ORIGINAL

Follow-up using fluorescence bronchoscopy for the patients with photodynamic therapy treated early lung cancer

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Abstract : Purpose : To evaluate the accuracy of fluorescence bronchoscopy by precise histological analysis of the photodynamic therapy (PDT) treated lesions. Methods : A retrospective study was conducted on thirteen patients (16 lesions) with centrally located early lung cancer (CLELC) had been undergone photodynamic therapy and had been followed up by fluorescence bronchoscopy. Fluorescence bronchoscopy was performed between 1 and 60 months after photodynamic therapy. Results : Of the 16 early carcinomas treated, 14 (87.5%) had a CR, 2 (12.5%) had a NR after initial PDT. Among the 14 carcinomas achieving a CR, 4 (29%) recurred locally from 6 to 12 months after initial PDT. A total of 62 surveillance auto fluorescence bronchoscopies (average ; 4.5/patient) and 47 biopsies (average ; 4/patient) were performed after PDT. The addition of the SAFE-3000 examination to conventional bronchoscopy increased the sensitivity of screening from 69% to 100%, which yielded a relative sensitivity of 145% with a negative predictive value of 100%. Out of 14 CR lesions, 9 lesions finally reverted to normal fluorescence. CR cases that did not show normal fluorescence were relapsed cases or a patient with complete response whose treated lesion showed fibrosis in the sub mucosa. Histopathological finding of the complete response sites which demonstrated temporal fluorescent defect consisted of inflammatory lesions, goblet cell hyperplasia, basal cell hyperplasia, squamous metaplasia or dysplasia. Conclusion : our results confirm that SAFE-3000 allows accurate assessment of the quality and efficacy of PDT. J. Med. Invest. 58 : 46-55, February, 2011

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INTRODUCTION

Lung cancer is a global epidemic and number one killer among all cancers. Morbidity is high and cure rate is only 13%. Many lung cancer patients

are diagnosed in a relatively advanced stage, precluding radical resection (1). The increase in the number of lung cancer deaths is mainly because it is detected at a late stage. However, central type early stage lung cancer has shown a good response to endoscopic treatment (2-4).

To improve the detection rate of early bronchial lesions, fluorescence diagnosis has been investigated and used clinically in several facilities (5-7). The principle of this diagnostic procedure is that normal bronchial tissue emits green auto fluorescence (500-600 nm) excited by blue light, while tumor or dysplasia lack green auto fluorescence because of differences in tissue architecture and auto fluorescence fluorophores (8-10). Although the value of fluorescence bronchoscopy in detecting early lung cancer/pre-invasive lesions has been evaluated in different clinical and research settings, its role in the routine follow-up of PDT treated early lung cancer has not been extensively evaluated.

The aim of this study was to objectively evaluate the efficacy of autfluorescence bronchoscopy (SAFE-3000) surveillance in PDT-treated early central lung cancer patients. Longitudinal follow-up of these patients will be necessary to determine the impact of fluorescence bronchoscopic surveillance in the identification of intraepithelial or invasive lesions. The present study reviewed the use of auto fluorescence bronchoscopy (SAFE-3000) during follow-up of PDT-treated early lung cancer.

SUBJECTS AND METHODS

Patient selection

A retrospective study was conducted between December 1999 and August 2010, on 13 patients with 16 centrally located early lung cancer (CLELC) lesions, have been treated by PDT and also been followed-up after the PDT by the auto fluorescence bronchoscopy (SAFE-3000). The patients had standard work up for lung cancer. Pretreatment examination included chest X-ray, bronchoscopy, auto fluorescence bronchoscopy (SAFE-3000 or AFI) Chest and abdominal computed tomography (CT), brain magnetic resonance imaging (MRI) and/or 2-deoxy-2-[F-18] fluoro-D-glucose-*positron emission tomography* (*FDG*-PET)/CT. Assessment bronchoscopy had been performed in all to evaluate the extent, topography and the number of lesions within the bronchial tree. All patients were staged according to the lung cancer staging system of International Union Against Cancer (UICC) (11).

Patients were considered candidates for PDT under the following conditions : 1) histologically proven squamous cell carcinoma 2) endoscopically visible distal tumor margins and accessibility to laser irradiation. 3) tumor size $\leq$ 2 cm. 4) no metastasis in hilar or mediastinal lymph nodes and no distant metastasis (stage 0 : TisNOM0 or stage I : T1NOM0) using chest and abdominal CT, brain MRI and/or PET/CT. 5) normal chest X-ray and CT imaging cannot detect primary tumor and 6) informed consent to undergo PDT was obtained.

Auto fluorescence Bronchoscope (SAFE-3000)

The newly developed video endoscopy-based auto fluorescence (AF) bronchoscope system is referred to as SAFE-3000 (12). In this system, normal bronchial tissue emits intense green auto fluorescence when excited by blue light from a diode laser (408 nm), whereas abnormal tissue lacks the green auto fluorescence due to the differences in the tissue structure, metabolic state, and blood flow. SAFE-3000 consists of a color CCD video endoscopy-based auto fluorescence system with two light sources, namely, a xenon lamp for white light (WL) and a diode laser (408 nm) as an AF mode excitation light source. Both white light (WL) mode and AF mode appear at the same time on the screen. WL findings were classified into two categories, normal and abnormal in our protocol. "Normal finding" means no visual abnormality. "Abnormal WL finding" suggests irregularity of the bronchial mucosa such as redness, hypervascularity, swelling, thickening, as well as nodular or polypoid lesions. Also, AF findings were classified into two categories, "normal sites" show green color images and "abnormal sites" lack this green fluorescence and show dark images.

PDT and follow-up

PDT procedures were performed using porfimer sodium (Wyeth Japan KK ; Tokyo, Japan) or talaporfin sodium (Meiji Seika, Japan) and an Excimer Dye Laser (Hamamatsu Photonics Co., Japan) or a diode laser system (Matsushita Electric Industrial Co., Japan) emitting continuous-wave laser light. For patients till June 2004, porfimer sodium (2 mg/kg) was given, 48 h before light irradiation. For patients after July 2004, talaporfin sodium (40 mg/m^2) was given 4 to 6 h before light irradiation. Laser irradiation (664 nm) for the PDT was performed via a quartz fiber inserted through the biopsy channel

of the endoscope. The total energy of the laser irradiation was 100 J/cm^2, 150 mW/cm^2, and the duration of irradiation was usually 10 to 20 min.

Before the PDT, we performed SAFE-3000 with a diode laser (408 nm) to define the base line fluorescence intensity emitted from the tumor. After the PDT, we performed SAFE-3000 to determine the change in the intensity of fluorescence emitted from the tumor as compared with that observed before the PDT. Cytological and histological examinations via fiber optic bronchoscope were performed at 1, 2 and 3 months and thereafter at 3-month intervals in the first year and 6-month intervals after the second years after PDT. The antitumor effect of the initial treatment was evaluated on the basis of the change in the intensity of the fluorescence emitted from the tumor after PDT compared with that observed before the PDT, morphologic appearance, and the findings on histopathologic examination of biopsy specimens. The tumors were then classified as showing complete response (CR) (no microscopically demonstrable tumor in brushing and/or biopsy specimens over period of 4 weeks) ; partial response (PR), showing a more than 50% shrinkage of the lesion at endoscopy, but persistent cancer at biopsy ; or no response (NR), that is a less than 50% reduction in tumor size, or stable or progressive disease. A second photodynamic treatment was performed in cases of PR or NR. If a less than complete response was obtained after a second treatment, the patient was referred for surgical resection.

Pathological diagnosis

Biopsy specimens were taken from all suspicious and abnormal lesions detected by AF bronchoscopy and WL bronchoscopy and fixed in formalin and embedded in paraffin. The pathological diagnoses were coded according to the World Health Organization lung cancer classification (13). In the present study, lesions in the bronchi were divided into the following three categories according to histopathological diagnosis ; 1) No malignancy : normal mucosa, fibrosis of sub mucosa, goblet cell hyperplasia, basal cell hyperplasia, 2) Premalignancy : Squamous metaplasia and dysplasia, 3) Malignancy : Carcinoma in situ and invasive cancer.

Statistical analysis

Data are presented as mean± standard deviation (SD). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of WL mode and AF mode of SAFE-3000 in detecting premalignant and malignant lesions (based on biopsy) were calculated. The relative sensitivity : the ratio of the sensitivity of AF to WL was compared. The Z-test was used to compare the diagnostic sensitivity and specificity. A P value< 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

At the Tokushima University Hospital between December 1999 and August 2010, 13 patients with 16 centrally located early lung cancers received PDT. All patients were men (mean age, 70.2± 5.34, and range 57-76) and smokers or ex-smokers (mean Brinkman index (1507.5± 953.95). The tumors were detected on endoscopic screening of asymptomatic high-risk patients or from symptomatic patients' complaints of haemoptysis or chronic cough. Of these, 9 patients had previously undergone resection surgery for invasive lung cancer ; most bronchoscopies were performed during postoperative follow-up. All cases were squamous cell carcinoma.

The Japanese Lung Cancer Society classifies CLELCs on the basis of the endoscopic findings into a thickened type, polypoid type, and nodular type (14-17). The thickened type is characterized by superficial lesions manifested by subtle mucosal changes on the bronchial surface, and it is the predominant type (14-17). Of the 16 lesions examined in this study, 11 of them were the thickened type, 4 lesions were nodular type and 1 was the polypoid type. Size of the tumors is ranged from 3-12 mm. The locations of the tumors are described in Table 1.

PDT results

Of the 16 early carcinomas treated, 14 (87.5%) had a CR, 2 (12.5%) had a NR after initial PDT. Among the 14 carcinomas achieving a CR, 4 (29%) recurred locally from 6 to 12 months after initial PDT (Table. 2). The CR period until the last follow up examination was between 3 to 60 months after photodynamic therapy. A complete response that lasted longer than 12 months after only one session of PDT was observed in 7 of the 14 cancers (50%). No severe early or late PDT-related sequelae were noted. PDT was well tolerated by all patients.

Table. 1. Tumors Characteristics.

Case	Location	Size (mm)	Shape	Histology*	Stage	Past History
1	Rt. B^3	5	Swelling	SCC	Early	Rt. lung cancer, Lobectomy
2	Lt. upper division br. Lt. B^{1+2}	10	Nodular	SCC	Early	Rt. lung cancer, Chemoradiation
	Rt.B^6	5	Redness			
3	Rt. B^6	8	Swelling	SCC	Early	Rt. lung cancer, Lobectomy
4	Rt. $B^{1,}$ B^2 spur	12	Redness	SCC	Early	Rt. lung cancer, Lobectomy
5	Rt. main br.	8	Swelling	SCC	Early	Left lung cancer, lobectomy,
6	Rt. B^9	7	Ulcer	SCC	Early	Bronchial cancer, Radiation
7	Lt. upper division br. Lt. B^3	5	Nodular	SCC	Early	Pulmonary emphysema
8	Lt. upper division br.	7	Swelling	SCC	Early	Rt. lung cancer, Lobectomy
9	Middle, Basal br. spur	10	Swelling	SCC	Early	None
10	Trachea	5	Nodular	SCC	Early	Rt. lung cancer, Lobectomy
	Carina	5	Nodular	SCC	Early	
11	Rt. B^{10} a	3	Ulcer	SCC	Early	Tuberculosis, Wedge resection
12	Rt. B^6	8	Swelling	SCC	Early	Rt. lung cancer, Lobectomy
13	Rt.B^2	6	Polypoid	SCC	Early	Rt. lung cancer, Lobectomy
	Rt.B^6	3	Swelling			

*SCC : Squamous cell carcinoma

Table 2. Photodynamic therapy for early central lung cancer.

Patients	Photosensitizer	Fluence dose	Number of lesions	PDT sessions	Complications	Response§	Recuurence	Follow-up months
1	Porfimer sodium	235	1	1	No	CR	-	40
2	Porfimer sodium	450	2	2	No	CR	-	27
	Talaporfin sodium	140				CR	Recurrence	6
3	Porfimer sodium	300	1	1	No	CR	-	28
4*	Porfimer sodium	250	1	2	No	CR	Recurrence	8
	Talaporfin sodium	400				CR	-	40
5	Porfimer sodium	400	1	1	No	CR	-	33
6	Talaporfin sodium	100	1	1	No	CR	-	15
7*	Porfimer sodium	400	1	2	No	CR	Recurrence	12
	Talaporfin sodium	70				CR	Recurrence	8
8	Talaporfin sodium	150	1	1	No	CR	-	60
9	Talaporfin sodium	175	1	1	No	CR	-	15
10	Talaporfin sodium	100	2	2	No	NR	-	3
	Talaporfin sodium	100				NR	-	3
11	Talaporfin sodium	100	1	1	No	CR	Recurrence	12
12	Talaporfin sodium	100	1	1	No	CR	-	6
13	Talaporfin sodium	200	2	2	No	CR	-	3
	Talaporfin sodium	350				CR	-	3

§CR : Complete response ; NR : No response.
*Case number 4 and 7 had one lesion which recieved two sessions of PDT.For case 4, CR occured after the first and the second PDT then recurrence occured only after the first CR. For case number 7, CR occured after the first and the second PDT then recurrence occured after the first and the second CR.

SAFE-3000 and histopathology findings after PDT

Over the period from December 1999 to August 2010, a total of 62 SAFE-3000 system bronchoscopies (average ; 4.5/patient) were performed on 13 patients who had undergone PDT for early central lung cancer as part of the post-PDT fluorescence bronchoscopy surveillance at the University of Tokushima. The follow-up time ranged from 1 to 60 months (median, 30 months) (Fig. 1). A total of

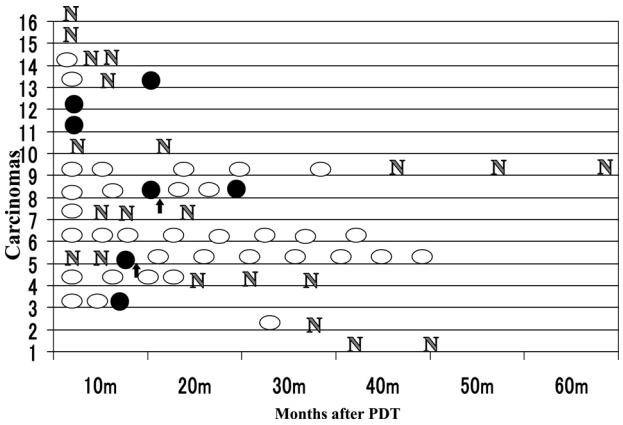

Figure 1. N : Fluorescence bronchoscopy showed no abnormal findings. ○ : Fluorescence bronchoscopy showed fluorescence defect in the treated lesion without histological evidence of malignancy. • : Fluorescence bronchoscopy showed fluorescence defect in the treated lesion with histological evidence of malignancy. Arrows mean second PDT. Longitudinal axis : number of samples, Horizontal axis : passage of time

47 biopsies were carried out (average ; 4/patient). The pathological diagnoses of these specimens were as follow : normal epithelium in 12 (25.5%) ; inflammation in 2 (4.25%) ; basal cell hyperplasia in 8 (17%) ; goblet cell hyperplasia in 4 (8.5%) ; fibrosis in 8 (17%) ; squamous dysplasia in 2 (4.25%) ; squamous metaplasia in 4 (8.5%) and cancer in 7 (15%) (Table. 3) (Fig. 2). Thus, 13 biopsy specimens (27.5%) were premalignant and malignant lesions. WL alone correctly identified 9 of 13 (69%) premalignant (squamous metaplasia, squamous dysplasia) and malignant (carcinoma *in situ* and invasive cancer) lesions compared with 13 of 13 (100%) premalignant and malignant lesions correctly identified by AF mode. The biopsy based sensitivity, specificity, PPV and NPV of WL and AF mode in post-PDT patients for both preinvasive and invasive

Table. 3. Relationships between the bronchoscopic findings and the pathological diagnoses of the biopsy specimens.

Histopathology(47)	WLB		SAFE-3000	
	Abnormal	Normal	Abnormal	Normal
Normal(12)	3	9	0	12
Inflammation(2)	1	1	2	0
Basal cell hyperplasia(8)	2	6	7	1
Goblet cell hyperplasia(4)	1	3	3	1
Fibrosis(8)	2	6	8	0
Squamous metaplasia(4)	3	1	4	0
Squamous dysplasia(2)	2	0	2	0
Carcinoma(7)	4	3	7	0

Fig. 2A

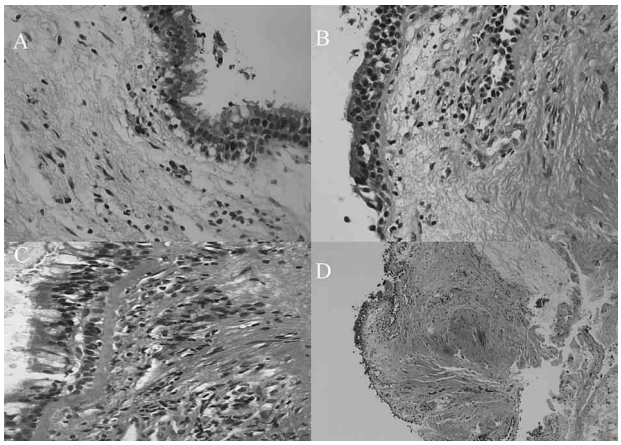

Fig. 2B

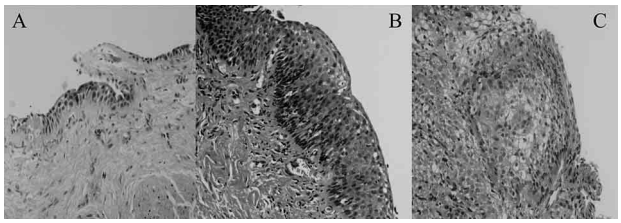

Figure 2. Histopathology findings after PDT.
Fig.2 A : (A) Normal brobchial epithelium. (B) Basal cell hyperplasia. (C) Goblet cell hyperplasia. (D) Fibrosis.
Fig.2B : (A) Squamous metaplasia. (B) Squamous dysplasia. (C) Carcinoma.

lesions are shown in Table. 4. The biopsy based sensitivity of AF bronchoscopy to detect premalignant and malignant lesions (100%) was significantly higher than WL bronchoscopy alone (69%) (P= 0.0148). However, specificity value was superior in WLB (P=< 0.0001). There was no statistically significant difference in either PPV (P=0.2) or NPV (P=0.07). However, NPV was superior in AF bronchoscopy (100% vs. 86%). The sensitivity of SAFE-3000 bronchoscopy for premalignant and malignant (intraepithelial and invasive) lesions in post-PDT patients far exceeded that of WLB, with a relative sensitivity of SAFE-3000 vs. WLB of 145%. The addition of the fluorescence examination to conventional WLB increased the sensitivity of post-PDT surveillance from 69% to 100%.

Tabel. 4. The sensitivity, specificity, PPV and NPV of WL and AF mode in SAFE-3000.

	Sensitivity	Specificity	PPV#	NPV¶
WL	69%	73.5%	50%	86%
AF	100%	41%	39%	100%
†*P* value	0.0148	< 0.0001	0.232	0.072

† Z-test to compare between 2 proportions.
#PPV : Positive predictive value.
¶NPV : Negative predictive value.

In 9 out of 14 lesions who presented complete response after photodynamic therapy, the treated lesions finally recovered normal fluorescence, though they temporary showed abnormal fluorescence in some cases. CR cases that did not show normal fluorescence were relapsed cases or a patient with complete response whose treated lesion showed fibrosis in the sub mucosa after two session photodynamic therapy. Histopathological finding of the complete response sites which demonstrated temporal fluorescent defect consisted of inflammatory lesions, goblet cell hyperplasia, basal cell hyperplasia, squamous metaplasia or dysplasia (Table. 5).

Case presentation

Case 9 : 57 years old man. Flat elevated lesion was noted in the membranous portion between the right middle and lower lobes during bronchoscopy. Fluorescence defect was observed during SAFE-3000 of the same lesion (Fig. 3A, B). The result of the biopsy was squamous cell carcinoma. PDT was performed using Talaporfin sodium and laser (175 J). Neoplastic lesion in bronchoscopy disappeared one month after treatment ; fluorescence by SAFE-3000 was approved in the treated area (Fig. 3C, D). SAFE-3000 follow up showed normal fluorescence

Table. 5. Realtionship between PDT dose and Post-PDT histopathology.

		Biopsy								
Case	PDT Dose	1 month	3 month	6 month	9 month	12 month	18 month	24 month	30 month	36 month
1	235		normal							
2	450						GH		normal	
	140		GH	Cancer						
3	300	Inflammation		GH		normal			normal	
4	250	BH	normal		cancer					
	400	BH	BH	GH	Fibrosis	fibrosis		Fibrosis	Fibrosis	fibrosis
5	400	Inflammation	BH	BH	BH	fibrosis	Fibrosis		Fibrosis	
6	100	sq.metaplasia	normal							
7	400	sq.metaplasia		sq.metaplasai	sq. dysplasia	cancer				
	70		BH	BH	cancer					
8	150		sq.metaplasia	sq.dysplasia			normal			
9	175		normal							
10	100		cancer							
	100		cancer							
11	100		normal			cancer				
12	100		normal							
13	200		normal							
	350		normal							

GH : Goblet cell hyperplasia ; BH : Basal cell hyperplasia ; sq.metaplasia : Squamous metaplasia ; sq,dysplasia : Squamous dysplasia.

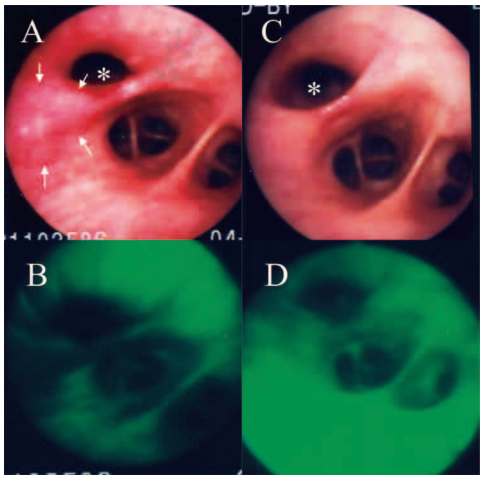

Figure 3. Bronchoscopic findings of the case 9. A : White light bronchoscopic finding of pre-PDT showed flatly elevated lesion in the membranous portion between the middle lobe bronchus and the right basal bronchus. B : Fluorescence bronchoscopic finding of A showed fluorescence defect at the same lesion. C : White light bronchoscopic finding at one month after PDT showed no tumorous lesion. D : Fluorescence bronchoscopic finding of C showed no fluorescence defect. *Middle lobe bronchus. Arrows show the border of the tumor.

after PDT (Fig. 1 ; lesion 10).

Case 3 : 73 years old man. The chest radiograph abnormality was noted when the patient referred from another hospital complaining of cough. CT scan showed a tumor in the right upper lobe, right upper lobe resection was done with intraoperative diagnosis of squamous cell carcinoma (pT2N0M0). In addition, upon receiving postoperative follow up bronchoscopy flat elevated lesion was pointed out to the entrance of the right central portion B^6. Fluorescence defect was observed during SAFE-3000 of the same lesion (Fig. 4A, B). The result of the biopsy was squamous cell carcinoma. PDT was performed using porfimer sodium and excimer laser (300 J). Neoplastic lesions in the white light bronchoscopy 5 months after treatment had disappeared, SAFE-3000 showed fluorescence defect around B^6 (Fig. 4C, D). The biopsy from fluorescence loss site showed basement membrane thickening. 14 months after treatment, SAFE-3000 showed fluorescence in the treated area (Fig. 4E, F). During SAFE-3000 follow-up, fluorescence loss was observed after PDT, followed by normal fluorescence (Fig. 1 ; lesion 4).

Case 4 : 74 years old man. Abnormal right lung shadow was found during preoperative evaluation for orthopedic lumbar compression fracture surgery. Detailed examination showed a large tumor about 5 cm in the right middle lobe. Another lesion was found during bronchoscopy in the right upper lobe bronchus ($rtB^{1,2}$ spur). Biopsy result was squamous cell carcinoma. Middle lobectomy and lymph node dissection (ND2a) was performed (pT2N0M0) for middle lobe lesion. PDT was performed for the lesion of the right upper lobe bronchus using porfimer sodium and Excimer Dye Laser (250 J). Residual lesion biopsy which was taken 8 months after treatment, showed recurrence. The second PDT (400 J) was performed. No recurrence has been noticed for 40 months. SAFE fluorescent is still missing (Fig. 5A, B). The histopathology examination showed tissue fibrosis (Fig. 5C). SAFE-3000 follow-up showed normal fluorescence after PDT, followed by fluorescence loss due to local recurrence. After second PDT, fluorescence is still missing due to fibrosis (Fig. 1 ; lesion 5).

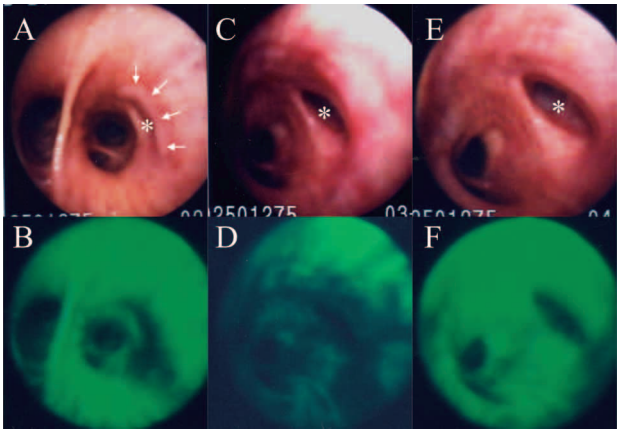

Figure 4. Bronchoscopic findings of the case 3. A : White light bronchoscopic finding of pre-PDT showed flatly elevated lesion prior to the right B^6. B : Fluorescence bronchoscopic finding of A showed fluorescence defect at the site of the lesion. C : White light bronchoscopic finding at 5 months after PDT showed no tumorous lesion. D : Fluorescence bronchoscopic finding of C showed fluorescence defect around the right B^6. E : White light bronchoscopic finding at 14 months after PDT showed no tumorous lesion. D : Fluorescence bronchoscopic finding of E showed no fluorescent defect around the right B^6. *Right B^6. Arrows show the border of the tumor.

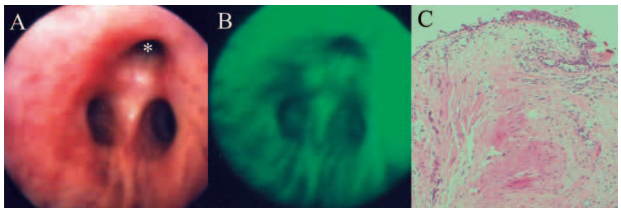

Figure 5. Bronchoscopic findings of the case 4. A : White light bronchoscopic finding at 40 months after PDT showed no tumorous lesion at the right upper bronchus where there had been a tumor. B : Fluorescence bronchoscopic finding of A showed fluorescence defect between the right B^1 and B^2 or B 3 . C : Histopathological finding of biopsy specimen at the site of fluorescence defect showed no malignant change but fibrotic change in the submucosa. *Right B 1.

Case 7 : 71 years old man. The patient had received medical treatment for emphysema at age of 50. Home oxygen therapy was introduced at the age of 65. The patient underwent regular bronchoscopy. Elevated lesion was seen during inspection of $Lt.B^3$ at the age of 71. The result of biopsy was squamous cell carcinoma. Because of severe emphysema and pulmonary hypertension, surgery was not considered. The PDT was performed by porfimer sodium and excimer laser (400 J). Evidence of recurrence was observed 12 months after treatment. The PDT was performed again using talaporfin sodium and laser (70 J). The tumor showed no obvious alteration in white light bronchoscopy 3 months after the second treatment. SAFE fluorescence loss was observed in the treated area (Fig. 6A, B). The biopsy showed bronchial epithelial hyperplasia and malignant findings. Bronchoscopy showed a recurrence 8 months after the second treatment (Fig. 6C). After PDT, SAFE-3000 showed fluorescence loss

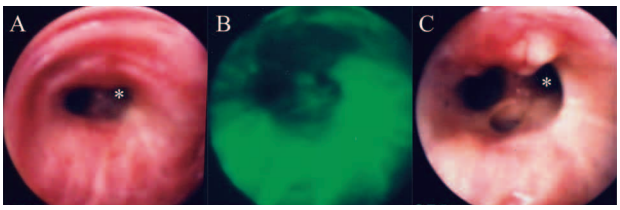

Figure 6. Bronchoscopic findings of the case 7. A : White light bronchoscopic finding at 3 months after second PDT showed no tumorous lesion at left upper division bronchus where there had been a tumor. B : Fluorescence bronchoscopic finding of A showed large fluorescence defect at left upper division bronchus though histopathological finding of biopsy specimen at the site of fluorescent defect showed no malignant lesion. C : Bronchoscopic finding at 8 months after second PDT showed recurrent tumor at left upper division bronchus. *Left B^3

due local recurrence after first and second PDT (Fig. 1 ; lesion 8).

DISCUSSION

Fluorescence diagnosis of the bronchial tree was initially reported by Lam *et al*. and this diagnostic procedure (LIFE system) has been adopted at several sites in recent years, resulting in increased detection rates of cancerous or precancerous lesions by conventional bronchoscopy plus additional fluorescence examination (6, 7, 18). Recently, Ikeda *et al*. reported the feasibility of use of SAFE-3000 as a very useful laser system for the early diagnosis of centrally located early cancers (12). The potential of AF bronchoscopy SAFE-3000 to follow up PDT treated lesions in the central airways is uncertain. This study was undertaken to evaluate a newly developed AF bronchoscopy (SAFE-3000) system as a follow up tool for patients who underwent PDT for early central lung cancer.

In the present study, we evaluated the role of PDT as a curative treatment in early-stage, radiologically node-negative early central carcinoma. We obtained a high CR rate for *in situ* lesions. Of the 16 early carcinomas treated, 14 (87.5%) had a CR after initial PDT. Our results were comparable with the response rates recorded in previous studies. Furukawa *et al*. (19) report CR and 5-year survival rates for patients with lesions < 1.0 cm of 92.8% (77/83 patients) and 57.9%, respectively, and there was a significant difference ($P < 0.001$) in the efficacy of PDT in terms of response and recurrence between lesions $<$ or > 1 cm. A small study from the Netherlands Cancer Institute, using i.v. Photofrin II, showed a CR in 10/11 patients with stage I NSCLC (20). Edell and Cortese (21) confirmed an impressive CR rate (13/14 cases) obtained in tracheobronchial tumors treated with hematoporphyrin-derivative phototherapy. Of the 16 early carcinomas treated, 2 carcinomas had a NR after initial PDT. This lesion has granular shape and 0.5 cm diameter.

Additionally, recurrence after CR was recognized in 4 of 14 CR lesions (29%) in the group of patients with lesions ≤ 1.0 cm in diameter. Despite the average diameter of the initial lesions being relatively small (0.5 cm), recurrence was recognized within 12 months. Furukawa *et al*. (19) reported that recurrence after CR was recognized in 9 of 77 lesions (11.7%) in the group of patients with lesions ≤ 1.0 cm in diameter. Despite the average diameter of the nine initial lesions being relatively small (0.46 cm), recurrence was recognized in eight of nine lesions (88.9%) within 12 months. The reasons why recurrences after CR were observed in the lesions $\leq$ 1.0 cm in diameter could be explained by inappropriate estimation of the peripheral margin in cases of local recurrence at the site corresponding to the peripheral margin and insufficient laser irradiation or miss estimation of tumor depth in the cases of local recurrence at the same site as the initial tumor. In our study, we did not use endobronchial ultrasonography before PDT which is essential for estimation of tumor depth before PDT. The accuracy of the initial evaluation of the lesion's depth is unquestionably fundamental to obtaining a better and more durable clinical response to treatment. Another reason, the site of the tumor is very important reason for recurrence, because difficult sites lead to insufficient dose of laser radiation.

There is wide variation in the follow-up strategies undertaken for post-PDT patients. Although chest roentgenography, computed tomography, bone scanning, bronchoscopy, sputum cytology were routinely performed by some and totally ignored by others, there are no specific guidelines suggested for post-PDT patients. Advances in endoscopic technology such as AF bronchoscopy have recently improved the detection of premalignant and malignant bronchial lesions in high risk individuals. To date, nearly all published AF bronchoscopy studies were done for early detection of bronchial premalignant and malignant lesions. No studies have evaluated the use of the AF bronchoscopy after PDT for early central lung cancer. Among AF bronchoscopies, we have used SAFE-3000. The advantages of this PDD system are as follows : increased sensitivity, ability to clearly define the tumor margin, a color CCD video endoscopy-based AF system equipped with a diode

laser and a hand switch to easily switch between the white light and AF modes. In the current study, the biopsy based sensitivity and NPV of AF mode were higher than WL mode. On the other hand, the specificity of WL was significantly higher than AF.

In our study the relatively high sensitivity of AF may be explained by due primarily to combination technique of both modes in one procedure because knowledge of white light-identified abnormalities might influence the bronchoscopist to also call AF identified abnormality in a given area. An important limitation of AF may be the high rate of false positive results which decrease the specificity and PPV of AF examination and may lead to more biopsies being evaluated at greater cost. Venman reported that LIFE is slightly more sensitive (89%) than white light alone (78%) in the diagnosis of dysplasia and CIS (7). However, in their report the specificity and positive predictive value of LIFE was lower (61 and 14%) than white light bronchoscopy (88 and 32%). The reasons for false positives in our study were mainly due to the thickened mucosal layer due to basal or goblet cell hyperplasia and sub mucosal layer due to chronic inflammation and fibrosis. Auto fluorescence emission was blocked by the thickened layer of the bronchus in subjects with chronic inflammation. It remains difficult to predict pathological diagnosis from the observed grade of auto fluorescence, as studies have found that some lesions identified as class III turned out to be inflammatory lesions on biopsy (22, 23). Although the specificity of AF in our study was statistically significantly lower than that of WL, we do not think that this difference is clinically relevant. The high sensitivity and low specificity of AF is similar to other imaging modalities such as low dose CT scanning in the diagnosis of small malignant nodules (24). There are many trials to increase the specificity. Quantitative fluorescence imaging or combined fluorescence-reflectance imaging may also be helpful in future bronchoscopic devices to address specificity. As AF system has higher sensitivity comparing with WL, AF system can detect recurrence after PDT early. AF system with higher NPV can avoid unnecessary biopsy. If AF system shows normal green, there is no recurrence after PDT.

Little is known about the natural history of CR carcinomas after PDT. Our data showed that in 9 out of 14 lesions who presented complete response after photodynamic therapy, the treated lesions finally recovered normal fluorescence, though they temporary showed abnormal fluorescence in some cases. CR cases that did not show normal fluorescence were relapsed cases or a patient with complete response whose treated lesion showed fibrosis in the sub mucosa after two sessions of photodynamic therapy. Histopathological finding of the complete response sites which demonstrated temporal fluorescent defect consisted of inflammatory lesions, goblet cell hyperplasia, basal cell hyperplasia, squamous metaplasia or dysplasia. However, fibrotic changes in sub mucosa give permanent fluorescent defect. Since it is known that early-stage lung cancer even when successfully treated with photodynamic therapy relapse, earlier detection of second primaries and/or local recurrence by the use of SAFE-3000 may expand the curative treatment options available to these patients. Careful mapping of post-PDT lesions with SAFE-3000 may allow us to better define the true rate of occurrence of these lesions in post-PDT patients. In addition, longitudinal monitoring with SAFE-3000 should help to better characterize their natural history. These findings strongly suggest that PDT treated carcinomas could be carefully followed with SAFE-3000.

In conclusion, The AF videobronchoscopy system (SAFE-3000) yields significantly higher sensitivity for the assessment of PDT treated lung cancer than WLB videobronchoscopy alone. Results of our study suggest that AF bronchoscopy is an efficient tool for follow up of PDT treated lung cancer. Further studies of AF videobronchoscopy should be widened on examination of its use as follow up tool after PDT.

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