Management of Multiple Primary Lung Cancer in Patients with Centrally Located Early Cancer Lesions

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Background: Patients with centrally located early lung cancer (CLELC) are often heavy smokers with a considerably high risk of multiple primary lung cancer (MPLC) lesions; treatment strategies for such patients must preserve the cardiopulmonary function.

Methods: Between July 2004 and July 2008, patients with CLELC underwent photodynamic therapy (PDT) using NPe6, second-generation photosensitizer at Tokyo Medical University Hospital. Among these patients, we retrospectively analyzed MPLC, which was treated by surgery plus PDT or PDT alone and examined the effectiveness of PDT, and we propose a treatment strategy for patients with MPLC.

Results: A total of 64 patients with CLECL received NPe6-PDT, and MPLCs were found in 22 patients (34.4%) using sputum cytology and a bronchoscopical examination using autofluorescence bronchoscopy. Among these 22 patients, 10 patients underwent surgery for primary lung cancer and underwent NPe6-PDT for the treatment of secondary primary CLELC, one patient underwent PDT for CLELC as a primary lesion followed by an operation for peripheral-type lung cancer as a secondary primary lesion, and 11 patients underwent PDT alone for MPLC lesions (28 lesions) that were roentgenographically occult lung cancers. Among these 22 patients with MPLC including peripheral-type lung cancers, which were resected by surgery, all 39 CLELC lesions exhibited a complete response after PDT, and all patients were alive.

Conclusions: For patients with lung cancer with a long-term history of smoking, careful follow-up examinations after surgical resection are needed considering the incidence of metachronous primary lung cancers. PDT can play an important role for the treatment strategy for MPLC.

Key Words: Multiple primary lung cancer, Photodynamic therapy, Centrally located early lung cancer.

(*J Thorac Oncol.* 2010;5: 62–68)

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ISSN: 1556-0864/10/0501-0062

Photodynamic therapy (PDT) is widely used as a treatment option for solid cancers and also for some noncancerous diseases.[1–3] Early lung cancers can be divided into two categories, the peripheral type and the central type, according to the site of origin of the tumor.[4,5] In Japan, PDT is recommended as a treatment option for centrally located early lung cancers (CLELCs), which are roentgenographically occult squamous cell carcinomas not located distal to the segmental bronchi that are histologically determined to be carcinoma in situ or carcinoma showing only limited invasion, with no evidence of invasion beyond the bronchial cartilage, as defined in the therapeutic guidelines for lung cancer established by the Japanese Ministry of Health, Labor and Welfare based on the principles of evidence-based medicine.[4,5] The second-generation photosensitizer talaporfin sodium (NPe6 or Laserphyrin), which has a major absorption band at 664 nm, has been approved by the Japanese government for use in the diagnosis/treatment of CLELC.[4–7] A phase II clinical study using NPe6 and a diode laser for early-stage lung cancer demonstrated excellent antitumor effects and safety, including a significantly lower skin incidence of photosensitivity compared with that observed using Photofrin (Wyeth Japan K.K., Tokyo, Japan).[6,7] The Japanese government approved the use of NPe6 for PDT in 2003, and the product has been available in Japan since June 2004.[4–7]

Roentgenographically occult lung cancers, which are located in the central bronchus, can be detected in high-risk patients using either sputum cytology or bronchoscopic evaluation.[8–11] One to 4% of these patients have a synchronous lung cancer, and the risk of a second lung cancer ranges from 1 to 25% per year.[12–14] Some reports have revealed that 17% of newly diagnosed early lung cancer cases have a synchronous lesion.[15,16]

Multiple primary lung cancer (MPLC) is not an uncommon event, and Nakata et al.[17] reported that 7.9% of patients with surgically resected non-small cell lung cancers and 8.4% of patients with adenocarcinomas exhibited multiple lesions. In 1975, Martini and Melamed[18] outlined the criteria for differentiating between MPLC and recurrence, and they proposed that tumors were 'synchronous' when they were detected or resected simultaneously and 'metachronous' when the second tumor was found some time later. Recently, the

incidence of MPLC has been increasing as a result of the widespread use of early detection tools such as multislice spiral computed tomography (CT) and fluorescence endoscopy.[12–15] Nevertheless, no guidelines have detailed recommendations for the selection and treatment of patients with synchronous or metachronous MPLC.

In particular, patients with CLELC are often heavy smokers and have a considerably high risk of a second primary lung cancer; thus, these patients require treatment that will preserve their cardiopulmonary function. It has been reported that 70% of carcinoma in situ is not detected during white-light bronchoscopy, and that the prevalence of synchronous occult lesions after fluorescence bronchoscopy assessment might be higher than the previously reported values of 7 to 14%.[8,19,20] Moreover, after the successful treatment of a first occult cancer, as many as 5% of the metachronous tumors detected per year might actually result from the progressive evolution of synchronous, undetected early lung cancers. For patients treated using PDT, we routinely perform follow-up examinations using autofluorescence bronchoscopy (SAFE-3000) to avoid missing occult lung cancers.[4–7,21] In such patients with synchronous or metachronous MPLC, PDT is an effective treatment that also preserves lung function and is recommended in the evidence-based clinical practice guidelines of the American College of Chest Physicians.[4–7]

In this study, we retrospectively analyzed MPLC with CLELC lesions, which were treated by surgery plus PDT or PDT alone, and examined the effectiveness of PDT for the treatment of patients with CLELCs, and we propose a treatment strategy for patients with MPLC.

MATERIALS AND METHODS

Photosensitizer

NPe6 (Meiji Seika, Tokyo, Japan) is a second-generation, water-soluble photosensitizer with a molecular weight of 799.69 and a chlorine annulus; its highest absorption peak occurs at a wavelength of 407 nm, and a second peak occurs at a wavelength of 664 nm.[4–7] NPe6 exhibits superior in tumor affinity, compared with Photofrin, and is excited by visible red light with a longer wavelength of 664 nm, enabling deeper and superior penetration into living tissues.[4,22]

Laser Unit

A diode laser (Matsushita Electric Industrial Co., Osaka, Japan) emitting continuous-wave laser light at a wavelength of 664 nm was used as the light source for the excitation of NPe6.[4–7]

Criteria for the Diagnosis of CLELC

Lung cancers not located distal to the segmental bronchi, diagnosed histologically as squamous cell carcinoma, and determined to be carcinoma in situ or carcinoma showing only limited invasion with no evidence of invasion beyond the bronchial cartilage were defined as CLELCs.[4–7] We routinely determined the tumor depth using endobronchial ultrasonography and confirmed that the tumors had not invaded the bronchial wall beyond the level of the cartilage and were confined to the basal membrane of the mucosa, submucosa, or intracartilaginous layers of the bronchial wall.[4,5,7,23] In 2003, the Japan Photodynamic Association and Japanese Society of Laser Surgery and Medicine established the following therapeutic criteria for PDT in cases with CLELC: patients with (a) endoscopically assessable early lung cancer, (b) a normal chest x-ray and CT, and (c) no metastasis to lymph nodes or distant metastasis as revealed using routine clinical diagnostic methods, including fluorodeoxyglucose-position emission tomography for staging.[4,5]

PDT Procedures and Follow-Up

Local anesthesia was performed using 4% lidocaine spray. Additional sedation was necessary. Laser irradiation (664 nm) for NPe6-PDT was transmitted by means of quartz fibers inserted through the biopsy channel of the endoscope, 4 to 6 hours after the administration of the photosensitizer, NPe6 (40 mg/m^2). The total energy of the laser irradiation was 100 J/cm^2 (150 mW/cm^2).[4–7] The Japanese government approved the use of NPe6 for PDT against CLELCs in 2003, and the product became available in Japan in June 2004.[4–7] Ever since, we have used NPe6 for PDT. A fiber-optic bronchoscopy with cytologic and histologic examinations was performed at 1, 2, and 3 months after the PDT and at 3-month intervals during the first year and 6-month intervals during the second year thereafter. The antitumor effect of the initial treatment was rated based on the endoscopic measurement of the tumor size using forceps, the morphologic appearance, and the pathologic findings of the biopsy specimens, in accordance with the general rules of the Japan Lung Cancer Society and the Japan Society of Clinical Oncology.[4–7] The antitumor effect was evaluated again at 3 months after the PDT. The tumors were then classified as showing a complete response (CR) (no microscopically demonstrable tumor in the brushings and/or biopsy specimens over a period of 4 weeks).[4–7,21] We used fluorescence bronchoscopy (SAFE-3000) as part of the follow-up examination after NPe6-PDT.[5,7]

Patient Selection

From 2004 to 2008 at the Tokyo Medical University Hospital, we found 64 patients with CLELC by bronchoscopical examination using autofluorescence bronchoscopy (SAFE-3000) because of abnormal sputum production and/or sputum cytologic abnormalities in mass survey or follow-up after surgical resection or PDT. All 64 patients with CLELC received NPe6-PDT. PDT was undertaken in patients who met the criteria for PDT after obtaining their informed consent in accordance with institutional guidelines.[4–7] The clinicopathological characteristics of the patients are listed in Table 1. Their median age at diagnosis was 74 years (range, 67–84). All the patients were men and heavy smokers with a smoking history of more than 30 pack-years.

Efficacy Evaluation

The antitumor effect was rated, based on endoscopic measurement of tumor size using forceps, morphologic observation, and histopathological examination by biopsy. The antitumor effect was rated at 2 months after PDT. Antitumor effect was rated as CR (no demonstrable tumor for 4 weeks),

TABLE 1. Clinicopathological Characteristics of the Patients Who Underwent NPe6-PDT (July 2004–July 2008)

Characteristics	No. of Lesions
Patients	64
Age	67–83
Gender	
Male	64
Female	0
Smoking history	
Positive	64 (>30 pack-years)
Patients with multiple lesions	22 patients
Synchronous	10 patients
Metachronous	12 patients

PDT, photodynamic therapy.

TABLE 2. Treatment for Multiple Lung Cancer Lesions (July 2004–July 2008)

Treatment	No. of Patients (Metachronous)
Surgery ➡ PDT	10 (8)
PDT ➡ surgery	1 (1)
PDT alone	11 (3)
Total	22 (11)

PDT, photodynamic therapy.

partial response (50% or greater reduction in tumor size), no change (less than 50% reduction or less than 25% increase in tumor size), and progressive disease (more than 25% increase in tumor size).

RESULTS

Clinicopathological Characteristics of the Patients Who Underwent NPe6-PDT

The clinicopathological characteristics of the patients with roentgenographically occult lung cancer, who underwent PDT with NPe6, are listed in Table 1. Their median age at the time of the diagnosis of CLELC was 74 years (range, 67–83 years). All the patients were men and were heavy smokers with a smoking history of more than 30 pack-years. We performed skin photosensitivity test 2 weeks after PDT, and all patients had no photosensitivity.

MPLCs were noted in 22 patients (34.4%, 22 of 64). Synchronous lesions were noted in 10 patients (15.6%), and metachronous lesions were noted in 12 patients (18.8%).

Treatment for MPLC Lesions

The characteristics of the patients with MPLC lesions are summarized in Table 2. Among these 22 patients, 10 patients underwent surgery for peripheral-type lung cancer as their first primary lesion followed by PDT for CLELC (Tables 3 and 4), one patient underwent PDT for CELC as a primary lesion followed by an operation for peripheral-type lung cancer as a secondary primary lesion (Table 5), and 11 patients underwent PDT alone for MPLC lesions that were all centrally located and roentgenographically occult lung cancers (Table 6).

TABLE 3. Surgery Followed by PDT (July 2004–July 2008)

Treatment	No. of Patients (Metachronous)
Surgery ➡ PDT	10 (8)
Lobectomy	
Adenocarcinoma	1 (1)
Squamous cell carcinoma	7 (6)
Small cell carcinoma	1 (1)
Pneumonectomy	
Squamous cell carcinoma	1 (1)

PDT, photodynamic therapy.

Surgery for Peripheral-Type Lung Cancer as Their First Primary Lesion Followed by PDT for CLELC

Ten patients underwent surgery (nine lobectomies and one pneumonectomy) for primary lung cancer at peripheral sites and then underwent NPe6-PDT for the treatment of secondary primary CLELCs (Table 3).

Information on 10 Patients Who Underwent Surgery Followed by PDT

Information on 10 patients, who underwent surgery (nine lobectomies and one pneumonectomy) for peripheral-type lung cancer as a first primary lesion and were then treated for CLELCs as secondary primary lung cancers, is presented in Table 4. The age distribution ranged from 63 to 70 years at the time of PDT for the treatment of secondary primary CLELCs. Two of these lesions (case 3 and case 6) were synchronous and eight were metachronous, and the interval between the diagnosis of the first and second cancers in this series ranged from 4 to 126 months (mean, 30 months). After operation, eight metachronous CLELCs were found by sputum cytology and bronchoscopical examination using autofluorescence bronchoscopy (SAFE-3000). Histologic examination of the surgically removed tumors before PDT revealed one adenocarcinoma, six squamous cell carcinomas, and one small cell carcinoma (Tables 3 and 4). In case 1, a left lower lobectomy was performed, and the pathologic diagnosis was adenocarcinoma (p-T1N0M0 stage IA); 72 months later, a CLELC was detected in the left main bronchus and PDT was performed. In case 2 and case 5, the pathologic stage was IIB (p-T2N1M0, squamous cell carcinoma); in case 10, the pathologic stage was IIIA (small cell carcinoma). In only one case (case 10), chemotherapy was performed after a right lower lobectomy. No evidence of metastasis or local recurrence was observed after the operation for the first primary lung cancer. In these 10 patients, the secondary tumors, all of which were roentgenographically occult, carcinoma in situ squamous cell carcinomas, were treated with NPe6-PDT. Three lesions were located in the trachea, and seven lesions were located in the segmental bronchus. In all 10 patients with CELCS, a CR was achieved after NPe6-PDT treatment (CR: 100%), and all the patients were alive at the time of writing.

TABLE 4. Surgery Followed by PDT (July 2004–July 2008)

Age (yr)	Operation	Pathology	Interval (mo)	PDT Lesion	PDT	Outcome
63	LL lobectomy	IA (adenocarcinoma)	72	Lt. main br. CR		Alive
63	LL lobectomy	IIB (sq.)	10	Rt. B1	CR	Alive
68	LL lobectomy	IA (sq.)	0	Rt. B3	CR	Alive
70	RL lobectomy	IA (sq.)	39	Rt. B6-basal CR		Alive
64	Lt. pneumonectomy	IIB (sq.)	17	Lt. main br. CR		Alive
66	RU lobectomy	IA (sq.)	0	Rt. B6	CR	Alive
67	RU lobectomy	IA (sq.)	49	Trachea	CR	Alive
69	RU lobectomy	IA (sq.)	4	Lt. B3	CR	Alive
70	RL lobectomy	IA (sq.)	43	Trachea	CR	Alive
65	RL lobectomy	IIIA (small)	126	Rt. B1	CR	Alive

PDT, photodynamic therapy; RU, right upper; LL, left lower; CR, complete response; Rt, right; Lt, left.

TABLE 5. PDT Followed by Surgery (July 2004–July 2008)

Age (yr)	Lesion	PDT	Interval (mo)	Operation	Pathology	Outcome
57	Lt. upper-lower	CR	25	RU lobectomy	IIIA (adenocarcinoma)	Alive

PDT, photodynamic therapy; CR, complete response; RU, right upper; Lt, left.

TABLE 6. PDT Alone for Multiple Primary Lung Cancers (July 2004–July 2008)

No. of Lesions	Patients (Metachronous)	Lesions	CR	Outcome
Two	7 (2)	14	14	Alive: 7
Three	3 (0)	9	9	Alive: 3
Five	1 (1)	5	5	Alive: 1
Total	11 (3)	28	28	Alive: 11

PDT, photodynamic therapy; CR, complete response.

Figure 1 shows case 4, a patient with metachronous double primary lung cancers. A 70-year-old man presented with coughing and hemoptysis. He had undergone a right upper lobectomy for squamous cell carcinoma 39 months previously. A chest CT scan revealed a clear lung field, and no mediastinal lymphadenopathy or abdominal lesions. A sputum cytologic examination revealed class V, squamous cell carcinoma. Conventional white-light bronchoscopy showed a 1.0 cm, thickened-type, roentgenographically occult lung cancer at the bifurcation between the right B6 and the basal bronchus that was identified as a secondary primary squamous cell carcinoma (Figure 1*B*). Four hours after the administration of NPe6 (40 mg/cm^2), we observed red fluorescence from the tumor using autofluorescence bronchoscopy (SAFE-3000) and were able to determine the tumor margin using a photodynamic diagnosis (Figure 1*C*); PDT was then performed using a diode laser (664 nm, 100J/cm^2, 150 mW) as previous reports.[4,5,7]

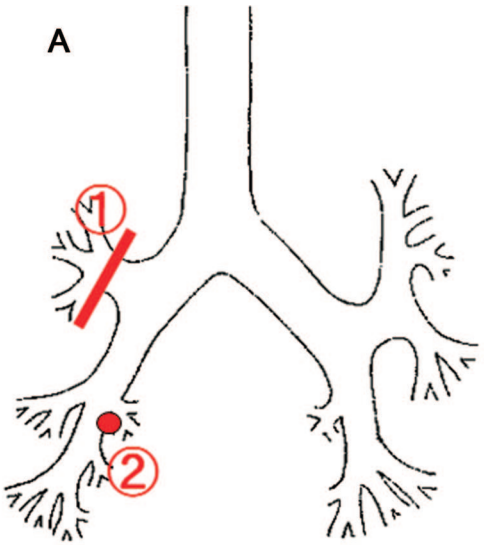
PDT for CELC as a Primary Lesion Followed by Surgery for Peripheral-Type Lung Cancer as a Secondary Primary Lesion

One patient underwent NPe6-PDT for a roentgenographically occult first primary lung cancer located at the bifurcation between the left upper and lower bronchus, and the metachronous lesion was resected by surgery (Table 5). This patient was followed using chest CT and sputum cytology, and 25 months later, a contralateral metachronous lesion (adenocarcinoma) was detected as a secondary primary lung cancer in the right S3 (Tables 2 and 5). The patient received a right upper lobectomy and then underwent chemotherapy because the pathologic stage was IIIA (T1N2M0) (Table 5).

PDT Alone for MPLC Lesions That Were All Centrally Located and Roentgenographically Occult Lung Cancers

In Table 6, the cases of multiple CLELCs that were treated with PDT alone are summarized. In 11 of the 22 patients, MPLCs (28 lesions in total) were observed. All lesions were roentgenographically occult lung cancers found by abnormal sputum production and were treated using NPe6-PDT alone (Tables 2 and 6). Seven patients had two roentgenographically occult lung cancer lesions, three patients had three lesions, and one patient had five lesions. Three of the 11 patients had metachronous occult lung cancer lesions and were followed using bronchoscopical examination with conventional and autofluorescence bronchoscopy after undergoing PDT (Tables 2 and 6). A CR was achieved in all 11 patients with a total of 28 roentgenographically occult lung cancer lesions (CR rate, 100%, 28 of 28); all the patients were alive at the time of writing.

Figure 2 shows a case with five CLELCs that were identified as metachronous MPLCs and treated using NPe6-PDT alone. This 65-year-old man with multiple CLELCs was diagnosed based on positive sputum cytologic findings performed during a mass screening. The performance status of this patient was 1 because of hemiparalysis caused by a cerebral infarction. All roentgenographic examinations were negative. The first tumor was a nodular-type early lung cancer located in the left B3, and NPe6-PDT was performed.



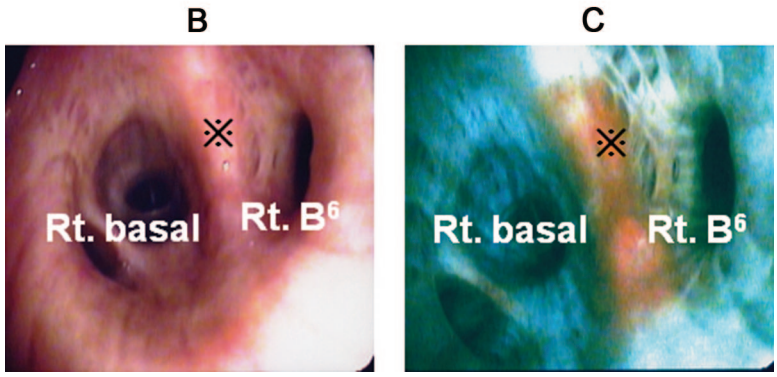


FIGURE 1. *A,* A schema of a 70-year-old man with metachronous multiple primary lung cancer. He underwent a right upper lobectomy for squamous cell carcinoma at S3. Thirty nine months later, centrally located early lung cancer was detected. *B,* Fiberoptic bronchoscopy revealed a thickened lesion. A thickened-type squamous cell carcinoma can be visualized at the bifurcation between right B6 and basal bronchus ※. *C,* Photodynamic diagnosis using SAFE-3000 system and NPe6 was conducted before the PDT. The red fluorescence excited by the diode laser (408 nm) from the SAFE-3000 system revealed the cancerous lesion ※.

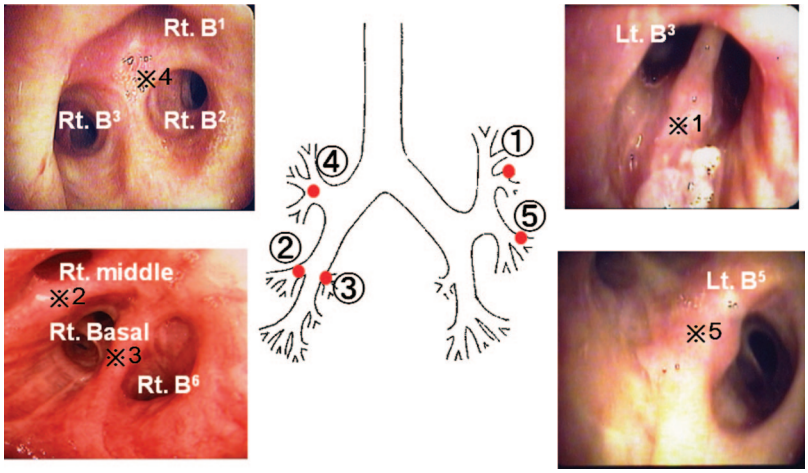


FIGURE 2. A 65-year-old man with metachronous multiple primary lung cancers. Fiberoptic bronchoscopy revealed five thickened-type lesions. First cancer lesions located at the left B3 (※ 1), second lesion at the bifurcation between the right middle lobe bronchus and the basal bronchus (※ 2), third lesion at the bifurcation between the right B6 and the basal bronchus (※ 3), fourth lesion at the right upper bronchus (※ 4) and fifth lesion at left B5 (※ 5). All five metachronous lesions were completely cured using PDT, and a CR was achieved.

Eight months after the PDT, a second tumor at the bifurcation between the right middle lobe bronchus and the basal bronchus was found, and the third tumor was found at the bifurcation between the right B6 and the basal bronchus during a routine bronchoscopic examination. Twenty months after the first PDT, a fourth tumor was detected in the right upper bronchus, and 29 months after the first PDT, a fifth tumor was detected in the left B5. These five lesions were thickened-type, roentgenographically occult lung cancers and were all treated using NPe6-PDT. All five metachronous lesions were completely cured using PDT, and a CR was achieved. No evidence of metastasis or recurrence was noted.

DISCUSSION

The criteria for MPLC were first proposed by Warren and Gates[24] in 1932. The most recent and recognized criteria

for differentiating between MPLC and recurrences are those reported by Martini and Melamed.[18] MPLC is not uncommon, and several authors have recently reported an incidence of 0.2 to 20%.[12–17] Johnson et al.[12,13] reported that the risk of developing a second lung cancer was 2 to 14% per patient per year, and that the risk increased twofold to sevenfold at 10 years after initial diagnosis. Nevertheless, no guidelines have detailed recommendation for the selection and treatment of patients with synchronous or metachronous MPLC. Moreover, CLELCs, which are roentgenographically occult and can be treated using PDT, cannot be detected using high-resolution computed tomography HRCT.[4,5,25–27] Fujimura et al.[11] reported that in 236 patients with roentgenographically occult lung cancers, a second primary lung cancer lesion was detected in 50 patients (22%), and 13 of these 50 patients had a third primary lung cancer lesion, whereas six of these 13 patients had a fifth primary lung cancer lesion. In an analysis of the Mayo Lung Project, only 54 patients with CLELC were identified, and synchronous lesions were found in four patients (7%).[2,28] Our results showed that multiple primary CLELCs were detected in 22 patients (34%, 22 of 64), providing an incidence rate that was higher than in previous reports (Table 1). We hypothesized that the incidence of MPLCs might have increased not only as a result of HRCT but also as a result of sputum cytologic examinations and bronchoscopical examination using fluorescence bronchoscopy, especially among patients with long history of smoking who have undergone surgery for peripheral lung cancers. In this report, eight patients (8 of 64, 11%) with roentgenographically occult secondary primary lung cancers were diagnosed based on sputum cytologic examinations, and their lesions were detected using autofluorescence bronchoscopy after surgical resection for peripheral-type lung cancer.

In 11 patients (11 of 64, 11%), multiple CLELCs were detected using routine bronchoscopical examination. These patients were all heavy smokers (more than 30 pack-years). The incidence of multiple primary CLELCs was similar to that in previous reports.[11,29] As shown Table 4, in case 1, a left lower lobectomy was performed because of peripheral-type lung cancer (adenocarcinoma) and 72 months later, a CLELC was found by abnormal sputum productions. These results suggest that for heavy smokers, there may be higher rate of incidence of squamous cell carcinoma as metachronous cancer compared with nonsmokers.

For heavy smokers with adenocarcinoma, who undergo surgery for primary lung cancer, sputum cytologic examinations should be a required part of their follow-up.[13,30,31] Careful follow-up using HRCT and sputum cytologic examination or fluorescence bronchoscopical examination might also be recommended, as suggested by the case history of patient 1 (Table 4). From our data, postoperative follow-up examinations should consider the incidence of MPLCs at peripheral or central sites in heavy smokers.

For synchronous or metachronous MPLCs, the performance of a pneumonectomy is a predictor of poor long-term survival, and a pneumonectomy should be avoided whenever possible.[15,16] Moghissi and Dixon[32] reported that PDT cured synchronous CLELCs 17 years after a pneumonectomy, and they concluded that PDT can enable long-term survival and serve as a potential cure for MPLCs. We also performed PDT for metachronous lung cancer 17 months after a left pneumonectomy, and the patients was still alive at the time of writing (Table 4). Moreover, as shown Figure 2, PDT cured all five MPLCs in another patient, enabling the patient's cardiopulmonary function to be preserved (Figure 2).

No guidelines detailing recommendations for the treatment of patients with MPLC have been published. Our present results suggest that minimally invasive treatments, such as PDT, should be performed for CLELCs of a synchronous or metachronous nature. Moreover, in heavy smokers who undergo surgery for lung cancer, sputum cytologic examination should be a necessary component of their follow-up care.

In conclusion, PDT is useful for extending the therapeutic options and improving the prognosis of patients with MPLCs. In particular, for patients with long-term history of smoking after surgical resection, careful follow-up with due consideration of the incidence of metachronous primary lung cancers is recommended, and PDT might play an important role for the treatment strategy for MPLC.

ACKNOWLEDGMENTS

Supported in part by a Grant-in-Aid for Scientific Research (C) from Japan Society for the Promotion of Science (JSPS), KAKENHI21591826 (to J. U.).

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