The low sensitivity and the large fraction of false-positive results indicate that CAD systems should be limited to complementary use to visual assessment of radiologists at present.

10.2. Evaluation of growth rate

Tumor growth can be more accurately estimated with a direct 3D volume measurement than with the conventional 2D method, because tumors often show asymmetric growth. Yankelevitz et al. [172] compared accuracy of 2D and 3D techniques for measurement of VDTs in 13 nodules less than 10 mm and found that 3D technique was more accurate than 2D technique. However, all malignant lesions in their series had a solid pattern (mean CT attenuation, 35 HU) with short VDTs (< 177 days). Solid lung cancers have much higher CT attenuation values than the lung parenchyma, whereas cancers of a GGO pattern show much lower CT attenuation values (mean, -590 HU), nearly reaching the lung parenchyma [173]. GGO nodules have longer VDTs than solid nodules and separation of nodules from the surrounding lung will be more difficult in GGO nodules than in solid nodules. Nonetheless, growth rate estimation with repeat 3D CT images in GGO nodules is awaited.

10.3. Quantification of GGO portions

Many investigators described that the evaluation of the extent of GGO components in lesion is useful not only for classification of subtypes of small lung adenocarcinoma but also for prediction of prognosis of patients with GGO tumors [31, 32, 174-176]. However, all authors estimated GGO areas quantitatively or semiquantitatively using a 2D technique. Takashima et al. [176] quantitatively evaluated GGO areas of lesion and described that among various HRCT findings, the percentage of GGO areas was the only significant factor for differentiation between type A or B tumor and type C tumor. Kuriyama et al. [31] semiquantitatively assessed GGO areas and described that GGO areas were significantly greater in type A or B tumor than in type C or type D-F tumors.

Takashima et al. [32] addressed the prognostic utility of GGO areas as well as other HRCT findings and pathologic data in patients with small adenocarcinoma, using multivariate analysis and reported that the percentage of GGO areas was an independent prognostic factor for survival. Kodama et al. [174] also described in a study of small adenocarcinoma that a 3-year survival rate was significantly better for patients with GGO areas greater than 50% than for patients with GGO areas less than 50%. Since more accurate quantification of GGO areas of lesion will be possible with a 3D volumetric analysis than with a 2D technique, a 3D estimate of GGO areas has potential for providing more exact information both on the diagnosis of GGO tumors and on prognosis of patients with replacement-type adenocarcinoma in the lung.

11. Conclusions

Detection of invasive carcinoma with screening CT at early stages will contribute to reduction of lung cancer mortality, whereas, discovery of indolent tumors will incur overdiagnosis. Real mortality will be the product of the balance of these factors. Ongoing randomized controlled trials will determine the true effectiveness of screening CT of the lung. In light of the past randomized controlled trials using CXR, well-designed studies and careful analysis should be conducted for screening CT.

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