43 of the 44 female patients and 153 of the 160 male patients. Gefitinib was given to 7 female and 25 male patients, and erlotinib to 1 female and 1 male patient. Thus, in all, EGFR-TKIs were given to 8 (18.2%) female and 26 (16.3%) male patients.

Table 1. Patient characteristics

Characteristics	Female ($n = 44$)		Male ($n = 160$)		P value
	N	%	N	%	
Age					
Median (range)	57 (29–74)		58 (35–78)		0.28
Smoking history					
Never	24	55	5	3	<0.001
Former	5	11	77	48	
Current	15	34	78	49	
Body weight loss					
≤4.9%	36	82	126	79	0.66
≥5.0%	8	18	34	21	
Performance status					
0	12	27	51	32	0.62
1	32	73	107	67	
2	0		2	1	
Histology					
Adenocarcinoma	32	73	88	55	0.034
Non-adenocarcinoma	12	27	72	45	
Stage					
IIIA	17	39	69	43	0.53
IIIB	27	61	91	57	
Period					
1994–99	17	39	47	29	0.24
2000–05	27	61	113	71	

Table 2. Grade 3–4 toxicity

Toxicity	Grade	Female ($n = 44$)		Male ($n = 160$)		P value
		N	%	N	%	
Leukopenia	3	23	52	79	49	0.44
	4	9	21	33	21	
Neutropenia	3	13	30	49	31	0.19
	4	15	34	51	32	
Thrombocytopenia	3	1	2	5	3	0.97
	4	0		1	1	
Febrile neutropenia	3	9	21	37	23	0.59
	4	1	2	1	1	
Esophagitis	3	2	5	14	9	0.79

Response and Survival

There were 3 patients showing complete response (CR), 38 showing partial response (PR) and 2 showing stable disease (SD) among the 43 female patients evaluable for response, and 10 patients showing CR, 116 showing PR, 24 showing SD and 7 showing progressive disease among the 157 male patients evaluable for response. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$). Disease progression was noted in 36 of the 44 (82%) female patients and 131 of the 160 (82%) male patients. The median PFS did not differ significantly between the sexes: 9.2 months in the females and 9.7 months in the males ($P = 0.67$, Fig. 1). The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$, Fig. 2). Survival analyses in subgroups showed the

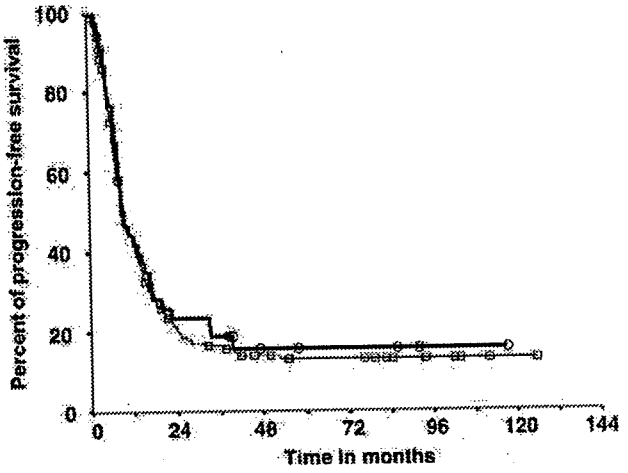

Figure 1. Progression-free survival by sex. Thick line, females; thin line, males.

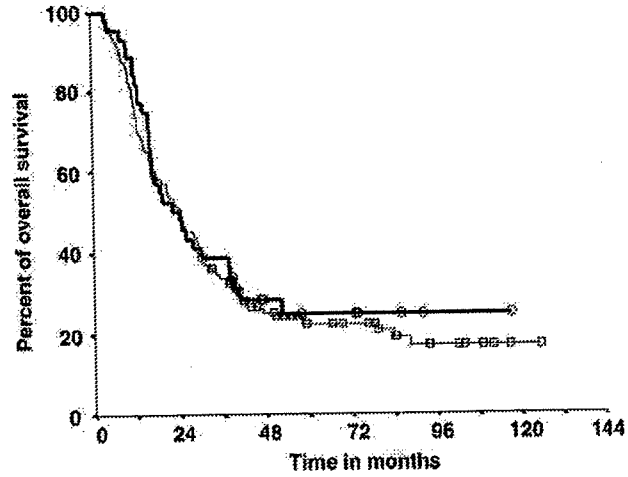

Figure 2. Overall survival by sex. Thick line, females; thin line, males.

Table 3. Factors associated with overall survival

Variables	Hazard ratio (95% confidence interval)	
	Univariate analyses	Multivariate analyses
Age	1.01 (0.99–1.03)	—
Sex		
Female	1	1
Male	1.10 (0.74–1.62)	1.16 (0.71–1.90)
Smoking habit		
No	1	1
Yes	1.00 (0.63–1.59)	0.75 (0.41–1.36)
Body weight loss		
≤4.9%	1	—
≥5.0%	1.19 (0.81–1.75)	—
Performance status		
0	1	1
1–2	1.59 (1.11–2.28)	1.44 (0.97–2.15)
Histology		
Adenocarcinoma	1	1
Non-adenocarcinoma	0.76 (0.53–1.10)	0.74 (0.51–1.08)
Stage		
IIIA	1	1
IIIB	0.96 (0.70–1.32)	0.79 (0.56–1.11)
Period		
1994–99	1	1
2000–05	0.62 (0.45–0.86)	0.65 (0.45–0.92)

absence of any gender differences either among patients with adenocarcinoma or among those with non-adenocarcinoma. Similarly, no gender differences were observed either among smokers or among never-smokers. Univariate Cox's proportional hazard analyses showed that the performance status and treatment period were significantly associated with the survival (Table 3). After adjustment for the smoking history and histological type, the gender had no impact on the overall survival (Table 3).

DISCUSSION

Although prospective cohort studies and a population-based study have reported better survival in women than in men with NSCLC, these results may be biased by potential confounding factors, because these studies included highly heterogeneous patients in terms of the stage, therapy, co-morbidities and other prognostic factors (2–4). Thus, whether there is any significant difference in survival between male and female patients receiving radiation-based treatment remained controversial, and this study failed to show any significant gender difference in the survival in NSCLC patients receiving concurrent chemoradiotherapy.

Several previous studies have suggested a better prognosis in female than in male NSCLC patients treated by surgery (2,14–18), whereas our results were inconsistent with this suggestion. This may be attributable to the difference in the distribution of the disease stage (pathological stages I, II and III) between these studies and our study, including pathological stages I, II and III. The magnitude of the gender difference in survival has been suggested to vary with the disease stage. Some studies have shown a diminishing gender difference as the disease stage advanced from stages I to III, with disappearance of the gender difference among patients with stage III disease (14,15), whereas others have shown relatively constant gender difference through all the disease stages (2,16,17). A study on the gender difference in the survival in surgically resected NSCLC patients showed a better overall survival in women than men, but no significant difference in the cancer-specific survival between the two sexes (18). These results suggest that the gender difference in survival in NSCLC patients undergoing curative surgery, especially patients with early-stage disease, can be explained by the mortality related to diseases other than lung cancer.

Among local or locally advanced NSCLC patients receiving radiotherapy-based treatment, the gender difference in survival has been controversial (5–9), but potential confounding factors in these studies prevent an accurate interpretation of the results. In these studies, as high as 30% of the patients had medically inoperable stage I–II disease and 3–22% of the patients had a performance status of 2. In addition, 36–100% of patients were treated by thoracic radiation alone, whereas the others also received some form of chemotherapy as part of the treatment. Neither the current study nor another previous study showed any gender difference in the survival (10). The patients in both of these studies were limited to stage III NSCLC patients with a performance status of 0–1 who were treated by concurrent chemoradiotherapy.

Several studies have been conducted on the gender differences in survival among patients with stage IIIB–IV disease treated by systemic chemotherapy (19–24). Of these, many showed a better survival in female patients than in male patients (19–22), but the causes of this gender difference in survival remain unknown. Our previous study also showed a better survival in female patients, which was explained partly by the large number of female patients (56% vs. 44%) receiving gefitinib, and the 4-fold longer duration of gefitinib treatment (144 vs. 35 days) in these patients (25). In contrast, only 18% of the female patients and 16% of the male patients received EGFR-TKIs in this study. Thus, treatment with EGFR-TKIs had little influence on the patient survival in this study.

Clear difference in the frequency of adenocarcinoma and smoking history between female and male patients has been reported repeatedly, and this study also showed that adenocarcinoma and never-smokers were more common among the female patients. Thus, it would be reasonable to think that differences in the tumor cell characteristics between the

female and male patients may be responsible for the difference in survival between the two sexes. However, survival analyses conducted separately in subgroups among patients with adenocarcinoma and those with non-adenocarcinoma, or among smokers and non-smokers have failed to reveal any gender differences in the survival among any subgroups. In addition, a multivariate analysis showed no difference in survival between the sexes after adjustment for the tumor histology and smoking history.

The threshold for drug toxicity may also differ between women and men. In general, chemotherapy-related toxicity is reported to be slightly more severe in women, and to the best of our knowledge, there are no reports on the gender difference in radiation-related toxicity. This study showed no difference in the severity of esophagitis or hematological toxicity between the two sexes. We did not examine pulmonary toxicity in this study, because our previous large retrospective study showed no difference in the incidence or grade of pulmonary toxicity between the sexes (26).

Among several limitations of this study, the most important is the small sample size that made it difficult to draw definitive conclusions. Indeed, small difference in survival between the sexes, if any, could not be detected in this small number of patients. It is difficult, however, to expand the study population without an increase in its heterogeneity. A population-based study with >20 000 patients, for example, included patients with all stages of lung cancer, and the therapies administered were not specified. Furthermore, the quality of data on diagnosis and treatment was not uniform (4). Thus, the results of that study may be biased, despite of the huge number of patients. We cannot overlook this problem especially when analyzing stage III NSCLC patients treated with radiation-based treatment, because the quality control of radiotherapy has not been fully developed in Japan, and therefore, indication, methods and outcomes of thoracic radiotherapy may vary among hospitals.

In conclusion, this study failed to reveal any significant differences in the treatment outcomes, including survival and treatment toxicity, between female and male patients with stage III NSCLC receiving concurrent chemoradiotherapy. These results are in sharp contrast to the reported better survival in female patients with localized disease treated by surgery or those with metastatic disease treated by systemic chemotherapy.

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Conflict of interest statement

None declared.

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CASE REPORT

CTガイド下気管支鏡検査で確定診断が得られた類上皮血管内皮腫の1例

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田辺裕子[4]；永易希一[5]；高橋和久[1]

要約 —— **背景**．Computed tomography(CT)ガイド下気管支鏡検査で診断確定に至った類上皮血管内皮腫の症例を報告する．**症例**．67歳女性．検診で左肺に結節影を指摘され，胸部CTで両肺野に多発する小結節影を認めた．CTガイド下経気管支肺生検を施行し，病理ではHE染色で類円形細胞を中心とした腫瘍細胞が索状の上皮様結合を示して増殖し，免疫染色でvimentinとCD34が陽性，cytokeratin AE1/AE3は陰性であり類上皮血管内皮腫（epithelioid hemangioendothelioma：EH）と診断した．定期的にCT検査を行い徐々に増大傾向を認めるが自覚症状はなく，経過観察をしている．**結論**．確定診断のために，過去のEH症例の多くは開胸術もしくは胸腔鏡下肺生検を行っている．今回，我々はhigh-resolution CT（HRCT）での責任気管支の同定を行いCTガイド下に気管支鏡肺生検を施行した．上記の検査方法は患者への侵襲を少なくし診断率を上げるために有効であると考える．

（気管支学．2010;32:67-71）

索引用語 —— 類上皮血管内皮腫，気管支鏡，CTガイド下経気管支肺生検

はじめに

類上皮血管内皮腫（epithelioid hemangioendothelioma：EH）の報告は本邦で約50例と稀な疾患である．診断方法としては開胸生検，肺切除あるいは剖検が多く，気管支鏡検査で診断に至った症例は検索した範囲では3件のみであった．今回，computed tomography（CT）ガイド下経気管支肺生検で診断確定に至った症例を経験したので若干の文献的考察を加え報告する．

症　例

症例：67歳，女性．

主訴：特記すべきことなし．

既往症：66歳から高血圧．手術歴なし．

喫煙歴：なし．

現病歴：2005年秋の胸部X線による検診で左肺に小結節を指摘され，胸部CTで両肺野に多発小結節影を認め，他臓器がんの転移を疑い精査をしたが原発巣を認めず，2カ月後に当院へ紹介となった．当院での初回の経気管支生検で陰性のため経過観察としたが，増大傾向を認めたため，7カ月後にCTガイド下に経気管支生検を再検した．

検査結果と経過：末梢血，生化学，血清学検査，腫瘍マーカーに異常なく，身体所見も異常は認めなかった．

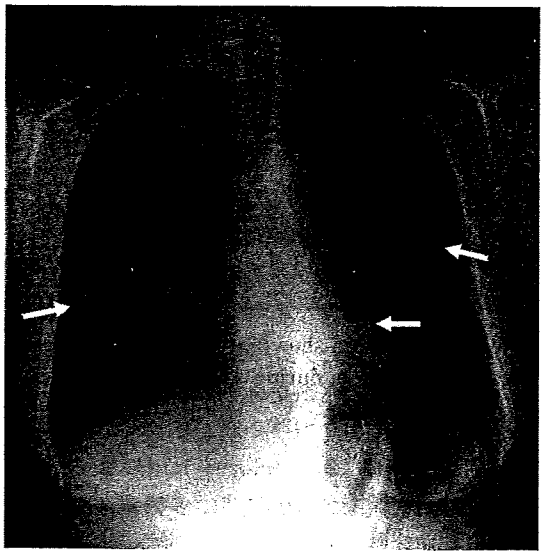

Figure 1. Chest X-ray on admission showing multiple nodules in bilateral lung fields.

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受付日：2008年12月12日，採択日：2009年9月1日．

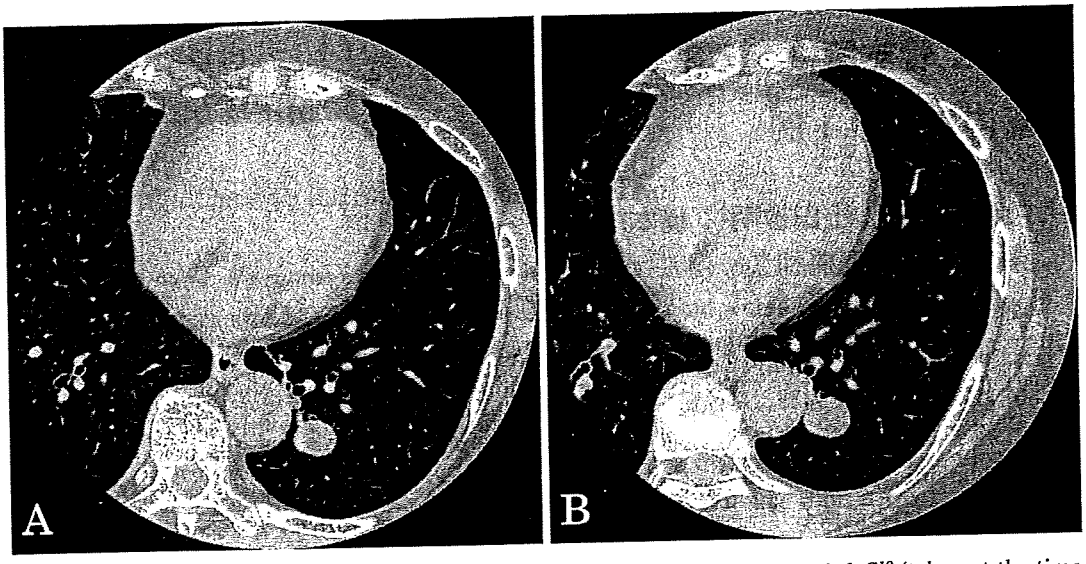

Figure 2. Chest CT findings. **A.** HRCT showing a well-defined nodule in the left S^{10} (taken at the time of the first hospital visit). **B.** HRCT showing a well-defined and slightly enlarged nodule in the left S^{10} (taken 3 months after the first hospital visit).

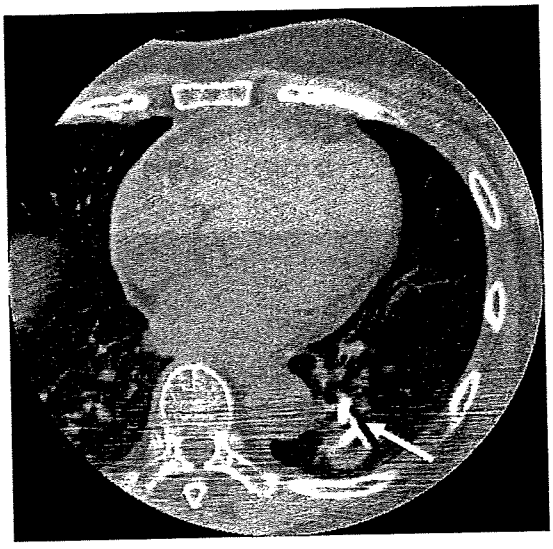

Figure 3. CT scan showing the forceps advanced towards the lesion during CT-guided transbronchial lung biopsy.

胸部X線単純撮影で両側肺野に多発結節影を認めた(Figure 1)．初診時のCTでは左S^{10}に17×15 mmの充実性結節と両肺野に約5 mm大の結節影を17個散在性に認め（Figure 2A)，3カ月後のCTで主病巣は19×16 mmと増大していた（Figure 2B)．

PET検査では主病巣にわずかな集積を認めたが，他の結節および臓器には異常集積を認めなかった．

2回目の気管支鏡検査では左$B^{10}{}_a$から鉗子を挿入して結節影に到達していることをCTにて確認し，生検を行った（Figure 3)．

病理組織学的所見ではHE染色で，類円形細胞を中心とした腫瘍細胞が索状の上皮様結合を示す胞巣の所見を認め，免疫染色ではvimentinとCD34が陽性となり，cytokeratin AE1/AE3は陰性であった（Figure 4A, 4B, 4C)．これらの病理所見と形態や臨床像からEHと診断した．

現在外来で経過観察しており，2008年4月のCTで主病巣が27×27 mmに，他の結節影も10 mm前後に増大している．

考　察

EHは1982年にWeissとEnzingerが低悪性度の血管性腫瘍の総称として提唱した[1]．DailとLiebowが1975年に報告した[2] intravascular bronchioloalveolar tumorと同一の範疇に含まれる疾患で，血管内皮細胞由来の腫瘍と考えられ，多臓器からの発生の報告がある[3-7]．

EHの診断は開胸生検や剖検による検体から確定されることが多い[8]．一般的な病理組織像は細胞質に空胞が見られ核は類円形で時に不整のものもあり，小さな核小体をもつ類円形，短紡錘形，あるいは多角形と多彩な形態の細胞を，豊富な間質の中に散在性に認める．一般に細胞密度は低いが，結節の辺縁部や血管・気管支腔内などでは細胞密度が高く，細胞も大きい．免疫組織学的にはvimentinと血管内皮細胞のマーカー（第VIII因子関連抗原，CD31，CD34，thrombomodulinなど)が陽性で上皮性マーカー陰性が特徴的な所見である．

今回の症例では細胞質の空胞は認めず，細胞密度が高

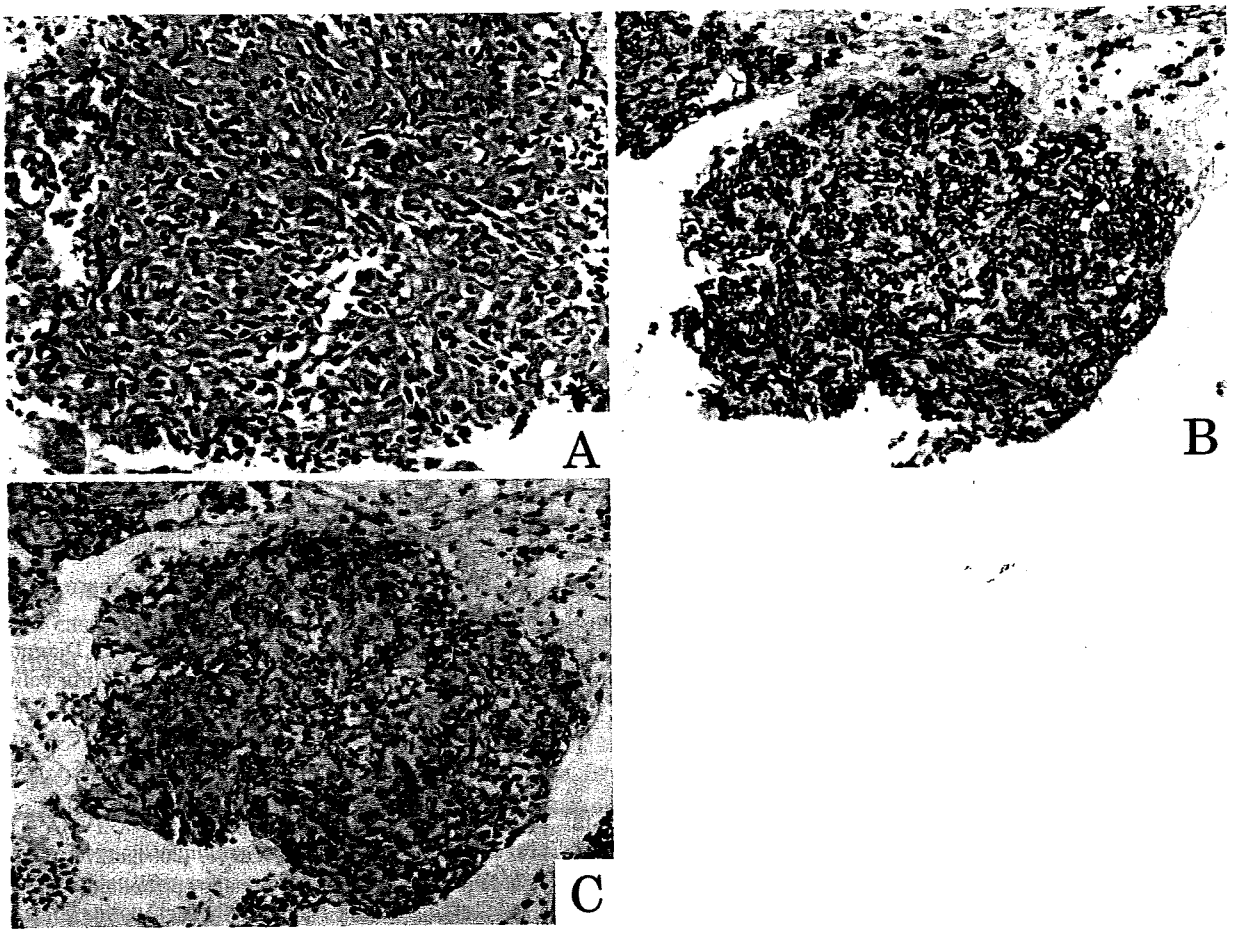

Figure 4. **A.** Histological sections showing cells with round or oval shaped nuclei forming trabecular epithelial networks (HE staining). **B.** Immunohistochemically stained sections demonstrating that the cells are positive for vimentin (vimentin staining). **C.** Immunohistochemically stained sections demonstrating that the cells are positive for CD34 (CD34 staining).

いのは気管支鏡にて腫瘍の辺縁部を採取したためと考えられ，HE 染色における所見と免疫染色の結果から EH と診断した．

画像が発見動機となることが多く，大多数の症例は肺野の多発結節影であり，病変の大きさは比較的そろっていることが多く，多中心性発生の可能性を示唆されている．本症例は 1 個だけが大きく，他は小さいために肺原発での肺内転移も考えられる．

確定診断の方法として開胸生検は最も確実ではあるが侵襲が大きく[9]，経皮針生検では診断率は高いが合併症の頻度も高い[10]．経気管支生検は診断率が低い[11]．本例では病変が多発していたため手術的な治療は不可能なこと，良性の可能性もあるので合併症の可能性がある経皮針生検は好ましくないと考え，経気管支鏡的生検を選択した．

気管支鏡検査の問題点として確実に病巣を捉えているかを確認する必要がある．

X 線透視下の気管支鏡検査の場合，病変が 20 mm 以下の場合は検出率が下がる[11]ため CT 下での検査が適応となる場合がある．CT ガイド下気管支鏡は，病巣へ鉗子が到達しているかをその都度 CT で確認しながら検査が行えるため検出率の向上が期待できる．ただし通常の透視下気管支鏡より検査時間が長く，CT を撮影しながら生検器具を病変部位に誘導する技術は熟練が必要であり，すべての検査が適応となるわけではない[12]．

責任気管支が high-resolution CT（HRCT）で確認できる場合には，小型の陰影でも気管支鏡で診断がつく可能性が高い．今回の検査でも HRCT の読影で責任気管支の同定を充分に行い，CT で鉗子が病変に到達していることを確認した．

EH は低悪性度の腫瘍とされているが予後が判明している症例での平均生存期間は肺原発においては 32 カ月と報告されている[13]．しかし，緩慢な経過の症例が多く予後について未報告例もあり，実際の予後は不明である．

治療法としては単発性の場合には手術が第一選択とさ

れている[14]．切除不能例の場合の治療として化学療法が有効であったとの報告[15]もあるが，症例数が少なくレジメンは確立していない．

今回我々は診断方法としてCTガイド下気管支鏡検査で診断に至った症例を経験した．HRCTでの責任気管支の読影とCTにより病変へ鉗子が到達したことを確認できることが診断率を上げるために有効であったと考える．

本症例は臨床的に典型的でない部分もあり今後の注意深い経過観察が重要で，EHの発生および進展形式についても何らかの示唆が得られる可能性があるかと思われる．

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A Case of Epithelioid Hemangioendothelioma Diagnosed by Computed Tomography-guided Bronchoscopy

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ABSTRACT —— ***Background.*** We report a case of epithelioid hemangioendothelioma (EH) diagnosed by computed tomography (CT)-guided bronchoscopy. ***Case.*** A 67-year-old woman had a medical examination, and a nodular shadow was pointed out in the left lung field on chest X-ray. Chest CT showed multiple small nodular shadows in both lungs. She underwent a CT-guided transbronchial lung biopsy at our hospital. Epithelioid tumor cells with round or oval shaped nuclei were found to form trabecular epithelial networks. Immunohistochemical staining demonstrated that these cells were positive for vimentin and CD34 and negative for cytokeratin AE1/AE3. We diagnosed EH based on the pathological findings and her clinical course. She has been followed up for 2 years without specific medication, and currently has a slightly enlarged nodule, but is asymptomatic. ***Conclusion.*** Almost all reported cases of EH in the literature have been diagnosed using open-lung or thoracoscopic biopsy specimens. We identified the bronchus with high-resolution CT (HRCT) and performed a CT-guided transbronchial lung biopsy. CT-guided bronchoscopy is therefore a minimally invasive and feasible examination technique for the diagnosis of EH.

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KEY WORDS —— Epithelioid hemangioendothelioma, Bronchoscopy, CT-guided transbronchial lung biopsy

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