医科大学 大槻）における臨床研究で構築された病理評価委員会と協同して開催評価をする予定であったが、環境省などの登録と委員が重複しており、新たに本登録において把握される症例が別に存在する可能性が極めて低いことから、環境省との連携関係を推進することが、適切と考えた。

全国集計データを用いた評価では、2008年症例で自施設診断・治療例は悪性胸膜中皮腫：465 症例、悪性腹膜中皮腫症例：45症例であり、本登録がなされた 64 例は約13%に当たる。倫理審査承認施設は21施設が拠点病院であり、全国集計データ提供施設357施設の6%にあたる。すなわち、約半数は拠点病院外からの提出であり、拠点病院だけでは中皮腫症例のカバーは不十分であると考えられた。また、都道府県単位で比較すると、全国集計データでは、兵庫県が123例と極めて多数で、次いで、神奈川県82例、福岡県69例、大阪府48例、埼玉県・千葉県・愛知県いずれも42例となっており、拠点病院の指定そのものに影響されたと考えられる偏った地域分布を示していた。

D．考察

本登録は、患者本人からの同意を得た上で、個人識別情報を含めた情報を取得し、重複の除外などを図りつつ、運用する形であるため、施設の倫理審査委員会において、研究参加のハードルが極めて高くなっていることが参加施設数の増加が見られない、主たる要因と考えられた。

個人識別情報の収集は、検体登録との関連において極めて重要であり、重複を許すことで、検体における各種検査の陽性率などが正確に評価できなくなることを危惧して、個人識別情報の収集とそれにより重複登録のチェックを実施する仕組みを構築したのであるが、結果的には登録数の増加などの足かせとなった事実は否めない。また、個人識別情報を収集は、人口動態統計情報の目的外利用等により、当該患者の情報をもとに、死亡情報との照合ができ、その結果、登録による患者の捕捉率の評価も可能となる。

このように背反した要求を満たしつつ、承認施設の増加を図るには、匿名化での登録についても受け付ける別の仕組みを構築し、登録実数を増加させることを検討する必要があろう。この場合、特定の施設からの登録のみ、連結可能匿名化した形を許容し、1）集計に際しては、こうした症例は除外した集計と重複がないと仮定した形での集計の2種類の集計を実施する。2）匿名化での実施医療機関から他の医療機関への紹介に際しては、他の医療機関へ登録ＩＤを紹介状に記載してもらい、紹介先医療機関からの登録に際しては登録ＩＤを付記してもらい、情報の一元化を図る、という方法が有効であると考えられたが、登録方法が二元化することによる煩雑さなどから実施を見送った経緯がある。しかしながら、今後、再検討を要すると考えられる。

その他、登録実施中に寄せられた登録協力施設からの意見の中には、臨床医師が記載する内容としてはかなり煩雑であるという、指摘も引き続き存在した。この点については、単純な報酬という仕組みでなく、1回に記載する内容をより簡略にして、簡略な項目で「該当あり」とされたケースについてのみ、時期をあらためて再度詳細な調査票を追加送付するなどの方策が考えられた。

全国集計データを用いた評価では、全国集計での症例数は510症例であり、本登録がなされた 64 例はその約 13%に当たる。2009年の本登録数は126症例と倍増してい

るが、2010年が極めて少なく、施設への登録勧奨不足が原因と考えられた。2009年症例で見る限りは、拠点病院で把握された症例の約20%のカバー率と考えられるが、労災病院などの指定が少ないことから、拠点病院のデータだけでは不十分と考えられた。また、施設の側から見ると倫理審査承認施設のうち、21施設が拠点病院であり、全国集計データ提供施設357施設の6%にあたる。すなわち、約半数は拠点病院外からの提出であり、こうした結果、中皮腫症例のカバーは不十分であると考えられた。

（とはいえ、重複を考慮して、拠点病院の参加を得ることで400症例程度が登録されれば、把握率は40%程度になるものと期待されるため、来年度には、症例数が多い拠点病院を中心に、登録勧奨活動を行う予定である。都道府県別では、神奈川県（82例）、広島県（35例）、福岡県（69例）など症例の多い都道府県において、神奈川県（0例）、広島県（0例）、福岡県（3例）と少数しか本登録には登録されておらず、地域により、登録協力施設に偏りがあることが明確となった。

E．結論

包括的な悪性中皮腫関連研究として、研究を進めたが、今年度の成果は極めて乏しく、体制の再構築が必要と考えられる。

来年度以降の実施については、現体制ではなく、環境省調査（救済法での症例蓄積）と連携し、医学的知見の集積を目的として、環境省調査をインデックスとした詳細な臨床情報を収集するという方向性で再構築をめざすべきと考えられる。現在までに確立したソフトウェアなどの資産を活用しつつ、悪性中皮腫のわが国における診断・治療の実態が把握されるよう、がん診療連携拠点病院のデータなども活かしつつ、新体制の確立を模索すべきである。

F．健康危険情報

特になし

倫理面への配慮

登録は疫学研究の倫理指針に基づいて実施しており、国立がんセンター倫理審査委員会の承認を得た上で実施している。個人情報の収集については全て患者本人あるいは代諾者の同意を得ており、倫理上問題ないと考えられる。

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H．知的所有権の取得状況

1．特許取得　なし

2．実用新案特許　なし

3．その他　なし

厚生労働科学研究補助金（がん臨床研究事業）
分担研究報告書

悪性胸膜中皮腫の診断および治療法の確立とアスベスト曝露の実態に関する研究

研究分担者　柿沼　龍太郎　　国立がん研究センターがん予防・検診研究センター
検診開発研究部 画像診断開発室長

研究要旨
低線量CTによる肺がん検診を2004年2月から2010年8月までに受診した10121名を対象に胸膜変化の所見について検討を行った。胸膜プラークの所見を有する頻度は全体で0.4%（男性0.6%、女性0.1%）であった。

A．研究目的

低線量CTによる肺がん検診画像における胸膜変化について2004年2月から2010年8月までに受診した10121名の胸膜病変の有無について検討する。

B．研究方法

低線量CTによる肺がん検診は、16列のmultislice CTを使用し、電圧120kVp、電流 30mA、0.5秒/回転、ヘリカルピッチ11にて撮影し、2mm毎に画像再構成した。読影は、9Mのモニター上にて、肺野条件WW2000、WL-600、縦隔条件WW600、WL50にて読影した。胸膜肥厚像などの所見はデータベースに記録した。2004年2月から2010年8月までに受診した10121名の胸膜肥厚像の所見等をデータベースより抽出した。その後、がん予防・検診研究センターの個人情報管理室にてファイルの匿名化を行なった。

（倫理面への配慮）
研究の実施にあたっては、個人情報の漏洩を防いだ。

C．研究結果

2004年2月から2010年8月までに受診した10121名の内訳は男性6010名、女性4111名であった。胸膜プラークを有していたのは、10121名中では40名（0.4%）であった。性別では、男性36名（男性6010名の0.6%）、女性4名（女性4111名の0.1%）であった。年代の内訳は、男性では、40代858名(14.3%)、50代2071名(34.5%)、60代2483名(41.3%)、70代552名(9.2%)、80代46名(0.8%)であった。胸膜プラークを有するのは40代1名(40代の0.1%)、50代9名(50代の0.4%)、60代19名(60代の0.8%)、70代7名(70代の1.3%)であった。
女性では、40代828名(20.1%)、50代1446名(35.2%)、60代1531名(37.2%)、70代285名(6.9%)、80代21名(0.5%)であった。胸膜プラークを有するのは40代1名(40代の0.1%)、60代2名(60代の0.1%)、70代1名(70代の0.4%)であった。職業歴に関しては、がん予防・検診研究センターを受診時に実施されたアンケート調査では、石綿関連について具体的な質問はしていない。男性36名中19名、女性4名中1名が、「専門的･技術的職業」と返答していたが、詳細に関しては、過去に遡った検討なので不明である。

D．考察

以前、2004年の受診者3628名を検討した際は、胸膜プラークを有する頻度は、約400人に1人であった。2005年1月から2008年12月は、約220人に1人の割合であった。2004年2月から2010年8月までは、初回受診者が1万人を越えたが、約253人に1人の割合であった。

E．結論

低線量CTによる肺がん検診を2004年2月から2010年8月までに受診した10121名中、胸膜プラークの所見を有する頻度は0.4%であった。

F．研究発表

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Anti-lung Cancer Association project: significance of repeated screening for lung cancer for more than 5 years with low-dose helical computed tomography in a high-risk cohort. Lung Cancer, 67: 318-324, 2010
3. Kakinuma R, Moriyama N, et al. Previously reported lung cancer growth curves, Chest, 137: 1002-1003, 2010

G．知的財産権の出願・登録状況（予定を含む）

1. 特許取得
   なし
2. 実用新案登録
   なし
3. その他
   なし

Ⅲ.　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
金子昌弘	肺がん検診の現状と将来	日本人間ドック学会誌	24増刊号	51-55	2010
Kaneko M	Changes and Current Stateof Diagnosis of Lung Cancer After Development of the Flexible Bronchofiberscope	Jpn J Oncol	40(9)	838-845	2010
Asamura H	Multiple primary cancers or multiple metastases, that is the question.	J Thorac Oncol	5(7)	930-931	2010
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Sakurai H, Asamura H, et al ; for the Japanese Joint Committee for Lung Cancer Registration.	Survival Differences by Gender for Resected Non-small Cell Lung Cancer: A Retrospective Analysis of 12,509 Cases in a Japanese Lung Cancer Registry Study	J Thorac Oncol	5(10)	1594-1601	2010
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Fujimoto N, Kishimoto T, Kishimoto T	Soluble mesothelin-related protein in pleural effusion from patients with malignant pleural mesothelioma	Experimental and Therapeutic Medicine	1	313-317	2010
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Kakinuma R, Seki N, et al.	Previously reported lung Cancer growth curves.	Chest	137	1002-1003	2010

Ⅳ．　研究成果の刊行物・別刷

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(9)838–845
doi:10.1093/jjco/hyq136

Changes and Current State of Diagnosis of Lung Cancer After Development of the Flexible Bronchofiberscope

Masahiro Kaneko*

Division of Endoscopy, National Cancer Center Hospital, Tokyo, Japan

*For reprints and all correspondence: Masahiro Kaneko, Division of Endoscopy, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo, Japan. E-mail: mhkaneko@ncc.go.jp

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The flexible bronchofiberscope developed by Ikeda et al. has brought about revolutionary changes in the diagnosis and treatment of lung cancer. Advances in this device are continuing to emerge and lesions even smaller than those visible to the naked eye can now be visualized. In addition, the use of ultrasound now enables diagnosis of extramural bronchial lesions. Bronchoscopy is also used for the treatment of early hilar lung cancer, and in patients with airway stenosis due to advanced cancer, laser therapy, brachytherapy, and stenting can be performed. The bronchofiberscope is also very useful for tissue sampling from the lung periphery. Further advances in computed tomography imaging have enabled bronchoscopy under computed tomography fluoroscopy, and virtual bronchoscopy images can be generated from computed tomography imaging. Navigation systems have been developed to show the target bronchus where instruments such as forceps should be guided. Computed tomography imaging has made remarkable advances, and computed tomography now plays a central role in chest imaging, including early detection of lesions by low-dose computed tomography, qualitative diagnosis by high-resolution computed tomography and diagnosis of disease progression by contrast computed tomography. Ikeda et al. introduced the concept of personal health data recording system to manage these various images but the technology was not mature enough at that time for implementation. With modern advances in information technology, this is likely to be realized using an electronic health record system.

Key words: flexible bronchofiberscope – lung cancer – computed tomography – mass screening

INTRODUCTION

The flexible bronchofiberscope was first developed by Ikeda et al. in 1966. This device is thinner and more flexible than previous rigid bronchoscopes, and its tip can be flexed using a lever in the handle, markedly increasing the range of visibility of the bronchi. In addition, instruments like biopsy forceps can be inserted through a working channel up to the lung periphery. The development of the flexible bronchofiberscope has brought about revolutionary changes in the diagnosis of lung cancer. These results were published in volume 1, issue 1, of the *JJCO* (1,2).

These research developments have subsequently undergone further dramatic advances. In this paper, we discuss these changes and the current state of diagnosis of lung cancer.

ADVANCES RELATED TO OBSERVATION OF THE AIRWAY LUMEN

The principle of the flexible bronchofiberscope is that light from an external light source, through glass fibers, is guided within the bronchi to illuminate the bronchial lumen, and the image is guided by separate glass fibers to an eyepiece lens in the handle for observation. Thus, image resolution is limited by the fineness and number of glass fibers.

Moreover, the image can only be viewed by the physician performing the examination. For display to multiple physicians, a large television camera must be connected to the eyepiece lens.

Development of Electronic Video Bronchoscope

To solve this problem, an electronic video bronchoscope was developed with a very small integrated charged couple

device at the tip of the bronchoscope (3). With the electronic video bronchoscope, findings directly from the lumen, not transmitted through glass fibers, are imaged, so the image obtained is comparable to or better than observed visually.

The image can also be viewed on an external monitor screen by several physicians at the same time. This facilitates objective evaluation and recording of images, improves diagnostic accuracy and is useful for educational purposes.

Development of Observation Methods Superior to the Naked Eye

Detailed Observation of the Bronchial Epithelium

Electronic imaging has enabled observation that is superior to that possible with the naked eye. Fluorescence imaging, narrow band imaging (NBI) and magnified imaging methods are available, and their use is starting to expand.

Fluorescence imaging was originally a photodynamic diagnosis (PDD) method whereby, after injection of a hematoporphyrin derivative, which is taken up in large amounts by tumors, the operator shines a laser light of a specific wavelength, and fluorescent light emitted from the tumor is detected. This later evolved to autofluorescence imaging (AFI), which detects autofluorescence from normal bronchial mucosa.

For PDD, a photosensitivity reaction to a photosensitive agent administered beforehand and a device that generates laser light of a specific wavelength are necessary. Therefore, this is now seldom used, except for the evaluation of lesions prior to photodynamic therapy (PDT), a laser treatment.

With AFI, administration of a photosensitive agent is not necessary, and very early lesions, which cannot be seen with the naked eye, can be detected. Originally, illumination with a laser light of a specific wavelength was required, but more recent devices can be used merely by passing standard white light through a filter (4). These small devices are convenient, and their use is beginning to expand. Figure 1 shows findings of early cancer at the tracheal bifurcation as observed with an AFI SAFE system. With white light, only a slight elevation is visible, but without any obvious abnormality. However, with AFI, there is a loss of green fluorescence compared with the normal area, thus permitting easy diagnosis of the abnormal area. In heavy smokers with positive sputum cytology, but in whom chest X-ray and computed tomography (CT) findings are negative, AFI is useful for the early detection of hilar lesions.

NBI is a method of observation using filters to select images of certain wavelengths. Because this enables depiction of small submucosal blood vessels, it is useful for diagnosis of lesion depth, direction of spread and determination of whether a lesion is benign or malignant (5).

Structure of the Bronchial Wall and Diagnosis of Extramural Lesions

To observe the structure of the bronchial wall and diagnose extramural lesions, endobronchial ultrasonography (EBUS) using ultrasound and optical coherence tomography (OCT) using reflected laser light can be used.

EBUS includes radial and convex types. With the radial type, an ultrasound probe is inserted through the working channel of a conventional bronchoscope for examination, but because a water-filled balloon must be placed in close contact with the bronchial wall, the airway must be temporarily blocked. This is mainly used to diagnose early hilar lung cancer and depth of invasion in the bronchial wall (6). Figure 2 shows the laminar structure of the wall on a bronchial cross-section as observed by radial EBUS.

The convex type requires the use of a special scope, but aspiration cytology can be performed at the same time. This can also be used for bronchial and extramural hilar and mediastinal lymph node biopsy (7).

For histological diagnosis of mediastinal lymph nodes, a large amount of tissue can be sampled by mediastinoscopy, thus permitting histological examination. This must be performed only by an experienced thoracic surgeon under general anesthesia. The tip of the needle is advanced under EBUS guidance, and lymph nodes and peripheral blood vessels can be depicted, so aspiration can be performed safely and reliably. Clinical use is rapidly expanding. Figure 3 shows an extramural lymph node and blood vessels in the lymph node as observed by convex EBUS.

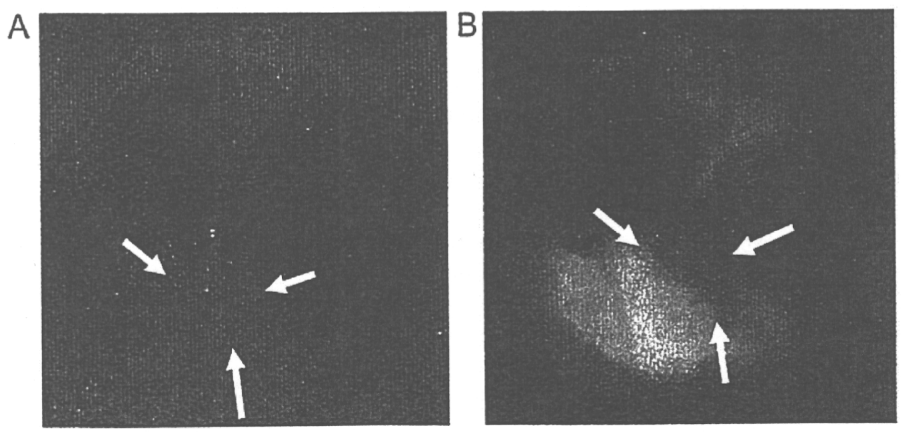

Figure 1. Early hilar-type lung cancer. (A) White light image and (B) autofluorescence image. Arrow symbols show a border of early cancer.

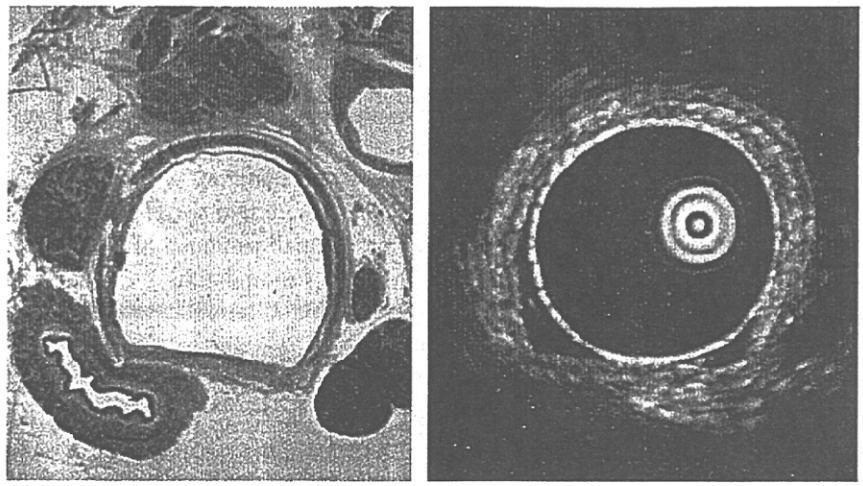

Figure 2. Endobronchial ultrasonographic (EBUS) image of normal trachea.

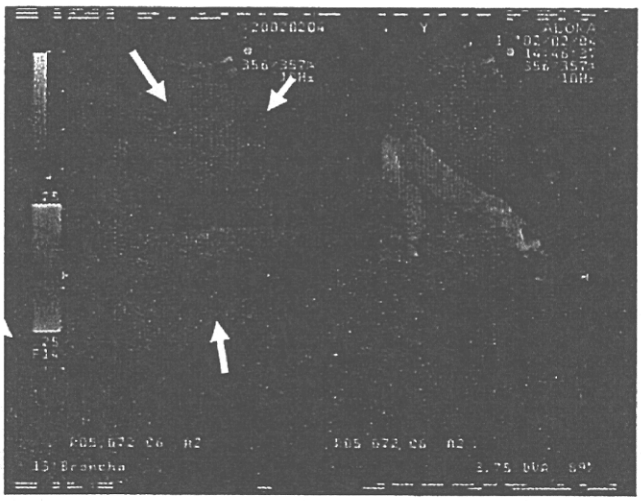

Figure 3. EBUS image of hilar lymph node. Arrow symbols show a border of swelling lymph node.

OCT is a non-contact test that uses laser radiation instead of ultrasound as in radial EBUS, so, unlike in ultrasound, expansion of a water-filled balloon is not necessary. OCT provides higher resolution than ultrasound to observe structures within the bronchial wall. However, depth of penetration is low, so structures outside the bronchial wall cannot be observed, thus severely limiting its range of use (8). In the future, OCT combined with AFI is expected to be useful to diagnose the extent of invasion of early hilar cancer. Figure 4 shows early hilar cancer as observed by OCT and confirms a lesion that extends beyond the bronchial wall.

TREATMENT OF LUNG CANCER BY BRONCHOSCOPY

The development of the flexible bronchofiberscope has enabled guidance of various instruments to any site in the bronchial lumen, so bronchoscopy is now also used in the treatment of lung cancer.

Treatment of Advanced Lung Cancer

Bronchoscopy is not used to treat advanced lung cancer itself, but it can be used to relieve stenosis of the trachea or main bronchus, thus alleviating symptoms of dyspnea. Methods to relieve stenosis include using a laser to cauterize a tumor protruding in the lumen or using a stent for dilation.

The YAG laser is often used for cauterization, but an argon plasma laser and a high frequency can also be used. In addition, local injection with ethanol has been effective.

Stents include silicone stents and metallic stents using shape memory alloys. Silicone stents themselves do not have expandable properties, so after dilation with a laser, they are often inserted to retain this state. Insertion still requires a rigid bronchoscope. Metallic stents can be tightly folded and then expanded in the airway, so dilation of the airway prior to insertion is not necessary. They can also be inserted with a flexible bronchoscope and are now widely used in general hospitals (9).

Treatment of Early Hilar Lung Cancer

Cancer lesions that are confined to the bronchial wall and whose entire extent is confirmed by bronchoscopy can be treated with a transbronchial approach.

Photodynamic Therapy

In PDT, a photosensitizing agent with an affinity for the tumor is administered beforehand, and when a high concentration has accumulated in the tumor, it is radiated with laser light of a specific wavelength. Atomic oxygen is released from the substance, whose cytotoxic effects on cells are used as treatment. This is an excellent method that selectively destroys only tumor cells, but the distance that laser light

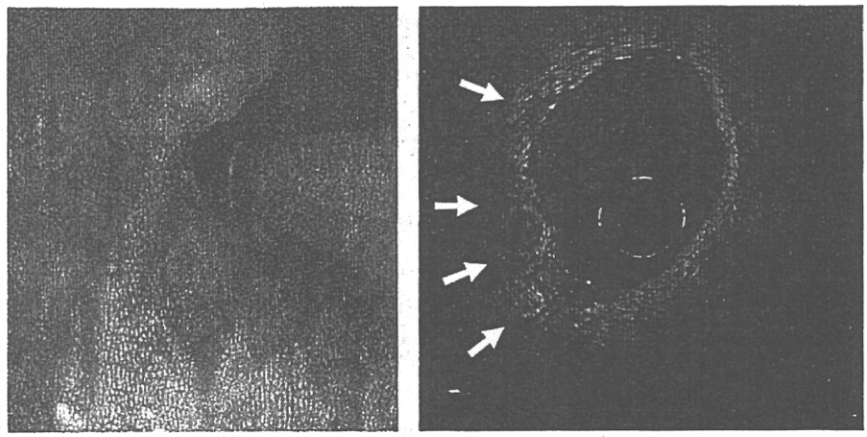

Figure 4. Optical coherence tomography image of early hilar-type lung cancer. Arrow symbols show a border of early cancer.

can reach in the bronchi is limited, so PDT is indicated in few cases (10).

Brachytherapy

In brachytherapy, a small source of radiation is guided by bronchoscopy into the bronchial lumen and radiation therapy is given from within. High-dose radiation is local only, so there are few effects on the peripheral lung, and respiratory function is not impaired. Compared with PDT, treatment can be deeper into the bronchial wall, but the applicator that guides the radiation source is not very flexible, so sites where treatment is possible are limited (11).

IMPROVED DIAGNOSTIC ACCURACY OF LESIONS IN PERIPHERAL LUNG FIELDS

At least 70% of lung cancers are in the peripheral lung and cannot be directly observed by bronchoscopy. For histological diagnosis of these types of lesions, tissue sampling from the lesion is required. Three types of procedures are usually available: the first is transbronchial biopsy, the second is percutaneous needle biopsy and the third is surgical open lung biopsy.

Open lung biopsy is the most reliable diagnostic method. The advantage is that if cancer is found, it can then be treated, but if cancer is not found, this is a major burden for the patient.

Transbronchial biopsy is a relatively safe procedure, although insertion into the airway may be uncomfortable. However, the relationship between the lesion and bronchi must be clearly defined. Therefore, before the flexible bronchofiberscope was developed, bronchography was performed to confirm the relationship between the lesion and bronchi. A Metras catheter with a curved tip is inserted into the bronchus, and through this, a curette is guided to the lesion for biopsy. However, it is difficult to change the curvature of a Metras catheter, so guiding the forceps to small lesions can be difficult. In addition, the airway lumen cannot be checked, so complications like bleeding are more difficult to treat (12).

Sample Collection with a Flexible Bronchofiberscope

When inserting biopsy forceps and a curette through the working channel of a flexible bronchofiberscope to biopsy a peripheral lung lesion, these instruments can be guided to the lesion reliably and safely, and diagnostic accuracy is increased. In addition, to more reliably guide biopsy forceps to a lesion, a 2 mm (outer diameter) ultrathin bronchoscope, which is even thinner than a conventional flexible bronchofiberscope, has been developed.

Bronchography can be very uncomfortable for patients, and contrast agents have become difficult to obtain. Thus, the relationship between lesions and bronchi is now being evaluated by interpretation of high-resolution CT imaging.

Recently, CT has been able to detect lesions that are too small to be seen on X-ray examinations. Because such lesions cannot be identified by X-ray fluoroscopy, the position of the biopsy forceps tip and lesion is determined under CT fluoroscopy (13). Figure 5 depicts a biopsy of a lesion in the right lung apex being performed by bronchoscopy under CT guidance.

For even more accurate guidance of biopsy forceps, ultrathin bronchoscopes are now being used. However, in the peripheral bronchi, the three-dimensional (3D) positional relationship between the lesion and bronchi is not easy to establish, thus making it difficult to determine in which bronchus to advance the biopsy instruments. To resolve this problem, navigation systems with virtual bronchoscopy imaging have also been developed.

These systems generate 3D images of the bronchial lumen from high-resolution CT imaging of serial 1 mm slices from the trachea to the lesion. A semi-automatically generated map of the bronchi shows the most reliable path to the lesion. The system indicates where the actual bronchoscope should be inserted at each bronchial branch (14).

Ultrasound of the peripheral lung is also now being performed to target the biopsy forceps to the lesion. This

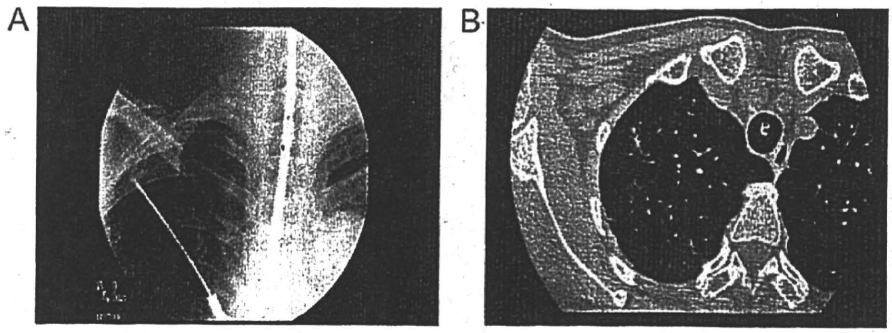

Figure 5. Transbronchoscopic biopsy (A) under X-ray fluorography guided and (B) under computed tomography (CT) guided.

involves insertion of a radial ultrasound probe into the lung periphery, and when the tip reaches within the lesion, findings different from normal lung tissue are obtained. The biopsy forceps cannot be directly guided, but a reliable biopsy from within the lesion can be confirmed, thus increasing the reliability of the biopsy results (15).

With the development of systems that enable reliable insertion of instruments such as forceps into peripheral lesions, the development of transbronchial treatment for peripheral lesions is highly likely and no longer just a dream.

ADVANCES IN IMAGING DIAGNOSIS

At the time of development of the flexible bronchofiberscope, imaging of the respiratory system primarily involved chest X-rays, tomography and bronchography. However, in the 1990s, the speed of CT scanning rapidly increased, serial imaging over a short time became possible and image quality improved. Tomography and bronchography are no longer being performed.

Advances in Chest CT

CT came into clinical use starting in 1974. At first, the devices used a single X-ray beam and one detector, and imaging of one cross-section required several minutes. Therefore, CT was used primarily for the head and was seldom used to evaluate the respiratory system.

In 1978, a CT system using a fan-shaped X-ray beam and linear detector was developed. Devices that could image one cross-section in only a few seconds appeared. Thus, several images during a single breath-hold could be acquired, and CT started to be used for diagnosis of lung lesions.

Then, in 1985, devices wherein the X-ray tube and detectors were continuously rotated were developed. Helical scan methods in which the images were acquired while the patient's body was continuously rotated were also developed. Imaging of the entire lung was made possible during a single breath-hold, and these devices became established for the diagnosis of respiratory tract disease.

Advances in CT devices have known no limits. The number of detectors has increased from 1 to 2, 4, 16 and 64, and recently, instead of linear detectors, area detectors have also been developed. The development of systems that can image the entire lung in a single rotation is also proceeding.

Along with advances in CT systems, changes in imaging protocols and display methods have changed. When a single image required a few seconds, only a few images, with 10 mm-thick slices focusing on the area of abnormality, were obtained. However, as imaging speed has increased, wider areas can easily be imaged, and the image slices are thinner.

With thinner image widths, resolution in a cephalocaudal direction is improved. This enables generation of images not only in the horizontal plane, but also in the coronal plane and sagittal plane, and even 3D images. Thus, 3D structural analysis of lesions is now possible (Figure 6).

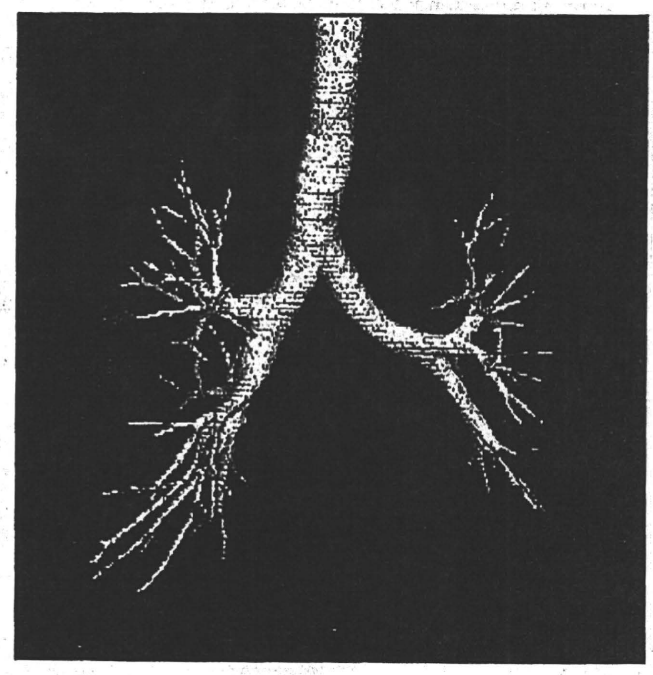

Figure 6. Three-dimensional image of bronchial tree made from high-resolution CT.

Advances in the Early Detection of Lung Cancer

With imaging of wide areas of the lung now easily possible, many lesions too small to be detected by conventional X-rays, even at other than the target site, can now be detected by CT. This is because compared with conventional X-rays, CT has superior concentration resolution, and faint concentration differences can be easily detected. Also, with CT cross-section images, fewer areas become blind spots, for example, due to the hilum, heart and diaphragm.

Therefore, CT screening was evaluated for the early detection of lung cancer. At first, even with third-generation scanners, whole lung imaging required several minutes, X-ray exposure was high and cost was high, so CT was not considered feasible for lung cancer screening.

However, in 1985, devices wherein the X-ray tube was continuously rotated, and helical scanning methods, in which images were acquired while the examination table was continuously moved, were developed. This markedly reduced imaging time and made whole lung imaging possible during a single breath-hold. Also, regarding detection of abnormal shadows in the lung fields, even with low-dose imaging, about 1/10 the exposure dose in conventional imaging, no differences in diagnostic performance were demonstrated. In 1993, the Anti-Lung Cancer Association (ALCA) became the first in the world to recommend low-dose CT for lung cancer screening. Low-dose CT screening started to be widely used in residential screening, occupational screening and routine medical examinations (16–19).

An effect of lung cancer screening by low-dose CT on reducing lung cancer mortality rates cannot yet be demonstrated, but compared with lung cancer screening with conventional X-ray imaging and sputum cytology, the lung cancer detection rates are increased 3–10 times. About 80% of detected lung cancer is Stage I, and the 5-year survival rate for detected lung cancer is also about 80%. To further improve the detection rate and enable safe diagnosis anywhere in the nation, the development of computer-aided diagnosis is now proceeding.

Advances in the Qualitative Diagnosis of Lung Cancer

With decreased CT slice thickness, magnified images and image processing that enhances margins, images can be obtained that appear just like black and white images of the resected lung. This enables evaluation of the characteristics of the border between the lesion and normal lung tissue and the interior of the lesion, thus improving diagnostic yield.

Currently, nodules about 1 cm in size that can be detected by CT are classified into three types: pure ground glass nodule (GGN), mixed nodules and solid nodules. In a pure GGN, pulmonary vasculature passing through the lesion can be identified, and the nodules consist only of ground glass opacity (GGO). Solid nodules have a high CT number and consist of areas where pulmonary vasculature passing through cannot be identified. Mixed nodules consist of both GGO and solid elements.

Pure GGN may be a mildly inflammatory lesion, atypical adenomatous hyperplasia (AAH: an adenocarcinoma precancerous lesion), or a very early well-differentiated adenocarcinoma. If inflammation is present, this often disappears in about 1 month. AAH often does not change for many years. In well-differentiated adenocarcinomas, changes such as enlargement or increased density occur. However, this process is very slow, and changes over the course of years are not uncommon. Therefore, these types of lesions, if there are no short-term changes, must be followed by CT for several years (20) (Fig. 7).

Meanwhile, mixed nodules are very likely to be an inflammatory healing process or well-differentiated adenocarcinoma. Inflammation, if present, should improve in 2–3 months. If re-evaluation shows no changes at this time, adenocarcinoma must be considered. Unless there are systemic contraindications to excision, an open lung biopsy should be performed. If excision is functionally difficult, bronchoscopic or percutaneous needle biopsy can be performed for a definitive diagnosis. If adenocarcinoma is confirmed, radiation therapy can be given (Fig. 8).

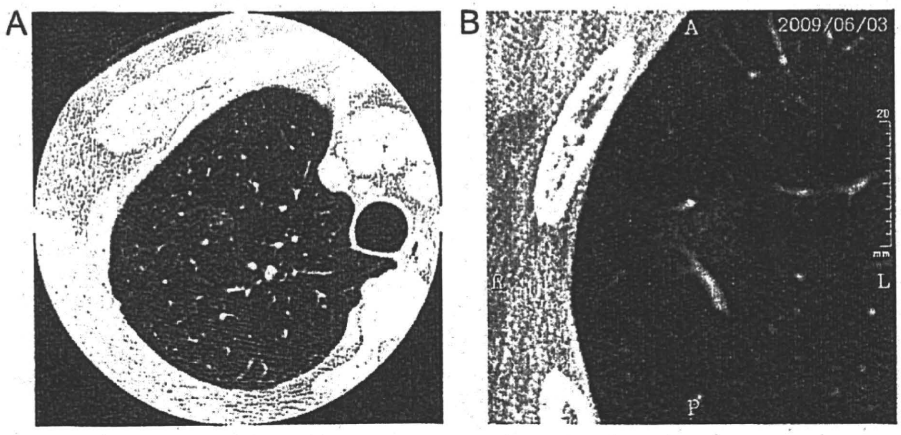

Figure 7. High-resolution CT image of pure GGN. (A) Atypical adenomatous hyperplasia and (B) adenocarcinoma.

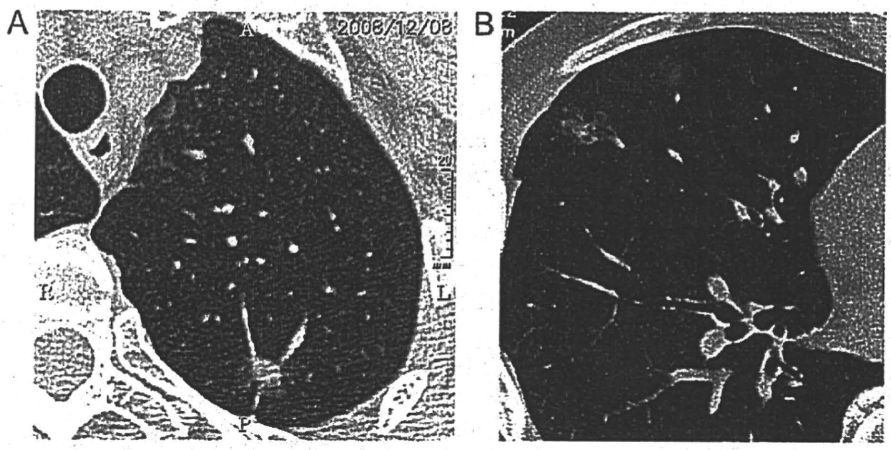

Figure 8. High-resolution CT image of a mixed nodule. (A) Adenocarcinoma and (B) adenocarcinoma.

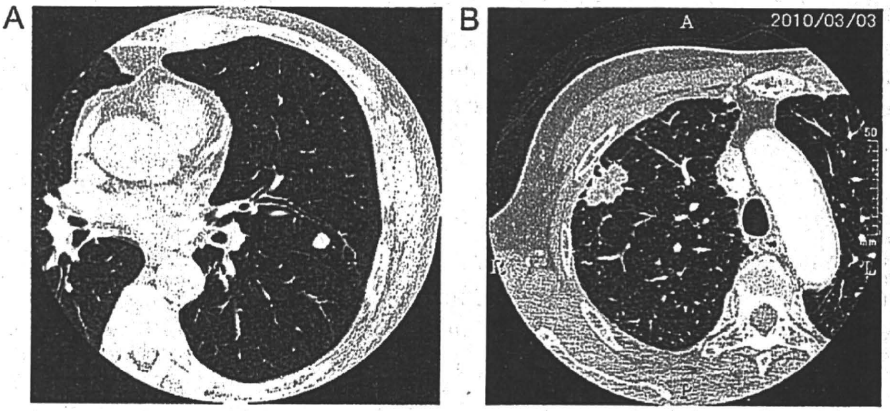

Figure 9. High-resolution CT image of a solid nodule. (A) Granuloma and (B) squamous cell carcinoma.

Up to 99% of solid nodules are benign lesions like granulomas or hamartomas, but occasionally, they may be squamous cell carcinoma or small cell carcinoma. Growth of these cancers is usually very rapid, so on follow-up evaluation after 1 and 3 months, if there is no change, they are likely benign. If enlargement is noted, malignancy is likely, and appropriate treatment is necessary. These types of lung cancers occur almost exclusively in smokers. In patients who are smokers, particularly careful follow-up observation is important (Fig. 9).

Advances in Quantitative Diagnosis of Lung Cancer

When lung cancer is strongly suspected by imaging diagnosis, or lung cancer is diagnosed by bronchoscopy, diagnosing the extent of progression is also important. Progression of lung cancer can be by local invasion of surrounding organs, by lymph node metastases or by hematogenous metastases to other organs.

To diagnose invasion of surrounding organs, CT with a contrast agent is useful. If a fat layer between the thoracic wall or mediastinal tissues is present, the absence of invasion is often diagnosed.

To diagnose lymph node metastases, CT with a contrast agent is also useful. For mediastinal lymph nodes, if the short axis is $\geq$10 mm, the likelihood of cancer metastases is high. For hilar lymph nodes, although not clearly defined, even when $\leq$10 mm, if lymph nodes are morphologically round, or there is strong contrast enhancement of lymph nodes, the likelihood of metastases is high, and a therapeutic modality is often selected. Recently, diagnosis by FDG-PET is being performed, but there are many false positives, so one cannot be too overconfident.

Hematogenous metastases commonly occur to the lungs, brain, liver, adrenal glands and bone. For these, whole body CT with a contrast agent, brain magnetic resonance imaging, abdominal ultrasound, FDG-PET or bone scintigraphy is performed.

UNIFORM MANAGEMENT OF MEDICAL INFORMATION

In the diagnosis of respiratory tract disease, a combination of imaging modalities and comparison with previous imaging is important. In particular, chest X-rays that have been taken

during medical check-ups and before treatment of many diseases are scattered and stored at each medical center. Because these cannot easily be compared, unnecessary examinations are often performed for benign disease, and malignant diseases originally diagnosed as benign end up progressing.

To eliminate this problem, Ikeda et al. introduced the concept of the 'personal health data recording system' in 1983. At that time, the elemental technology was not mature enough for clinical application, but with today's information technology environment, electronic health records (EHRs) are now possible.

With implementation of EHRs, when a patient goes to any medical facility in the nation, that individual's past medical history, including laboratory results and treatment, will be readily available. This will become just like a single medical facility, in which medical clinics throughout Japan can share one electronic medical record. This will reduce unnecessary tests, and comparison with previous imaging studies will be easy, thus improving diagnostic accuracy. In addition, records of diagnosis and treatment at each medical facility will always be accessible, leading to an improved level of medical care.

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Conflict of interest statement

None declared.

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シンポジウム2

肺がん検診の現状と将来

金子昌弘

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肺がん検診の現状と将来

金子昌弘

キーワード
肺がん検診，胸部X線写真，喀痰細胞診，低線量CT

はじめに

現在日本人の死亡原因の首位は「がん」であり，中でも肺がんが男女とも最も多数を占めている．がんの部位別の罹患数で見ると，肺がんは男性では胃がんに次いで2位，女性では乳がん，胃がん，結腸がんに次ぎ4位と最多ではない．しかし他のがんに比べ予後が不良のために死亡数ではこれらよりも多くなっている[1]．

一方進行肺がんに対する治療成績は，各種の抗がん剤の開発や放射線治療機器の進歩により延長はしているが，切除のような根治までは期待できない．従って，肺がん死亡を減少させるには検診で早期肺がんの時期に確実に発見し外科的に切除するか，喫煙率の低下をはかり肺がん自体の発生を下げることが急務である．

本稿では，肺がん検診の現状と問題点およびその解決方法としての新しい検診方法，さらにはそれらの検診と禁煙指導の結びつきについて述べる．

現状の肺がん検診

胸部の検診は，結核予防法による胸部の間接X線撮影が以前から行われてきたが，その後の疾病構造の変化により肺がんの早期発見にも用いられるようになり，実質的には肺がん検診となってきた．

1987年に当時の老人保健法に肺がん検診が取り入れられるにあたり，補助金の対象になる検診の方法は，40歳以上の男女に対し胸部X線撮影を行い，喫煙指数（1日の本数×喫煙年数）が600を超える50歳以上の受診者には3日間の蓄痰による喀痰細胞診を行うことと義務づけられた．またX線撮影の方法は直接あるいは100mmのフィルムでの間接の高圧撮影を行い，読影は2名の医師によるダブルチェックと必要に応じて過去の画像との比較読影を行うこと，と定められた．

現在，老人保健法は廃止されているので補助金による制約はなくなり，実施方法はそれぞれの自治体の判断に任されているが，おおむねこの方法で行われている．しかし一部では積極的に後述の低線量CTを取り入れている地域も出てきている．

現状の肺がん検診の効果

肺がん検診について，本邦では結核検診から移行する形で行われ始めたが，欧米ではそのような基盤がなかったので，検診を行うかどうか，その効果の検証から検討が行われた．

その中で最も信頼されているのが米国のメイヨークリニックのデータ[2]で，約1万人の喫煙男性を検診群と非検診群に無作為に割り付けるRandomized Control Trial：RCTが行われ，検診群には年に3回胸部X線と喀痰細胞診の検診を行い，それぞれの群での肺がん罹患と死亡を比較したところ，罹患数では検診群の方が多かったが

国立がんセンター中央病院 内視鏡部

連絡先：〒104-0045　東京都中央区築地5-1-1
Tel: 03-3542-2511　Fax: 03-3542-2628

死亡数に差がないことから，肺がん検診は効果がないと断定されてしまった．

しかしその後の検討で，非検診群も大半が年に1回程度は何らかの形で胸部X線撮影を受けており，逆に検診群も必ずしも全員が毎回の検診を受けていたわけではないことも判明し，その結果については見直しが必要という意見も強くなっている．

一方本邦では既に結核検診が行われていたので，非検診群を設定してのRCTは行うことができず，肺がん死亡例と性年齢，喫煙歴をマッチさせた健常例との検診受診歴を比較する，症例対照研究が複数行われた．特に老人保健法施行以降については宮城県，新潟県，群馬県，岡山県での全県を挙げての研究が行われ，その結果では定期的に毎年肺がん検診を受診することにより肺がん死亡は44%低下することが証明されている[3]．

新たな検診技術の導入

肺がん検診の有効性は定められた方式を遵守して行えば，一定の死亡数減少効果は証明されたものの，他の臓器の検診に比べ精度は低いことも事実で，精度向上のための方策も検討された．

喀痰細胞診では，区域気管支までの肺門部がんでは肉眼では指摘が困難なほどの微小ながんをみつけることができるが，X線写真でみつかる末梢部がんの場合は病巣の大きさの平均は3 cm程度で，病期も肺内に病変が留まるI期は半数に満たないのが現状である．従って肺がん検診の精度向上には，末梢部肺がんの早期発見の精度を高める必要があるとして，その工夫が行われてきた．

100 mmの間接写真の画質はほとんど直接撮影と遜色がないほどに向上したので，それ以上の進歩は望めず，むしろデジタル化による画像処理や経時的な引き算による新たな陰影の抽出なども行われたが，時間がかかることなどから一般化はしなかった．

次に導入が研究されたのが，Fuji Computed Radiography（FCR）の導入で，これはデジタルデータなので，肋骨を取り除いた画像の作成（エネルギーサブトラクション）などで診断の精度を上げることが可能になり，一部の自治体の検診に導入されたが，一般的に広まるには至らなかった．

低線量ヘリカルCTの肺がん検診への導入

一方1990年代からCTは濃度分解能が高く盲点が少ないことから肺野末梢病巣の発見率の高いことは知られていたが，撮影に時間がかかること，被曝が多いこと，費用が高いことなどの面から検診への導入は困難と考えられていた．しかし螺旋状に撮影できるヘリカルCTの開発や，異常な結節を指摘するだけであれば低線量にして被曝を10分の1程度まで下げても診断能に差がないことの証明などで，これらの問題が解決された．このような研究をもとに1993年から会員制の肺がん検診組織である「東京から肺がんをなくす会」の検診に世界で最初に取り入れられCTによる肺がん検診がスタートした[4]．

その後1990年後半から多くの人間ドックをはじめ，千葉県，長野県，愛媛県，大阪府などの一部の自治体や，日立などの職域の検診でも導入が進められている[5,6]．1994年には胸部CT検診研究会（現：NPO法人日本CT検診学会）も発足した．一方海外でもほぼ同時期に主に研究目的のCTによる肺がん検診がスタートし，国際的な研究組織もできあがり全世界的なレベルでのデータの集積も行われている[7,8]．

CTでの肺がん検診は当初はシングルスライスCTで始められたが，最近はマルチスライスCTで行う施設も多くなってきている．いずれも基本は50 mA以下の低線量で行い，全肺を15秒前後の一回の呼吸停止の間に撮影する．画像の再構成はシングルの場合は10 mm幅10 mm送りがほとんどであるが，マルチの場合は10 mm～1 mmまでの様々な厚みで行われている．読影は10 mmの場合はフィルムでも可能であるが1~2 mmの場合には画像の枚数が多くなるのでモニター読影で行われている．

検診を主体に行っている施設でのCT検診の場合は，低線量で撮影している施設が多いが，人間ドック学会での瀧澤らの報告によると，実際に低線量で撮影しているのは3分の1程度に過ぎず，他の施設では通常の外来や入院患者と同じ線量で