CHEST

Original Research

INTERVENTIONAL PULMONOLOGY

Results of Long-term Follow-up of Photodynamic Therapy for Roentgenographically Occult Bronchogenic Squamous Cell Carcinoma

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Background: **Photodynamic therapy (PDT) is considered a useful and minimally invasive modality for treating centrally located early lung cancer. To date, there has been limited information on the long-term outcome of patients treated with PDT, especially those who are medically operable.**
Methods: **Beginning in 1994, patients with roentgenographically occult bronchogenic squamous cell carcinoma (ROSCC) who met our criteria underwent PDT at Tohoku University Hospital and were followed up through 2006. Our criteria were as follows: (1) ROSCC without distant metastasis; (2) medically operable by means of lobectomy or further resection; (3) longitudinal tumor length of ≤ 10 mm; and (4) superficial bronchoscopic tumor findings.**
Results: **A total of 48 patients with ROSCC underwent PDT. The complete response (CR) rate was 94% (45 of 48 of patients). Nine patients (20%) had local recurrence after CR. A total of 11 deaths was observed, with 6 resulting from multiple primary lung cancer and only 1 from the original ROSCC. The 5-year and 10-year overall survival rates for all 48 patients were 81% and 71%, respectively. The Cox proportional hazard model showed that only metachronous multiple primary lung cancer was an independent poor prognostic factor.**
Conclusions: **PDT is thought to be a first-line modality for patients who have ROSCC with a tumor length of ≤ 10 mm, even if the tumor is medically operable. Most local recurrence can be cured by active therapy such as surgery, radiotherapy, or PDT. Multiple primary lung cancer subsequent to PDT is an important issue from the viewpoint of survival.**
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Abbreviations: AFB = autofluorescence bronchoscopy; CR = complete response; DFS = disease-free survival; OS = overall survival; PDT = photodynamic therapy; RFS = relapse-free survival; ROSCC = roentgenographically occult bronchogenic squamous cell carcinoma

Photodynamic therapy (PDT) is considered a useful and minimally invasive modality for treating centrally located early lung cancer. Based on the results of a prospective phase II study,[1] PDT is considered a first-line modality for nonsurgical patients with central-type early lung cancer with a longitudinal extent of ≤ 10 mm. The American College of Chest Physicians guidelines[2] stated that there was limited experience using PDT for patients who were surgical candidates. In the current study, patients with centrally located early lung cancers who were medically operable underwent PDT at Tohoku University Hospital, and underwent long-term follow-up.

Materials and Methods

Patients

PDT has been performed at Tohoku University Hospital since 1994. Patients who had roentgenographically occult bronchogenic squamous cell carcinoma (ROSCC) were examined with

bronchoscopy, chest CT scan, upper abdominal CT scan/ultrasonography, brain CT scan/MRI, and bone scintigraphy. Patients were considered candidates for PDT under the following conditions: (1) no metastatic lesions were observed; (2) the longitudinal extent of ROSCC was ≤ 10 mm; (3) the distal edge of ROSCC was visible by bronchoscopy; (4) bronchoscopy findings categorized the tumor as minute or hidden using our classification system (described later); (5) patients were medically operable by means of lobectomy or further lung resection; and (6) informed consent to undergo PDT was obtained. This study was approved by the Institutional Review Board of Tohoku University Hospital.

Bronchoscopic Findings

Our classification of ROSCC bronchoscopic findings has been described previously.[3] In brief, findings were classified into the following three categories: remarkable, minute, and hidden. "Remarkable" meant that a lesion could be identified easily as a tumor > 2 mm in height. "Minute" indicated that a lesion could be identified as a tumor only with difficulty, and was ≤ 2 mm in height. A "hidden" lesion was one that could not be seen using a conventional bronchoscope or that showed no characteristic changes related to carcinoma. Hidden lesions could be detected only by bronchial biopsy, brushing cytology, or autofluorescence bronchoscopy (AFB). Since 1997, AFB (LIFE system; Xilix Technologies; Vancouver, BC, Canada) and endobronchial ultrasonography have also been used for the evaluation of ROSCC. AFB is useful for precisely determining the size of the lesion,[4,5] whereas endobronchial ultrasonography may prove beneficial in evaluating the depth of tumor invasion.[6,7]

PDT

PDT procedures were performed with porfimer sodium (Photofrin; Wyeth Japan KK; Tokyo, Japan) and an excimer dye laser (EDL-1; Hamamatsu Photonics; Hamamatsu, Japan). All patients received 2 mg/kg porfimer sodium IV, 48 h before light irradiation. A quartz fiber was used to carry the laser light through a bronchoscope to the lesions. The total energy of the laser irradiation was 100 J/cm^2, and the duration of irradiation was usually 10 to 20 min. Bronchial toileting to remove necrotic tissues produced by PDT was routinely performed at 7 days after PDT. The lesions were evaluated by brushing cytology and biopsy specimen histology at 1, 2, and 3 months after PDT. Thereafter, patients were assessed with bronchoscopy, sputum cytology, and chest CT scan every 3 months for the first year, and every 6 months from the second through the fifth years. After that, patients were examined annually using sputum cytology and chest CT scan.

Tumor response to PDT was classified into the following two categories: complete response (CR); and non-CR. A CR was defined as the absence of any demonstrable tumor by biopsy or brushing cytology for at least 4 weeks.

Local recurrence was defined as a tumor that recurred at the same lesion as the PDT lesion after CR. Multiple primary lung cancer was defined according to the criteria of Martini and Melamed.[8]

Statistical Analysis

Overall survival (OS), relapse-free survival (RFS), and disease-free survival (DFS) were calculated using the Kaplan-Meier method. OS was defined as the time from PDT to death from any cause. RFS was defined as the time from PDT to local recurrence or death. DFS was defined as the time from PDT to local recurrence or metachronous multiple primary lung cancer or death. For non-CR cases, RFS and DFS times were defined as zero. Subgroup comparisons of survival curves were performed using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard model to determine factors significantly associated with survival. A p value of < 0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 48 ROSCC patients who met our criteria have undergone PDT at Tohoku University Hospital since 1994 and were followed up through 2006. As shown in Table 1, all patients were men, and their average age was 70 years. All patients were current or ex-smokers, and the average smoking index was 50 pack-years. Forty-five of the 48 patients were detected by sputum cytology mass screening,[9,10] and the remaining patients were detected by medical examination for other diseases (arrhythmia, GI disorder, and cerebrovascular disease).

Synchronous multiple primary lung cancer was diagnosed in four patients (Table 2). Three of these patients were treated with surgery; the other patient underwent radiotherapy.

Table 1—*Baseline Patient Characteristics (n = 48)*

Characteristics	Description
Gender	All men
Age,* yr	70 (6.7)
Smoking index,* pack-yr	50 (11.1)
Detection method	Sputum cytology mass screening (45 patients) Medical examination for other diseases (3 patients)
Synchronous multiple primary lung cancer	4 patients

*Values are given as the mean (SD).

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Table 2—*Synchronous Multiple Primary Lung Cancer (n = 4)*

Patient, No.	PDT Lesion	PDT Efficacy	Synchronous Cancer Lesion (Histology)	Treatment for Synchronous Cancer	Prognosis
1	LB^{3}	CR	RB^{1} (Sq)	Surgery (lobectomy)	Alive
2	LUD	CR	RB^{3} (Ad)	Surgery (partial resection)	Dead from AMI
3	LB^{3}	CR	RB^{4} (Sq)	Radiotherapy	Dead from synchronous cancer
4	RB^{1}	CR	RB^{8} (Sq)	Surgery (lobectomy)	Alive

Ad = adenocarcinoma; AMI = acute myocardial infarction; LUD = left upper division bronchus; Sq = squamous cell carcinoma.

Tumor Response to PDT

Forty-five of the 48 patients (94%) achieved CR. Non-CR was seen in three patients. Among these, two patients had ROSCCs in segmental bronchi, and the other had disease located in a subsubsegmental bronchus. There was no statistically significant relationship between tumor response and tumor location ($p = 0.64$ [Mann-Whitney *U* test]). Two of the three non-CR cases underwent radiotherapy, and the other one underwent left lung lobectomy. As a result, all of the non-CR patients were free of lung cancer at the last follow-up.

Local Recurrence

Local recurrence after CR was found in 9 of the 45 CR patients (20%) [Table 3]. Among these, ROSCCs were found in segmental bronchi in five cases, in subsegmental bronchi in three cases, and in a subsubsegmental bronchus in the remaining case. There was no statistically significant relationship between local recurrence and tumor location ($p = 0.29$ [Mann-Whitney *U* test]). The relapse-free interval of the nine patients ranged from 3 to 47 months (average, 25 months). Treatments for recurrence were as follows: radiotherapy, five patients; surgery, two patients; additional PDT, one patient; and chemotherapy, one patient. As a result, eight of the nine patients were alive at the last follow-up.

Metachronous Multiple Primary Lung Cancer

During the follow-up period, a total of 10 patients had metachronous second primary lung cancers, and only 1 patient had metachronous third primary lung cancer (Table 4). The time from PDT to metachronous primary lung cancer ranged from 12 to 89 months (average, 45 months). Nine of the 10 patients received some form of active therapy (*ie*, surgical resection, 2 patients; radiotherapy, 2 patients; laser therapy, 2 patients; PDT, 2 patients; and chemotherapy, 1 patient). Five deaths occurred among these 10 patients, all from metachronous lung cancers.

Survival

The median follow-up time for all 48 patients was 63 months. The median follow-up time for living patients was 70 months. Only two patients were lost to follow-up, and their follow-up times were 21 and 27 months.

Among these 48 patients, a total of 11 deaths were observed, with only 1 patient dying from the original ROSCC. Five patients died from metachronous multiple lung cancer, one patient died from synchronous multiple lung cancer, two patients died from myocardial infarction, one patient died from cerebral hemorrhage, and the remaining patient died from an unknown cause. This last case was counted as an original lung cancer death in the survival analysis.

Table 3—*Local Recurrence of PDT*

Patient, No.	PDT Lesion	Months From PDT to Local Recurrence	Treatment for Local Recurrence	Prognosis
1	RB^{1}ai/ii	46	Radiotherapy	Alive
2	LB^{1+2}a+b/c	34	Left lung lobectomy	Alive
3	LB^{3}a/b+c	16	Radiotherapy	Alive
4	LB^{9}	15	Left lung lobectomy	Alive
5	RB^{1}	26	Radiotherapy	Alive
6	LB^{3}	7	Radiotherapy	Alive
7	LB$^{1+2/3}$	29	Chemotherapy	Dead from original lung cancer
8	LB^{3}a/b+c	47	Radiotherapy	Alive
9	LB^{6}	3	PDT	Alive

See Table 2 for abbreviations not used in the text.

Table 4—*Metachronous Multiple Primary Lung Cancer (n = 10)*

Patient, No.	PDT Lesion	PDT Efficacy	Metachronous Cancer Lesion (Histology)	Treatment for Metachronous Cancer	Time From PDT to Metachronous Cancer, mo	Prognosis
1	RB^{1}	Non CR	RB^{7} (Sq)	Radiotherapy	38	Dead from metachronous cancer
2	LB^{1+2}	CR	LLB (Sq)	PDT	57	Alive
3	LB^{3}	CR	RB^{8} (Sq)	Laser	50	Alive
4	LB^{1+2}	CR	RB^{3} (Sq)	Surgery (lobectomy)	71	Dead from metachronous cancer
5	LB^{3}	CR	RS^{3} (Sq)	Surgery (lobectomy)	29	Alive
6	LB^{3}	CR	RLL (NSCLC)	Supportive care	43	Dead from metachronous cancer
7	LB^{1+2}	CR	LB^{6} (Sq)	Radiotherapy	44	Dead from metachronous cancer
8	RB^{10}	CR	RB^{7}/RB^{8} (Sq)	Laser/Radiotherapy	89	Alive
9	RB^{1}	CR	RB^{3} (SCLC)	Chemotherapy	12	Dead from metachronous cancer
10	LB^{1+2}	CR	LB^{8} (Sq)	PDT	14	Alive

LLB = left lingual bronchus; NSCLC = non-small cell lung cancer; RLL = right lower lobe; SCLC = small cell lung cancer. See Table 2 for abbreviations not used in the text.

The 5-year and 10-year OS rates were 81% and 71%, respectively. The relationships among survival, local recurrence, and metachronous multiple primary lung cancer were examined. The 5-year OS rate of patients with local recurrence showed no statistically significant difference from that of patients without local recurrence (log-rank test $p = 0.62$) [Fig 1]. The 5-year OS rate of patients with metachronous multiple lung cancer was 56%, which was statistically lower ($p = 0.031$ [log-rank test]) than that of patients without it (88%) [Fig 2]. The 5-year and 10-year RFS rates were 60% and 54%, respectively; the 5-year and 10-year DFS rates were 56% and 43%, respectively.

The Cox proportional hazard model showed that metachronous multiple primary lung cancer was an independent poor prognostic factor (hazard ratio, 1.99; 95% confidence interval, 1.01 to 4.03). Tumor location, local recurrence, and tumor response were not significant prognostic factors (Table 5).

Discussion

The long-term results of PDT for a total of 48 patients with ROSCC are reported in this article. Our cases differed from those in previous studies[1,11–15] in the following respects. First, all patients were medically operable; they selected PDT after fully informed consent. We offered two options (*ie*, surgical resection and PDT) to patients with ROSCC who were medically operable and met our PDT criteria, as mentioned earlier. Most of them selected PDT after fully informed consent, although we did not have the precise number of patients who selected surgery. Second, all lesions were marked by

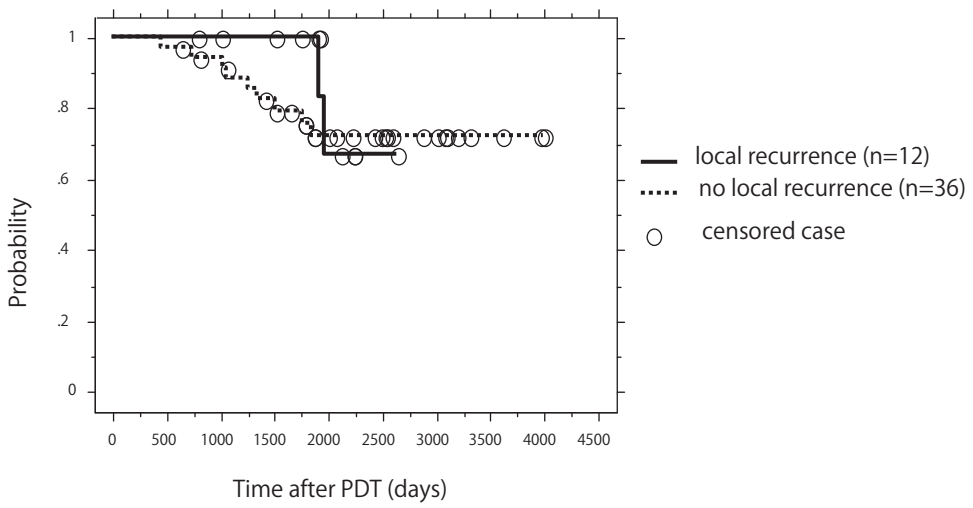

Figure 1. OS and local recurrence. The 5-year survival rates of patients with and without local recurrence were 100% and 76%, respectively, indicating no statistically significant difference (log-rank test $p = 0.62$).

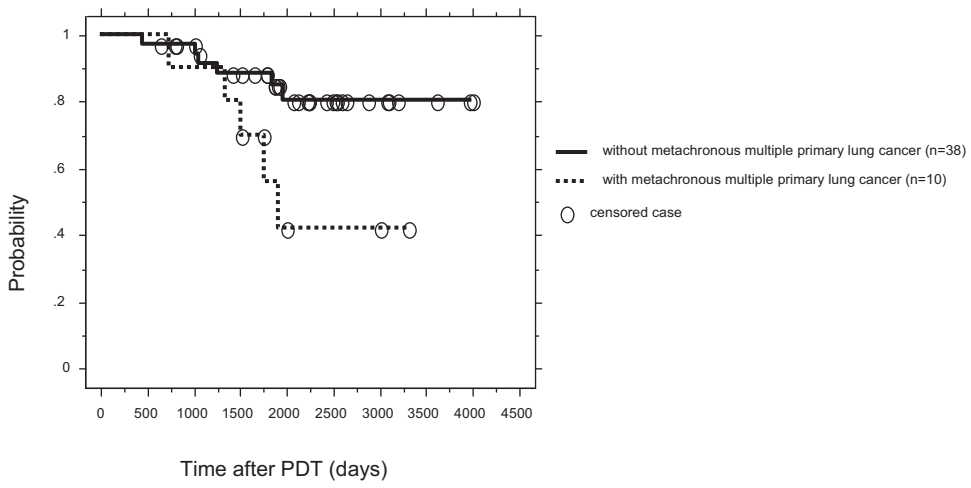

FIGURE 2. OS and metachronous multiple primary lung cancer. The 5-year survival rates of patients with and without metachronous multiple primary lung cancer were 56% and 88%, respectively, indicating a statistically significant difference (log-rank test p = 0.031).

only a superficial change in the bronchial epithelium. In previous articles,[1,13–18] some lesions had nodular findings, which meant that not all cases necessarily possessed superficial changes in the bronchial epithelium. It has been shown[14,19–21] that some tumor qualities make successful treatment by PDT less likely. One of these qualities is tumor invasion into or beyond the cartilaginous layer of the bronchus. We reported previously that the depth of tumor invasion would be within the cartilaginous layer if the bronchoscopic finding was either "minute" or "hidden" according to our classification system.[3] An ROSCC with a bronchoscopic finding of "remarkable" sometimes invades beyond the cartilaginous layer. It was therefore supposed that the tumors found in our patients were less likely to invade beyond the bronchial cartilaginous layer and would therefore be more suitable for PDT. Last, our study followed up patients for a longer period than did those in other reports. Accordingly, the local recurrence rate and the incidence of metachronous multiple primary lung cancer should be more precise. Local recurrence was found only within 4 years of PDT. However, metachronous primary lung cancer was found even after that. To our knowledge, this is the first report where 10-year OS, RFS, and DFS after PDT have been described.

Table 5—*Multivariate Survival Analysis Using the Cox Proportional Hazard Model*

Variables	Hazard Ratio	95% Confidence Interval
Tumor location (segment or more peripheral bronchus)	0.71	0.31–1.94
Local recurrence (+)	0.71	0.16–1.70
Tumor CR	0.69	0.13–3.51
Metachronous multiple primary lung cancer (+)	1.99	1.01–4.03

The Cox proportional hazard model showed that metachronous multiple primary lung cancer was an independent poor prognostic factor (hazard ratio, 1.99; 95% confidence interval, 1.01 to 4.03). Tumor location, local recurrence, and tumor response were not significant prognostic factors. + = positive.

CR was achieved in 94% of patients, with a recurrence rate of 20%. Even if PDT is used only in patients in whom ROSCC is marked by a superficial change of the bronchial epithelium, some patients will have local recurrence. However, most of these patients can be cured by salvage therapy. Both the log-rank test and multivariate survival analysis with the Cox proportional hazard model showed that local recurrence had no influence on survival after PDT. However, the Cox proportional hazard model showed that multiple primary lung cancer was an independent prognostic factor. We have previously reported[22] the frequency and the treatment of multiple primary lung cancer in patients with resected roentgenographically occult lung cancer, where the cumulative rate of postoperative metachronous multiple primary lung cancer was 0.11 5 years after the initial operation, and the OS rates for solitary and multiple resected occult lung cancers 5 years after the initial operation were 0.90 and 0.59, respectively, which is a statistically significant difference ($p < 0.01$). Multicentricity in roentgenographically occult lung cancer is a very important matter in terms of prognosis after the initial treatment. Although the main themes in studying the effectiveness of PDT for lung cancer have so far been tumor response or local

recurrence, we also have to consider metachronous multiple primary lung cancer after PDT and its impact on prognosis.

As stated in the American College of Chest Physicians guidelines,[2] the use of PDT for patients who are surgical candidates has so far remained limited. Because all of our patients were medically operable, the current study could offer new important information. In our previous report[19] on the results of surgical treatment for ROSCC, the 5-year OS rate of the 94 ROSCC patients was 80%, which was comparable to the results of the current study. However, the 10-year OS rate of 207 patients undergoing surgical treatment for ROSCCs was 40%,[23] which was much lower than the 70% 10-year OS rate found in the current study. We do not know the precise reason for a greater 10-year survival after PDT than after surgery. However, the following could be the reason. PDT does not result in the pulmonary function loss, so that adequate therapy, including surgery, can be undertaken for either local recurrence or the subsequent primary lung cancer after PDT. However, pulmonary resection would cause pulmonary function loss, so that an additional resection may be impossible even if surgery is the most curative therapy for local recurrence or the subsequent primary lung cancer after the initial resection. Moreover, quality of life after PDT should be better than that after pulmonary resection.

The current study is one of the largest assessing the effectiveness of PDT for early lung cancer. The design of the study was retrospective and observational, so its information might be limited. However, when PDT is employed with curative intent, its main targets are centrally located, early bronchogenic squamous cell carcinomas, which account for a very small percentage of all lung cancers. Given this fact, even retrospective studies can offer important information. Actually, to date, only one prospective study[1] has been published.

In summary, the current study indicates that PDT is thought to be a first-line modality for patients who have ROSCC with a tumor length of $\leq$ 10 mm, even if they are medically operable. After PDT, a 5-year OS rate of about 80% and a 10-year OS rate of 70% can be expected for these patients after PDT. Most local recurrence can be cured by salvage therapy such as surgery, radiotherapy, or PDT. During long-term follow-up after PDT, lung cancer was the most frequent cause of deaths, and multiple primary lung cancer was the most important issue from the viewpoint of survival. Further study, especially a prospective study, should be conducted to get a robust data of PDT for medically operable patients with ROSCC.

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