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Computed tomography-guided intraluminal brachytherapy in recurrent bronchogenic carcinoma: A clinical trial in a small group

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Abstract

Objective: The overall survival (OS) of lung cancer patients has been significantly extended as a consequence of chemotherapy and targeted drug utilization, which has resulted in an increase in local recurrences. The present study followed patients to evaluate the short-term and long-term efficacies and the safety of high-dose rate intraluminal brachytherapy (ILBT) in recurrent bronchogenic carcinoma patients, and investigate the factors that influence prognosis.

Methods: The clinical records, treatment, curable effects, and adverse events of 15 patients treated in the First Affiliated Hospital of Soochow University, Suzhou, China, who were diagnosed with recurrent bronchogenic cancer between 1 June 2009 and 30 September 2015 were reviewed, and survival analysis was assessed by the Kaplan–Meier method.

Results: A total of 15 recurrent bronchogenic carcinoma patients received ILBT, and information on curable effects and safety was available. The group consisted of two complete response (2/15), 11 partial response (11/15), one stable disease (1/15) and one progression disease (1/15). The response rate was 86.7% (13/15), and disease control (complete response + partial response + stable disease) was 93.3% (14/15). The dyspnea indexes of the patients decreased significantly in weeks 1, 2, 4, and 8 after ILBT treatment ($P < 0.001$). The average post-ILBT partial remission period was 5.27 ± 3.35 months, and the median partial remission period was 3.24 months. The combination therapy of ILBT and bronchofiberscope ($P = 0.013$), and a total ILBT dose of ≥20 Gy could produce a partial effective rate. The progress-free survival of patients was 9.5 months (95% CI 12.2–16.5 months), average progress-free survival was 15.8 ± 14.4 months, median OS was 32.0 months (95% CI 25.0–30.0 months), 1-year OS was 93.3% (14/15), and 3-year OS was 40.0% (6/15). The main adverse events were bronchospasm and hemoptysis (grade III); others were grade I–II.

Conclusion: Computed tomography-guided ILBT is a safe, effective palliative treatment for recurrent bronchogenic carcinoma, but it requires further study in larger groups.

KEYWORDS
external beam radiation therapy, high-dose rate, intraluminal brachytherapy, lung neoplasms, palliative care

1 | INTRODUCTION

The overall survival (OS) of lung cancer patients significantly expands as sufficient chemotherapeutic and targeted medicines are applied, which results in an increasing number of local recurrences. The quality of life and OS of patients are threatened by the loss of distal pulmonary function caused by airway obstruction. Researchers all over the world use various intracavitary treatments, including endotherm

knife, laser, cryotherapy, and stent implantation, to dredge airways in the short term and to improve pulmonary function.[1–5] However, the control rate of the tumor in surrounding bronchial walls and cavities does not increase largely after those treatments. Intraluminal brachytherapy (ILBT) can suppress tumor cell growth, eliminate local tumor tissues, release the airway quickly, delay the airway narrowing procedure, improve ventilator function, and improve therapeutic efficacy and quality of life. It is regarded as a secondary treatment that can be applied in patients with bronchial malignant tumors who have no chance for clinical surgery.[6] Other studies show that regular radiotherapy; that is, external beam radiation therapy (EBRT), can extend the catabatic period in combination with ILBT and can achieve ideal palliative treatment results.[7] The present study treated 15 recurrent bronchial cancer patients with high-dose ^{192}Ir afterloading produced by Nucletron (Veenendaal, the Netherlands), and a small sample clinical trial was carried out to evaluate the therapeutic efficacy and safety of computed tomography (CT)-guided ILBT.

2 | METHODS

2.1 | Patient selection and general information

Clinical data of 15 recurrent bronchial cancer patients who received bronchoscope-guided ILBT at the First Affiliated Hospital of Soochow University, Suzhou, China, from 1 June 2009 to 30 September 2015 were selected (13 men and 2 women). Participant age ranged from 42 to 70 years, with an average age of 60.13 ± 8.41 years and a median age of 63 years. Among all patients, 14 had non-small cell lung cancer, and one had small cell lung cancer. One of the patients was classified as stage II, three were stage III, and 11 were stage IV, according to the TNM classification of Malignant Tumors by the Union for International Cancer Control, 2009, 7th edition, and imaging results such as chest CT (non-contrast and contrast-enhanced scan), abdomen ultrasound, cranial CT, and bone scan. A total of 13 patients had chronic obstructive pulmonary disease, three patients had hypertension, one patient had type II diabetes, and one patient had atrial fibrillation.

Recruiting standards for ILBT: (1) confirmed recurrent central lung cancer; (2) patients without a chance of undergoing surgery or who were denied surgery; (3) severe bronchiostenosis or bronchial closure diagnosed with a bronchoscope (diagnosis for serious stenosis: a mean trachea or main trachea wall thickness of >2/3 the lumen diameter, and at least one narrow trachea, and a main trachea wall thickness of >2/3 lumen diameter); (4) pulmonary function: FEV1 ≤90%; (5) an expected survival period of >3 months; (6) no serious hemoptysis; (7) the applicator could easily reach the focus; (8) overall evaluation scores: external beam radiation therapy (EBRT; Zubrod-ECOG-WHO, 5 points) ≤2; and (9) the patients had signed informed consent forms.

2.2 | Evaluation of focus via fibrobronchoscope

Comprehensive evaluations were carried out via enhanced chest CT and fibrobronchoscope on the focus and stenosis of the trachea and bronchus, including the focus-related sites of largest diameter and grade; the cause of stenosis, including internal lumen invasion, external pressure or mixture; and the blood supply of the focus and local hemorrhage. The focus-invasive sites of recruited patients included the main airway in three patients, the left main bronchus in four patients, the right main bronchus in eight patients, and the simple lumen recurrence in six patients; nine patients had an airway mass of ≤2 cm, and all patients had a mass larger than 1 cm.

2.3 | ILBT method

After the patient received general anesthesia, the fibrobronchoscope was inserted through the nose, and the respiratory physician and radiation oncologist decided whether electrocoagulation diathermy or cryosurgery should be used on the airway focus before radiotherapy. Afterwards, the applicator was implanted by the respiratory physician through the sputum aspiration tunnel of the fibrobronchoscope (the two ends of the tumors and the relative position of the applicator were recorded according to the scales on the source applicator surface); then, the end of the applicator reached the distal focus. The operator retracted the fibrobronchoscope when the assistant fixed the tube. The scope was inserted from the other side of the nasal cavity to optimize the applicator's location, and the applicator was immobilized. A CT location image was uploaded to the planning system, and the radiation oncologist delineated the gross tumor volume (GTV) on the ONCENTRA treatment planning system (Nucletron, Veenendaal, the Netherlands), per the bronchoscope results and tumor images obtained by CT scanning. The GTV of the exophytic tumor into the tracheal cavity included all tumors, and the GTV of tumors infiltrated into the trachea included tumors that were only 0.5–1 cm beneath the mucosa; the main blood vessels surrounding the tumor and organs at risk, such as the esophagus and spinal cord, were delineated, the dose limits were determined, and the inverse intensity modulated radiation plan was made, optimized, and submitted to the radiation unit with approval from the attending physician. The applicator was connected to the Selectron ^{192}Ir-HDR brachytherapy afterloading unit (Nucletron, Veenendaal, the Netherlands), and the treatment was started. A single dose to the target region was 4–8 Gy, and each patient received 1–6 fractions, for a total dose of 5–32 Gy.

2.4 | Combination therapy summary

Eight of fifteen (8/15) patients had been treated with tumor-relevant surgeries; 11 patients had received surgeries under fibrobronchoscope (1–12 times), which included endoloop resection, endotherm knife, laser, cryotherapy, and stent implantation; 13 patients had received systemic chemotherapy, 84.6% of whom switched to secondary chemotherapy or higher; 11 patients received pulmonary EBRT (total dose 45–60 Gy), and eight patients received EBRT followed by ILBT.

2.5 | Observation index

2.5.1 | Clinical sign evaluation

The recruited patients were evaluated according to breath shortness standards of the American Thoracic Society before ILBT, and at the end of 1, 2, 4, and 8 weeks post-ILBT.[8] Grade 0: normal; grade 1: dyspnea

TABLE 1 Evaluation of airway stenosis recanalization and restenosis

Local efficacy	Standards
Complete response	The foci in cavity disappeared completely and functions recovered
Partial response	>50% of narrow cavities were recanalized, functions generally recovered, subjective signs improved
Slight response	Stenosis recanalization of <50%, but distal pulmonary inflammatory effects disappeared after drainage
No response	No objective or subjective improvements in clinical parameters
Restenosis	Cavity stenosis of >50% with or without signs like chest distress and dyspnea

when walking fast; grade 2: dyspnea in normal walking pace; grade 3: stop normal pace walking due to dyspnea; and grade 4: dyspnea in slight activity. The evaluation was carried out by specified personnel.

2.5.2 | Local relief evaluation

The standards for airway stenosis recanalization are presented in Table 1. Total efficiency equals complete response plus partial response. Short-term efficacy was based on Response Evaluation Criteria In Solid Tumors (RECIST) standards and consisted of complete response (CR), partial response (PR), stable disease (SD), and progression disease.[9] For Table 1, CR stands for complete response, PR indicates partial response and slight response, SD indicates no response, progression disease indicates airway restenosis, and response rate indicates the portion of CR and PR among total patients.[10] The partial relief period is the period defined by multiple fibrobronchoscopic examinations. In addition, the factors affecting local relief rate were analyzed.

2.5.3 | Long-term efficacy evaluation

For the survival analysis, the survival index consisted of progression-free survival (PFS), which is the period from the start of the clinical intervention to disease progression, and OS, which is the time period between the clinical intervention start to disease progression, recurrence, death or the last follow-up visit.

2.5.4 | Adverse effects

The adverse effects were evaluated as grades 0–IV, according to adverse reaction evaluation standards (NCI-CTC, edition 3.0) recommended by the US National Cancer Institute.

2.6 | Follow up

A total of 15 patients received hospital and communicative evaluations until 30 September 2015, and no patients were missing. The follow-up periods ranged from 8.5 to 73 months, with a median value of 23 months.

2.7 | Statistical analysis

All data were processed with SPSS 19.0 (IBM China (Nanjing branch), Nanjing City, China). Measurement data were presented as $\bar{x} \pm s$; dyspnea grades before and after ILBT were analyzed by one-way analysis of variance (ANOVA). When the data passed the sphericity test, the LSD (Least–Significant Difference)-*t* test was used in the pairwise comparison of different time-points. Fisher's test was used to compare the different factors that influenced therapeutic efficacy; the Kaplan–Meier method was used to calculate the mean local relief period, median local relief period, median PFS, mean PFS, mean survival period, median survival period, and survival rate. The test level α was 0.05.

3 | RESULTS

All 15 patients received GTV delineation and radiotherapy plan optimization via the ONCENTRA treatment system (Fig. 1). During the treatment procedure, no side-effects, such as airway perforation, ambustion in the airway or other parts of the body, or mediastinal emphysema, were noted, neither was death caused by radiation pneumonitis, thoracic wall pain, rib fracture, or an obvious skin reaction.

3.1 | Dyspnea index comparison

The dyspnea index was evaluated in 15 patients at pretreatment (3.13 ± 0.64), the end of week 1 (2.40 ± 0.83), week 2 (2.00 ± 0.76), week 4 (1.13 ± 0.59), and week 8 (1.53 ± 0.52). In the one-way ANOVA analysis, the dyspnea index satisfied the sphericity test ($P = 0.086$), and the variances between indexes of different time-points were statistically significant, $F = 27.746$, $P < 0.001$. The LSD-*t* test was then used in the pairwise comparison of different time-points, and the indexes at the end of weeks 1, 2, 4, and 8 remarkably decreased compared with the pretreatment index, with *t* values of 0.786, 1.214, 1.500, and 1.643, respectively (all $P < 0.001$).

3.2 | Short-term efficacy

In the whole group, two patients were CR, 11 patients were PR, one patient was SD, and one was progression disease. Overall, the response rate was 86.7% (13/15 patients), and the cancer control rate (CR + PR + SD) was 93.9% (14/15). Relief of subjective cough and chest distress was noted in 11 patients who received ILBT. Fisher's test was used to compare the factors that affected local efficacy (Table 2). A total of 11 patients who underwent bronchoscopy plus ILBT were CR + PR ($P = 0.013$), nine of whom were patients who had a local catabatic period of ≥2 months; this indicated that the combination of fibrobronchoscope and ILBT was beneficial for local relief. The total dose in 11 patients was >20 Gy, and the total dose in the other four patients was ≤20 Gy. GR + PR of former patients was 100.0% (11/11), but was just two out of four in other patients, which showed that ILBT >20 Gy could increase the local relief period, $P = 0.013$. The mean relief period of 15 patients was 5.27 ± 3.35 months, and the median value was 3.24 months. The mean local relief period for patients who

TABLE 2 Analysis on factors that influenced local efficacy in recurrent lung cancer patients

Subject	Factor	Local focus		Statistics
		CR + PR	SD + PD	*P*
Sex	Male	2	0	0.432
	Female	11	2	
Smoking history	Yes	2	0	0.432
	No	11	2	
Age (years)	<60	6	0	0.134
	≥60	7	2	
Distance from carina	≤2 cm	8	1	0.759
	>2 cm	5	1	
Surgery	Yes	6	1	0.919
	No	7	1	
Chemotherapy	Yes	11	2	0.432
	No	2	0	
Chemotherapy-resistant time	<3 lines	6	1	0.919
	≥3 lines	7	1	
Fibrobronchoscope intervention	No	2	2	0.013
	Yes	11	0	
Fibrobronchoscope Operation	<3 times	7	2	0.134
	≥3 times	6	0	
EBRT	Yes	10	1	0.446
	No	3	1	
ILBT and EBRT order	Pre-BRT	7	1	0.919
	Post-EBRT	6	1	
ILBT accumulated dose	≤20 Gy	2	2	0.013
	>20 Gy	11	0	

Total $n = 15$. CR, complete response; EBRT, external beam radiation therapy; ILBT, intraluminal brachytherapy; PD, progression disease; PR, partial response; SD, stable disease.

only received ILBT (4 patients) was 2.87 ± 2.75 months, whereas the mean local relief period of patients who received fibrobronchoscope and ILBT (11 patients) was 6.18 ± 3.12 months. The survival rate of patients who received ILBT was 73.3% (11/15) after 3 months, 46.7% (7/15) after 6 months, and 33.3% (5/15) after 9 months.

3.3 | Long-term efficacy

The median PFS of all patients was 9.5 months (5% CI 12.2–16.5 months), the mean PFS was 15.8 ± 14.4 months, the median OS was 23.0 months (95% CI 25.0–30.0 months), the mean OS was 28.0 ± 17.0 months, and survival rates after 1 year and 2 years were 93.3% (14/15) and 40.0% (6/15), respectively (Fig. 2).

3.4 | Adverse effects

Adverse effect information was available for all patients. The main adverse effects included bronchospasm and hemoptysis, and the secondary adverse effects were cough, dyspnea, emesis, and myelosuppression. Two aged male patients withdrew from ILBT due to cough (grade III) after an initial ILBT, but the remaining patients did not withdraw due to adverse effects.

4 | DISCUSSION

Studies have shown that distant metastasis was noted in 75% of patients with stage III bronchial cancer or surgery dissection, and the local recurrence rate was 50–75%.[11] Chemotherapeutic drugs made little contribution to the survival rate.[12,13] Therefore, radiotherapy played an important role in the comprehensive treatment of bronchial cancers.[14] However, a single EBRT takes 3–4 weeks or longer to achieve sufficient efficacy, and the re-expansion rate of pulmonary atelectasis was only approximately 21.0%;[15] 33–50% of patients had a tumor progression rate of 50% within the radiation field 15 months after EBRT.[16] This indicated that single EBRT was not effective for local advanced or recurrent bronchial cancer treatment, particularly in terms of an improvement in clinical signs, such as cough, obstruction, dyspnea, and severe hemoptysis. As ILBT constantly develops, radiotherapy was used in close brachytherapy for tumors in narrowed bronchi. The advantages of ILBT include a high dose in the treated region, a short therapeutic distance, a sharply decreased surrounding dose, and the improvement of clinical signs, such as pulmonary atelectasis as a result of obstructive lung disease or hemoptysis as a result of tumor invasion in the airway. CT-guided ILBT has been used gradually, and has led to a new method of accurate intracavitary radiotherapy to treat recurrent bronchial cancer.[17]

High-dose rate ILBT is commonly used as a secondary or palliative treatment method for local advanced bronchial cancer, particularly when OS cannot be prolonged in the last stage. The increased local relief rate is essential in the improvement of the quality of life of patients. In terms of local efficacy in the short term, 11 patients subjectively reported that ILBT was effective as expected, and improvements were noted in ventilatory function, severe cough, and hemoptysis in all 15 patients with recurrent bronchial cancer who received ILBT. In addition, fibrobronchoscope examinations showed that ILBT reached a local objective relief rate of 86.67% (13/15). Zorlu *et al.* arrived at the same conclusion regarding the obvious short-term relief of clinical signs; chest distress was improved in 79% of recurrent lung cancer patients after high-dose rate ILBT.[18] The study by Hennequin *et al.* showed that 59.4% of patients with localized metastatic bronchial tumors experienced relief 3 months after high-dose rate ILBT, and the improvements had pathological significance.[19]

In the present study, recurrent bronchial cancer patients received ILBT combined with EBRT. The local relief period was 6.18 ± 3.12 months, which is longer than that of patients after single EBRT (2.87 ± 2.75 months) and longer than the relief period in the study by Zorlu *et al.* (45 days).[18] The differences showed that EBRT contributed to the therapeutic benefits of ILBT for recurrent bronchial cancer treatment, and most researchers agreed that ILBT combined with EBRT was the best way to maximize ILBT. The combination therapy could guarantee prescribed dose uniformity, suppress tumors in the cavity and surrounding invasive lesion, control potential

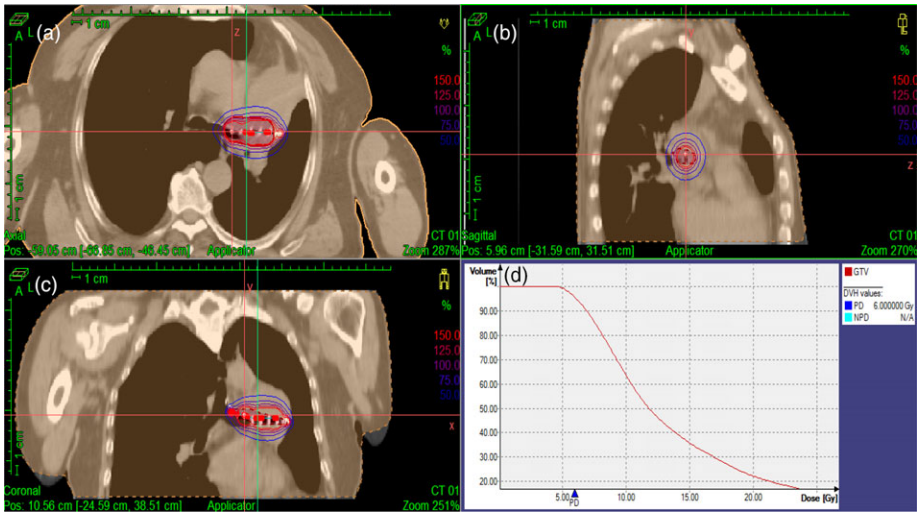

FIGURE 1 The lineation of gross tumor volume (GTV) of a recurrent bronchial lung cancer, and the radiotherapy planning optimization. (a) Lineation of GTV in an axial thoracic computed tomography image. (b) Lineation of GTV in a sagittal thoracic computed tomography image. (c) Lineation of GTV in a coronal thoracic computed tomography image. (d) Dose–volume histograms (DVH) of intracavitary radiotherapy planning

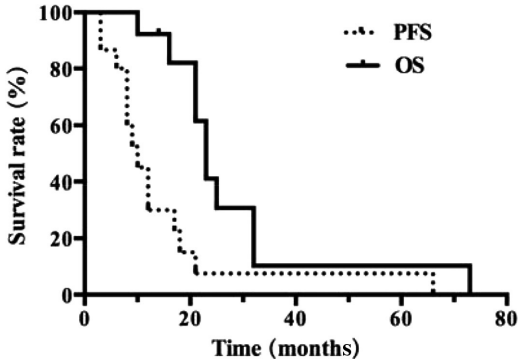

FIGURE 2 Overall survival (OS) and progression-free survival (PFS) curves of recurrent bronchial lung cancer patients ($n = 15$)

lymphocytic metastases, and reduce the risk of recurrent airway obstruction by tumor cell infiltration.[20] Regarding a simple bronchus tumor, specifically, a patient with occult lung cancer detected by X-ray radiograph, the PFS after ILBT combined EBRT was 87.3%, and the 5-year survival rate was 72.3%.[21] The combined therapy was less harmful to normal tissues, and was regarded as a promising replacement for surgery. As for recurrent bronchial cancer patients, the tumors could grow large in size, eccentrically or with infiltration, and with a subclinical focus. The pulmonary function dramatically decreased, and the airway reaction was usually induced by source applicator implantation, while a large-scale breath could lead to the axial displacement of the applicator.[17] In that situation, the ILBT dose might be insufficient because of a lack of treatment distance and incomplete coverage over the entire tumor focus. The combination of EBRT and ILBT could guarantee dose uniformity, increase the control rate of the tumor focus outside the trachea, and achieve control of the tumor in the long term.

In the present study, patients with >20-Gy ILBT had a high local relief rate in the short-term clinical evaluation, which was identical to the high local relief rate observed with a 20–30-Gy dose level in the previous studies. In contrast, the survival rate after ILBT decreased with time: 73.3% in 3 months, 46.7% in 6 months, and 33.3 in 9 months, and the decrease showed that ILBT could not extend OS, even though it improved the local relief rate. This was considered to be related to the following: (1) in the present study, masses in the airway were <1 cm in the long diameter, and the locations were ≤2 cm close to the carina in most cases. It was easy for the source applicator to reach and be implanted properly, and the middle size tumors shrank under high-dose radiation in a short time-period, resulting in the improvement of clinical signs. (2) Related with the deterministic effect of normal tissues, high accumulated dose ILBT deposited higher exposure doses in the airway mucosa, induced acute radiation injuries, such as tissue edema, bronchospasm, and hemoptysis, and increased the risk of chronic radiation injuries. A total of 11 patients had a previous history of EBRT. A high dose of EBRT could result in airway mucosa necrosis, and a large amount of necrotic tissue could lead to airway obstruction and dyspnea. The side-effects impacted patients' OS to a certain degree.[22] Therefore, the control of the local dose was essential to avoid airway mucosa necrosis and to remove tracheal debridements following afterloading therapy. Additionally, regarding the limited samples from the follow up, some of the patients were in the last stage and were intolerant to consistent ILBT; thus, they benefited little from the therapy. The study by Speiser *et al.* showed that the cancer itself, the patient's cachexia or advanced bronchial cancer with low ECOG grades or operative injuries would lead to short local relief after ILBT.[23] Hence, it might be more important and essential to achieve the endpoint of palliative relief than prognostic outcome for those patients.

In addition, we discovered that local efficacy was significantly increased by ILBT combined with fibrobronchoscope in the present study. Previous studies showed that ILBT combined with cryotherapy and endotherm knife sufficiently reduced local tumor loads.[1,2] ILBT combined with microwave could suppress the recovery from radiation caused by sublethal tumor cell injury, and could potentially cause lethal damage by initiating fever and generating S phase cells with radiation resistance. ILBT combined with stent implantation could extend the restenosis time due to tumor growth or muscular spasm, and

could permit multiple ILBT treatments.[24] Nevertheless, the risks of bleeding, perforation, pneumothorax, infection, and severe and paroxysmal cough exists in endoscopic operations. Those risks could result in disadvantages for ILBT combination therapy, and could overlap with acute/chronic injuries in radiotherapy. They would conceal ILBT efficacy in terms of tumor cell elimination, reduce patients' subjective feelings, and even lead to massive hemoptysis. It was not difficult to confirm that two patients in the present study experienced irritable bronchial spasm and hemoptysis (both grade III) after ILBT combined with fibrobronchoscope in the follow-up visit, and discontinued ILBT because of a lack of subjective benefits. Therefore, it is necessary for respiratory physicians and radiation oncologists to evaluate the clinical advantages and disadvantages together, and to decide on endoscope intervention applications during ILBT therapy.

In conclusion, the results of the present study showed that CT-guided ILBT was effective and safe in treating recurrent bronchial cancer. The rate of tumor shrinkage was increased by high-dose accumulated ILBT (>20 Gy), in combination with fibrobronchoscope, and clinical signs, such as dyspnea and the quality of life, of end-stage cancer patients were improved. ILBT is promising as an innovative palliative treatment, and worthy of further large-scale prospective studies.

CONFLICT OF INTEREST

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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