Photodiagnosis and Photodynamic Therapy 30 (2020) 101698

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Clinical trial of photodynamic therapy for peripheral-type lung cancers using a new laser device in a pilot study

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ARTICLE INFO

Keywords:
Photodynamic therapy (PDT)
Peripheral type lung cancer
Laser
Photosensitizer
Endobronchial treatment
Clinical trial

ABSTRACT

Introduction/Aim: Photodynamic therapy (PDT) involves the use of a tumor-specific photosensitizer and laser irradiation, and is one of the treatment options recommended for early centrally located lung cancers, but not yet for peripheral-type lung cancers. We developed a new laser probe, the composite-type optical fiberscope (COF), which allows accurate laser irradiation of a cancer lesion with simultaneous visualization of the lesion. In this study, we attempted a new endobronchial PDT technique using the new laser probe, and evaluated the effectiveness and feasibility of this novel PDT technique for peripheral lung cancers.

Methods: This phase I study was conducted in 7 patients with peripheral lung cancers (primary tumor ≤ 20 mm in diameter). We performed endobronchial PDT for these patients using the new laser probe and talaporfin sodium as the photosensitizer.

Results: We performed PDT for 3 patients with peripheral lung cancer using a laser dose of 50 J/cm^2 at 120 mW, and confirmed the feasibility of using this dose. Then, we escalated the laser dose to 100 J/cm^2 in 4 additional patients. A total of 7 patients met our inclusion criteria. Evaluation at 2 weeks and 3 months after the PDT revealed no complication such as pneumonia or pneumothorax. At the evaluation conducted 6 months later, we found CR in 3 cases and SD in the remaining 4 cases.

Conclusion: PDT was found to be a feasible and non-invasive treatment modality for early peripheral-type lung cancer. In the future, PDT could become a standard treatment option for peripheral-type lung cancer.

1. Introduction

Introduction Recently, the number of elderly patients with lung cancer has been increasing, and prompting the need for exploring minimally invasive treatment techniques. New pathological classifications for peripheral lung adenocarcinomas have been proposed, and new concepts, such as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), have been introduced [1,2]. Lung cancers of this type are often visualized as GGOs on chest CT and have a relatively good prognosis. In the future, for the treatment of AIS and MIA, neither surgery nor RT may be required. Minimally invasive treatments, such as endoscopic treatments, are unmet medical needs for such cancers..

For definitive diagnosis of small nodules in the peripheral lung, bronchoscopy using radial endobronchial ultrasound (R-EBUS) and a combination of this modality with virtual bronchoscopic navigation (VBN) are very useful [3–5]. Bronchoscopic diagnosis using these new techniques of R-EBUS and VBN has improved the diagnostic yield for small peripheral pulmonary lesions measuring less than 3.0 cm in diameter [6,7]. Especially, peripheral pulmonary lesions are easy to access by electromagnetic navigation bronchoscopy (ENB), such as that using the superDimension navigation system, and the accessibility and diagnostic rates of peripheral lung cancers have improved [8,9].

Photodynamic therapy (PDT) consists of using a tumor-specific photosensitizer and laser irradiation to induce the production of reactive oxygen species in cancer cells [10–12]. Since the first modern clinical trial of PDT reported by Dougherty et al., the photosensitizer photofrin has been applied for the treatment of many kinds of cancers

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https://doi.org/10.1016/j.pdpdt.2020.101698
Received 20 January 2020; Received in revised form 11 February 2020; Accepted 24 February 2020
Available online 18 March 2020

[13–16]. The second-generation photosensitizer, talaporfin sodium (Laserphyrin®) well known as mono-L-aspartyl chlorine e6 (NPe6), which has a major absorption band at 664 nm, was approved for the treatment of centrally located early lung cancers (CLELCs) by the Japanese Ministry of Health, Labour and Welfare in 2004 [17,18]. Kato and Furukawa et al. reported, based on a phase II clinical study, that PDT using talapofin and a diode laser was safe, including being associated with a significantly lower frequency of skin photosensitivity than photofrin-PDT, and showed excellent antitumor effect in patients with CLELs [17]. Usuda et al. reported that PDT using talaporfin exerted a strong antitumor effect against CLELCs measuring > 1.0 cm in diameter (19). According to their report, the CRs of centrally located lung cancers measuring ≤1.0 and > 1.0 cm in diameter were 94 % (66 of 70 cases) and 90.4 % (19 of 21 cases), respectively. We analyzed the relationship between the tumor size and clinical response and found no significant correlation between the tumor size and clinical response [19]. Moreover, there was no significant difference in the efficacy of talapofin-PDT between tumors ≤1.0 and > 1.0 cm in diameter.

However, until now, PDT has only been approved for centrally located lung cancers, but not for peripheral lung cancers, even though the accessibility and diagnosis rate of peripheral lung cancers have improved with the use of R-EBUS and/or VBN (5–7). This could be explained as there was no laser probe that could be inserted into peripheral lung lesions.

In this study, we report the use of a new laser probe developed by us, the composite-type optical fiberscope (COF), which allows accurate laser irradiation with simultaneous visualization of the cancer lesion. Oka et al. reported applying the COF technology to develop a new device for laser surgery to treat twin-to-twin transfusion syndrome [20,21]. In this study, we developed a new minimally invasive laser device using a COF with an external diameter of 1.0 mm, which can be introduced into peripheral lung lesions for laser irradiation. We conducted this phase I clinical study to investigate the feasibility and antitumor effect of PDT using talaporfin sodium and the new laser probe for peripheral-type lung cancers.

2. Methods and patients

2.1. Study design

This study was a phase-I, single-arm clinical trial conducted with the participation of 4 hospitals (Nippon Medical School Hospital, National Cancer Center Hospital, Tokyo Medical University Hospital, and Asahikawa Medical College Hospital) in Japan (Clinical Trial Japanese Registration URL: www.umin.ac.jp. Unique identifier: UMIN000021501), after obtaining approval from the ethics committee of each of the participating institutions. The clinical study was supported by Research on Development of New Medical Device, Japan Agency for Medical Research and Development.

At first, we used a target dose for laser irradiation of 50 J/cm^2 of the lesion on the maximum-section plane on sliced CT in 3 cases. If there were no adverse events of grade 3 or greater severity, the laser dose was to be increased to 100 J/cm^2 of the lesion on the maximum-section plane (Fig. 1). Thus, the dosing conditions for laser irradiation were the same as those used for PDT of centrally located early lung cancers [17–19]. If the maximum tumor cross-sectional area was greater than 1.0 cm^2, irradiations were undertaken from multiple directions to irradiate the entire tumor.

2.2. Patients

Patients with clinical stage IA (7th edition of the TNM classification for lung cancer) were included if they were 20 years of age or older, and had cytologically or histologically confirmed (by transbronchial lung biopsy (TBLB) diagnosis of non-small cell lung cancer. Other eligibility criteria were presence of measurable disease (lesions were ≤20 mm in diameter as measured on CT images), with no metastasis to the hilar/mediastinal lymph nodes or distant metastasis, patients who were unsuitable candidates for, or did not desire, surgery or radiation therapy, and an Eastern Cooperative Oncology Group performance status of 0–2. Written informed consent was obtained from each patient prior to his/her participation in the study.

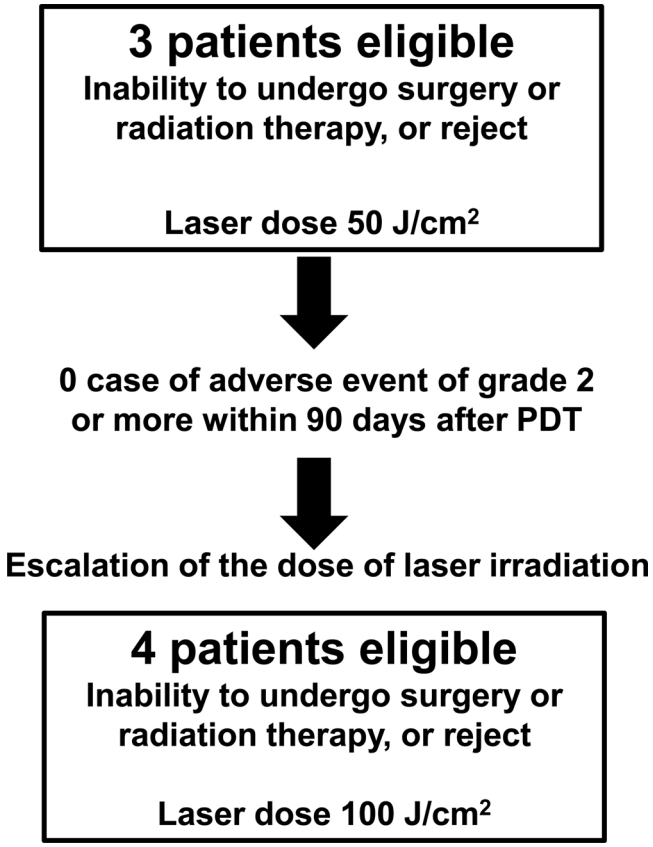

Fig. 1. Study design of talaporfin-PDT for peripheral-type lung cancers. Patients who were unsuitable candidates for surgery, or not desirous of undergoing surgery or radiation therapy, were enrolled in this study. PDT was to be undertaken for the first three patients at a laser dose of 50 J/cm^2 of the lesion on the maximum-section plane on sliced CT; if there were no adverse events of grade 3 or greater severity, the laser dose was to be increased to 100 J/cm^2 of the lesion on the maximum-section plane of sliced CT.

2.3. Photosensitizer

Talaporfin sodium, or NPe6 (Laserphyrin®, Meiji Seika Pharma Co., Ltd., 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 [17–19]. Talapofin sodium exhibits superior tumor affinity, and is excited by visible red light with a longer wavelength of 664 nm.

2.4. Laser unit

A diode laser (OK Fiber Technology Co., Kyoto, Japan) emitting continuous-wave laser light at a wavelength of 664 nm was used as the light source for the excitation of NPe6.

2.5. Laser probe

We developed the composite-type optical fiberscope (COF), a new laser probe, which allows accurate laser irradiation with simultaneous

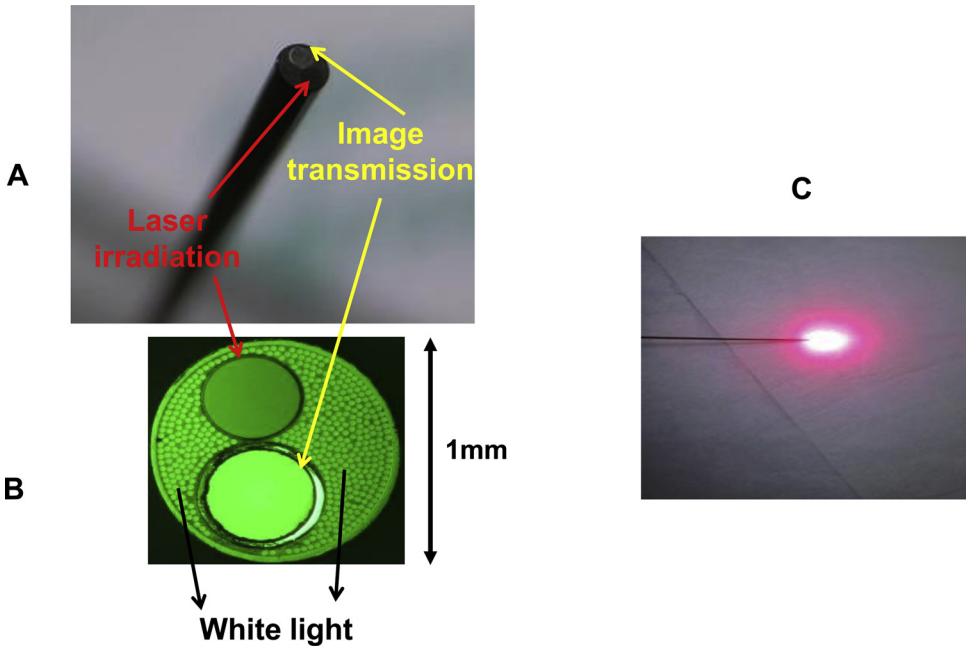

Fig. 2. Composite optical fiberscope. Red arrow shows the lens on the tip that focuses the red light laser. Yellow arrow shows the lens on the tip that transmits the images for visualization. A) Tip of the composite-type optical fiberscope with an external diameter of 1.0 mm. The red arrow shows the port of the laser irradiation, and the yellow arrow shows the port of image transmission. There are a lot of fibers that pass white light around the two pots. (B) The COF was a straight-type laser probe, not a cylindrical-type.

visualization of the cancer lesion. Oka et al. reported applying the COF technology to develop a new device for laser surgery to treat twin-to-twin transfusion syndrome [20]. For this study, we designed and developed a new minimally invasive laser device using a COF with an external diameter of 1.0 mm, which can be introduced into peripheral lung lesions for laser irradiation (Fig. 2). The COF has one optical fiber with diameter of φ0.4 mm for laser transmission and the image transmission of approximately 10,000 optical fibers with φ0.5 mm lens on the tip, which were surrounded by many thin optical fibers for white light transmission (Fig. 2A, B, C).

2.6. PDT procedure

The photosensitizer, talaporfin sodium (40 mg/m^2), was administered 4–6 hours prior to the laser irradiation for PDT. First, under general anesthesia, we introduced a guide sheath (GS) into the peripheral lung cancer lesion, and examined the lesion by radial endobronchial ultrasound (R-EBUS) and chest X-ray. The R-EBUS probe and laser probe can be introduced repeatedly to the same site with the use of the GS [5–7].

Before inserting the COF, we inject a little of saline buffer (about 1 ml) into the guide sheath to make it clearly visible. Then, the COF was introduced through the GS into the cancer lesion, followed by laser irradiation at the dose of 50 J/cm^2 (150 mW/cm^2) or 100 J/cm^2 (150 mW/cm^2). A few days after the PDT, the patient was discharged.

2.7. Follow-up and endpoints

This multicenter single-arm study was performed with the objective of investigating the feasibility and efficacy of PDT for peripheral-type lung cancers. The primary endpoint was the rate of occurrence of grade 2 or more severe adverse events within 90 days after the PDT, because adverse events occurring in the short term after PDT are often more serious and considered more important.

The secondary endpoints were as follows: 1) local-progression-free survival (PFS)rate 90 days after the PDT, 2) local-PFS rate 1 year after the PDT, 3) adverse events from the time of the primary assessment to 1 year after the PDT.

TBLB was performed 3 months after the PDT, to evaluate local control. Chest CT was performed at 3, 6, 9, and 12 months after the PDT.

2.8. Evaluation of outcomes

If the cancer lesions were no longer visible on thin-section CT at 90 days after the PDT, it was judged as complete response (CR). Alternatively, a negative transbronchial biopsy/cytology at the same time was also judged as CR. Thereafter, if there was no increase in the tumor size on thin-slice CT, the CR was continued. Even if the tumor was malignant by biopsy after PDT, it was determined to be stable disease (SD) if the tumor size was not increased by chest CT.

Progressive disease (PD): According to the RECIST guidelines (revised version 1.1), target lesions were evaluated by chest CT. When the sum of the major axes of the target lesion increases by 20 % or more compared to the minimum sum of the major axes up to the evaluation including the baseline, and the absolute value of the sum of the major axes increases by 0.5 cm or more.

2.9. Adverse event reporting

The first patient was enrolled in March 2016. Enrolment was closed in April 2017, and last follow-up was performed in April 2018. Adverse events in this protocol were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (CTCAE v4).

3. Results

Seven patients, including five male and two female patients, were treated by talaporfin-PDT using the new laser probe, COF, which allows accurate laser irradiation of a lung cancer lesion with simultaneous visualization of the lesion (Table 1). We could simultaneously observe and irradiate the cancer lesions in the peripheral regions of the lung. To obtain a definitive histopathological/cytological diagnosis, we performed TBLB using a GS and/or R-EBUS for the peripheral lung tumors.

The mean age was 77.1 years (72–90), and the average size of the nodules was 16.7 mm (13.6–20). The histological type was adenocarcinoma in 6 patients and squamous cell carcinoma in 1 patient. The tumor lesion was in the upper lobe in 4 patients, and in the lower lobe in the remaining 3 patients.

For the first three patients, laser irradiation was performed at 50 J/cm^2 according to the protocol. Ninety days after the PDT, the occurrence rate of adverse events of grade 2 or higher severity was 0%. One

Table 1
The clinicopathologocal data of patients who were treated by talaporfin-PDT using the new laser probe.

	Age	Gender	Localization	Histology	Size (mm)	energy (J/cm2)	3 months	1year	adverse event
1	90	Man	Rt.S2	Adeno Ca	20	50	CR	CR	–
2	71	Woman	Lt. S3	Adeno Ca	10	50	CR	CR	Skin photosensirtivity (Grade 1)
3	81	Man	Lt. S3	Squamous cell Ca	14	50	SD	SD	–
4	76	man	Lt. S9	Adeno Ca	19	100	SD	SD	–
5	82	Woman	Rt. S6	Adeno Ca	16	100	CR	CR	–
6	72	man	Lt. S1 + 2	Adeno Ca	12	100	CR	CR	–
7	73	man	Lt.S8	Adeno Ca	19	100	SD	SD	–

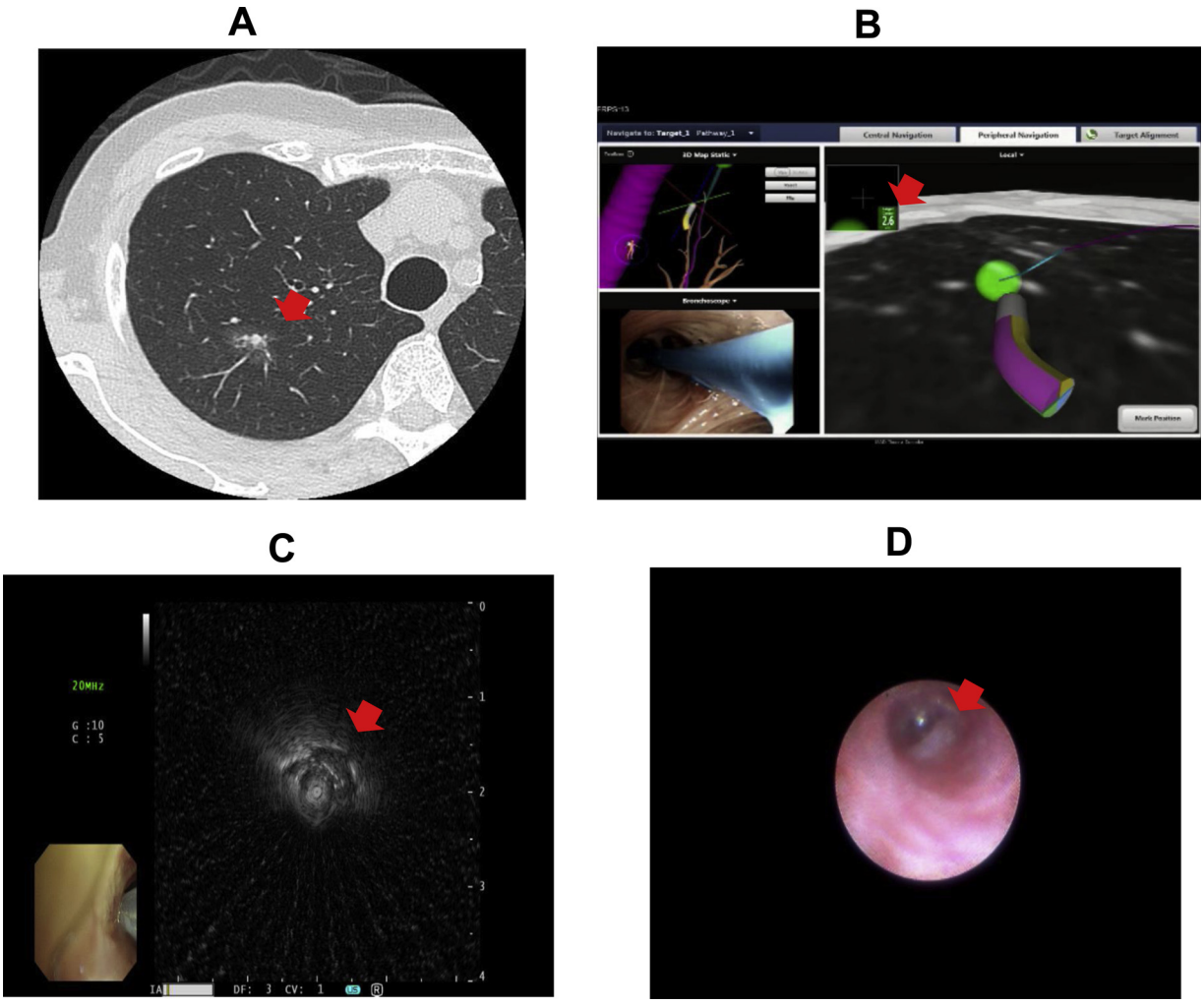

Fig. 3. A) Chest CT showing the cancer lesion in rt S^2. The tumor is visualized as a GGO with a solid component, and measured 20 mm in diameter. B) A navigational bronchoscopy image using superDimension. The green ball represents the right upper nodule at rt S^2 in the apical segment. The red arrow shows the alignment of the guide sheath with the target at 2.8 cm distance. C) R-EBUS image of the tumor. The red arrow shows the tumor lesion. D) Image of the peripheral-type lung cancer lesion as visualized by the COF. The red arrow shows the tumor.

patient (Case 2) showed grade 1 skin photosensitivity. We confirmed that talaporfin-PDT using the new laser probe was feasible after successful treatment of 3 patients at the laser dose 50 J/cm^2. According to the protocol, we administered PDT at an escalated laser dose of 100 J/cm^2 to the remaining 4 patients. Of the total of 7 patients in this clinical study, one case (Case 2) showed photosensitivity; no other treatment-related complications were encountered (Table 1). There were no major complications such as pneumothorax, hemothorax or pneumonia. Fig. 3 shows the clinical profile of Case 1. The patient was a 90-year-old man; the diagnosis was definitively established by TBLB as adenocarcinoma, c-T1bN0N0 stage IA in rt S^2 (Fig. 3A). The patient refused surgical resection and SBRT, and desired to undergo PDT using the new laser probe. Talaporfin sodium at the dose of 40 mg/m^2 was administered by intravenous injection 4 h before the PDT. We introduced the guide sheath (GS) into the cancer lesion using superDimensionTM ENB, a bronchoscopic navigation system (Fig. 3B). Using this system, it is easy to determine the distance to the target lesion in real time and accurately introduce the GS. In addition, the ultrasound probe was introduced though the GS and the cancer lesion was located accurately (Fig. 3C). Subsequently, we removed the EBUS probe from within the GS. A saline buffer was injected into the peripheral side of the bronchus, and the peripheral bronchus was dilated. We inserted the new laser probe, the COF, into the cancer lesion, visualized the tumor and irradiated the tumor with red laser (664 nm) (Fig. 3D). The endpoint of this study was

the occurrence rate at 90 days after the PDT of adverse events of grade 2 or higher severity in the patients, and the rate was 0%. At 3 months after the PDT, 4 patients showed CR, and at 1 year after the PDT also, CR was observed in 4 patients (Table 1). As the secondary endpoint, the local-progression-free survival rate at 90 days and at 1 year after the PDT was 100 %. From these results, we concluded that PDT using the new laser probe for peripheral-type lung cancer is feasible and very effective.

4. Discussion

Recently, use of chest CT imaging and implementation of lung cancer screening have expanded, and the detection rate of peripheral lung nodules is increasing [7–9]. At present, for lung cancer lesions in the lung periphery measuring less than 30 mm in diameter, surgical resection remains the treatment modality of choice. However, the prognosis of small nodules visualized as GGOs may be good, and surgical resection may not be necessary. For these cancers, minimally invasive treatments, such as bronchoscopic treatment, may be desirable. Okunaka et al. reported that percutaneous-PDT for peripheral lung cancer was effective and promising [22]. However, the percutaneous approach for PDT may cause pneumothorax, and cerebral infarction by air embolism [7]. Therefore, recently, bronchoscopy-guided radiofrequency ablation (RFA) has been developed and applied for the treatment of peripheral lung cancers [7,23,24]. It has been reported that RFA and microwave treatment generate heat and bubbles around the tumor [7,23,24]. However, lasers used for PDT have low power and do not generate heat, and are safer than RFA. Even if RFA or microwave treatment can be performed, PDT may be more feasible and perhaps better.

In this study, 4 of the 7 enrolled patients showed CR, both at 3 months and at 1 year after the PDT, because histopathological examination of TBLB specimens showed no evidence of malignancy. However, no significant reduction of the tumor size was observed on the chest CT images. In a study conducted by our colleagues, Okunaka et al., in which nine patients with peripheral lung cancers were enrolled for treatment of the cancer by PDT using catheters placed percutaneously under CT guidance [22], the tumor size did not change much. It is also difficult to evaluate the antitumor effect of SBRT on the chest CT. Although PET-CT assessment may be an option to determine the efficacy of SBRT and PDT, it is not a sufficient assessment.

This is because inflammatory effect was induced after PDT, and PETCT does not always reflect the therapeutic effect. It is important to properly evaluate the antitumor effect of PDT, so that it can be established as a valid treatment modality for the future.

To improve the feasibility and efficacy of PDT, guidance of the COF, the laser probe, is very important. To guide the probe precisely to the cancer lesion, cylindrical-type rather than straight-type fibers would be more effective. In the future, we think that it is necessary to develop these two types of laser probes, and consider how to use them properly for accurate placement at the cancer lesion. Moreover, establishment of the laser irradiation method and simulation of the irradiation dose as in radiation treatment planning are future problems to be addressed.

This multicenter clinical trial was the world's first trial of talaporfin-PDT for c-stage IA peripheral lung cancer. PDT was found to be a feasible and non-invasive treatment modality for early peripheral lung cancers. In the future, talaporfin-PDT could become a useful treatment modality for non-invasive adenocarcinomas, such as AIS, MIA, and the standard option for stage IA peripheral lung cancers.

Acknowledgments

This study was supported by Research on Development of New Medical Device, Japan Agency for Medical Research and Development (17hk0102025h0003).

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