○低線量CTでの肺癌検診では80%前後が病期IA期で発見される.
○CT検診はまだ研究段階なので精度管理を確実に行う必要がある.
○CT検診では肺癌以外にも冠疾患，肺気腫，内臓脂肪も発見できる.

指導，特に禁煙指導の効果は高いと報告されている．喫煙は肺癌のみならず多部位の発癌やCOPDや心筋梗塞，脳梗塞など多くの致命的な疾患に関与することが明らかになってきているので，CT画像を元に禁煙指導を行い喫煙率を下げることは，関連するあらゆる疾患による死亡率を下げることになる．

低線量CT検診は，少ないとはいえ，通常の間接撮影の10倍程度の被曝量を与えるので，それに見合う効果を得るためには，利用できるデータはすべて利用し，受診者に還元することで，総合的な効果を高める必要があると思われる．

まとめ●

現行の肺癌検診も定められた基準を遵守して行えば一定の効果はあるが，他の癌検診に比べ有効性は低い．

精度向上のために低線量CTの導入がはかられ，発見率や早期癌の占める率で著明な改善がみられるが，肺癌死亡数を低下させるかどうかの証明はまだされていない．

内外でRCTを含む有効性証明のための研究がスタートしているが，肺癌は喫煙や年齢による罹患率の変動が大きく，発育速度もきわめて多様なので，研究結果を評価するためには，その研究対象集団の特性にも十分な注意を払う必要がある．

低線量CTの画像は肺癌の早期発見のみならず，多種の疾患のハイリスク群の抽出にも有効で，これらを対象にした禁煙指導の効果も大きいとされ，禁煙などの効果も含めた総合的な評価も必要と思われる．

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肺門部肺癌

藤田 佳嗣・関 順彦・江口 研二

ポイント

- 胸部X線上，肺野の肺炎様陰影では，病変領域の容積減少を伴うか否かが陰影中枢側の太い気道病変を推測するヒントとなる．
- 胸部X線上，肺門部肺癌では腫瘤陰影自体は異常影として描出されず，病変の末梢側に起こる2次性の閉塞性肺炎の陰影によって発見されることが多い．
- 肺門部肺癌の診断では，病変の部位や閉塞性肺炎の広がりだけでなく，手術の可否を決めるために，中枢気道の内腔所見と肺門部血管への浸潤所見を，CTや気管支鏡を用いて診断する必要がある．

■ 症例1

【病状経過】

63歳男性．2年前に食道癌の手術を施行され，その後外来で経過観察していたが，1年6カ月後に胸部異常陰影を指摘された．喫煙歴は20本/日×41年(喫煙指数820)，食道癌術後禁煙．

【画像所見】

図1(胸部単純X線)：左上肺野の内側にエアブロンコグラムを伴った境界不明瞭な浸潤影を認める(矢印)が，大動脈弓・下行大動脈のシルエットは保たれており，陰影は左上区前方に存在する．左上葉支口の透亮像を認めるが，左B^3bの気管支輪状影は不明瞭である．左中肺野に左心縁と平行に垂れ下がるように走行する血管影は舌区のもので，左主気管支の位置，左横隔膜の高さと合わせて，左上区の容積減少は少ないと考える．左下肺野の血管陰影(下葉各枝)は右下葉に比べ減弱しており，肺門部病変による血流低下の可能性が考えられる．

図2(胸部単純X線左側面像)：左右の上葉支口の透亮像は認められる．胸骨後方で気管透亮像前方に浸潤影を認める(矢印)．左上区S^3b，c領域付近の陰影と考えられる．

図3，4(胸部CT画像)：大動脈弓のレベルの肺野条件(図3)では，左上区B^{1+2}を認め，S^{1+2}領域の含気が保たれているが，左B^3b，cは認められない．含気のない左B^3b，cに沿う領域(矢印)に縦隔条件のCT画像(図4)では，円形低吸収域も混在し，気管支内粘液栓を考える．その末梢にエアブロンコグラムを伴った浸潤影と含気の残存する部分を認め，隣接するS^{1+2}領域が代償性の広がりを示していることからS^3b，c領域の部分的な容積減少を伴う閉塞性肺炎と考えられる．

図5，6，7(胸部CT画像．肺野条件・縦隔条件)：さらに気管分岐部レベルおよびやや上方のレベルでは，左上区に広がるB^{1+2}は認められるが，B^3b，c根部は腫瘤に隠れている(図5〜7)．縦隔#5リンパ節も腫大している(図6

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図1　胸部X線正面像

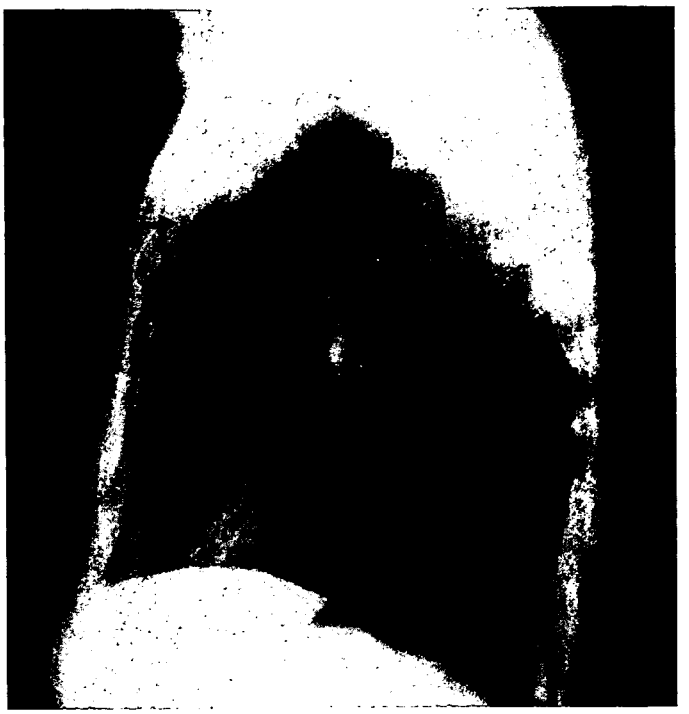
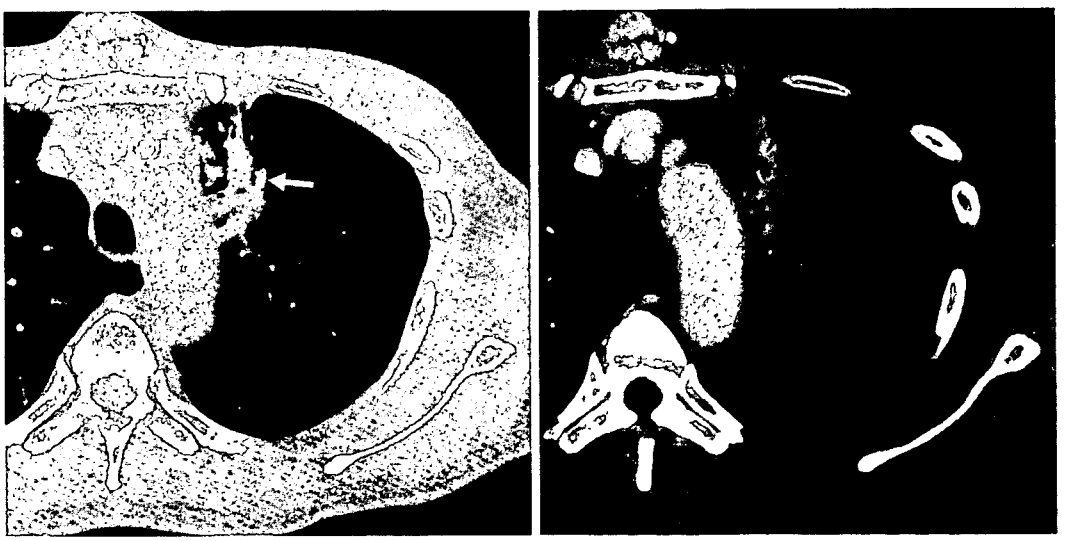


図2　胸部X線左側面像

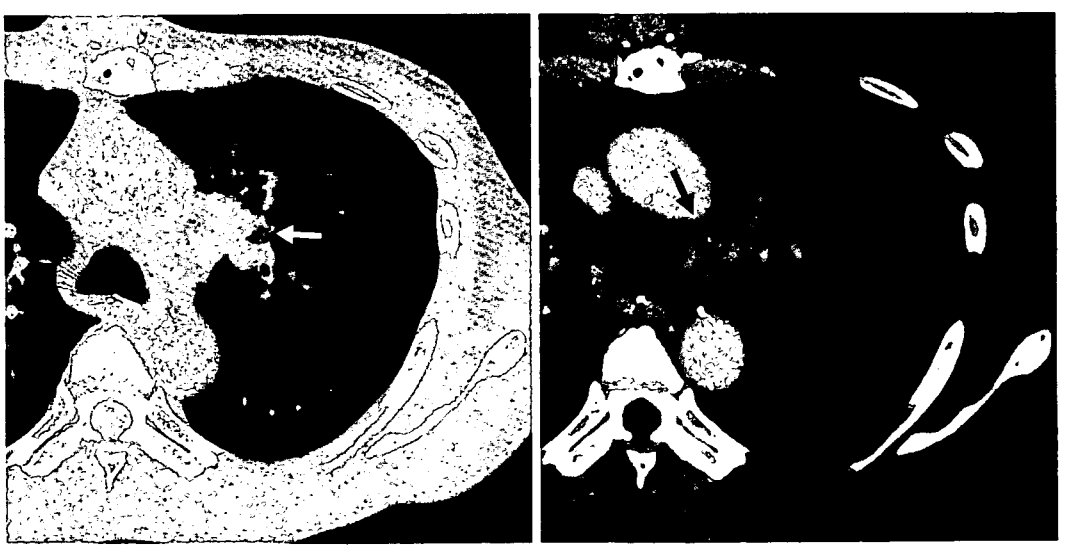
3 | 4



胸部CT画像（肺野条件）

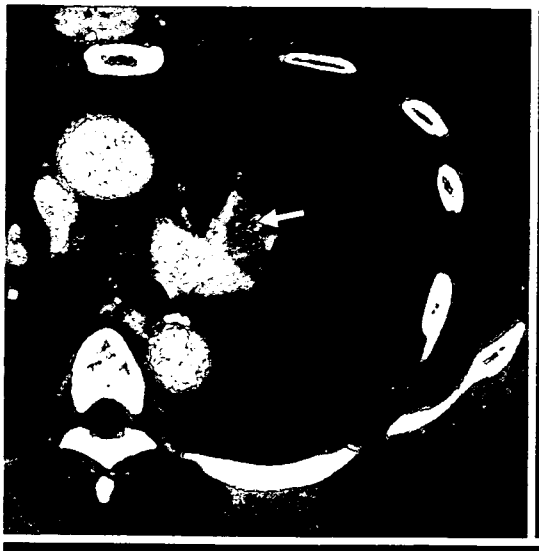
胸部CT画像（縦隔条件）

5 | 6



胸部CT画像（肺野条件）

胸部CT画像（縦隔条件）



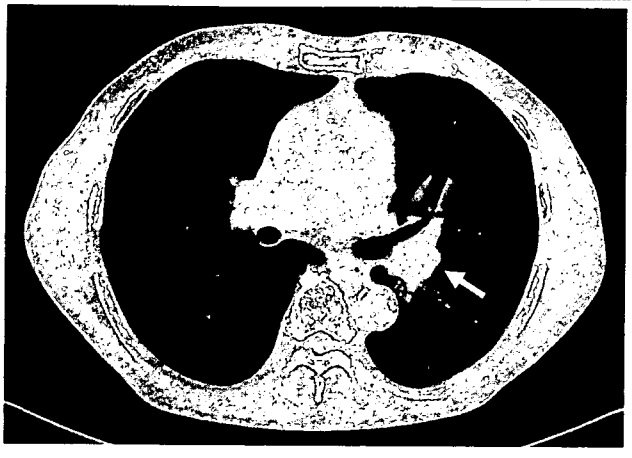


図7　胸部CT画像（縦隔条件）
図8　胸部CT画像（肺野条件）
図9　気管支鏡

矢印）．肺内#13リンパ節腫大によりS^3肺動脈起始部の圧排像を認める（図7矢印）．

図8（胸部CT画像．肺野条件）：舌区気管支は開存している．さらに，肺門#11リンパ節の腫大を認める（矢印）．

図9（気管支鏡）：左上葉支口では，上区舌区支分岐のB^3側に上皮の顆粒状変化を認める（矢印）．さらに奥では左上区B^3の入口部が閉塞しており，B^{1+2}が圧排されていた．気管支鏡生検組織により，扁平上皮癌と診断．胸腔鏡下で左上葉切除，リンパ節廓清を施行された．左上区B^3b，c根部付近から生じたと思われる扁平上皮癌であった．

■ 症例2

【病状経過】

71歳男性．3カ月前に胸部異常陰影で紹介される．喫煙歴30本/日×50年（喫煙指数1,500）．

【画像所見】

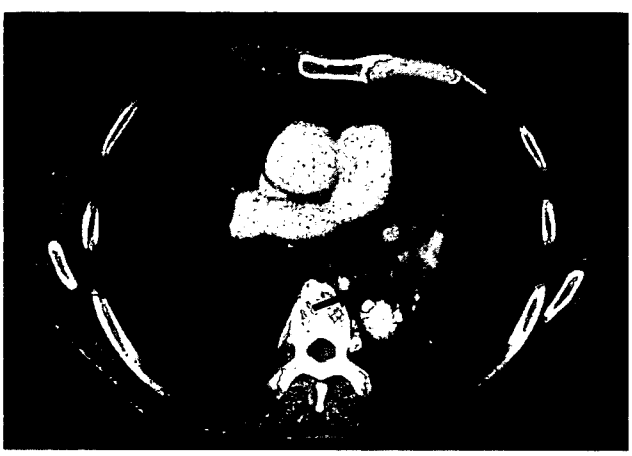
図10，11（胸部単純X線）：初診時および初診3カ月前の2枚である．比較すると撮影体位のずれはあるが，3カ月前にくらべ主に肺動脈影からなる左肺門陰影の明らかな増大と高濃度化を認める（矢印）．血管影の走行などから判断して，左上葉下葉の広がりには，明らかな容積変化などを認めない．

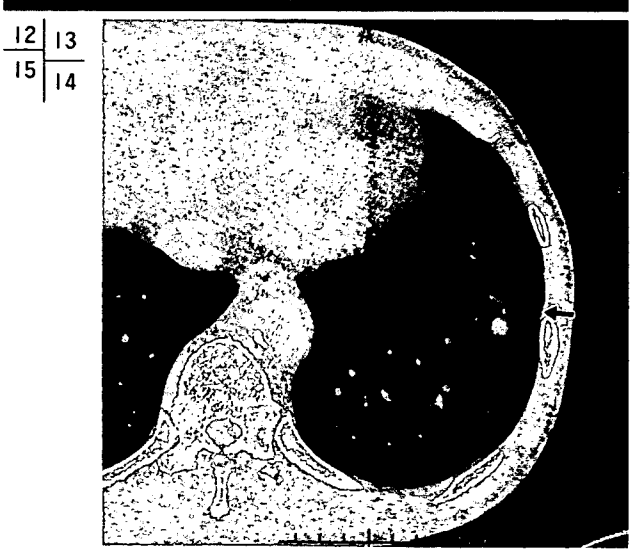
図12，13，14（胸部CT画像）：左舌区支と左下葉B^6のレベルの縦隔条件画像（図12）では，左下葉枝肺動脈をB^6側から圧排するような腫瘤影（矢印）を認めたため，肺門リンパ節と一塊となった肺門部肺癌を考えた．冠状再構成CT画像（図13，14）と併せると左肺門の腫瘤と造影された下葉肺動脈との位置関係を理解しやすい．ただし，X線写真上で二次性の閉塞性肺炎像を認めず，気管支鏡所見では左B^6入口部は圧排所見のみであったので，肺門部の扁平上皮癌としては，前例のような画像所見に乏しく診断が難しくなった．気管支鏡擦過細胞診で異型細胞あり，class IIIとされた．

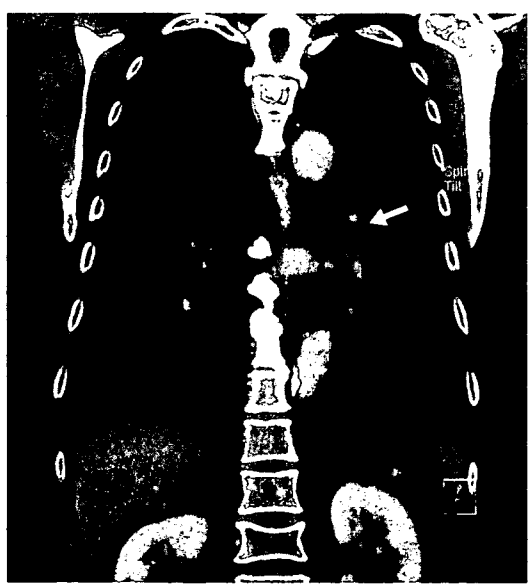
図15　胸部CT画像（肺野条件）：左S^8b末梢に末梢気管支に接する8mm大の充実結節影を認めた（矢印）．左下葉切除術後，病理組織学的に左S^8b原発の末梢型扁平上皮癌肺門リン

図10　胸部単純X線(初診3カ月前)

図11　胸部単純X線(初診時)







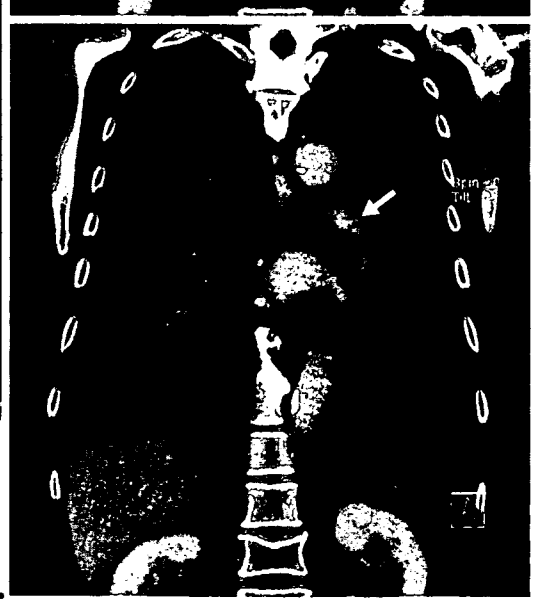


図12　胸部CT画像(縦隔条件)
図13　冠状再構成CT画像
図14　冠状再構成CT画像
図15　胸部CT画像(肺野条件)

パ節転移と判明した．左肺門部はリンパ節腫大による所見のみであった．

■ 読影のポイントとCTの意義

肺門部肺癌を疑う所見として，①無気肺や含気減少による肺の容積変化がある，②正常では見えるはずの領域が不明瞭になっている，などがポイントである．胸部単純X線でいつも見えている肺の構造，例えば，気管から左右主気管支の透亮像，左右B^3bの位置，両下葉枝の肺動静脈の陰影と走行などについて一定の順序で読影することによって肺葉の容積変化を読みとり，見落としのないように注意したい．

肺門部肺癌は，厚生省の研究班により，3次気管支(亜区域支)までに発生したと考えられる肺癌と定義され，組織学的にはほとんどが扁平上皮癌であり，小細胞癌もある．ただし近年，肺野末梢に発生する肺癌にくらべ症例頻度の減少が世界的に指摘されている．管腔器官である気道粘膜上皮に発生するので，胸部X線写真や胸部CT画像では腫瘍自体が描出されにくく，より小型の早期癌を発見することは難しい．いわゆるハイリスク群(重喫煙者)に関しては，冒頭の読影ポイントを念頭において慎重な読影と，喀痰細胞診検査が必要となる．特に同一部位に繰り返す肺炎像には要注意であり，その部位に拡がる気管支の中枢部の病変の有無を診断すべきである．最近の胸部CTとしては，造影マルチスライスCT(MDCT)による肺門部の再構成画像は，気道病変の範囲についてより詳細に描出されるので，有力な情報を与えるものである．今後はさらに気管支鏡検査の補助手段として，virtual bronchoscopyによる太い気道の狭窄病変の診断や生検ガイドにもMDCT再構成画像が活用されると思われる．

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An Operating Support System for CT Screening for Lung Cancer

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Abstract: The lung cancer occupies 1st place in the man in the cancer death of Japan and the woman occupies 3rd place. The death toll is in the increasing tendency every year. It is a pressing need to do the early stage detect of the lung cancer for this. The lung cancer medical examination with CT device is tried in the medical institution. The medical examination business divides into the clerical work section, the radiation section, and the diagnosis section and it divides into three sections. These business is operation using paper and it exists in an inefficiency situation. In this thesis, the CT screening for Lung cancer Operating support system that efficiently operates the information management of the medical examination business is researched and developed. The clarification of the analysis of business process, the computerization of the work contents, and the Visualization are researched, and for this, these results are mounted and systematized. Utility is evaluated by the business processing time and the user questionnaire survey, etc. by using this development system on the medical examination site.

Keywords: CT screening for lung cancer, Database, Operating support system, Business process, Visualization

1. Introduction

The medical examination from which the cancer medical examination indicator is shown from the Ministry of Health, Labour and Welfare in Japan and the improvement and the effect of the consultation rate of a mortality rate decrease are expected is recommended [1,2]. Perhaps, an active research in each internal organs is advanced in the field in relation to it. Even if the decrease of the lung cancer death is attempted by using the CT device to find the lung cancer, the CT Screening for Lung Cancer (CT Screening for Lung Cancer) of the early stage of the inclusion is executed in that as for the lungs internal organs.

The execution form of the CT Screening for Lung Cancer of the implementing agency are the municipality medical examination, the occupation medical examination, and the human dry dock, etc [3]. , and is executed in a medical examination specialized agencies, a general medical institution, a highly developed special medical institution, and various organizations where features exist [4,5,6]. Moreover, the section that takes charge of this medical examination business is a composition to which it is composed of three sections (the clerical work section, the radiation section, and the diagnosis section) and information circulates with the person. It is significant to achieve the improvement of accuracy with the operating effectiveness to share between the three sections by the accurate intelligence promptly and to achieve the accumulation of the detailed data for the those who consult a physician management and the rational valuation. However, it is operation in present using paper and the inspection delay etc. occur in the advance preparation of the medical examination with people by coming in succession with requiring medical examination business, outpatient, and in-patient's inspection business at time. Moreover, transmission shortage between sections occurs from the manpower shortage and there are adverse effects in acquisition and the reference to necessary information [7]. In addition, because the number of CT Screening for Lung Cancers of execution facilities is the report that it is few and the consultation rates are worse than medical examinations of another internal organs, will concentrate by those who consult a physician in the future, and have the possibility of a consultation rate increase, it is requested to improve it immediately. Therefore, the CT Screening for Lung Cancer Operating support system that can be efficiently safely operated based on the accurate intelligence is researched and developed.

This medical examination Operating support system achieves efficient operation by not only information on the instruction request, the record, and the display but also doing grasp of activities and clarification of the demand [8], and making information on the business process electronic.

SY0001/08/0000-0065

2. Operating support system of CT Screening for Lung Cancer

1. The business support in the clerical work section: Consultation person's type can be easily recognized from the reservation screen referring to consultation . Moreover, the progress report for the processing of those who consult a physician can be easily understood regardless of the section and the information recognition is matched.

2. The business support in the radiation section: The radiology technician has them facilitate the content of the instruction before from the change to a morbid state position grasp and the diagnostician master from the integrated judgment result and the key image by two or more doctors from the screen where the history can be immediately understood.

3. The business support in the diagnosis section: The interview sheet can be referred to easily, and another doctor's judgment result can be shared. Moreover, it researches . Information that can be used when there is a cooperation request of the investigation report is collected.

3. Design specification of CT Screening for Lung Cancer Operating support system

Figure 1 shows the outline of the system. This composes four those who consult a physician essential information, municipality code, Zip code, key image, and those who consult a physician cards by using card type data model. These are done in relations and it makes it to the data base. The those who consult a physician card that becomes the nucleus of this system is progress information, those who consult a physician essential information (ID, name, age, sex, and date of birth) that displays the flow, and consultation people's place of residence region information examining on business. It consists of business management information that collects information necessary for the articles of consumption usage condition, the business report, and the irradiation record, etc. and consultation person's reservation information, consultation , diagnosis result information, the image information, information of examining in an interview, and change to a morbid state details information. It is a mechanism that the person in charge of each section inputs necessary information respectively at each consultation and the those who consult a physician card is completed. Those who consult a physician essential information is connected with ID even by those of passing year who consult a physician when the card is made one card's making without fail when consulting a physician every time and making it to the data base, and the municipality code and the Zip code are connected by the ZIP code.

After it refers for the image, the key image is stuck directly on the those who consult a physician card. The self-relation function is put by using that the consultation person's repetition registration is generated, same consultation person's diagnosis history and image history are made the same, and the consultation history display is displayed. To input and to retrieve it to the those who consult a physician card in each section for this, the operation screen is made.

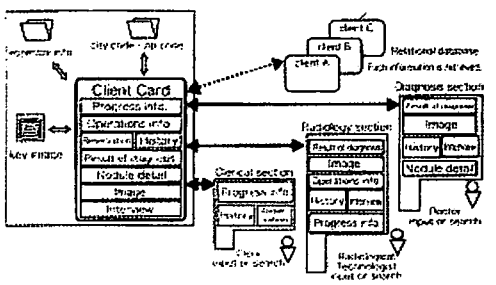

Fig. 1: Overview of an operating support system.

4. System implementation and evaluation

4.1 Construction of operating support system

Construction is comparatively easy because it is the one that it specialized in the CT Screening for Lung Cancer business and there are not small number of relating sections with three sections either. System construction has gone from valuing the profit by filing the common type. Because it is possible to facilitate it comparatively when customizing and current accumulation data are shifted after it distributes it of each medical examination organization, development with this product is consistently advanced. When distributing it, FileMaker Advanced that the development of the runtime version is possible is used.

4.2 Achievement of operating support screen in clerical work section

The congestion of the over-the-counter customer service is avoided by other patients even when there are a lot of those who consult a physician. The dissemination in the electronic medium can be smoothly done to a print and a corporate medical examination destinations of the presence and mailing destination of the judgment result that is information that the clerical work section of information generated in the other business segment needs with this system. Moreover, login information is left the history concerning the information control as security. Moreover, it is possible to correspond to the inquiry of can the saving of the time of the report between sections and those who consult a physician early

because the progress report is displayed in detail in each those who consult a physician.

4.3 Achievement of operating support screen in radiation section

The key image information, the content of the instruction, and the diagnosis were made to be efficiently enforceable. The sick position pointed out by the list display can be promptly understood even in the key image that two or more doctor selected the image from it is possible to judge it promptly when CT is operated important in the site by the click.

4.4 Achievement of operating support screen in diagnosis section

One CT image and one pathology image a change to a morbid state can be registered about the image information. This CT image is registered as a key image and necessary information in the next medical examination and introduction. The diagnostic information on the change to a morbid state for which doctors hoped in achieving these is made electronic and the system that can use it to be doing statistical analytical and to report on information management to research laboratories is achieved.

4.5 Before Operating support system is introduced in each section and comparison of the following processing time

It is done that the processing time after the business process is introduced in the operating support system is compared with the processing time before it introduces it.

The evaluation item of the clerical work section

1. Time to be going to require consultationby grasp.

2. Registration time of those who consult a physician essential information.

3. It is time that hangs to the grasp and the diagnosis result sending work completion of the progress report.

The evaluation item of the radiation section

4. Input time of vote of examining in an interview answer.

5. Time required from diagnostic outcome and doctor's content of instruction and key images to confirmation of change to a morbid state position before.

6. It is an input that has been executed and label making time.

The evaluation item of the diagnosis section

7. Time until image is diagnosed based on table of examining in an interview, consultation vote, and key image reference.

About the evaluation item of all sections.

8. Time at all stages.

As a results, time at all stages was shortened at 3.7 minutes from 14.8 minutes. The time crunches were able to be achieved up to about 1/4.

4.6 Questionnaire investigation

To evaluate the effectiveness of the business support function of this system, the questionnaire was executed.

To evaluate the effectiveness of the business support function of this system, the questionnaire was executed.

1. Is there "It is useful for cooperation with the other business segment" effect?

2. Is it effective of "Intuitive operation"?

3. Is there "Consultation can be referred promptly beforehand" effect?

4. Is there "The progress report is understood" effect?

5. Is it effective of the vita information on "Grasp, integrated judgment result display, and instruction content display at the key image and the change to a morbid state position"?

6. Is there "The vote of examining in an interview input is compared with the paper before" effect?

7. Is it effective of "Judge while easily referring to the judgment result, the interview sheet, and the key image before"?

8. Is it effective of "Screen where information on change to a morbid state can be recorded and the statistical analysis be done"?

Q1 question on the cooperation between section sections of the operating support system. Q2 question on the experience to the display. Q2-Q8 is a question to each section. It went by two systems of the operating support function to specialize in the impression and the section in the reaching display for the section.

Table 1: Result of questionnaire.

Question.No.	clerical work	radiology	diagnostic
Q1	3	3	2
Q2	3	3	3
Q3	4	-	-
Q4	4	-	-
Q5	-	4	-
Q6	-	4	-
Q7	-	-	4
Q8	-	-	4

Table 1 shows the result. It was obtained that it clerked and both excellent results of the radiological technologist in a common question to the section from the result. Because the doctor strongly considered and had been demanding special functions of the case and the follow-up survey, etc. . the problem was pointed out.

5. Conclusions

The CT Screening for Lung Cancer business does, and information's the computerization of the analysis and the work contents in the business process of each section doing and visible having made of the clarify them in this thesis This was systematized, and the operating support system was achieved. Utility was evaluated by the user questionnaire survey by using this system on the medical examination site at the business processing time. The system that proposed it showed the reduction of the business load on a clinical site and operation surely.

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Comparative Evaluation of Physicians' Pulmonary Nodule Diagnosis with Thin and Thick Section Multislice CT Images at Lung Cancer Screening

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Abstract: The physicians pulmonary nodule diagnosis of using thin-section and thick-section images at MCT screening for lung cancer was quantitatively and statistically analyzed. MSCT images of 360 subjects with 2 mm and 10 mm slice thicknesses were read and interpreted by six physicians. The diagnosis criteria were nodules for further exact examination (NFE), nodules for no further examination (NNFE), non nodule (NN) and no abnormality (NA) case. Descriptive statistics was used to evaluate the diagnosis results. Lung lobe classification algorithm was used to identify nodule location. Semi-automated extraction and quantitative analysis were carried out to determine the diagnostic capabilities of two slice thicknesses on physicians' diagnosis of pulmonary nodules

Keywords. MSCT, thin and thick section images, pulmonary nodules, diagnostic capabilities, lung cancer MSCT screening

1. Introduction

The accurate identification of pulmonary nodules, may lead to the successful detection and characterization, and treatment of a myriad of lung diseases[1].Therefore, earlier and more certain detection with more effective screening methods can be expected to improve cure rates[2]. Over the past 10 years, lung cancer screening studies using CT have detected up to 85% of lung cancers in stage1, offering promise in what has been a disease with a dismal outlook[1]. Lung cancer is now the leading cancer cause of death in Japan[3]. Recently, attempts have been made in Japan to apply helical computed tomography (CT) to lung cancer[4].

Evaluation of pulmonary nodules may provide a more reliable and accurate detection of lung cancer. With the nodule features, some studies findings revealed that nodule size and nodule location can influence nodule detection

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Feature values of the nodules such as size, average CT value, contrast and the location in the lung lobes are examined. Size as one factor influencing the probability of lung cancer in a pulmonary nodule has been recognized that it correlates with the risk of cancer[1].

This study was conducted to show and evaluate the extent of diagnostic capabilities of thick and thin section MSCT images at MSCT screening on physicians' diagnosis of pulmonary nodules. The objective is to quantitatively and statistically evaluate the diagnostic capabilities of 10 mm thick and 2 mm thick MSCT images on physicians' diagnosis of pulmonary nodules.

2. Materials and Methods

We used MSCT images of 360 people obtained from lung cancer MSCT screening. The subjects were composed of 236 male and 124 female. The lung cancer MSCT screening was conducted between September 2000 to September 2001. The images were taken using the following measurement conditions: slice thickness, 2 mm and 10 mm; tube current, 30 mA, tube voltage 120 kV; reconstruction interval 1 mm and 10 mm; helical pitch 5.5; pixel size 0.625 mm and image size 512 × 512 pixel.

Table 1. Physicians' criteria for pulmonary nodule diagnosis

Criteria for Pulmonary Nodule Diagnosis
NFE nodule for further examination :
1. lung cancer is suspected strongly
2. nodule other than lung cancer (granuloma, inflammation but possibly a cancer)
3. disease believed to be other than lung cancer but further examination is necessary
4. tuberculosis (TB) is suspected strongly
NN- non nodule : active pulmonary diseases other than lung cancer and TB for treatment
NNFE- nodule for no further examination: old inflammatory lesion
NA- no abnormality case: diagnosed as normal

The comparative reading test was carried by 6 physicians through the following steps: Initially, the individual reading of each physician was carried out. Based on the individual reading, group consensus reading was formed. The images were distributed in a way that no two physicians can read the images of the same person. Seventy (70) people were assigned to each physician. The NN diagnosis was excluded from analysis due to its GGO characteristics.

The diagnosed nodules at the comparative reading were further analyzed through a semi-automated extraction. The nodule features such as size, average CT value and contrast were calculated. The relationship between average CT value and size; between contrast and size of 2 mm and 10 mm MSCT detected nodules were analyzed through a scatter plot. Furthermore, the relationship between average CT value and size; between contrast and size, using physicians' diagnosis with 2 mm thick as the gold standard were compared with the 10 mm thick physicians' diagnosis result.

The identification of nodules in each lung lobe was carried out using the lung lobe classification algorithm developed in our laboratory. The classification algorithm has the following steps: first, extraction of the lung field region and the lung blood vessel using thresholding; second, classification of the lung blood vessel adjoining each lobe of bronchial tube into lobe units by connectivity; third, compilation of the space which wraps the lung blood vessel and finally, classification of lung field region into lobe units.

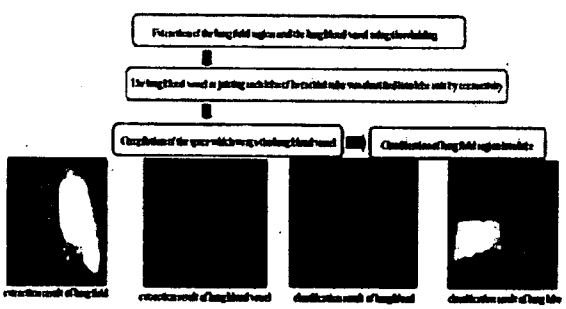


Fig. 1: Lung lobe classification algorithm

The measurement of nodule distance from chest wall was carried out based on the concept that the mediastinum is the contour of the lung field which is not connected. Then taking into consideration the lung field region, distance from the chest wall was calculated.

Table 2. Cross tabulation of physicians' overall diagnosis

		10 mm thick MSCT			
		NFE	NNFE	NA	Total
2 mm thick MSCT	NFE	65	33	35	133
	NNFE	43	152	164	359
	NA	21	37	-	58
	Total	129	222	199	550

Table 3. Cross tabulation of physicians' diagnosis of nodule at RUL

		10 mm thick MSCT at RUL			
		NFE	NNFE	NA	Total
2 mm thick MSCT at RUL	NFE	14	9	15	38
	NNFE	13	61	57	131
	NA	8	13	-	21
	Total	35	83	72	190

Table 4. Cross tabulation of physicians' diagnosis of nodule at RML

		10 mm thick MSCT at RML			
		NFE	NNFE	NA	Total
2 mm thick MSCT at RML	NFE	11	3	0	14
	NNFE	3	9	8	20
	NA	1	1	-	2
	Total	15	13	8	36

Table 5. Cross tabulation of physicians' diagnosis of nodule at RLL

		10 mm thick MSCT at RLL			
		NFE	NNFE	NA	Total
2 mm thick MSCT at RLL	NFE	17	9	5	31
	NNFE	13	27	25	65
	NA	7	8	-	15
	Total	37	44	30	111

Table 6. Cross tabulation of physicians' diagnosis of nodule at LUL

		10 mm thick MSCT at LUL			
		NFE	NNFE	NA	Total
2 mm thick MSCT at LUL	NFE	5	7	10	22
	NNFE	9	24	42	75
	NA	2	6	-	8
	Total	16	37	52	105

Table 7. Cross tabulation of physicians' diagnosis of nodule at LLL

		10 mm thick MSCT at LLL			
		NFE	NNFE	NA	Total
2 mm thick MSCT at LLL	NFE	18	5	5	28
	NNFE	4	31	31	66
	NA	5	9	-	14
	Total	27	45	36	108

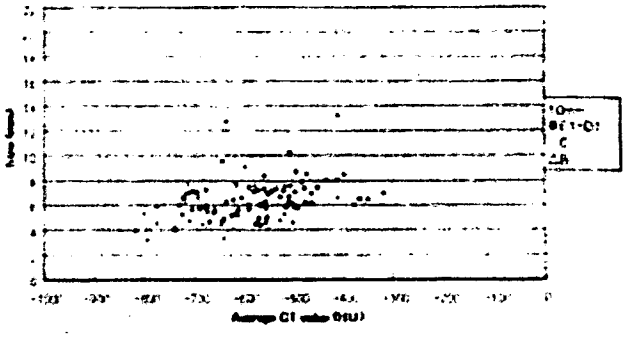


Fig. 2: Relationship of average CT value and size of 2 mm thick MSCT diagnosed NFE as compared with the diagnoses with 10 mm image

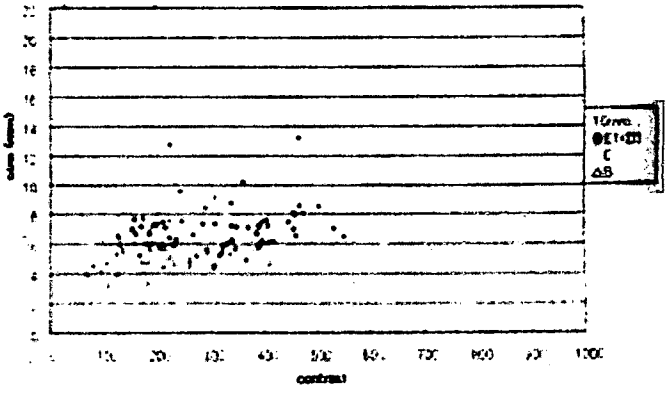
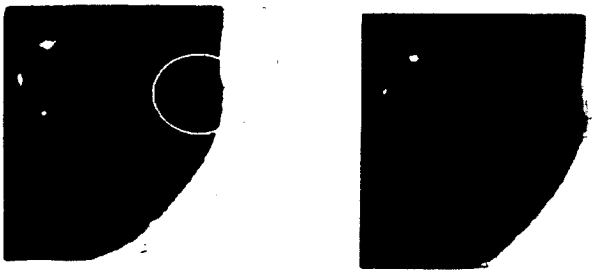


Fig. 3: Relationship of contrast and size of 2 mm thick MSCT diagnosed NFE as compared with the diagnoses with 10 mm image

3. Results

We did the cross tabulation of 2 mm and 10 mm 550 nodules obtained from the 6 physicians' interpretations of the MSCT images of 360 subjects. The 2 mm and 10 mm identified NFE, NNFE and NA were133 and 129; 359 and 222 and 58 and 199 respectively. The ratio of the nodule of 2 mm and 10 mm per person was; NFE: 1 and 1; NNFE: 2 and 1, and NA: 1 and 2. The NFE diagnosis rate of 10 mm over 2 mm as the gold standard, were 48.87% for overall

diagnosis, 36.84%, 78.57%, 54.83%, 22.72% and 64.28% for RUL, RML, RLL, LUL and LLL respectively. There were 33 NNFE and 35 NNFE with 10 mm out of 133 NFE with 2 mm. Most of the missed nodules were at the lung upper lobe, anterior and inferior borders of the lung and have a pixel size of ≤5. Four lung cancers were depicted as NFE with both slice thicknesses. With 2 mm thick image, NFE of ≤ 3.3 mm in diameter, ≤-820 H.U average CT value, and ≤ 68 contrast were missed. With 10-mm thick image, using the physicians' diagnosis result with 2 mm diagnosed NFE as the gold standard: nodules of ≤4.4 mm in diameter, ≤-730 H.U. average CT value and ≤152 contrast were missed or misinterpreted.



a. 4.52 mm nodule at LUL (diagnosed as NFE with 2 mm)

b. no abnormality (with 10 mm)

Figure 3. Physicians' diagnosis difference with thick and thin section MSCT images

4. Conclusions

Thin sections enhance resolution and decrease volume averaging from slice to slice and should result in more accurate depiction of small nodules [5]. But by thin sections large numbers of axial images lead to reviewers' fatigue during interpretation. This shows two facets of using thin section MSCT image in pulmonary nodule detection. Thick section on the other hand may not be able to detect smaller nodules compared to what the thin section can do but the convenience and lesser burden for interpreting physicians and radiologist should be taken into consideration. It is also important to emphasize that the thick section CT has a limitation of depicting calcification in nodules of smaller diameter than the section thickness [6].The study disclosed the strengths and weaknesses of the two slice thicknesses on physicians' diagnosis of pulmonary nodules. Both can depict lung cancer. Thin section may not be effective for nodules with ≤3 mm in size, ≤-820 H.U., ≤ 68 contrast. Whereas, thick section maybe not be an option for nodules with ≤5 mm in size, ≤-730 H.U., ≤ 152 contrast. Thick section was not good at depicting nodules located at the lung upper lobe and at the lung borders and those which have a pixel size ≤5. This information may serve as a useful reference to determine in which particular situation the two slice thicknesses can be effectively used for pulmonary nodule that may lead to early detection of lung cancer.

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Modern Pathology (2007) 20, 215–220

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Immunohistochemical detection of GLUT-1 can discriminate between reactive mesothelium and malignant mesothelioma

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The separation of benign reactive mesothelium (RM) from malignant mesothelial proliferation can be a major challenge. A number of markers have been proposed, including epithelial membrane antigen, p53 protein, and P-glycoprotein. To date, however, no immunohistochemical marker that allows unequivocal discrimination of RM from malignant pleural mesothelioma (MPM) has been available. A family of glucose transporter isoforms (GLUT), of which GLUT-1 is a member, facilitate the entry of glucose into cells. GLUT-1 is largely undetectable by immunohistochemistry in normal epithelial tissues and benign tumors, but is expressed in a variety of malignancies. Thus, the expression of GLUT-1 appears to be a potential marker of malignant transformation. Recently, in fact, some studies have shown that GLUT-1 expression is useful for distinguishing benign from malignant lesions. The purpose of the present study was to evaluate the diagnostic utility of GLUT-1 expression for diagnostic differentiation between RM and MPM. Immunohistochemical staining for GLUT-1 was performed in 40 cases of RM, 48 cases of MPM, and 58 cases of lung carcinoma. Immunohistochemical GLUT-1 expression was seen in 40 of 40 (100%) MPMs, and in all cases the expression was demonstrated by linear plasma membrane staining, sometimes with cytoplasmic staining in addition. GLUT-1 expression was also observed in 56 out of 58 (96.5%) lung carcinomas. On the other hand, no RM cases were positive for GLUT-1. GLUT-1 is a sensitive and specific immunohistochemical marker enabling differential diagnosis of RM from MPM, whereas it cannot discriminate MPM from lung carcinoma.
Modern Pathology (2007) **20,** 215–220. doi:10.1038/modpathol.3800732; published online 22 December 2006

Keywords: Glut-1; reactive methothelium; malignant pleural mesothelioma; immunohistochemistry; lung carcinoma

The separation of benign reactive mesothelium (RM) from malignant mesothelial proliferation can be a major challenge. The common cytomorphological features associated with malignancy, such as high cellularity/proliferation, marked cytonuclear atypia and high mitotic rate are of very limited use in this setting. Thus, it is sometimes very difficult, or almost impossible even for expert pathologists to make a definite diagnosis of malignant mesothelioma, especially in small specimens, unless there is unequivocal invasion of adjacent tissues by tumor cells.[1] On the other hand, early diagnosis of malignant pleural mesothelioma (MPM) in small closed pleural biopsy samples, or by cytology, is crucial for patient management and may facilitate the avoidance of invasive surgical procedures.

A number of immunohistochemical markers have been proposed to assist conventional morphological diagnosis, including epithelial membrane antigen (EMA)[2–5] p53 protein,[2–11] and P-glycoprotein.[2,5,12] Other markers tested have included Bcl-2,[2,3,13] platelet-derived growth factor receptor (PDGF-R) β-chain[2,5,8] and desmin.[2] To date, however, no single immunohistochemical marker that can unequivocally discriminate RM from MPM has been available.

GLUT-1 is one of 14 members of the mammalian facilitative glucose transporter (GLUT) family of passive carriers that function as an energy-independent system for transport of glucose down a concentration gradient.[14] GLUT-1 is not detectable

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Received 30 August 2006; accepted 23 October 2006; published online 22 December 2006

in a large proportion of cells from normal tissues and benign lesions, except for erythrocytes, germinal cells of the testis, renal tubules, perineurium of peripheral nerves, endothelial cells in blood–brain barrier vessels, and placenta (trophoblasts and capillaries).[15,16] In contrast, GLUT-1 is expressed in a variety of carcinomas such as those of the breast, head and neck, bladder, renal cells, and lung.[15–24] Previous reports suggest that the expression of GLUT-1 may be a potential marker for malignancy.

Recently, some studies have shown that GLUT-1 expression is useful for resolving the common diagnostic dilemma of distinguishing benign from malignant lesions.[25,26] Although a few studies have demonstrated that GLUT-1 is useful for distinguishing RM from metastatic adenocarcinoma in body cavity effusions,[27–29] the study cohorts did not include MPM. Using immunohistochemistry, Godoy *et al*[16] analyzed coexpression of GLUT-1 and other GLUT isoforms (GLUT-2 to -6 and GLUT-9) in a variety of benign and malignant tumors, and demonstrated that two of four MPMs were positive for GLUT-1. However, they did not analyze reactive and normal mesothelium.

The purpose of the present study was to evaluate the diagnostic utility of GLUT-1 detection for differential diagnosis between RM and MPM.

Materials and methods

Case Selection

The materials for the present study were extracted from cases deposited in the pathology files of the National Cancer Center Hospital, Tokyo, between 1971 and 2005. They comprised 40 cases of RM, 48 cases of MPM (epithelioid, 36 cases; biphasic, 11 cases; sarcomatoid, 1 case), and 58 cases of lung carcinoma (squamous cell carcinoma, 28 cases; adenocarcinoma, 30 cases). All diagnoses had been made on the basis of conventional histopathologic features evident in slide preparations stained with hematoxylin and eosin, some special stains, and immunohistochemical techniques available at that time.[30,31] In the present study, immunohistochemistry for D2-40 and calretinin was added for all cases to confirm the identity of mesothelial cells (see below).

Immunohistochemistry

For immunohistochemical staining, 5-μm-thick sections were deparaffinized and treated with 3% hydrogen peroxide for 30 min to block endogenous peroxidase activity, followed by washing in deionized water for 2–3 min. Heat-induced epitope retrieval with Target Retrieval Solution (DAKO, Carpinteria, CA, USA) was performed for GLUT-1 and calretinin. After the slides had been allowed to cool at room temperature for 40 min, they were rinsed with deionized water and then washed in phosphate-buffered saline for 5 min. The slides were then stained by overnight incubation with primary antibodies against GLUT-1 (1:200, polyclonal, Dako), D2-40 (1:200, clone D2-40, Signet Laboratories, Dedham, MA, USA), and calretinin (1:100, polyclonal, Zymed, San Francisco, CA, USA). Immunoreactions were detected by the labeled streptavidin–biotin method, and visualized with 3, 3′-diaminobenzidine, followed by counterstaining with hematoxylin. Appropriate positive and negative controls (red blood cells for GLUT-1) were used for each antibody. The area of GLUT-1 staining was evaluated on a sliding scale of 0 to 3+ to represent the percentage of positive cells among mesothelial cells (indicated by D2-40 and calretinin immunostain) or tumor cells (0 = <1%, 1+ = 1–25%, 2+ = 26–50%, 3+ = >51%). Immunohistochemical staining was scored independently by two observers (YK and KT).

Results

The results of immunohistochemistry are summarized in Table 1. GLUT-1 expression was demonstrated by distinct linear plasma membrane staining, sometimes with cytoplasmic staining in addition

Table 1 Immunoreactivity of GLUT-1

	n	*GLUT-1 positive (%)*	*Staining area*			
			0	*1+*	*2+*	*3+*
Mesothelioma, all subtypes	48	48 (100)	0	15	15	18
Epithelioid	36	36 (100)	0	9	12	15
Biphasic	11	10 (90.9)[a] 7 (63.6)[b]	1[a] 4[b]	6[a] 3[b]	3[a] 2[b]	1[a] 2[b]
Sarcomatoid	1	1 (100)	0	1	0	0
Reactive mesothelium	40	0 (0)	40	0	0	0
Lung carcinoma	58	56 (96.5)	2	12	9	35
Squamous cell carcinoma	28	28 (100)	0	1	3	24
Adenocarcinoma	30	28 (93.3)	2	11	6	11

[a]Epithelioid areas.
[b]Sarcomatoid areas.

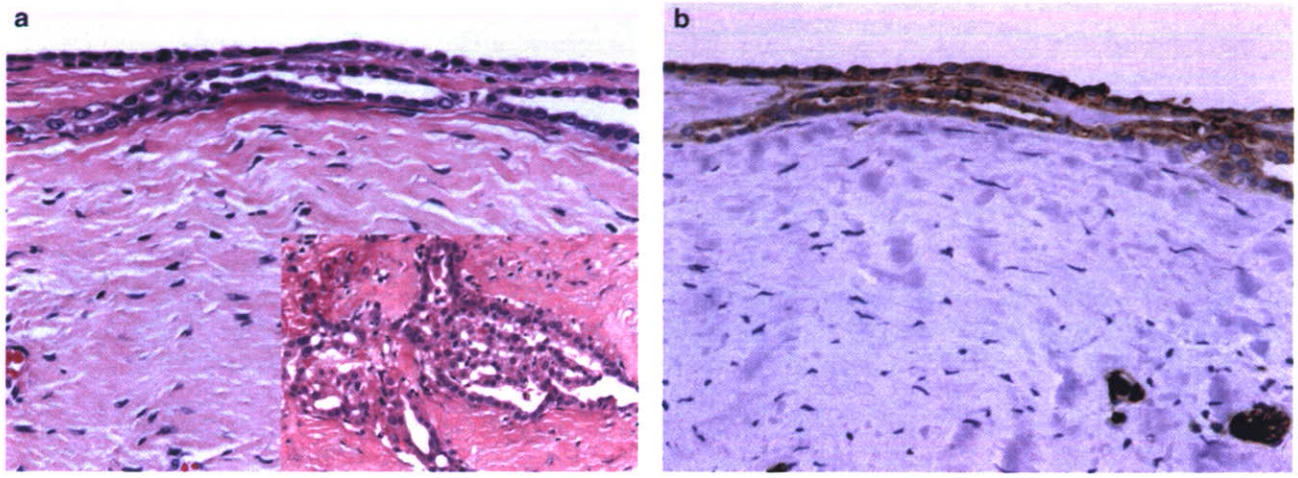

Figure 1 (**a**) In the surface area, the tumor cells showed bland cytologic atypia, nevertheless malignant mesothelioma(HE stain, × 10). Inset: the tumor cells arranged complex branching tubular formation (HE stain, × 10). (**b**) Most of the tumor cells in the epithelioid MPM were positive for GLUT-1 and red blood cells were served as internal positive control (× 10).

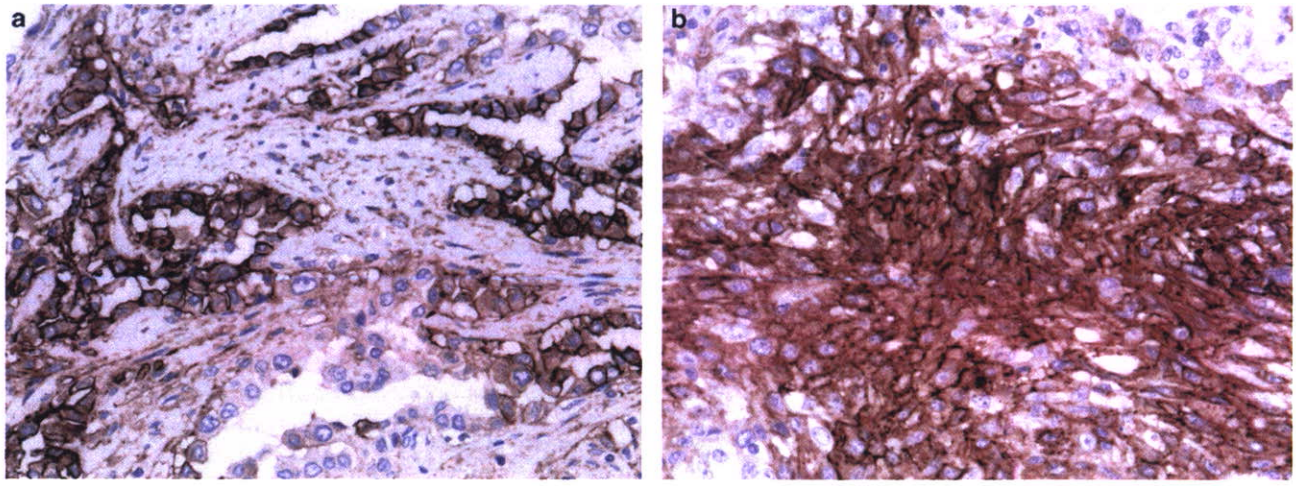

Figure 2 (**a**) More than half of the epithelioid tumor cells were positive for GLUT-1 (× 10). (**b**) Most of the sarcomatoid tumor cells were positive for GLUT-1 (× 10). The immunoreactivity was observed as distinct linear plasma membrane staining, with weak cytoplasmic staining in addition.

Table 2 GLUT-1 immunoreactivity acording to MPM histological subtype

	n	*GLUT-1-positive (%)*	*Staining area*			
			0	*1+*	*2+*	*3+*
Epithelioid area	47	46 (97.8)	1	15	15	16
Sarcomatoid area	12	8 (66.7)	4	4	2	2

(Figure 1a and b). GLUT-1 immunoreactivity was seen in 48 of 48 (100%) MPM cases, whereas no RM cases were positive for GLUT-1.

We also evaluated GLUT-1 immunoreactivity according to histological subtype, as shown in Table 2. Immunoreactivity was observed in 46 of 47 (96.7%) epithelioid mesothelioma (Figure 2a) including epithelioid areas of biphasic mesothelioma, and in seven of 12 (66.7%) sarcomatoid mesothelioma (Figure 2b) including sarcomatoid areas of biphasic mesothelioma. However, immunoreactive cells more than half of tumor cell was only 16 of 47 (34%) of epithelioid mesothelioma including epithelioid areas of biphasic mesothelioma, and two of 12 (14.1%) of sarcomatoid mesothelioma including sarcomatoid areas of biphasic mesothelioma. The GLUT-1-positive cells varied from a few cells to almost all cells in the clusters, but no characteristic staining pattern was observed in MPM.

GLUT-1 immunoreactivity was also seen in 56 of 58 (96.5%) cases of lung carcinoma. According to histological subtype, immunoreactivity was

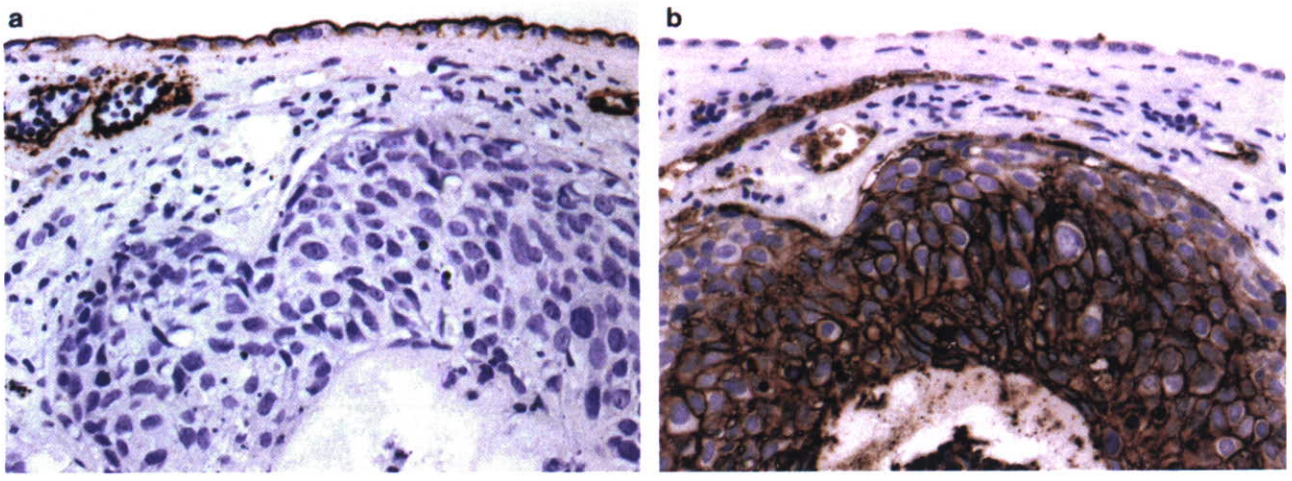

Figure 3 (**a**) D2-40 immunoreactivity was observed in the RM and lymph vessels beneath the pleura, but no immunoreactivity was observed in the poorly differentiated squamous cell carcinoma (× 10). (**b**) Most of the tumor cells without peripheral lesion in of the poorly differentiated squamous cell carcinoma were positive for GLUT-1 (red blood cells were served as internal positive control). On the other hand, RM showed no immunoreactivity for GLUT-1 (× 10).

observed in 28 of 28 (100%) cases of squamous cell carcinoma (Figure 3a and b) and 28 of 30 (93.3%) cases of adenocarcinoma. In squamous cell carcinoma, the area of positive staining was 3+ in 24 of 28 (85.7%) cases, compared with only 11 of 30 (36.7%) in cases of adenocarcinoma. Also in squamous cell carcinoma, a characteristic staining pattern was observed; tumor cells showed more intensely positive staining in the central area of tumor nests than in the peripheral area (Figure 3b).

Discussion

Morphologic differentiation between RM and MPM in small specimens can be a diagnostic challenge. The difficulty is compounded when neoplastic cells demonstrate only slight atypia. In addition, there are currently no reliable markers that allow immunohistochemical discrimination between RM and MPM. In the present study, we clearly demonstrated that GLUT-1 is a sensitive and specific immunohistochemical marker that can differentiate RM from MPM. To our knowledge, this is the first report to describe the usefulness of GLUT-1 immunostaining for discriminating between RM and MPM.

Elevated levels of expression or activation of GLUT-1, or both, have been shown to be associated with transformation of cells and malignancy, and to be modified by changes in the physiological microenvironment in tissues.[32,33] High GLUT-1 expression correlates with increased metabolism and glucose utilization in a number of normal tissues, and this transporter is overexpressed in a variety of human tumors.[15,16] Increased expression of GLUT-1 is also seen in conditions that induce greater dependency on glycolysis as an energy source, such as ischemia, hypoxia, or both.[34] These data suggest that overexpression of GLUT-1 may play an important role in the survival of tumor cells by maintaining an adequate energy supply to support their high metabolism and rapid growth in an often less-than-ideal physiological environment.[35]

GLUT-1 expression has been revealed in a variety of carcinomas, such as those of the breast, head and neck, bladder, and renal cells.[15–19,23] In the lung, about 34.3–100% of lung adenocarcinomas[16,20–22,24] and 100% of lung squamous cell carcinomas[20–22,24] are reported to express GLUT-1 at the primary site. With regard to MPM, only one article has describe that two of four studied cases were positive for GLUT-1.[16] In the present study, GLUT-1 immunoreactivity was observed in all MPMs and 56 out of 58 (96.5%) cases of lung carcinoma. These results indicate that GLUT-1 cannot discriminate between MPM and lung carcinoma. Therefore, additional appropriate positive and negative mesothelial markers are needed in order to differentiate between MPM and lung carcinoma.[31]

The heterogeneity of GLUT-1-positive areas has been reported previously. In squamous cell carcinoma, cells in the center of cancer nests, close to the necrotic area, were stained more strongly than those in peripheral areas. In adenocarcinoma, poorly differentiated areas such as the solid central area were stained more strongly than well differentiated areas such as those showing lepidic growth.[20–22,24] In the present study, more than half of all tumor cells were positive for GLUT-1 in 37.5% of MPMs, 85.7% of lung squamous cell carcinomas, and 36.7% of lung adenocarcinomas. These results indicate that GLUT-1 negativity in small samples such as those obtained by biopsy does not exclude malignancy, and that positive immunoreactivity for GLUT-1 may be an aid to accurate diagnosis of malignancy.

The GLUT-1 positivity rate in RM has been reported to be 0% (present study and Afify *et al*[29]), 3% (Zimmerman *et al*[28]), and 20% (Burstein *et al*[27]).

However, Zimmerman *et al* and Burstein *et al* reported that GLUT-1-positive cells of RM showed equivocal-to-weak staining and were easily distinguishable from unequivocal positivity of other cell types, so that the specificity of GLUT-1 was not diminished. According to them, a number of 'false-positive' cases occurred in patients with cirrhosis. The RM resulting from cirrhosis may be prompted by glucose intake to compensate for the unfavorable environment in effusion. Our cohort of RM consisted of surgically resectable cases within the physiological range or without effusion.

Positron emission tomography (PET) measurements of fluorodeoxyglucose (FDG) accumulation in different animal tumors has shown a correlation between tracer FDG uptake and the GLUT-1 mRNA content. GLUT-1 has been found to be overexpressed in tumor cells and to promote glucose metabolism and FDG accumulation in humans.[22,24] In MPM, Carretta *et al*[36] have reported that FDG-PET can differentiate RM from MPM. These findings are consistent with the present immunohistochemical results.

In summary, GLUT-1 appears to be a sensitive and specific marker for differentiating between RM and MPM, although it is unable to discriminate between MPM and lung carcinoma.

Acknowledgement

This work is supported in part by Special Coordination Funds for Promoting Science and Technology of Japan.

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