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The Efficacy and Safety of Acupuncture for Preventing Radiation Pneumonitis in Patients With Lung Cancer: A Prospective, Single-Blinded, Randomized Pilot Proof-of-Principle Study

Moonkyoo Kong, MD, PhD[1], Seung Hyeun Lee, MD, PhD[1], Jaehyo Kim, KMD, PhD[2,3], Beom-Joon Lee, KMD, PhD[2], and Kwan-Il Kim, KMD, PhD[2]

Abstract

Purpose: We evaluated the efficacy and safety of acupuncture for prevention of radiation pneumonitis in patients with lung cancer. **Methods:** Twenty-five patients were prospectively enrolled in this study and randomized to either intervention group or control group. The patients assigned to the intervention group received 15 minutes of acupuncture treatment twice a week. The patients assigned to the control group received RT alone without acupuncture treatment. The primary endpoint was incidence of radiation pneumonitis. The secondary endpoints were FEV1 (forced expiratory volume in 1 second), DLCO (diffusing capacity for carbon monoxide), 6-minute walk distance, and modified Borg scale. **Results:** The intervention group showed lower incidences of grade 3 and grade ≥2 radiation pneumonitis than the control group (10% vs 30% for grade 3 and 50% vs 60% for grade ≥2). In the control group, mean DLCO value was decreased from 62.1% at baseline to 49.1% after RT ($P = .004$). The DLCO was also decreased after RT in the intervention group, but the decrement was not statistically significant (56.7% at baseline and 50.9% after RT, $P = .204$). The FEV1 and 6-minute walk distance were decreased after RT in the control group. However, FEV1 and 6-minute walk distance were increased after RT in the intervention group. **Conclusions:** This study found that patients who received acupuncture treatment showed a lower incidence of radiation pneumonitis and a protective effect against aggravation of pulmonary function after RT in patients with lung cancer. To confirm the results of this study, well-designed randomized studies with large sample sizes will be required.

Keywords

radiation pneumonitis, lung cancer, radiotherapy, acupuncture, pulmonary function

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Introduction

Radiotherapy (RT) plays an important role in lung cancer. For early-stage lung cancer, stereotactic radiosurgery has been used as a standard treatment for patients who are not candidates for or refuse surgical resection. For patients with locally advanced lung cancer, definitive RT with concurrent chemotherapy remains the standard treatment. Radiation pneumonitis is the most common complication of thoracic RT and causes clinical and economic problems in patients with lung cancer.[1-4] Although many clinical studies attempting to reduce radiation pneumonitis have been conducted, no effective agents currently exist.[5] Amifostine has been considered an effective protective agent for radiation toxicities;

[1]College of Medicine, Kyung Hee University, Seoul, Republic of Korea
[2]College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
[3]College of Medicine, Yonsei University, Seoul, Republic of Korea

Corresponding Author:
Beom-Joon Lee, Division of Allergy, Immune and Respiratory System, Department of Internal Medicine, Kyung Hee University Medical Center, College of Korean Medicine, Kyung Hee University, 26 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Republic of Korea.
Email: franchisjun@naver.com

however, the results of clinical trials are controversial. In addition, systematic reviews do not support the effectiveness of amifostine for the prevention of radiation pneumonitis.[6]

In recent years, the interest of physicians in traditional medicine to treat modern medical conditions has increased. In Korea, several herbal medicines have been used to prevent radiation pneumonitis. A recent meta-analysis reported that incidence of radiation pneumonitis decreased significantly in the groups of patients who received RT combined with herbal medicine compared with those who received RT alone. However, a definitive conclusion could not be drawn due to the poor methodological quality of the included studies.[7] Acupuncture is another representative treatment modality of traditional medicine in Korea. Several studies have reported that acupuncture improved dyspnea and lung function in patients with chronic obstructive pulmonary disease (COPD),[8,9] and a review of 16 randomized controlled trials concluded that acupuncture is a potentially effective intervention for improvement of dyspnea in patients with COPD and asthma.[10] In 2015, a pilot study also reported that acupuncture exhibited relief of dyspnea in patients with lung cancer.[11] In addition, because acupuncture treatment has been shown to reduce pulmonary inflammation,[12,13] we can hypothesize that acupuncture has beneficial effect for prevention of radiation pneumonitis. However, there are no reports that analyzed the effect of acupuncture on radiation pneumonitis. In this pilot proof-of-principle study, we evaluated the efficacy and safety of acupuncture in the prevention of radiation pneumonitis in patients with lung cancer.

Materials and Methods

Inclusion criteria were histologically proven primary lung cancer, receipt of RT with or without chemotherapy, receipt of a total RT dose ≥50 Gy, Eastern Cooperative Oncology Group performance status ≤3, no prior thoracic irradiation, no previous or concurrent illness that would compromise completion of RT, and available follow-up data. Patients who underwent pre-RT surgical resection were excluded from this study. Patients who underwent radiosurgery were also excluded. The institutional review board of our institution approved this study (KMC IRB 2016-08-046), and all research was conducted in compliance with the Declaration of Helsinki guidelines. We obtained written informed consent from all patients. This trial was retrospectively registered in the CRIS registration system (KCT0004550).

The initial diagnosis was pathologically confirmed in all patients based on either endoscopic bronchial or percutaneous needle biopsy. The cancer stage was ascertained according to the eighth edition of the American Joint Committee on Cancer Staging System. At 1 week before the RT start, the forced expiratory volume in 1 second (FEV1), diffusing capacity for carbon monoxide (DLCO), 6-minute walk distance, and modified Borg scale were assessed in all patients.

From August 2017 through July 2018, 25 patients were prospectively enrolled in this study and randomized to either the intervention group or the control group. The randomization was stratified according to concurrent chemotherapy status (yes vs no) using a computer-generated random number list. The patients assigned to the intervention group received 15 minutes of acupuncture treatment twice a week. The acupuncture treatment was conducted from the first week of RT throughout the RT period. Because the planned RT duration was 6 weeks, scheduled acupuncture treatment sessions were scheduled for a total of 12 times. The practitioners were licensed Traditional Korean Medicine Doctors with at least 2 years of clinical experience and were not allowed to talk to patients to minimize other effects. The acupuncture points were decided in accordance with previous research on acupuncture for pulmonary inflammatory diseases and the literature describing the traditional prescription of acupuncture points.[8,11,14] The standardized acupuncture points used in this study were in total 27 and were as follows: both sides of acupoints of (1) LR3 (Taichong), (2) LI4 (Hegu), (3) LU1 (Zhongfu), (4) LU2 (Yunmen), (5) LU9 (Taiyuan), (6) BL13 (Feishu), (7) BL 20 (Pishu), (8) BL23 (Shenshu), (9) KI3 (Taixi), (10) GB12 (Wangu), (11) ST36 (Zusanli), and (12) PC6 (Neiguan), and single acupoint of (13) GV14 (Dazhiu), (14) CV4 (Guanyuan), and (15) CV12 (Zhongwan). The essential acupuncture points were LR3, LI4, LU1, LU2, LU9, BL13, BL20, BL23, ST36, and PC6. The additional acupuncture points were KI3, GB12, GV14, CV4, and CV12. Sterile disposable acupuncture needles, 40 mm in length and 0.25 mm in diameter (Dong Bang Acupuncture Inc, Seoul, Republic of Korea), were used and inserted to a depth ranging from 5 mm to 25 mm. A sensation of *De-qi* (tingling, numbness, heaviness) was achieved during the manipulation of needles at every point. Compliance with the acupuncture treatment was evaluated weekly by one of the investigators. The patients assigned to the control group received RT alone without acupuncture treatment. Any medications for radiation pneumonitis were not allowed in either group during RT period. After completion of RT, the patients who suffered from radiation pneumonitis received proper management depending on symptoms and grade of pneumonitis.

All patients received computed tomography (CT)-planned RT. RT targets encompassed the primary tumor and grossly involved lymph nodes. The patients who cooperated well with the instructions of medical staff underwent 4-dimensional CT. Elective nodal irradiation was not performed in all patients. A daily dose of 2 to 2.2 Gy was delivered at 5 fractions per week, resulting in a total dose of 60 to 70 Gy. The sequence and regimen of chemotherapy

were individualized based on patient performance status and compliance.

Patients were evaluated with weekly chest X-rays during RT. Follow-up visits were scheduled 2 weeks after completion of RT and every 1 to 2 months thereafter. Visits were more frequent for those who experienced treatment-related toxicities. Complete history and physical examination, basic laboratory studies, and chest radiograph were conducted at each follow-up visit. Chest CT and positron-emission tomography were also performed as needed. Radiation pneumonitis was diagnosed by a treating radiation oncologist on the basis of clinical symptoms and characteristic imaging findings within the RT field. Radiation pneumonitis was scored prospectively according to the toxicity criteria of the Radiation Therapy Oncology Group. To minimize interscorer variability, only one investigator scored the grade of radiation pneumonitis. This investigator was not involved in patient assignment or assessing patients' compliance with treatment. Therefore, we could maintain blinding throughout the study. Patients presenting with severe symptoms unresponsive to antitussive agents with suspicious radiologic changes were treated with steroids and scored as grade 3 radiation pneumonitis. Because a previous study reported that a significant decrease in pulmonary function was observed 3 months after RT completion,[15] we reassessed FEV1, DLCO, 6-minute walk distance, and modified Borg scale in all patients at 3 months after RT completion. Any adverse events associated with acupuncture treatment were evaluated using Common Terminology Criteria for Adverse Events, version 4.0.

The primary endpoint was incidence of radiation pneumonitis. The secondary endpoints were FEV1, DLCO, 6-minute walk distance, and modified Borg scale. FEV1 and DLCO were expressed as a percentage of normal values. Change in pulmonary function parameters (FEV1, DLCO, 6-minute walk distance, and modified Borg scale) was defined as the differences between baseline and post-RT 3 months values (post-RT 3 months value − baseline value). Baseline characteristics between the groups were compared using a χ^2 test for discrete variables and independent *t* test for continuous variables. The incidence of radiation pneumonitis between the groups was compared using a χ^2 test. To evaluate the changes in pulmonary function parameters after RT, we compared the baseline values with post-RT 3 months values using the paired *t* test. To investigate whether changes in pulmonary function parameters were different between intervention and control groups, the independent *t* test was used. All tests were 2-tailed, and a $P < .05$ was considered statistically significant. All analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY).

Results

Of the 63 patients who received RT for treatment of lung cancer from August 2017 to July 2018, 25 patients were enrolled in this study. Among the 14 patients assigned to the intervention group, 3 patients refused to receive acupuncture treatment after undergoing 1, 2, and 2 sessions of acupuncture treatment because they were busy and had no time for acupuncture treatment. In addition, 1 patient declined to receive RT after 4 sessions of RT. Among the 11 patients assigned to the control group, 1 patient refused to receive RT after 3 sessions of RT. The remainder of the patients completed scheduled RT and acupuncture treatment without interruption and complied well with the instructions of investigators. Therefore, 10 patients in the intervention group and 10 patients in the control group were included in efficacy and safety analyses (Figure 1). Patient characteristics are summarized in Table 1.

All patients were followed for more than 6 months. During the follow-up period, all patients experienced radiation pneumonitis. Grade ≥2 radiation pneumonitis developed in 11 patients (55%) and grade 3 in 4 patients (20%). No patient experienced grade ≥4 radiation pneumonitis. All radiation pneumonitis developed within 4 months after RT completion. Cumulative incidence of radiation pneumonitis is depicted in Figure 2. All patients with radiation pneumonitis were successfully treated with conservative management. One patient with grade 3 pneumonitis in the intervention group and 2 patients with grade 3 pneumonitis in the control group were treated with 0.5 mg/kg of prednisone for 1 week, followed by tapering over 4 weeks. One other patient with grade 3 pneumonitis in the control group recovered well without steroid agents. Mean FEV1 value was 67.4% (range, 42-103) at baseline (1 week before RT start) and 66% (range, 41-86) at 3 months after RT completion ($P = .375$). Mean DLCO value significantly decreased from 59.4% (range, 39-85) at baseline to 50% (range, 35-67) at 3 months after RT completion ($P = .006$). Mean 6-minute walk distance was 371 m (range, 165-531) at baseline and 361 m (range, 30-531) at 3 months after RT completion ($P = .375$). Median modified Borg scale was 3 (range, 0-7) at baseline and 3 (range, 0-5) at 3 months after RT completion ($P = .693$).

The results of the primary and secondary endpoints are summarized in Table 2. In the intervention group, only 1 patient (10%) experienced grade 3 radiation pneumonitis and 5 patients (50%) experienced grade ≥2 radiation pneumonitis. In comparison, 3 patients (30%) experienced grade 3 radiation pneumonitis and 6 patients (60%) experienced grade ≥2 radiation pneumonitis in the control group. The intervention group showed lower incidences of grade 3 and grade ≥2 radiation pneumonitis than the control group (10% vs 30% for grade 3 and 50% vs 60% for grade ≥2).

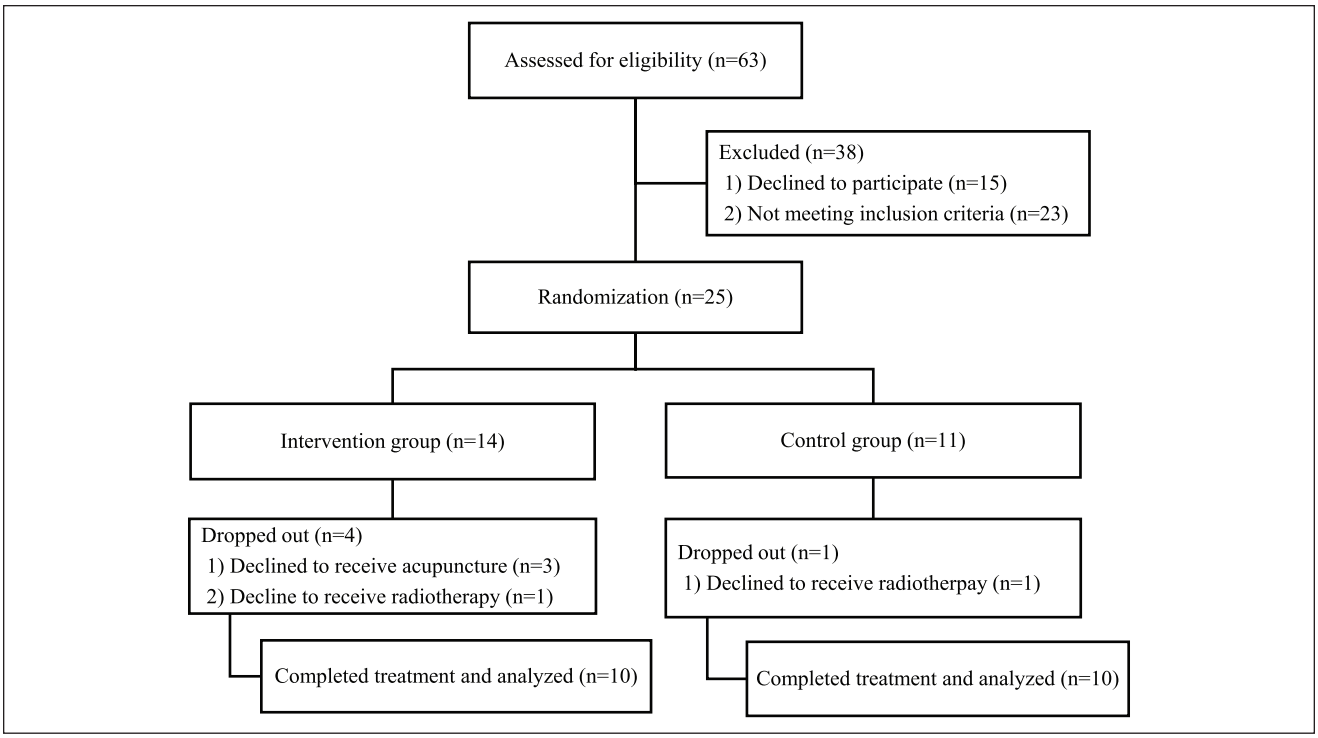

Figure 1. Study participant flow diagram in this pilot study.

In the control group, DLCO was significantly decreased after RT. The mean DLCO value was decreased from 62.1% (range, 47-85) at baseline to 49.1% (range, 35-66) at 3 months after RT completion ($P = .004$). The DLCO was also decreased after RT in the intervention group, but the decrement was not statistically significant. Mean DLCO value was 56.7% (range, 39-74) at baseline and 50.9% (range, 37-67) at 3 months after RT completion ($P = .204$). The intervention group showed a protective effect against aggravation of DLCO after RT.

The FEV1 and 6-minute walk distance were decreased after RT in the control group. Mean FEV1 decreased from 73.6% (range, 48-103) at baseline to 69.7% (range, 54-83) at 3 months after RT completion, and mean 6-minute walk distance decreased from 358 minutes (range, 180-434) at baseline to 350 minutes (range, 165-420) at 3 months after RT completion. However, FEV1 and 6-minute walk distance were increased after RT in the intervention group. Mean FEV1 increased from 61.2% (range, 42-86) at baseline to 62.3% (range, 41-86) at 3 months after RT completion, and mean 6-minute walk distance increased from 365.7 minutes (range, 30-502) at baseline to 384.1 minutes (range, 295-531) at 3 months after RT completion. The intervention group showed an improvement of FEV1 and 6-minute walk distance after RT.

The modified Borg scale was not changed after RT in both groups. Adverse events associated with acupuncture including subcutaneous hemorrhage, pain, nerve injury, nausea, vomiting, and headache were evaluated in all patients assigned to the intervention group. However, no patient experienced side-effects from acupuncture treatment.

Discussion

In this prospective randomized study, we evaluated the efficacy and safety of acupuncture treatment in the management of radiation pneumonitis in patients with lung cancer. Although this is a pilot study with small sample size, we found that patients who received acupuncture treatment showed lower incidence of radiation pneumonitis and protective effect against aggravation of pulmonary function after RT. In addition, acupuncture treatment did not cause any side-effects. To the best of our knowledge, this is the first study to report the efficacy of acupuncture treatment on radiation pneumonitis.

This pilot study was conducted to investigate whether acupuncture treatment is safe and effective for preventing radiation pneumonitis in a descriptive manner. Statistical significance was not an essential assessment criterion because the results were expected to form the basis for the power calculation for further large sample size studies. Although we did not find significant statistical differences, acupuncture treatment seemed to reduce the incidence of radiation pneumonitis and prevent aggravation of pulmonary function after

Table 1. Patient Characteristics.

Characteristics	Intervention Group (n = 10)	Control Group (n = 10)	*P*
Age (years)			
Median (range)	65 (52.2-77.7)	69.9 (62-83.1)	.112
Gender			
Male/female	7/3	8/2	.574
ECOG performance status			
0/1/2	3/4/3	4/5/1	.241
AJCC stage			
II/III	3/7	2/8	.868
Site 1			
Right/left	7/3	6/4	.722
Site 2			
Upper/lower or middle	5/5	5/5	.963
Smoking status			
Current/former/never	5/1/4	5/3/2	.495
Alcohol status			
Current/former/never	4/0/6	4/2/4	.284
Histology			
SqCC/adenoca/SCLC	4/3/3	6/2/2	.179
Underlying lung disease			
Yes/no	2/8	3/7	.636
Diabetes mellitus			
Yes/no	4/6	3/7	.461
Chemotherapy			
Yes/no	7/3	7/3	.974
V20 (%)			
Median (range)	23 (4.2-45)	18.1 (6-40)	.457
Mean lung dose (Gy)			
Median (range)	13.4 (1.5-21.2)	10.2 (3.8-21.3)	.554
RT technique 1			
3D-CRT/IMRT	2/8	1/8	.736
RT technique 2			
3D simulation/4D simulation	3/7	3/7	.961
Total RT dose (Gy)			
Median (range)	66 (60-70)	66 (60-70)	.807
Daily RT dose (Gy)			
Median (range)	2 (2-2.2)	2 (2-2.2)	.917
GTV (cc)			
Median (range)	97.6 (18.2-444.4)	126 (38.3-258.3)	.431

Abbreviations: ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; SqCC, squamous cell carcinoma; adenoca, adenocarcinoma; SCLC, small cell lung cancer; RT, radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; 3D, 3-dimensional; 4D, 4-dimensional; GTV, gross tumor volume.

thoracic RT. We believe that the results of our study can be an important basis for further large-scale clinical trials. Based on the results of this study, we plan to conduct additional studies to confirm the efficacy of acupuncture treatment for preventing radiation pneumonitis in patients who received thoracic RT.

Although the pathophysiologic process of radiation pneumonitis is complex and has not yet been clarified, ionizing radiation-induced cell damage, cytokine release from damaged lung cells, cytokine recruitment of inflammatory cells to the alveoli and pulmonary interstitium, and subsequent acute pulmonary inflammation are fundamental steps for development of radiation pneumonitis.[16-19] In East Asia, acupuncture treatment has been used for various inflammatory diseases such as rhinitis, rheumatoid arthritis, and inflammatory bowel disease for hundreds of years.[20] Moreover, acupuncture treatment has been shown to reduce pulmonary inflammation in asthma and COPD.[8-10,12,13] Several studies reported the possible mechanisms for the anti-inflammatory effect of acupuncture treatment. There

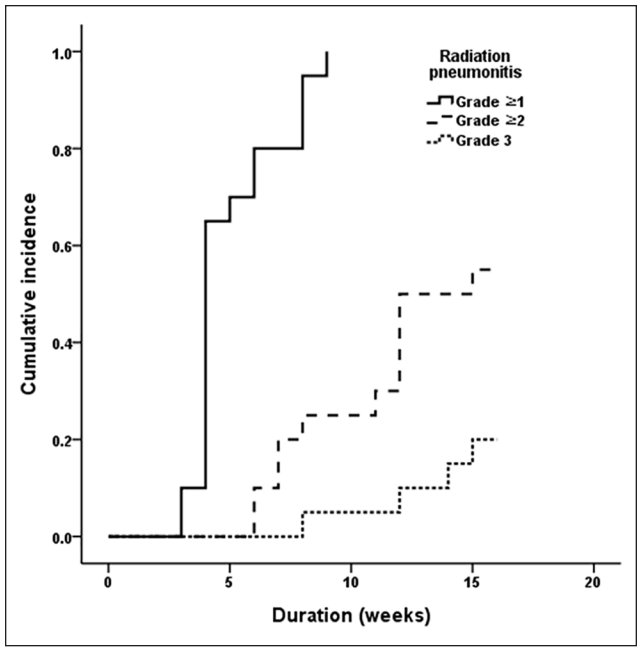

Figure 2. Cumulative incidence of radiation pneumonitis. Grade ≥1 radiation pneumonitis developed in all patients, grade ≥2 in 11 patients (55%), and grade 3 in 4 patients (20%).

are a few representative mechanisms. First, acupuncture regulates the cytokine expression through the cholinergic inflammatory pathway. Acupuncture regulates the autonomic nervous system via the increase of acetylcholine and inhibits the expression of pro-inflammatory cytokines.[21] Acupuncture has also been reported to reduce the secretion of pro-inflammatory cytokines such as tumor necrosis factor, interleukin-1β and interleukin-6, all of which are important cytokines in the development of radiation pneumonitis.[22] In addition, the efferent vagus nerve is stimulated by acupuncture and mediates cholinergic signaling that inhibits pro-inflammatory responses via the inflammatory reflex.[23,24] Second, acupuncture acts on the hypothalamic-pituitary-adrenal axis through stimulating the vagus nerve leading to subsequent secretion of glucocorticoids and inhibition of pro-inflammatory cytokine synthesis. Finally, acupuncture showed opioid-like anti-inflammatory effects via a chemokine-mediated proliferation of opioid-containing macrophages in inflamed tissues.[24,25] Given this background, we evaluated the efficacy and safety of acupuncture treatment on preventing radiation pneumonitis in patients who received thoracic RT.

Although many studies have been conducted to find effective agents to prevent and reduce the incidence of radiation pneumonitis, there are no established guidelines for the treatment of radiation pneumonitis.[5] Many physicians use systemic glucocorticoids to treat symptomatic radiation pneumonitis, and many patients experience marked symptomatic relief after systemic glucocorticoid administration. However, long-term administration of glucocorticoids can cause several side-effects, and relapse of radiation pneumonitis is common after glucocorticoids withdrawal.[26] Randomized trials reported that amifostine has efficacy in reducing the incidence and severity of radiation pneumonitis,[27] and amifostine is the only radioprotective agent approved

Table 2. Analysis of Primary and Secondary End Points.

End Point		Intervention Group (n = 10)	Control Group (n = 10)	P^a
Incidence of radiation pneumonitis (%)	Grade ≥2	50	60	.653
	Grade 3	10	30	.264
FEV1 (%), mean (range)	Baseline	61.2 (42-86)	73.6 (48-103)	.037
	Post-RT 3 months	62.3 (41-86)	69.7 (54-83)	.261
		P^b .385	P^b .262	
	Change value[c]	1.1 (−21 to 17)	−3.9 (−49 to 10)	.481
DLCO (%), mean (range)	Baseline	56.7 (39 to 74)	62.1 (47 to 85)	.204
	Post-RT 3 months	50.9 (37 to 67)	49.1 (35 to 66)	.380
		P^b .204	P^b .004	
	Change value[c]	−5.8 (−13 to 0)	−13.0 (−44 to 1)	.112
6-minute walk distance (m), mean (range)	Baseline	365.7 (30 to 502)	358 (180 to 434)	.418
	Post-RT 3 months	384.1 (295 to 531)	350 (165 to 420)	.213
		P^b .281	P^b .795	
	Change value[c]	18.4 (−69 to 265)	−0.6 (−56 to 191)	.621
Modified Borg scale, median (range)	Baseline	3 (2 to 7)	3 (0 to 7)	.365
	Post-RT 3 months	3 (0 to 5)	3 (0 to 4)	.330
		P^b .500	P^b .497	
	Change value[c]	0 (−3 to 2)	0 (−4 to 2)	.864

Abbreviations: FEV1, forced expiratory volume in 1 second; RT, radiotherapy; DLCO, diffusing capacity for carbon monoxide.
[a] Intervention group value was compared with control group value using the independent *t* test.
[b] Post-RT 3 months value was compared with baseline value using the paired *t* test.
[c] Change value was defined as the difference between baseline and post-RT 3 months values (post-RT 3 months value − baseline value).

by the US Food and Drug Administration. However, many patients experience significant side-effects such as hypotension and nausea after amifostine administration. Moreover, because amifostine should be only injected intravenously, its use is limited in clinical practice. Some studies have also reported effectiveness of pentoxifylline, azathioprine, and cyclosporine for treatment of radiation pneumonitis,[28-31] but the results of these studies are not yet confirmed. Therefore, a current standard of care for radiation pneumonitis has not yet been established. If the results of our study are confirmed through well-designed randomized studies with large sample sizes, acupuncture treatment can be used as new treatment option for radiation pneumonitis in patients who received thoracic RT.

There were some limitations in this study. First, this is a preliminary study with small sample size. Second, because the patients were not blinded to their group assignment, possible confounding factors might have been present. Therefore, this study lacks sufficient power to make definite conclusions regarding the efficacy of acupuncture treatment on radiation pneumonitis. However, to minimize interobserver and/or intraobserver variation, only 1 investigator, who had more than 10 years of experience in evaluating and treating radiation toxicities, scored the grade of radiation pneumonitis. Moreover, the 2 experimental groups were well-randomized and had comparable patient and tumor characteristics.

In conclusion, this single-blinded randomized study found that patients who received acupuncture treatment showed a lower incidence of radiation pneumonitis and a protective effect against aggravation of pulmonary function after RT in patients with lung cancer. To confirm the results of this study, well-designed randomized studies with large sample sizes will be required.

Declaration of Conflicting Interests

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ORCID iDs

Moonkyoo Kong https://orcid.org/0000-0003-3703-0417
Beom-Joon Lee https://orcid.org/0000-0002-9567-4520

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