68 Ga/Ge rod source. The images were reconstructed iteratively (ordered-subset expectation maximization method, two iterations, eight subsets). The standardized uptake value (SUV) was semiquantitated in cases where the uptake suggested abnormal findings. The SUV was calculated as the ratio of the FDG uptake in a small region of interest (placed over the lesion in attenuation-corrected images) to the administered activity per body weight.

In our institute, a whole-body CT scan was performed just prior to the FDG-PET and was used as a reference for FDG-PET diagnosis or image fusion in cases with suspicious accumulations on the FDG-PET images because a PET/CT scanner was scheduled for installation 1 year or 2 years after the start of the study, and we wished to perform an examination that would approximate a PET/CT examination. Whole-body CT images were obtained using a 16-line multidetector row CT scanner (Aquilion 16, Toshiba, Tokyo, Japan). The CT examination was performed from the head to the mid-thigh according to a standardized protocol with the following settings: axial 2.0-mm collimation · 16 modes; 120 kVp; 5–100 mAs, adjusted to the participants' body weights (35 mAs at 170 cm, 70 kg); and a 0.5-s tube rotation, pitch 15.0. The subjects were requested to maintain a normal, shallow respiration during the three-dimensional CT scan acquisition. Iodinated contrast material was not administered.

The study population was defined as consecutive subjects who participated in the RCCPS cancer-screening program and underwent FDG-PET examinations between February 2004 and January 2005. A total of 2911 individuals, including 1629 men and 1282 women were enrolled. The mean overall age was 59.79 years (men 61.08 years; women 58.18 years).

When a cancerous lesion was suspected based on the results of the RCCPS program, the participant was referred to National Cancer Hospital (NCH Central or East) or another local hospital for follow-up, further examination or treatment. The final diagnosis was obtained by a pathological examination. The cancer stagings were based on the 1977 TNM classification of the International Union Against Cancer (UICC) [9]. The records of the cancers detected at NCH can be directly viewed via the electronic record system of NCH, which is also utilized by the RCCPS program. The information regarding the cancers detected at local hospitals was obtained from the patients' doctors. The information regarding false-negative RCCPS results was obtained from the annual responses of the participants. The collection rate of the annual responses was about 90%. This study was approved by the Institutional Review Board of the National Cancer Center.

Data analysis

Each examination was interpreted in a blinded manner, without any information from any of the other examinations. The PET and whole-body CT images were interpreted by a single board-certified radiologist.

The criterion for a positive PET finding was a visible, focally increased uptake of FDG that appeared to differ from the physiologic uptake or the uptake of well-recognized benign lesions [8], occasionally referring to the SUV. The PET diagnosis was performed using no information obtained during the other examinations (with the exception of the whole-body CT). The PET diagnosis was also performed by referring to the whole-body CT scan ("PET and CT" diagnosis), especially for pulmonary focal accumulations of FDG. Even if a focally strong uptake was detected in the lung, the PET finding was regarded as negative when the corresponding CT finding was negative for malignancy. On the other hand, even if malignancy was suspected on the basis of the CT images, the FDG finding was regarded as being negative when abnormal accumulation was not observed.

The positive rate, detection rate, sensitivity, specificity, and positive predictive value of FDG-PET for whole-body screening (with or without information from the whole-body CT scan) were calculated using data obtained from all the examinations and from the 1-year follow-up examinations. In addition, PET-positive or PET-negative cancers were also investigated. Further investigations were also performed for lung, breast, and colorectal cancers, which are the major targets of cancer screening. Moreover, focal pulmonary and colorectal accumulations, which are considered to be the major causes of PET false-positive cases [10, 11], were also investigated.

Statistical analysis

Differences in the mean SUVs between malignant and benign lesions in the lung or colorectal region were analyzed for statistical significance using Student's t test. The difference in the mean size between PET-positive and -negative lung cancers was also analyzed using Student's t test. A P value < 0.05 was considered statistically significant.

Results

Of the 2911 asymptomatic participants, malignant tumors were detected in 153 participants (157 tumors; 97

men and 56 women) within 1 year after screening. All the malignant tumors were detected during thorough examinations, including FDG-PET. Cancer was not detected during any of the 1-year follow-ups. The number of PET-positive cases without information from whole-body CT scanning totaled 246 from among the 2911 participants. The number of PET-positive cases with information from whole-body CT scanning (PET- and CT-positive cases) totaled 226. True-positive PET findings were obtained for 28 malignant tumors in 12 men and 16 women. The details of the PET-positive cancers are shown in Table 2. The cancers comprised seven colorectal cancers, four lung cancers, four thyroid cancers, three breast cancers, two gastric cancers, two prostate cancers, two small intestinal sarcomas (gastrointestinal stromal tumors), one malignant lymphoma, one head and neck malignancy (nasopharyngeal carcinoid tumor), one thymoma, and one hepatocellular carcinoma. Most of the PET-positive tumors were early stage lesions (stages 0 or I according to the TNM classification). Three of the PET-positive tumors were stage II (one breast cancer and two colorectal cancers), and one was stage III (one gastric cancer).

A total of 129 of the 157 detected cancers were PET-negative. The details of the PET-negative cancers are shown in Table 2. These cancers comprised 28 colorectal cancers, 23 lung cancers, 22 gastric cancers, 20 prostate cancers, 9 thyroid cancers, 8 breast cancers, 7 urologic cancers, 6 esophageal cancers, 4 malignant lymphomas, 1 pancreas cancer, and 1 gallbladder cancer. Four of the participants had double cancers: three participants had colorectal cancer and prostate cancer, and one participant had gastric cancer and prostate cancer. All the PET-negative cancers were early stage lesions (stages 0 or I) according to the TNM classification.

The overall positive rate and the detection rate of FDG-PET for whole-body screening without whole-body CT were calculated to be 7.76% and 0.96%, respectively (Table 3). The positive rate of "PET and CT" diagnosis was 8.58%. The overall sensitivity, specificity, positive predictive value, and accuracy of PET without whole-body CT were estimated as 17.83%, 95.15%, 11.20%, and 87.94%, respectively. Specificity, the positive predictive value, and the accuracy of "PET and CT" diagnosis were 95.20%, 12.39%, and 88.78%, respectively.

Tables 4, 5, 6, and 7 show the details of several kinds of detected cancers such as lung cancer, breast cancer, and colorectal cancer, which are among the main targets of cancer screening. The average tumor diameters of the detected lung cancers, the PET-positive lung cancers, and the PET-negative lung cancers were 15.2 mm (5–32 mm), 16.8 mm (10–24 mm), and 14.9 mm (5–32 mm), respectively. The difference between the mean size of the PET-positive and PET-negative lung cancers was not significant ($P > 0.05$, Table 4). All the PET-positive lung cancers were solid-type nodules and were pathologically identified as adenocarcinomas. The PET-negative lung

Table 2 Detected cancers

	PET-positive cases	PET-negative cases
Lung cancer	4	23
Breast cancer	3	8
Colorectal cancer	7	28
Thyroid cancer	4	9
Malignant lymphoma	1	4
Esophageal cancer		6
Gastric cancer	2	22
Hepatocellular carcinoma	1	
Pancreas caner		1
Gallbladder cancer		1
Prostate cancer	2	20
Renal/bladder cancer		7
Others	4	
Total	28	129

Others in PET-positive cases contain two gastrointestinal stromal tumors, one thymoma, and one nasopharyngeal carcinoid tumor

Table 3 Result of screening value

	PET (%)	PET and CT* (%)
Positive rate	8.58	7.76
Detection rate	0.96	0.96
Sensitivity	17.83	17.83
Specificity	95.15	95.20
Positive predictive value	11.20	12.39
Accuracy	87.94	88.78

*Whole-body CT

Table 4 Size of PET-positive lung nodules

	Cancer	Benign	*P*
Number	4	23	
Average size	16.8 mm	14.9 mm	0.05

Table 5 Detected lung cancers

	Total	Solid nodule	Part-solid nodule	Non-solid nodule
PET-positive case	4	4	0	0
PET-negative case	23	8	12	3

Table 6 Detected breast cancers

	Total	DCIS	IDC
PET-positive case	3	0	3
PET-negative case	8	7	1

DCIS ductal carcinoma in situ, *IDC* invasive ductal carcinoma

Table 7 Detected colorectal cancers

	Depth Total	*m* 18	sm1 3	sm2 3	mp 0	ss 2	se 0
PET-positive case	7	4	0	1	0	2	0
PET-negative case	28	23	3	2	0	0	0

m intramucosal tumor, *sm1* slight to moderate submucosal invasion, *sm2* massive submucosal invasion, *mp* invasion to proper muscle layer, *ss* subserosal invasion, *se* serosal invasion

Table 8 Benign focal colorectal accumulations

Physiological uptake	84
Benign adenoma	11
Hyperplastic polyp	2
Hemorrhoid	4
Inflammation (ulcerative colitis)	2
Reactive lymphoid hyperplasia	1
Total	104

Table 9 Focal colorectal accumulations

	Cancer	Benign	*P*
Number	7	104	
Average of SUV_{max}	8.31	5.66	>0.05

SUV_{max} maximum standardized uptake value

cancers comprised 8 solid nodules, 12 part-solid nodules, and 3 non-solid nodules. Pathologically, the PET-negative cancers comprised 18 adenocarcinomas and 5 bronchioloalveolar carcinomas. All the lung cancers were stage I, according to the TNM classification.

Of the breast cancers, all the PET-positive cancers were duct-invasive carcinomas (DIC): two were stage I lesions, and one was stage II. The PET-negative breast cancers comprised four DIC and four ductal carcinomas in situ (DCIS). All the PET-negative breast cancers were at an early stage.

All the detected colorectal cancers were pathologically identified as adenocarcinomas. The PET-positive colorectal cancers comprised four intramucosal tumors, one submucosa-invaded tumor, and two advanced cancers. The PET-negative colorectal cancers comprised 26 intramucosal tumors and 5 submucosa-invaded tumors, respectively.

A total of 104 of the 111 PET-positive cases for the colorectal region were false-positive (Tables 8, 9). The

Table 10 Focal pulmonary accumulations

	Cancer	Benign	*P*
Cancer by CT* diagnosis	4	2	
Benign by CT* diagnosis	0	20	
Average of SUV_{max}	3.76	3.71	>0.05

*Whole-body CT

PET false-positive cases comprised 84 physiological accumulations, 11 adenomas, 2 hyperplastic polyps, 4 hemorrhoids, 2 inflammations (ulcerative colitis), and 1 reactive lymphoid hyperplasia. The average maximal SUVs were 8.31 (3.88–16.25) for the colorectal cancers and 5.66 (2.94–16.77) for the benign accumulations. The difference between the SUVs of the colorectal cancers and the benign uptakes was not significant ($P > 0.05$).

Focal pulmonary FDG uptake was observed in 26 cases, including 4 cancers and 22 inflammations (Table 10). The average maximal SUVs were 3.76 (2.07–4.96) for the lung cancers and 3.71 (1.20–4.39) for the inflammations. The difference between the SUVs of the lung cancers and the lung inflammations was not significant ($P > 0.05$). Of the 26 cases of focal pulmonary uptake, 2 cases of inflammation were misdiagnosed by "PET and CT" diagnosis.

Discussion

FDG-PET is a promising screening modality targeting the whole body. In our study, cancers of many organs were detected, mostly at an early stage, by FDG-PET. A few participants had either a head and neck malignant tumor or a malignant lymphoma that was only detected using FDG-PET. However, the detection of some cancers using FDG-PET is known to be difficult: the detection of urologic cancers is hampered by the renal excretion of FDG [12], and cancers with a low cell density (bronchioloalveolar carcinoma [13], gastric cancer [14], and schirrhous-type breast cancer [8]), small cancers (smaller than 10 mm in diameter) [15], and hypometabolic cancers (renal cell carcinoma [16], and hepatocellular carcinoma [17]) are also difficult to detect. In our study, such cancers were hardly detected as early gastric cancers, small lung cancers containing ground glass opacity on CT scans, DCIS of the mammary gland, intramucosal carcinomas of the colon, prostate cancers. FDG-PET sometimes showed a physiological uptake in the gastrointestinal tract that led to a false-positive PET result [11]. Most of the false-positive PET findings in our study were caused by physiological gastrointestinal uptake. FDG often accumulates in areas of inflammation [10] or in benign

tumors [18]. In our study, a differential diagnosis between tumor and inflammation in the lung or between malignant tumor and benign tumor in the thyroid gland was difficult. Reference to CT images was useful for differentiating lung tumors and inflammation in our study. It has to be kept in mind that FDG-PET has these limitations and some types of cancer are likely to be missed in cancer screenings using only FDG-PET.

The detection rates for PET cancer screening reported by several institutions, including ours, were about 1.0% (from 0.96% to 2.34%) [19]. These detection rates are much higher than the sum of the detection rates for other screening modalities whose efficacies have been already assessed; these other screening modalities include chest X-ray and sputum cytology, MMG and physical examination, upper gastrointestinal (GI) tract X-ray, fecal occult blood test (FOBT), and cytology of the uterine cervix [20, 21]. On the basis of these data, FDG-PET may be considered to be useful in cancer screening. However, a high detection rate is insufficient for an assessment of validity because the detection rate depends on the prevalence of the population [20].

Sensitivity is the most important value in assessing the accuracy of screening, which is relevant to the quality control of screening [20]. However, the sensitivity of PET cancer screening has not been sufficiently measured because of the difficulty in following up PET-negative cancers, which require simultaneous and thorough examinations for each organ or an adequate follow-up system. Each examination conducted as part of the RCCPS program is thorough, and the RCCPS program also has an adequate follow-up system. Therefore, the sensitivity of PET cancer screening targeting the whole body could be measured in the RCCPS program and was estimated to be 17.83%. In an earlier report on PET cancer screening that was based on a large-scale questionnaire survey sent to 99 PET facilities in Japan, the reported sensitivity (79.0%) was higher than that of our data [22]. There are two possible explanations for this difference. First, a large proportion of the population in our study had undergone a prior screening test within 1 year of the present study, according to a report investigating profile of the participants in the RCCPS screening program [1]. Therefore, a considerable proportion of the patients in our study did not have advanced cancers that were easily detected using FDG-PET. Second, the screening sensitivity is a relative value that depends on combined examinations or follow-up systems that affect the detection of PET-negative cancers. These two reasons probably led to the high overall detection rate (5.26%) of the thorough examinations and the low sensitivity by FDG-PET in our study.

The PET sensitivity in our study was considerably lower than the reported sensitivities of examinations that have already been assessed their effectiveness in reducing mortality [20]. However, concluding that FDG-PET is not effective for cancer screening would be hasty because the validity of a cancer-screening modality is not confirmed by a high sensitivity, but rather by a reduction in mortality [20]. Studies to determine the efficacy of FDG-PET for cancer screening of the whole body are underway.

Of note, some cancers with a minimal effect on mortality were included among the PET-negative cancers identified in our study, such as small lung cancer containing ground glass opacity on CT scans, DCIS of the mammary gland, and intramucosal carcinoma of the colon. FDG-PET is presumed to be capable of detecting cancers that are advanced enough to be treated [21]. However, the progression of these PET-negative cancers is not well understood, and further investigation is needed.

To obtain evidence supporting PET cancer screening, the validity of this modality must be assessed. However, assessing reductions in mortality over a short time period is difficult. The United States Preventive Services Task Force (USPSTF) recommends an "analytic framework" that demonstrates a chain of logic in which the evidence supports a link between the preventive service and improved health outcomes [23]. Using such an analytic framework, validity can be assessed not only by using direct evidence, such as a reduction in mortality, but also by using indirect evidence connected to the validity of the modality. Such a framework may enable a shortcut for assessing the validity of PET cancer screening by measuring the relative sensitivity when compared with other modalities such as chest X-ray or FOBT [24] for which sufficient evidence is already obtained.

A few problems regarding PET cancer screening remain; specifically, a risk analysis and economic assessment were not sufficiently investigated in our study. These problems are as significant to the evaluation of a screening modality as the assessment of accuracy [20]. A major risk of PET cancer screening is radiation exposure, which is estimated as 0.7 mSv per 37 MBq of FDG as the effective radiation dose. Although a risk–benefit analysis of PET cancer screening was not sufficiently investigated in this study, efforts to reduce radiation exposure, such as reducing the FDG dose using three-dimensional scans, are needed. From the aspect of the economic assessment of PET cancer screening, no obvious evidence of cost-effectiveness is available, even though PET examinations involve a substantial cost when compared with other screening modalities [19, 21]. At present, PET cancer screening is

categorized as an opportunistic screening modality because the efficacy of PET cancer screening has not been confirmed. Therefore, each subject must pay for the cost of the PET examination by himself or herself, without the support of public funding. If evidence of PET cancer-screening efficacy is obtained in the future, debates surrounding issues of cost-effectiveness will arise.

In conclusion, FDG-PET can detect a variety of cancers at an early stage as part of a whole-body screening modality. The detection rate of PET cancer screening was higher than that of the other screening modalities which had already demonstrated evidence of efficacy. However, the sensitivity of PET cancer screening was lower than that of other thorough examinations performed at our institute. FDG-PET has some limitations, and cancer screening using only FDG-PET is likely to miss some cancers.

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報告

肺がんCT検診認定技師の要件
― 撮影およびスクリーニングにおけるminimum requirement ―

低線量肺がんCT検診(以下，CT検診)における今後の受診者数の増加とそのニーズに応じてCT検診を実用的に、同時に精度良く行うためには、従来と異なる新しい検診ステムの構築が不可欠となる。この課題に対し日本CT検診学会を中心に肺がんCT検診分野における読影認定医と認定技師(胸部CTスクリーナー)の構想が進んでいる。後者の認定技師の資格は、専門的なトレーニングを受けた後、認定試験によって与えられる。またその業務は肺がんCT検診画像読影の専門知識をもつ認定医師の下でのみ行われることを前提としている。ここにCT検診分野における認定技師に求めるminimum requirementと今後の展望について考察する。

キーワード：低線量CT、肺がん検診、認定技師、CTスクリーナー

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1．目的と背景

肺がんCT検診は、1990年初めより金子、森山らにより肺がんの早期発見のための手段としてその試みが導入され、本邦での1996年[2]、1998年[3]の報告に続き、1999年には米国においてもCT検診の実施とその成績が報告[4]されている。本邦において現行の胸部X線写真による肺がん検診の受診者数は年間700万人以上であり、その中でCT検診は既に6万人以上が行われている。しかし，その割合は全受診者の1%であり，現行の肺がん検診をCT検診で置き換えるには読影医の確保と養成に限界があることは明白である。

このような状況の中で，受診者数の増加とニーズに応じて国民が，いつ、どこの施設でも精度の高いCT検診を受けることができる体制つくるためには、従来と異なる新しい検診ステムの構築が不可欠となる。この課題に対し日本CT検診学会ではCT検診のための読影認定医と胸部CTスクリーナーが議論されてきた[5]。この中で胸部CTスクリーナー(以下，肺がんCT検診認定技師)とは、診療放射線技師が専門的なトレーニングと認定試験を受けることで，CT装置の保全とスキャン条件の管理、受診者の被曝管理、受診者情報の管理を行う能力を身につけると共に，検診CT画像の肺結節に対する存在診断の能力を身につけることで肺がんCT検診認定技師として1次読影[6-7]を担当することである。これにより読影能率の向上と読影医の負担軽減を行いながら、厳密な被曝線量低減の下にCT検診全体を精度良くかつ実用的なレベルで行って行く。この新しい検診システムによりCT検診を実用的な運用と共に、その量的拡大と質的維持を行うことで国民がそのニーズに応じて，今後検討が予定されている肺がんCT検診認定医師が勤務する認定施設において精度の高いCT検診を受けられる体制の構築を目指して行くものである。

2．肺がん CT 検診認定技師の業務内容(案)

肺がん CT 検診認定技師の業務は CT 検診における役割の中で、①撮影業務、②装置管理、③線量(被ばく)管理、そして④1次読影としての肺結節の拾い上げ(以下、存在診断と呼ぶ)の4つである。

2.1.1　撮影業務

CT 検診では健康な人を対象とする。このために受診者の X 線被曝を最大限に抑えつつ、検診のための読影に適した最適なスキャンパラメーターによる撮影が必須な業務となる。同時にリスクとしての X 線被曝に対して得られる診断情報を最大にするためのスキャンデータに対する画像処理が必要となる。

a)シングルスライスCT(Single slice CT) を用いた検診において

一定の大きさの肺結節に対してスキャン終了後,その場で 2 から 3mm 厚の Thin section CT (TSCT)を実施する。これにより要精査受診者の再来院などに伴う負担軽減を行ない読影精度と検診能率の向上を図って行く。ここでは得られた CT 画像に対して存在診断を行なうことで積極的に結節の拾い上げを行い、適切に TSCT を実施できる能力が要求される。この場合に受診者に対して TSCT の実施に伴う医療被曝を過度に与えることのないように解剖と疾患に対する十分な知識、および撮影技術を持つことが要求される。

b)マルチスライスCT (Multislice CT : MSCT) を用いた検診において

検診現場の MSCT では1～2.5mm前後の撮影スライスでデータ収集された後、5mm～8mm のスライス画像として再構成され読影されることが多い [8]。この場合に結節の存在を的確に判断しスキャン終了と同時に結節に対する拡大処理を含む 1 から 2.5mm 厚の TSCT 画像を作成し、また必要に応じた多断面画像 (sagittal, coronal 像) の作成、生データ(投影データ)の保存[1]などスキャンデータに対し最善な処理を行なう能力が要求される。これにより MSCT の特徴であるアイソトロピックなスキャン情報を有効に生かすためのスキャンデータの運用を可能とし, MSCT の性能を最大限に生かした診断情報の高い CT 画像を読影医に提供する。

これらの業務は既に多くの検診施設で行なわれている (土屋班：全国検診施設アンケート調査より)。しかしその判断基準は施設、担当技師により異なるのが現状 [8,9] である。この課題に対し肺がん CT 検診認定技師によって, これらの業務を統一した基準で行なうことで、常に読影医に対して最新の撮影技術に対応した最高の画像情報 [10] 提供して行く。

2.1.2　装置管理、線量(被曝)管理

多くの検診施設では CT 装置は1台であり代替装置はない。この場合に装置の故障に伴うダウンタイムの延長は円滑な検査の実施に大きな影響を与える。CT 装置を安全に管理し、その予防保全を行うことで故障を未然に予防し、装置の稼働率と信頼性を維持しながらその性能を最大限に発揮させる [10] ことは必須な業務となる。同時に、最小限の被曝線量 [11,12] で肺結節を検出するための最適スキャン条件の設計, 画像描出条件, 線量管理などの環境の整備を行ってゆく

2.1.3　1次読影としての肺結節の拾い上げ

今後, 予想される検診施設と受診者数の増加 [8]、MSCT に代表される膨大な画像データは読影医に対し過度な負担となり, 読影能率と検診能率を低下させる。これに対し

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[1] ディスク内の生データ容量には制限がある。再構成画像と異なり、生データはスキャンの繰り返しにより上書きされ消去される。TSCT に必要な拡大再構成、高分解能関数処理は生データに対して再構成処理を行うことで得られる。

て画像データに対して肺結節の拾い上げ(存在診断)という1次読影の業務を担うことにより読影医の負担を軽減し、検診能率を向上させて行く。ただしこの業務は肺がんCT検診認定医師の監督下でのみ,行われることが前提となる。また、そのための専門的トレーニングによる肺解剖と疾患、読影に関する十分な基礎知識の習得が行われることが必須条件となる。到達目標の1つは肺がんCT検診認定技師による1次読影、その結果を参考にして行なわれる読影医による2次読影(責任読影)というダブルチェックシステムである。

3.スクリーニングと肺がんCT検診認定技師としての要件

3.1 スクリーニングを行なうための minimum requirement

スクリーニングを行なうための必要条件として次の2つがある。1つは肺がんCT検診認定技師の1次読影の業務は肺がんCT検診認定医師の下でのみ行われなければならない。第2には、肺がんCT検診認定技師における1次読影の業務は肺に関する解剖と疾患、読影に関ずる専門的なトレーニングを受け、基礎知識を十分に習得した後、認定試験に合格した技師のみが担当することである

肺がんCT検診認定技師による1次読影、肺がんCT検診認定医師による責任読影というダブルチェックシステムの問題点は診断結果の責任[13]にある。肺がんCT検診認定技師はCT撮影業務を行うと共に、その読影結果をレポートする。しかし現行において医師でない肺がんCT検診認定技師にその読影結果の医学的(法的)責任は取れない。医師は法的責任が取れない肺がんCT検診認定技師が読んだ読影結果を参考にし,2次読影、すなわち責任読影を行なうことになる。従ってこの場合の医師には肺がんCT検診認定技師の読影結果の採否に関し医学的責任がとれる高度な低線量CT画像に対する読影能力と専門性が求められる。また肺がんCT検診認定技師の独り歩きを防ぐために、その業務は肺がんCT検診認定医師の下でのみ行なえるようにしなければならない。さらに医師との連携した読影業務が行えるように、医師には肺がんCT検診認定技師を指導、管理する義務と責任が伴う。肺がんCT検診認定技師と肺がんCT検診認定医師は同時に機能し、業務を行なうことが必要条件[13]である。

3.2 スクリーニング手順の minimum requirement

スクリーニング手順を図1*に示す。方法-1として従来までの医師によるダブルチェックシステムの運用がある。方法-2として、肺がんCT検診認定技師が1次読影を行い、肺結節のある画像を積極的に拾い上げ、その後、肺がんCT検診認定医師が責任を持って判定する方法である。この場合に読影医は責任読影という立場を堅持するためにも再度,全てのCT画像を読影することが必要条件と考える。この場合にも肺がんCT検診認定技師からの読影結果を基に読影医側は2次読影(責任読影)を行なうことで負担が軽減され検診能率の向上が図れる。方法-3として、肺がんCT検診認定技師の1次読影と並行してコンピュータ診断支援(computer-aided diagnosis: CAD)[14,15]の使用が考えられる。肺がんCT検診認定技師がCADを用いてより確かな情報を2次読影側に提供する方法[15,16]である。しかし、現時点では、日常的に使用できるCADはなく、今後の研究の結果を待つ必要がある。

3.3 肺がんCT検診認定技師としての minimum requirement

肺がんCT検診認定技師は専門的トレーニング受けた後、以下の能力を習得していることを必要条件とする。能力の有無は筆記および読影試験により行なわれ、定められた成績と感度を持つことが要求される

1．10mm以上の大きさを持つ結節の確実な拾い上げ
2．5-9mmの大きさの結節の拾い上げ(95%以上の感度で)
3．被検者に合った最適なスキャン条件による検査を行なう能力
4．受診者の被曝管理と被曝低減を行なえる能力
5．受診者情報保護・管理の能力

図1．肺がんCT検診画像の2重読影の方法

4．　報告様式

拾い上げた結節を医師に伝える報告用紙(レポート)の記載内容および方法に関して以下の方法を班研究として検討した。1)現在の報告様式の延長として結節の存在する位置をシェーマ上にマークする方法，2)結節の存在するスライス位置、スライスNoの記載，3)フイルム上に赤鉛筆でマーキング[6,7]，4)肺がんCT検診認定技師のマーキングした結節の座標を記録し，2次読影の際に参照表示できるビューアーシステムの使用などが挙げられる。

特に4)の報告様式はマルチスライスCTを用いたモニターによる読影システムと併用が可能であり、読影能率を向上させるために有用な手段と考えられる。4)のシステムの1例は、現在、新潟大学（和田真一研究室)、放射線医学総合研究所(松本 徹)、富士通の共同研究にて開発中である。

5．　肺がんCT検診認定技師養成のための教育研修（案）

5.1　Web，CDを利用した受講準備システム

講習会（教育研修）はこれを受講し，その内容を修得することで肺がんCT検診認定技師に必要な解剖・疾患に関する知識、そして業務を行うため必要な肺結節に対する検出基準に達することが前提となる。このためには、いかに講習会を能率良く行うかが課題となる。このためには講習会の前に時間をかけての自己学習が必須条件となる。この課題に対して，①Web，CDを利用したティーチングファイル、②東京から肺がんをなくす会の症例を用いたソフト「The Simulation」の利用、③マルチスライスCT検診の肺がん症例ソフトを用いることが提案され、準備されている。これらを講習会受講前に十分に学習することで肺がんCT検診認定技師の肺結節に対する検出能力を短時間で目標レベルに到達させることが可能と考える。

5.2　講習会案

講習会は2日間を想定している。肺がんCT検診認定技師の受講科目の内容の中で基礎項目の習得はWeb，CDで講習会の受講前に済まし、講習会では存在診断に関するトレーニングに重点を置く。また2日目の最終に認定試験と読影試験を実施し、肺結節の検出能力が目標としている感度に達しているか否かの試験を行なうことが計画されている。この計画に対しては平成18年度には斎藤班の小班として、読影能力試験を想定した駒沢大学IT教室(50台のパソコンとサーバーのローカルエリアネットワークシステム)にて、保健学科学生と診療放射線技師の合計25名にて検診CT画像の読影認定試験のシミュレーションが実施され，どのように肺がんCT検診認定技師の読影能力を認定するのかの検討が行われた（図

2)。 ビュアーシステムでは受講者がＣＴ画像上にマーキングした結節の座標を記録し，2 次読影の際に参照表示できる．読影結果はリアルタイムで主制御 PC に集められ試験終了と同時に、それぞれの読影者の感度や偽陽性などを算出することも可能である。

図２専用画像ビュアーを用いた肺がん CT 検診の読影認定試験のシミュレーション実験

6.　肺がん CT 検診認定技師の実現に向けての課題

制度の実現に向けた今後の課題として、その有効性の評価と効果的な教育方法、認定制度準備委員会の設置、技術力の向上などがある。

第１の肺がん CT 検診認定技師の存在を保証するエビデンスとして、専門的なトレーニングを受けた肺がん CT 検診認定技師は，実際に肺がん CT 検診画像を読影している医師と比較し、結節の存在診断において差がないということの証明が必要となる。この課題に対しては 2007 年２月の第 14 回日本 CT 検診学会において、土屋班研究結果として柿沼らは、5mm 以上の pure ground-glass opacity (GGO)や mixed GGO の結節や、6mm 以上の充実型の結節の存在診断において有意差がないことを報告[17]している。その他、土屋班の研究として、インターネット上での教育ソフトウェアの開発、講習会テキスト（案）の作成などが行なわれている。第２の効果的な教育方法については講習会の受講，インターネット上での教育ソフトでの自己学習などの前と後での結節検出能に関する比較実験などを通じての学習効果に関する検討が必要となる。第３に現在、検討されている認定構想(①肺がん CT 検診認定医師、②肺がん CT 検診認定技師、③認定施設)のオーソライズ、それらの維持管理のための関連学会からなる委員会の設置(仮称：低線量 CT 検診精度管理中央委員会)が検討されなければならない。

今後，肺がん CT 検診認定技師制度が真に役立つ制度となるためには医師側は肺がん CT 検診認定技師に対して CT 画像から必要最低限のどのような所見を読み取り、どのようなレポートが欲しいのか、具体的な要求が必要となる(例としては 10mm 以上の結節に対して 100%、5－9mm に対して 95%の感度で検出、検出結果をモニター上に円形マークで表示など)、それに対して肺がん CT 検診認定技師側は医師からの要求に答えられるように１次読影のための具体的な方法と得られる読影結果を医師と共に検討し、十分な協力体制による読影力向上を図った上で実務に入ることが必要となる。さらに肺がん CT 検診認定技師および肺がん CT 検診認定医の技術向上のために，結果をフィードバックする施設内および精検施設、治療施設との合同カンファレンスの設置、あるいは精度管理への積極的な参加が行われる体制を作ることが必要と考える。また臨床的に緊急な対応を要する病態の存在を検出した場合の CT 検診認定医に対する連絡体制のルールの検討も必要となる。

5.　まとめ

低線量肺がん CT 検診は日本が世界に先駆けて行なった画期的な早期肺がん発見の

ためのシステムである。日本はこの検診システムを実用的レベルで運用するための体制を構築しておく責務がある。このためには読影医に対する支援、および低線量 CT 検診の幅広い実施を目的として，CT 検診の分野に特化した肺結節の発見を目的する肺がん CT 検診認定技師の養成が必要となる。肺がん CT 検診認定技師は、精度の高い CT 検診を実施していくために構想されている①肺がん CT 検診認定医師、②認定施設などの制度の中に位置づけられて検討されることが必要である。

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低線量CTによる肺がん検診の現状

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肺がんは近年増加の一途をたどり現在日本人におけるがん死亡原因の第1位となっている．本邦では1993年から低線量CTによる肺がん検診が開始されている．その後，研究，実地検診，人間ドック，自治体のモデル事業として日本の中では広まってきている．代表的な低線量CTによる肺がん検診の概要を表1に示した[1]．検診発見肺がんの病理病期IA期の占める割合は50～93%と報告されており，肺がん発見率は0.36～3.3%であった[2]．通常のシングルヘリカルCTの場合の被曝線量は7.62 mSvと多かったが撮影電流を100～210 mAから25 mAに減らして撮影すると

表1　低線量CTによる肺がん検診の対象，撮影条件，検診期間，被験者数，発見肺がん，病理病期IA期の割合の比較

	ALCAP	信州	ELCAP	Mayo	Munster	SMC
年齢(歳)	≧40	≧40	≧60	≧50	≧40	≧45
喫煙(pack-years)	NL	NL	≧10	≧20	≧20	NL
期間	1993～1998	1996～1998	1993～1998	1999～2001	1995～1999	1999～2003
CT撮影条件						
Tube voltage (kVp)	120	120	140	120	120	120
Tube current (mA)	50	25～50	40	40	50 ¶	48～50 ¶
Collimation (mm)	10	10	10	5	5	5
Pitch	2	2	2	1.5	2	0.75～1.5
検出器の数	1	1	1	4	1	1, 4, 8, 16
検診間隔(月)	6	12	3, 6, 12	12	3, 6, 12, 24	6, 12
被験者数	1,611	5,483	1,000	1,520	817	6,406
CT発見肺がん	36	60	33	38	12	23
病理病期IA期	28 (77)	53 (93)	27 (82)	21 (60)	6 (55)	13 (62)

ALCAP：anti-lung cancer association project, ELCAP：early lung cancer action project, SMC：Samsung Medical Center, NL：制限なし
カッコの中の数字は%である．¶mAs

(文献1)より引用，Lee先生の御好意による)

1345-1553/07/¥100/頁/JCLS

低線量CTの被曝線量は1.27 mSvに減らすことができる[3]．CTによる検診がはじまってから多くの小型肺がんの画像所見の知見が蓄積されてきたが，最近のmultislice CTの機器の進歩により微小結節がさらに多数発見されるようになってきている．

最近の報告としては，International Early Lung Cancer Action program (I-ELCAP) studyでは1993年から2005年まで3万1,567人の肺がんCT検診を行い，484人の肺がんを発見し，その85%が病期Iで10年生存率が88%であったと報告した[4]．しかし肺がんCT検診は胸部単純X線による検診に比べ，発見可能前臨床期preclinical detectable phaseの長さが長いためlead time bias(見かけ上発見後の観察期間が長い)，length bias(進行の遅いがんほど発見されやすい)，過剰診断バイアス(overdiagnosis bias：致死的でないがんを含む)の影響を強く受けると考えられるため，肺がんCT検診が有効であるかの直接的な証拠とはならない．

また，肺がんCT検診は，肺がんと診断されて切除されるものは増加するが，肺がんによる死亡率を低下させる効果がないとの報告もある[5]．この調査は，肺がんリスクの高い喫煙者と過去喫煙者3,246人を対象に，4年間，毎年1回の肺がんCT検診を実施し，この間肺がんで死亡したり，進行肺がんと診断された患者の割合を予測モデルと比較したものである．

米国国立がん研究所では2002年9月から5万人規模の無作為化比較対照試験randomized control trial(RCT)を開始している．肺がん高危険群を低線量肺がんCT検診群と胸部単純写真群とに無作為割付し，肺がん死亡率を両群で比較する研究計画で3年間年1回の検診を実施した後，2009年まで経過観察し結果が報告される予定である．また，他のRCTとしては，オランダとベルギーのNelson Trial(2万人を対象，CT検診対非検診)も開始されている．日本では，第三次対がん総合戦略研究事業の研究班により，コホート研究(肺がんCT検診対胸部単純写真)が進行中である[2]．

低線量CTによる肺がん検診により，より小型で早期の肺がんが発見されるようになったが，肺がん死亡を減少させるかどうかのエビデンスはまだなく，研究途上であることを十分認識し，エビデンス確立に役立つようなデータ収集の体制を極力整備して実施することが望まれる．

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LUNG CANCER

Phase II trial of carboplatin and paclitaxel in non-small cell lung cancer patients previously treated with chemotherapy

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Summary The purpose of this phase II trial was to evaluate the efficacy and toxicity of carboplatin plus paclitaxel in the treatment of advanced non-small cell lung cancer (NSCLC) previously treated with chemotherapy. Patients with a performance status (PS) of 0 or 1 who had received one or two previous chemotherapy regimens for advanced NSCLC were eligible. Paclitaxel 200 mg/m^2 was infused over 3 h and followed by carboplatin (area under the curve 6) infusion over 1 h, once every 3 weeks. Thirty patients were enrolled. A complete response was observed in 1 patient and a partial response in 10 patients, for an overall response rate of 36.7%. The median time to progression was 5.3 months. The median survival time was 9.9 months, and the 1-year survival rate was 47%. Hematological toxicity in the form of grade 3/4 neutropenia occurred in 54%, but grade 3 febrile neutropenia developed in only 3%. Non-hematological grade 3 toxicities were less frequent. There were no treatment-related deaths. The combination of carboplatin plus paclitaxel is an active and well-tolerated regimen for the treatment of NSCLC patients who have previously been treated with chemotherapy and have a good PS.
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1. Introduction

Lung cancer remains a major cause of death from cancer in many countries. More than half of all patients diagnosed with non-small cell lung cancer (NSCLC) have advanced stage IIIB or IV disease at presentation, and patients with advanced NSCLC are candidates for systemic chemotherapy. Platinum-based chemotherapy is considered the standard first-line treatment for patients with advanced NSCLC, and prolongs survival, palliates symptoms, and improves quality of life [1,2]. Many patients with good performance status (PS) when progression occurs after first-line chemotherapy are suitable candidates for second-line chemotherapy [3].

The taxanes are an important class of new agents for the treatment of advanced NSCLC. Paclitaxel, in combination with carboplatin, is the most common regimen

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used as first-line chemotherapy for advanced NSCLC, and this combination has a more favorable toxicity profile and is more convenient to administer than other platinum-based regimens [4,5]. Docetaxel has been investigated more extensively than any other agent for second-line treatment of advanced NSCLC, and the results of two randomized phase III trials of second-line chemotherapy in patients with advanced NSCLC demonstrated that docetaxel monotherapy significantly improved survival compared with best supportive care or other single agents (vinorelbine or ifosfamide) [6,7].

Belani et al. recently reported that results of a phase III trial comparing a carboplatin plus paclitaxel regimen with a cisplatin plus etoposide regimen for first-line treatment of advanced NSCLC [8]. Carboplatin plus paclitaxel yielded a higher response rate (23% versus 15%), time to progression (121 days versus 111 days), and overall quality of life benefit than cisplatin plus etoposide, but the median survival time was better in the cisplatin plus etoposide arm than in the carboplatin plus paclitaxel arm (274 days and 233 days, respectively [$P = 0.086$]). The authors reported that a substantially greater proportion of patients in the cisplatin plus etoposide arm received second-line chemotherapy with a taxane-containing regimen than in the carboplatin plus paclitaxel arm, and suggested that treatment with taxanes in a second-line setting may have had an impact on the survival in their study. Remarkably, more than half of the regimens that were used in the second-line setting of their study consisted of paclitaxel alone or carboplatin plus paclitaxel, not docetaxel. While the efficacy of paclitaxel-containing regimens as first-line chemotherapy for advanced NSCLC has been established in many randomized phase III trials [9], the data on the efficacy of paclitaxel-containing regimens in second-line settings are limited [10,11].

Based these considerations we conducted a phase II trial to evaluate the efficacy and toxicity of carboplatin plus paclitaxel in the treatment of advanced NSCLC previously treated with chemotherapy.

2. Patients and methods

2.1. Eligibility criteria

The inclusion criteria were: pathologically confirmed advanced NSCLC patients with measurable disease who had received one or two previous chemotherapy regimens for their disease. Patients were required to submit evidence of failure of prior chemotherapy. Patients who were previously treated with carboplatin or paclitaxel were excluded if the best response was progressive disease (PD). Patients who had received prior radiotherapy were eligible provided that at least 30 days had elapsed between the completion of radiotherapy and entry into the study. Patients were also required to be 20–75 years of age, have an Eastern Cooperative Oncology Group PS of 0 or 1, and have adequate organ function as indicated by the following parameters: absolute neutrophil count $\geq 1500\,mm^{-3}$, platelet count $\geq 100{,}000\,mm^{-3}$, hemoglobin $\geq 9.0\,g/dl$, AST and ALT $\leq 2.0 \times$ the institutional upper normal limits, total bilirubin $\leq 1.5\,mg/dl$, creatinine $\leq 1.5\,mg/dl$, $PaO_2 \geq 65$ Torr. Exclusion criteria were: uncontrolled pleural or pericardial effusion, active concomitant malignancy, prior irradiation to areas encompassing more than a third of the pelvis plus spine, active infection, myocardial insufficiency or myocardial infarction within the preceding 6 months, uncontrolled diabetes mellitus or hypertension, any other condition that could compromise protocol compliance, pregnancy and/or breast-feeding. All patients were required to provide written informed consent before entry into the study. The study was approved by the institutional review board of our institution.

2.2. Treatment plan

Treatment was started within a week of entry into the study. Patients received paclitaxel $200\,mg/m^2$ diluted in 500 ml of 0.9% saline as a 3-h intravenous infusion followed by carboplatin (area under the curve [AUC] 6; Calvert formula) diluted in 250 ml of 5% glucose as a 1-h intravenous infusion, every 3 weeks. All patients were premedicated with dexamethasone (24 mg i.v.), famotidine (20 mg i.v.), and diphenhydramine (50 mg orally) 30 min before the paclitaxel infusion to prevent a hypersensitivity reaction. A 5-HT3-receptor antagonist was intravenously administered as an antiemetic before carboplatin. Therapy was continued for at least two cycles unless the patient experienced unacceptable toxicity or had PD. The maximum number of cycles of chemotherapy was six. In the event of grade 4 leukopenia or thrombocytopenia or of grade 3 neutropenic fever, the dose of carboplatin and paclitaxel was reduced to AUC 5 and $175\,mg/m^2$, respectively, in the following cycle of chemotherapy. The next cycle of chemotherapy was started if the neutrophil count was $\geq 1500\,mm^{-3}$, the platelet count $\geq 100{,}000\,mm^{-3}$, AST and ALT $\leq 100\,IU/l$, total bilirubin $\leq 2.0\,mg/dl$, creatinine $\leq 1.5\,mg/dl$, PS 0 or 1, and the patient was afebrile.

Pretreatment evaluation included a medical history, a physical examination, vital signs, height and body weight, PS, complete blood count, biochemical studies, arterial blood gas analysis, electrocardiogram, chest radiograph and computed tomography scan (CT), abdominal ultrasound or CT, and brain magnetic resonance imaging or CT. A complete blood count, biochemical studies, and chest radiograph were performed weekly during the first cycle of chemotherapy, and 2 weekly starting with the second cycle.

2.3. Response and toxicity assessment

Objective tumor response was assessed as complete response (CR), partial response (PR), stable disease ≥ 8 weeks (SD), or PD according to the Response Evaluation Criteria in Solid Tumors. Measurable lesions were defined as lesions whose longest diameter was ≥ 2 cm. Imaging studies were repeated every 4 weeks until the objective tumor response was confirmed. All responses were reviewed by an independent radiologist. Toxicity was graded using National Cancer Institute-Common Toxicity Criteria version 2.0.

2.4. Statistical analysis

The primary endpoint of this study was the response rate, defined as the proportion of patients whose best response was CR or PR among all enrolled patients in the intent-to-treat analysis. The secondary end points were toxicity and overall and progression-free survival (PFS) from the date of enrollment in this study.

According to Simon's minimax two-stage phase II study design, the treatment program was designed for a minimal response rate of 5% and to provide a significance level of 0.05 with a statistical power of 80% in assessing the activity of the regimen according to a 20% response rate. The upper limit for first-stage drug rejection was no response in 13 evaluable patients. The upper limit for second-stage drug rejection was three responses in 27 evaluable patients. Overall survival time was defined as the interval between enrollment in this study and death or the most recent follow-up visit. PFS was defined as the interval between enrollment in this study and the first documented PD, death, or the most recent follow-up visit. Survival was estimated by the Kaplan–Meier analysis method. All comparisons between proportions were performed by Fisher's exact test.

3. Results

3.1. Patient characteristics

Between October 2002 and November 2003, 30 patients were enrolled in this study, and their characteristics are shown in Table 1. Twenty-six (87%) patients were men, and 21 (70%) patients had adenocarcinoma. Median age was 60 years. The majority of the patients (93%) had received prior platinum-based chemotherapy, and seven (23%) patients had received two prior chemotherapy regimens. The platinum-based chemotherapy regimens that had been used were: cisplatin plus vinorelbine ($n = 26$), cisplatin plus gemcitabine ($n = 1$), and carboplatin plus gemcitabine ($n = 1$). There were 15 (50%) responders to any of the prior chemotherapy regimens and 12 of them had experienced a response (CR/PR) to cisplatin-based chemotherapy. Twenty-one (70%) patients had a treatment-free interval of 3 or more months since the final dose of the prior chemotherapy regimen.

A total of 94 cycles of chemotherapy were administered, and the median number of cycles per patient was three (range, 1–6). Four patients had received only one cycle of treatment either because of toxicity (two patients, grade 3 rash), the patient's refusal (one patient), or PD (one patient).

3.2. Response and survival

Two patients were not evaluable for response because the protocol treatment had been terminated because of toxicity (grade 3 rash) during the first cycle of chemotherapy, and they subsequently received further chemotherapy without PD. There was 1 CR and 10 PRs among the 30 patients, and the objective response rate in the intent-to-treat analysis was 36.7% (95% confidence interval [CI], 19.9–56.1%) (Table 2). Treatment outcomes of all patients are listed in Table 3. The response rate of patients who experienced a response (CR/PR) to prior cisplatin-based chemotherapy was 43% (6/14), as opposed to 23% (3/13) among the non-response patients ($P = 0.41$). The response rate of the patients who had received one prior chemotherapy regimen was 39% (9/23), as opposed to 28% (2/7) among the patients who had received two regimens ($P > 0.99$). According to the treatment-free interval since the final dose of the prior chemotherapy regimen, the response rate of patients whose interval was 3 months or more was 33% (7/21), com-

Table 1 Patient characteristics

Characteristic	No. of patients (%)
Patients enrolled	30
Sex	
Male	26
Female	4
Age, years	
Median	60
Range	39–75
ECOG performance status	
0	7
1	23
Stage	
IIIB	11
IV	19
Histology	
Adenocarcinoma	21
Squamous cell carcinoma	7
Large cell carcnioma	2
Prior treatment	
Platinum-based chemotherapy	28 (93)
Docetaxel	5 (16)
Chest radiotherapy	4 (13)
No. of prior chemotherapy regimens	
1	23
2	7

Table 2 Treatment efficacy ($n = 30$)

	No. of patients	%
Response		
Overall response rate	11	36.7
Complete response	1	3.3
Partial response	10	33.3
Stable disease	12	40
Progressive disease	5	16.7
Not evaluable	2	6.7
Survival		
Median (months)	9.9	
1 year (%)	47	
Progression-free survival		
Median (months)	5.3	

Table 3 Treatment outcomes of all patients

Patient No.	Prior first-line therapy		Prior second-line therapy		Time from last therapy (months)	CBDCA + PTX, best response	PFS (months)	Survival (months)
	Regimen	Best response	Regimen	Best response				
1	CDDP + VNR	SD	DOC	PD	1.8	SD	1.4	25.2
2	CBDCA + GEM	NE	Gefitinib	PD	0.8	PR	3.8	8.8
3	CDDP + VNR	SD	–		6.8	SD	7.6	18.1
4	CDDP + GEM	PR	–		9.5	PR	7.5	33.8+
5	CDDP + VNR	SD	–		4.8	SD	2.8	7.0
6	CDDP + VNR + DOC + RT	PR	–		6.0	PR	8.0	21.6
7	GEM + VNR	SD	–		23.0	PD	1.2	7.8
8	CDDP + VNR + RT	PR	–		13.6	SD	6.7	25.0+
9	CDDP + VNR	SD	–		5.0	SD	2.1	3.7
10	CDDP + VNR	SD	–		5.0	PD	1.2	6.7
11	CDDP + VNR	PR	–		8.9	NE	1.1	3.3
12	CDDP + VNR	SD	Gefitinib	CR	1.9	SD	6.3	6.3
13	CDDP + VNR	PR	–		5.4	NE	1.0	13.4
14	CDDP + VNR	PR	–		1.7	SD	4.8	5.7
15	CDDP + VNR + RT	PR	–		9.3	SD	5.0	15.7
16	CDDP + VNR	SD	–		2.8	PR	3.7	15.8
17	CDDP + VNR	SD	DOC + GEM	SD	3.8	SD	5.3	21.6+
18	CDDP + VNR + DOC + RT	PR	–		3.9	SD	4.5	9.0
19	CDDP + VNR	PR	–		12.9	PR	9.4	16.0
20	CDDP + VNR	PR	–		11.5	CR	24.8+	24.8
21	CDDP + VNR	PD	–		1.1	PR	9.2	23.6+
22	CDDP + VNR	SD	DOC	SD	4.5	PD	2.3	5.5
23	Gefitinib	SD	–		0.9	PR	8.8	12.7
24	CDDP + VNR	PR	–		11.1	PR	5.3	10.2
25	CDDP + VNR	PR	Gefitinib	PR	4.4	PR	5.5	9.9
26	CDDP + VNR	NE	–		11.7	PR	7.0	12.2
27	CDDP + VNR	PR	–		5.4	SD	6.2	9.4
28	CDDP + VNR	SD	–		0.8	PD	1.4	2.5
29	CDDP + VNR	PR	–		4.4	PD	0.2	8.4
30	Gefitinib	PD	CDDP + VNR	PD	0.9	SD	3.1	3.3

CBDCA, carboplatin; PTX, paclitaxel; PFS, progression-free survival; CDDP, cisplatin; VNR, vinorelbine; GEM, gemcitabine; DOC, docetaxel; RT, chest radiotherapy; SD, stable disease; NE, not evaluable; PR, partial response; PD, progressive disease; CR, complete response.

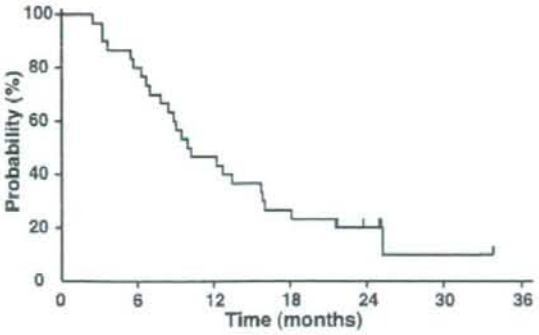

Fig. 1 Kaplan–Meier curve for overall survival.

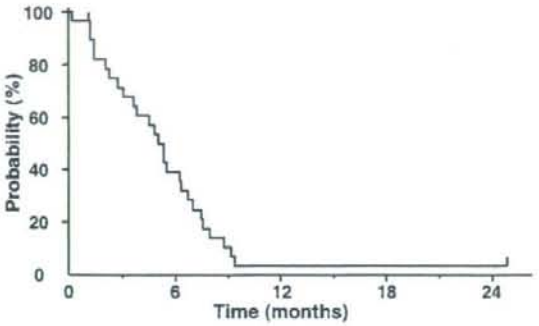

Fig. 2 Kaplan–Meier curve for progression-free survival.

pared with 44% (4/9) in patients in whom it was less than 3 months ($P = 0.68$).

The median follow-up time was 24 months. The median survival time (MST) was 9.9 months (range, 2.5–33.8 months), and the 1-year survival rate was 47% (95% CI, 29–65%). The median PFS was 5.3 months. The Kaplan–Meier curve for overall survival and for PFS is shown in Figs. 1 and 2, respectively. Nineteen patients (63%) received at least one subsequent chemotherapy regimen, and their regimens are shown in Table 4. Fourteen of them were treated with gefitinib, and a PR was achieved in three of them.

3.3. Toxicity

The common toxicities associated with carboplatin plus paclitaxel are listed in Table 5. Grade 3/4 neutropenia occurred in 54% of the patients in our study, but grade 3 febrile neutropenia developed in only 3%. Grade 3/4 anemia and thrombocytopenia were observed in five patients (16%) and two patients (13%), respectively. Non-hematological grade 3 toxicities were less frequent. Grade 3 hyponatremia was observed in five (16%) patients, but they were all asymptomatic. Grade 2 neuropathy occurred in 33% of the patients. There were no treatment-related deaths.

Table 4 Post-study chemotherapy

Regimen	No. of patients	Responder (%)
Gefitinib	14	3 (21)
Docetaxel	9	0
Gemcitabine plus viborelbine	1	0

4. Discussion

Docetaxel, pemetrexed, and erlotinib have been approved for second-line treatment of advanced NSCLC on the basis of the results of phase III trials [6,7,12,13]. Hanna et al. reported a phase III study comparing 3-weekly pemetrexed 500 mg/m^2 with 3-weekly docetaxel 75 mg/m^2 as second-line treatment for advanced NSCLC. The overall response rate with pemetrexed and docetaxel was 9.1% and 8.8%, respectively, and MST was 8.3 months and 7.9 months, respectively. Although efficacy in terms of the outcome as measured by survival time and response rate was similar for both treatments, the pemetrexed group experienced less grades 3–4 hematological toxicity and alopecia of all grades [12]. In the trial reported by Shepherd et al. 731 NSCLC patients previously treated with chemotherapy were randomized to receive either erlotinib at a dose of 150 mg daily or placebo, and the response rate in the erlotinib group was 8.9%. MST was 6.7 months in the erlotinib group and 4.7 months in the placebo group ($P < 0.001$). The results of their trial showed that erlotinib significantly prolonged the survival of patients with advanced NSCLC who had previously been treated with chemotherapy [13]. Despite the positive results of these phase III trials, the response rate of advanced NSCLC to second-line chemotherapy remains low, and the life expectancy of advanced NSCLC patients remains short. Alternative effective chemotherapy option is needed for second-line treatment of advanced NSCLC.

The combination of carboplatin plus paclitaxel has proved effective as one of the standard platinum-based doublet regimens for first-line treatment of advanced NSCLC [4,5,14]. However, since the efficacy of carboplatin plus paclitaxel used in a second-line setting had hardly been assessed, in the present study we evaluated the efficacy and toxicity of carboplatin plus paclitaxel in the second- or third-line treatment of advanced NSCLC. The results in the 30 patients with advanced NSCLC previously treated with chemotherapy indicated that the combination of carboplatin plus paclitaxel yielded an objective response rate of 36.7% and an MST of 9.9 months, with a 1-year survival rate of 47%. Our study had not included patients who were treated with the platinum/taxane combination chemotherapy. Most of the toxicity observed in our study was hematological. Grade 3/4 neutropenia, anemia, or thrombocytopenia occurred in 54, 16, or 13% of the patients in our study, respectively. Hematological toxicity of carboplatin plus paclitaxel used in first-line treatment for Japanese patients with advanced NSCLC has been reported that grade 3/4 neutropenia, anemia, or thrombocytopenia occurred in 88, 15, or 11% of the patients [15]. The toxicity observed in our study appeared similar to that of carboplatin plus paclitaxel, which was administered as the first-line treatment, although the number of patients in our study was not large. The combination of carboplatin plus paclitaxel seems to be effective and tolerable, not only as first-line therapy for advanced NSCLC but

Table 5 Hematological and non-hematological toxicity ($n=30$)

Toxicity	NCI-CTC Version 2.0, grade							
	0–1		2		3		4	
	n	%	n	%	n	%	n	%
Leukopenia	11	37	10	33	9	30	0	0
Neutropenia	10	33	4	13	14	47	2	7
Anemia	7	23	18	60	3	10	2	7
Thrombocytopenia	27	90	1	3	2	7	0	0
Febrile neutropenia	29	97	–		1	3	0	0
Nausea	27	90	3	10	0	0	–	
Fatigue	30	100	0	0	0	0	0	0
Neuropathy	20	67	10	33	0	0	0	0
Arthralgia	21	70	8	27	1	3	0	0
Rash	28	93	0	0	2	6	0	0
Infection	29	97	0	0	1	3	0	0
Arrhythmia	29	97	0	0	1	3	0	0
Alopecia	21	70	9	30	–		–	
AST/ALT	29	97	1	3	0	0	0	0
Hyponatremia	25	83	–		5	17	0	0

as second-line therapy as well if the patients had not been previously treated with the platinum/taxane combination chemotherapy.

Hotta at al. reported a meta-analysis based on abstracted data to compare the effect of carboplatin-based chemotherapy with that of cisplatin-based chemotherapy on overall survival, response rate, and toxicity in the first-line treatment of patients with advanced NSCLC [16]. The results indicated that combination chemotherapy consisting of cisplatin plus a third generation agent produced a significant survival benefit compared with carboplatin plus a third generation agent, although the toxicity profiles of the two modalities were quite different. Recently, Pignon et al. reported a pooled analysis from five randomized clinical trials of cisplatin-based chemotherapy in completely resected NSCLC patients [17]. Their analysis suggested that adjuvant cisplatin-based chemotherapy improved survival in patients with NSCLC. Based on the results of their meta-analysis, cisplatin-based chemotherapy should be recommended as first-line therapy for patients with advanced NSCLC. Moreover, in view of the results of our own study, we speculate that the combination of carboplatin plus paclitaxel may be suitable as second-line treatment for advanced NSCLC patients who had experienced progression after first-line cisplatin-based chemotherapy.

Care must be exercised in interpreting the favorable outcome in our study. One concern is that it was a single-institution phase II study, and therefore patient selection may have influenced the outcome. The responders to any of the prior chemotherapy regimens accounted for 50% of the 30 patients enrolled in this study, and about 80% of the patients had received only one prior chemotherapy regimen. The selection criteria, such as an ECOG PS of 0 or 1, may also have contributed to this favorable outcome. Another concern is that our study had included only five patients who were previously treated with chemotherapy using taxanes. Therefore, the efficacy of carboplatin plus paclitaxel as the secondary therapy after chemotherapy using taxanes is not clear. A further randomized study is warranted to be able to draw definitive conclusions about our results.

Conflict of interest statement

None declared.

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