



Feasibility of Aerobic Exercise and Tai-Chi Interventions in Advanced Lung Cancer Patients: A Randomized Controlled Trial

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Abstract

Background: A majority of lung cancer patients are diagnosed at advanced stages. Although there is considerable evidence of the benefits of aerobic exercise and tai-chi for lung cancer patients, little is known about the comparative effectiveness of the 2 exercise modes in advanced lung cancer patients. **Objectives:** To explore the feasibility and preliminary effects of aerobic exercise and tai-chi interventions on survival and well-being among advanced lung cancer patients. **Methods:** In an assessor-blinded, exploratory randomized controlled trial, 30 advanced lung cancer patients were randomized to an aerobic exercise group, a tai-chi group (both attending 12-week, twice-weekly supervised sessions), or a self-management control group (receiving written exercise guidelines). The primary outcomes focused on feasibility including intervention completion, exercise adherence, and adverse events, while the secondary outcomes addressed preliminary effects and included 1-year survival, cancer symptoms (Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Score, Brief Fatigue Inventory), quality of life (EORTC QLQ-C30, QLQ-LC13), physical performance (6-minute walk test, up-and-go, sit-to-stand, 1-leg standing), activity levels (actigraph), and circadian rhythms (salivary cortisol). **Results:** Intervention feasibility was established with a satisfactory completion rate at post-intervention for the aerobic exercise group (80%) and the tai-chi group (78%). The tai-chi group attained higher adherence than the exercise group in terms of attendance in supervised sessions (89% vs 75% of scheduled classes) and self-practice (225% vs 87% of the prescribed amount). Higher adherence to self-practice in the tai-chi group remained at the 6-month follow-up (81% vs 38% of the prescribed amount). No adverse event as a result of the intervention was reported. Effect-related outcomes did not show statistically significant changes in any group, except an improvement post-intervention in the up-and-go (−2.26, 95% CI: −4.04, −0.48) and sit-to-stand tests (4.52, 95% CI: 2.19, 6.85) in the aerobic exercise group. **Conclusions:** The findings support the feasibility of aerobic exercise and tai-chi interventions in advanced lung cancer patients. A future study with a larger sample from multiple sites is recommended to confirm the comparative effects of the 2 exercise interventions relative to the self-management group and to enhance the generalizability of the findings.

Keywords

advanced cancer, lung cancer, aerobic exercise, tai-chi, survival, quality of life

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Introduction

Lung cancer is the leading cause of cancer-related death. Despite progress in clinical therapies for the disease, survival rates remain low. Approximately 72% to 76% of lung cancer patients are diagnosed at Stage III or IV, which have 1-year survival rates of 48.7% and 19.3%, respectively.¹ Meanwhile, lung cancer patients experience higher symptom burden than other cancer patients.^{2,3} They have high levels of dyspnea, coughing, fatigue, pain, anxiety, depression,

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sleep disturbances,^{4,5} and circadian rhythm disruptions.⁶ Strategies to reduce patients' symptom burden, improve quality of life (QoL), and potentially prolong survival in advanced lung cancer patients are necessary.

There is considerable evidence of the benefits of exercise for lung cancer patients, with improvements in QoL, psychological well-being, exercise tolerance, and postoperative recovery.^{7,8} However, most studies have involved patients in early-stage disease. Relatively less is known about the achievability of these benefits in those with advanced disease, many of whom are older with comorbid disease. A meta-analysis based on 3 randomized controlled trials (RCTs) in 59 advanced lung cancer patients demonstrated that aerobic exercise training improved exercise capacity and disease-specific QoL over the usual care.⁹ However, the authors graded the overall quality of evidence as low because the included studies had significant risks of bias and most studies had small samples. On the survival benefits of exercise, even less is known. One observational study reported that lung cancer patients with higher levels of self-reported exercise have better survival rates than the physically inactive.¹⁰ In the general cancer population, 2 newly published meta-analyses have demonstrated significant benefits of exercise for cancer survival.^{11,12} Of note, most data have come from breast cancer patients or patients with mixed cancer types. Also, most included studies were observational, so bias from confounding and reverse causation is of concern. Given that lung cancer is the leading cause of cancer deaths worldwide, and in light of the highly suggestive observational findings compiled thus far, there is an urgent need for a well-designed RCT examining the effect of exercise on cancer symptoms, QoL, and survival in advanced lung cancer patients.

While aerobic exercise is the most frequently studied exercise modality in lung cancer patients,⁸ mind-body exercise is also gaining popularity worldwide. There was little research comparing the effects of the 2 exercise modes. A meta-analysis has shown that both aerobic and mind-body exercise were effective in improving sleep post-intervention among cancer patients, while only the benefit of aerobic exercise remained evident at 3 to 6 months post-intervention.¹³ A large-scale RCT in patients with fibromyalgia has demonstrated that tai-chi results in greater improvement in fibromyalgia symptoms (eg, pain, physical function) and anxiety than aerobic exercise.¹⁴ A randomized, cross-over trial conducted with 24 patients with mixed advanced lung and gastrointestinal cancers found that aerobic exercise resulted in more improvement in exercise capacity than qigong; however, the beneficial effects of aerobic exercise markedly reduced or diminished during the second intervention period.¹⁵ There is no definitive conclusion on the comparative effectiveness of the 2 exercise modes.

Tai-chi is a mind-body exercise of low-to-moderate intensity rooted in traditional Chinese medicine.^{8,22} It combines

slow physical movements with deep, controlled breathing exercises and relaxation techniques. Tai-chi is less physically demanding than aerobic exercise, which is likely acceptable for a wider range of advanced lung cancer patients, who are often elderly and suffer from fatigue and poor cardio-respiratory fitness after surgery, chemotherapy, or other targeted treatments. Meta-analyses have shown that tai-chi has beneficial effects on cancer-specific QoL, fatigue, immune function, and cortisol levels in cancer patients,^{16,17} while the survival benefit of tai-chi has yet to be evaluated. To our knowledge, no rigorous RCT comparing the effects of aerobic exercise and tai-chi on survival, QoL, and cancer symptoms has been conducted. An RCT is thus warranted to compare the effects of these 2 popular exercise modes comprehensively to guide clinical recommendations.

The primary aim of this study was to test the feasibility and acceptability of implementing 12-week aerobic exercise and tai-chi interventions among advanced lung cancer patients. The effect-related outcomes include survival, cancer symptoms (sleep, psychological distress, and fatigue), QoL, physical performance, activity levels, and circadian rhythms. Although this exploratory pilot study was not powered for formal statistical significance testing, the feasibility results obtained will inform the design for a fully powered trial.

Material and Methods

Study Design

This feasibility study was an assessor-blind, 3-arm RCT conducted from 10 May 2018 to 31 August 2019. The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 18-154). After baseline assessment, patients were stratified by their primary cancer treatment (targeted therapy or non-targeted therapy) and randomized into 3 arms (exercise, tai-chi, and self-management control groups). Randomization was performed using software that allows for replication by an independent randomizer. Block randomization was adopted, in which varying block sizes of 3 and 6 were used to ensure allocation concealment. The allocation sequence was kept by the randomizer. Whenever a participant was recruited, the research assistant contacted the randomizer for the group allocated. Outcome assessors were blinded to study allocation.

Participants

A total of 30 patients were recruited from oncology and respiratory medicine out-patient clinics of a public-funded hospital in Hong Kong. Patients could participate if they were: (i) aged 18 or above, (ii) diagnosed with Stage IIIB or IV non-small-cell lung cancer confirmed by pathology, (iii) not

currently engaged in other research or participating in other exercise or mind-body classes, (iv) able to communicate in Cantonese, Mandarin, or English, (v) not doing regular exercise, defined as <150 minutes weekly, (vi) Karnofsky Performance Scale (KPS) scores ≥ 80 , and (vii) without other cancer diagnosis within the previous year. Patients suffering from diagnosed active neurological, substance abuse, and/or psychiatric disorders were excluded. All patients signed informed consent forms before participating.

Treatment Conditions

Aerobic exercise intervention group. Patients attended a 60-minute exercise class in a gym twice a week for 12 weeks. Patients engaged in both aerobic and strengthening exercises in each class (30 minutes each). Aerobic exercises included walking on a treadmill and cycling on a stationary bike, at a set pace individually tailored for moderate exercise of 50% to 60% of the heart rate reserve as measured by a chest strap heart-rate monitor.¹⁸ A set of 4 strengthening exercises was included in 1 class every week to increase arm, leg, and abdomen strength and to improve trunk stability (10 repetitions of each exercise each time). In the initial assessment, patients performed 10 repetitions of each exercise to decide on the appropriate resistance (60% 1-RM).¹⁹ The exercise classes were led by 2 licensed exercise trainers. The design of the classes was based on the American College of Sports Medicine guidelines for individuals with multiple chronic disease and health conditions.²⁰ For self-practice, patients were instructed to perform moderate-intensity aerobic exercise for at least 90 minutes per week during the intervention period. Moderate intensity aerobic exercise was rated at 3 to 4 on the Rating of Perceived Exertion (range 0-10).²¹ After the intervention, patients were encouraged to practice moderate-intensity aerobic exercise for at least 150 minutes per week and to practice 2 sets of strengthening exercises with 10 repetitions each on alternate days. A standardized exercise log was distributed to patients to record their daily exercise sessions (type, duration, intensity) up to the end of intervention.

Tai-chi intervention group. Patients attended tai-chi classes twice a week for 12 weeks with each session lasting approximately 60 minutes. The class was based on a 24-form Yang style of tai-chi exercise set and led by a tai-chi master with more than 5 years of teaching experience. Each session included a warm-up, a guided run-through of the movements, breathing techniques, relaxation in tai-chi, and cool-down. The theory behind tai-chi and the principles of the techniques were also explained during class. During the intervention period, patients were encouraged to self-practice tai-chi (30 minutes) at least 3 times per week. After the intervention, patients were encouraged to self-practice at least 5 times per week (150 minutes total). A standardized

exercise log was distributed to patients to record their daily exercise up to the end of intervention.

Self-management group. Patients were given written information on the recommended levels of physical activity by the World Health Organization (WHO) (at least 150 minutes of moderate-intensity or 75 minutes of vigorous aerobic exercise per week).²² A standardized exercise log was distributed to patients to record their daily exercise pattern up to Week 12. At the end of the evaluation stage of the study, survivors could take part in an intervention of their choice.

Data Collection

Outcome assessment was conducted by trained research assistants blinded to group allocation. Feasibility outcomes were assessed post-intervention (after 12 weeks), while effect-related outcomes were assessed at 4 times: baseline, post-intervention (after 12 weeks), 6-month (3 months post-intervention), and 1-year follow-up (9 months post-intervention), except that survival was recorded at 1-year follow-up only and circadian rhythms were measured at baseline and 1-year follow-up only (Figure 1).

Feasibility outcomes. Feasibility was measured by intervention completion, adherence, patient satisfaction, and tolerance of exercise. Intervention completion was defined as the percentage of patients who completed the intervention. Adherence was calculated as (i) the percentage of supervised exercise sessions completed and (ii) total time of self-practice in minutes per week out of the prescribed amount. To assess patient satisfaction with intervention classes (aerobic exercise and tai-chi groups) and study logistics, an investigator-designed questionnaire composed of 14 items (Supplemental Material 1) was administered. Tolerance of exercise was assessed by the number of adverse events reported relating to the exercise intervention.

Effect-related outcomes

One-year survival rate. Information on 1-year survival was obtained from patients' electronic medical records. Causes of death were also recorded.

Cancer symptoms. Subjective quality of sleep was assessed by the Chinese version of the Pittsburgh Sleep Quality Index (PSQI). It comprises 19 items with a total score ranging from 0 to 21, with scores higher than 5 denoting poor sleep quality. The PSQI has been validated in the Chinese population.²³ Psychological distress (anxiety and depression) was measured by the Chinese version of the Hospital Anxiety and Depression Score (HADS). It includes 7 items to assess anxiety and depression, respectively, with each item scored on a 4-point scale. It is a reliable tool widely used to assess patients with cancer.²⁴ Fatigue

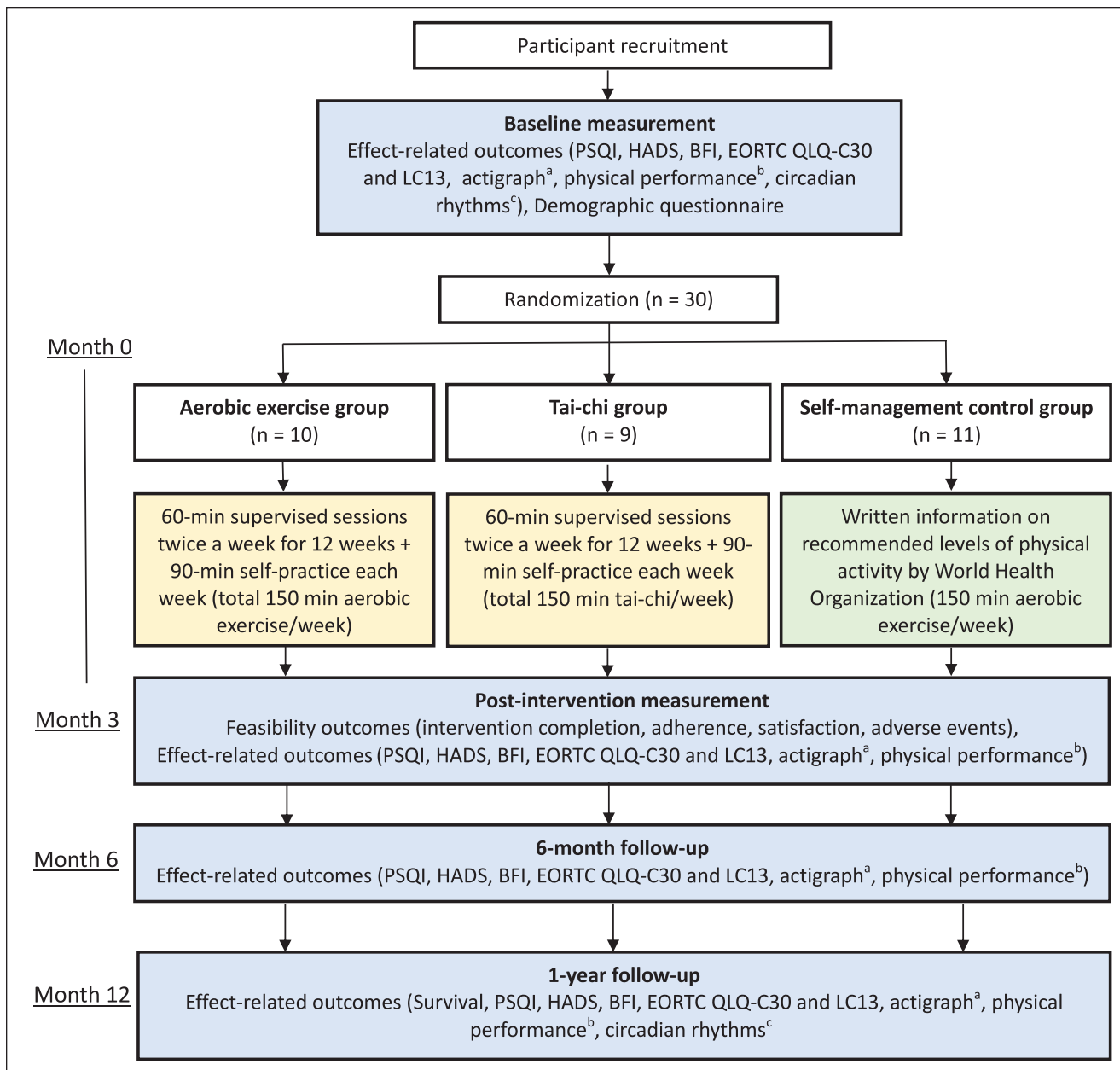


Figure 1. Data collection points.

Abbreviations: BFI, Brief Fatigue Inventory; EORTC QLQ-C30 and LC13, European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire and corresponding lung cancer-specific module; HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburg Sleep Quality Index; WHO, World Health Organization.

^aFor measuring activity levels (step counts) and objective sleep parameters (total sleep time, sleep efficiency).

^bBy conducting 6-minute walking test, timed up-and-go, 30-second sit-to-stand test, 1-leg standing test.

^cBy measuring levels of cortisol in saliva samples.

was measured by the Chinese version of the Brief Fatigue Inventory (BFI).²⁵ The BFI consists of 9 items, with the first 3 questions on fatigue severity (0=“no fatigue” to 10=“as bad as you can imagine”) at current, usual, and worse levels, and the remaining 6 questions on fatigue interference (0=“does not interfere” to 10=“completely interferes”). A higher score in BFI denotes a higher level of fatigue.

Quality of life. Health related QoL was assessed by the Chinese version of the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and the corresponding lung cancer-specific module (QLQ-LC13). A higher score in the EORTC QLQ-C30 functional scale denotes a healthier level of functioning, while higher values in the EORTC QLQ-

C30 symptom scale and QLQ-C30-LC13 indicate higher levels of symptomatology. These questionnaires are valid and reliable to measure QoL in Chinese cancer patients.²⁶

Level of physical activity and objective sleep parameters. Wrist-worn accelerometers (Actigraph; Ambulatory Monitoring Inc., New York) were used to determine level of physical activity (step count),²⁷ total sleep time (total time spent asleep), and sleep efficiency (the ratio of the total sleep time to total time in bed multiplied by 100).²⁸ Patients were asked to wear the actigraph for 3 consecutive 24-hours spans, along with recording in a sleep diary.

Physical performance. Four aspects of physical performance were assessed: (i) exercise capacity with the 6-minute walk test (6MWT), (ii) agility by timed up-and-go (time to get out of chair, walk 3 m, and return to sitting on the chair), (iii) leg strength by a 30-second sit-to-stand test (number of unassisted chair stands performed in 30 seconds), and (iv) balance ability by a 1-leg standing test (length of time the subject can maintain their balance with a single leg). All physical performance tests were conducted using standardized protocols.²⁹⁻³²

Circadian rhythms. Saliva was collected by each participant using Salivettes at 0.5 hour, 4, 8, and 12 hours after habitual wake time. Concentrations of cortisol in the saliva were analyzed with enzyme-linked immunosorbent assay kits (SKGE008, R&D Systems, Inc., Minneapolis, MN, USA) according to the manufacturer's instructions. Standards of cortisol were 0.156 to 10 ng/ml. Standards and samples collected were assayed simultaneously. All samples were quantified by colorimetric analysis at 450 nm (with the correction wavelength set to 570 nm).³³ Circadian rhythms were indicated by a diurnal cortisol slope which was calculated by regressing the 4 cortisol levels on sample collection times. The cortisol levels for the regression were log-transformed.³⁴ Total cortisol area under curve (AUC) with respect to ground (ie, total area under the curve of all measurement) was also calculated. Normal diurnal cortisol production peaks at 30 minutes after waking and declines steadily during the day, reaching its lowest point at bedtime. A flatter diurnal slope and larger AUC indicate more circadian rhythm disruption.

Demographic questionnaire. Patients' demographic and clinical data were collected at baseline from self-administered questionnaires and electronic medical records if necessary. Information collected included age, sex, marital status, education level, employment status, financial condition, and cancer-related characteristics (eg, KPS scores, stages of disease, cancer treatment, current medication).

Statistical Analyses

Given that testing of statistical significance is not appropriate for pilot studies, our analysis focused on descriptive

statistics.³⁵ It was performed by an independent researcher who was unaware of the group allocation using an intention-to-treat approach with SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The background characteristics between the intervention and the waitlist control groups were assessed by a chi-square test and *t* test for categorical and continuous data, respectively. Feasibility-related outcomes (completion and adherence) were presented as descriptive statistics. For effect-related outcomes, descriptive analysis was performed using the mixed-effects model because it can accommodate missing data without manual imputation, thereby providing a natural way to deal with missing values or dropouts.³⁶

Results

Recruitment

Figure 2 presents the recruitment flow diagram. A total of 2820 cancer patients were assessed for eligibility from May through July 2017, of whom 2589 patients were excluded mostly due to not meeting the eligibility criteria of cancer type and stage (n=2532). Among the 231 eligible patients, 163 patients were approached. Ultimately, 30 consented to participate, indicating a recruitment rate of 18.4%. The major reasons for refusal to participate were lack of interest (n=59), inconvenient venues (n=25), conflicts with schedule (n=19), self-perceived as physically incapable (n=19), and sufficient exercise (n=11).

Baseline Characteristics

Table 1 shows information on participants' demographics. Almost half the participants (46.7%) were female. Participants in aerobic exercise classes were aged 61.00 ± 12.12 , tai-chi classes were 61.11 ± 7.01 years, and those in control group were 58.36 ± 9.32 years on average. The average number of months since diagnosis was 24.20 ± 17.26 , 14.11 ± 8.05 , and 28.09 ± 18.11 in aerobic exercise, tai-chi, and control groups, respectively. More than half the participants (60%) were receiving targeted therapy. There were no significant baseline differences between the groups.

Feasibility Outcomes

At post-intervention, 8 (of 10) patients in the aerobic exercise group and 7 (of 9) patients in the tai-chi group completed data collection (reasons for withdrawal: 1 lost interest; 1 treatment side effects; 2 deteriorated condition), while 8 (of 11) patients in the control group completed data collection (2 deaths; 1 not satisfied with group allocation). For the overall dropout unrelated to death at 1-year follow up, a total of 7 participants (3 in aerobic exercise, 2 in tai-chi, 2 in the control group) withdrew from the trial, with the major reason being deteriorated condition. Out of the 24 supervised exercise classes, study

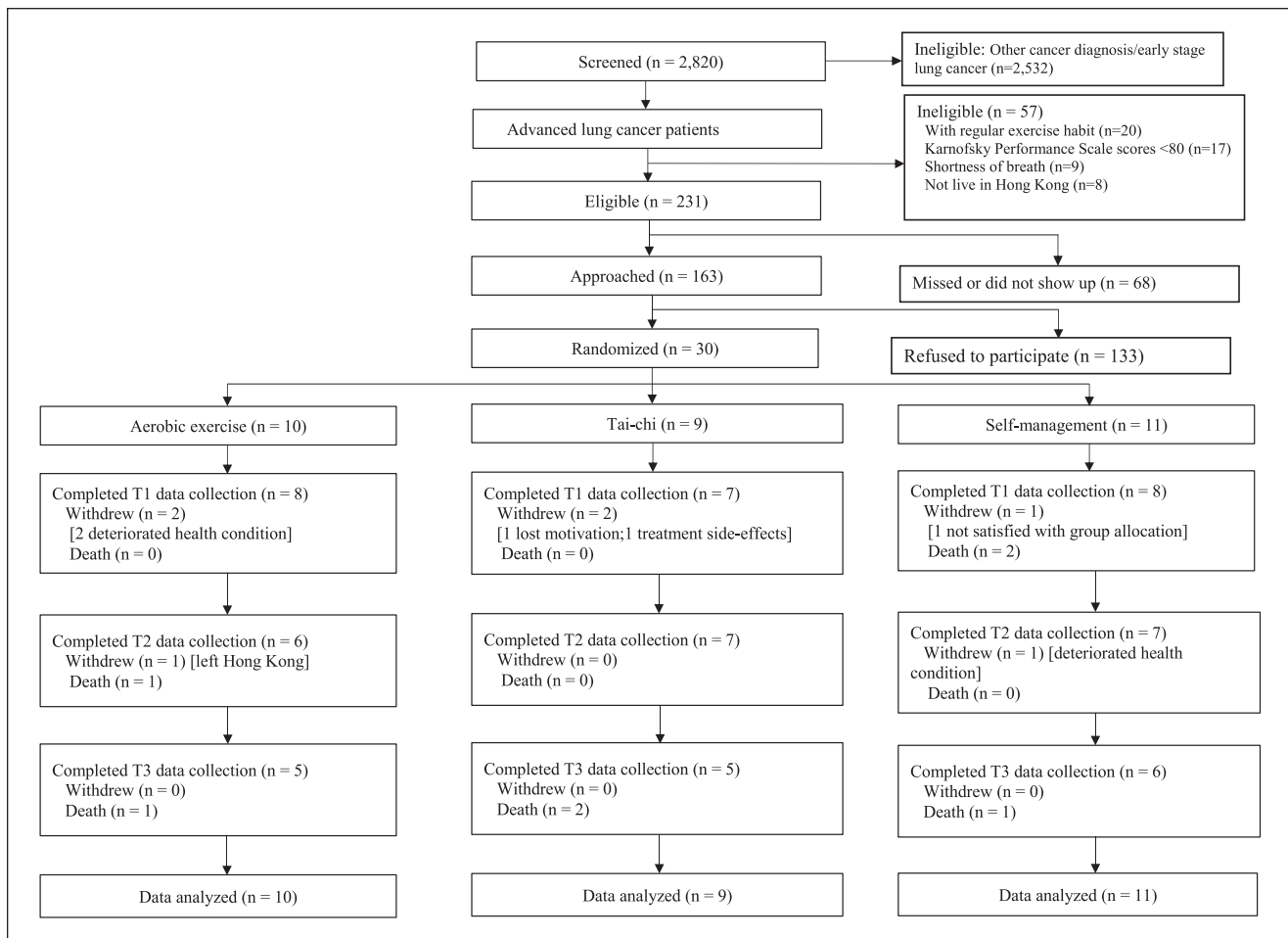


Figure 2. Flow chart.

completers in the aerobic exercise group attended a mean of 17.88 ± 2.70 classes (75% of classes, with 75% of participants completing 60%-80% of supervised sessions and 25% of participants completing >80%), while those in tai-chi classes attended a mean of 21.30 ± 3.55 classes (89% of classes, with 14% of participants completing 60%-80% of supervised sessions and 86% of participants completing >80%). From baseline to post-intervention (target 90 minutes/week), the aerobic exercise group self-practiced moderate intensity aerobic exercise for 78.22 ± 76.70 minutes per week on average (87% of prescribed amount), while the tai-chi group self-practiced tai-chi of 229.29 ± 161.37 minutes per week (255% of the prescribed amount). For the mean self-practice time (minutes/week) from post intervention to 6-month follow-up (target 150 minutes/week), the aerobic exercise group was 56.25 ± 36.62 minutes/week (38% of prescribed amount), while the tai-chi group was 121.43 ± 230.25 minutes/week (81% of the prescribed amount). Control group participants, who received recommendations of 150 minutes of exercise, reported aerobic exercise of 177.86 ± 189.64 (119%) and 162.86 ± 134.00 minutes/

week (109%) from baseline to post-intervention, and from post-intervention to 6-month follow-up, respectively. None of the control group participants performed tai-chi.

A total of 7 aerobic exercise and 7 tai-chi group participants returned the post-intervention satisfaction questionnaire. Half rated the intervention classes as very enjoyable and 28.6% as quite enjoyable. Positive ratings were given for intervention classes and study logistics. One participant in the aerobic exercise group reported numbness around the lips during the supervised class and was diagnosed with traumatic hematoma, which was likely unrelated to the exercise intervention. There was no adverse event in the tai-chi and control group.

Effect-Related Outcomes

Table 2 presents the descriptives of all effect-related outcomes. Regarding cancer symptoms, the tai-chi group showed improvement in anxiety at post-intervention (-1.45 , 95% CI: $-4.62, 1.72$), 6-month (-2.13 , 95% CI: $-5.30, 1.04$), and 1-year follow up (-1.98 , 95% CI: $-5.18, 1.22$) relative to

Table 1. Baseline demographic characteristics of study participants.

Variables	Aerobic exercise group (n=10)	Tai-chi group (n=9)	Control group (n=11)	P-value
	n (%) or M ± SD	n (%) or M ± SD	n (%) or M ± SD	
Age, years	61.00 ± 12.12	61.11 ± 7.01	58.36 ± 9.32	.770
Gender (female)	5 (50.0)	3 (33.3)	6 (54.5)	.628
Marital status				
Married	8 (80.0)	6 (66.7)	8 (72.7)	.187
Unmarried	2 (20.0)	3 (33.3)	3 (27.3)	
Education				
Primary	3 (30.0)	2 (22.2)	3 (27.3)	.918
Secondary	2 (20.0)	1 (11.1)	2 (18.2)	
High school	1 (10.0)	3 (33.3)	3 (27.3)	
University or above	4 (40.0)	3 (33.3)	3 (27.3)	
Months since diagnosis	24.20 ± 17.26	14.11 ± 8.05	28.09 ± 18.11	.143
Treatment modalities				
Targeted therapy	6 (60.0)	6 (66.7)	6 (54.5)	.872
Non-targeted therapy	4 (40.0)	3 (33.3)	5 (45.5)	
Chemotherapy	2 (20.0)	2 (22.2)	3 (27.3)	
Radiotherapy	1 (10.0)	0 (0)	0 (0)	
No treatment	1 (10.0)	1 (11.1)	2 (18.2)	
Karnofsky Performance Scale scores				
100	4 (40.0)	1 (11.1)	4 (36.4)	.498
90	6 (60.0)	8 (88.9)	6 (54.5)	
80	0 (0)	0 (0)	1 (9.1)	
Smoking habit				
Yes	1 (10.0)	0 (0)	1 (9.1)	.639
No	9 (90.0)	9 (100)	10 (90.9)	
Alcohol drinking behavior ^a				
Yes	0 (0)	0 (0)	1 (9.1)	.422
No	10 (100.0)	9 (100.0)	10 (90.9)	
Employment				
Employed	2 (20.0)	1 (11.1)	2 (18.2)	.866
Unemployed	8 (80.0)	8 (88.9)	9 (81.8)	

^aSelf-reported as drinking 3 or more alcoholic drinks (can/bottle) per typical week.

the baseline, while the aerobic exercise and control groups reported smaller improvements. For physical performance, the aerobic exercise group showed more improvement post-intervention in time up-and-go (-2.26, 95% CI: -4.04, -0.48) and 30s sit-to-stand tests (4.52, 95% CI: 2.19, 6.85) than the tai-chi group and control group, while the tai-chi group showed more improvement in balance post-intervention (28.25, 95% CI: -37.08, 93.58) and 6MWT post-intervention (19.42, 95% CI: -44.83, 83.67) than the aerobic exercise group. Of note, none of the aforementioned changes from baseline were statistically significant except the improvement in time up-and-go and 30s sit-to-stand test in the aerobic exercise group post-intervention.

Regarding 1-year survival, 2 in the control group had died post-intervention, but none in the other groups. At 6-month follow-up, 1 in the aerobic exercise group had also died. At

12-month follow-up, a further 1 in the aerobic exercise group, 2 in the tai-chi group, and 1 in control group had died. Overall, 2 in the aerobic exercise group, 2 in the tai-chi group, and 3 in the control group died within the study period.

Discussion

To our knowledge, this is the first study to examine the feasibility of a 3-arm RCT comparing the effects of aerobic exercise, tai-chi, and self-management among advanced lung cancer patients. The findings from this study suggest that the 2 exercise interventions are feasible and acceptable for the target population in view of the high adherence rate. Tai-chi group patients are more likely to adhere to the prescribed intervention and continue to practice it after completion of the intervention. A wide range of objective and

Table 2. Effect-related outcomes.

Outcomes	Aerobic exercise group (n = 10)		Tai-chi group (n = 9)		Control group (n = 11)	
	Mean ± SE	Within-group change from baseline (95% CI)	Mean ± SE	Within-group change from baseline (95% CI)	Mean ± SE	Within-group change from baseline (95% CI)
BFI						
Baseline	1.78 ± 0.72		1.21 ± 0.76		3.78 ± 0.69	
Post-intervention	1.97 ± 0.77	0.19 (-2.00, 2.39)	2.48 ± 0.82	1.27 (-1.07, 3.61)	3.25 ± 0.76	-0.53 (-2.70, 1.64)
6-month follow-up	2.48 ± 0.87	0.70 (-0.67, 2.08)	2.13 ± 0.90	0.92 (-0.39, 2.23)	4.78 ± 0.83	1.00 (-0.28, 2.29)
1-year follow-up	2.45 ± 1.03	0.67 (-1.27, 2.62)	1.80 ± 1.05	0.59 (-1.27, 2.45)	4.95 ± 0.97	1.17 (-0.63, 2.97)
HADS anxiety						
Baseline	4.30 ± 1.35		4.67 ± 1.42		5.09 ± 1.28	
Post-intervention	4.20 ± 0.93	-0.10 (-3.09, 2.89)	3.22 ± 0.99	-1.45 (-4.62, 1.72)	2.75 ± 0.91	-2.34 (-5.25, 0.56)
6-month follow-up	4.25 ± 1.36	-0.05 (-3.32, 3.22)	2.54 ± 1.35	-2.13 (-5.30, 1.04)	4.38 ± 1.28	-0.71 (-3.78, 2.37)
1-year follow-up	5.61 ± 1.01	1.31 (-1.75, 4.36)	2.69 ± 1.04	-1.98 (-5.18, 1.22)	4.67 ± 0.96	-0.42 (-3.34, 2.50)
HADS depression						
Baseline	3.10 ± 1.14		4.56 ± 1.21		6.45 ± 1.09	
Post-intervention	5.18 ± 1.13	2.08 (-1.68, 5.83)	6.37 ± 1.20	1.81 (-2.18, 5.80)	5.11 ± 1.12	-1.35 (-5.03, 2.33)
6-month follow-up	5.40 ± 1.39	2.30 (-2.50, 7.11)	5.82 ± 1.32	1.26 (-3.52, 6.04)	5.97 ± 1.30	-0.48 (-5.02, 4.05)
1-year follow-up	7.24 ± 1.42	4.14 (-0.38, 8.65)	4.96 ± 1.38	0.40 (-4.04, 4.84)	6.67 ± 1.32	0.21 (-4.00, 4.43)
PSQI						
Baseline	5.30 ± 1.55		8.44 ± 1.63		8.18 ± 1.47	
Post-intervention	4.37 ± 1.12	-0.93 (-4.87, 3.02)	8.88 ± 1.19	0.44 (-3.74, 4.62)	5.91 ± 1.10	-2.27 (-6.10, 1.56)
6-month follow-up	5.99 ± 1.29	0.69 (-3.37, 4.76)	6.80 ± 1.26	-1.65 (-5.72, 2.43)	6.62 ± 1.21	-1.56 (-5.40, 2.29)
1-year follow-up	6.61 ± 1.49	1.31 (-1.57, 4.20)	5.95 ± 1.54	-2.50 (-5.41, 0.41)	6.34 ± 1.44	-1.84 (-4.68, 1.00)
EORTC QLQ-C30 functional						
Baseline	88.44 ± 4.10		85.19 ± 4.32		78.99 ± 3.91	
Post-intervention	90.56 ± 3.41	2.12 (-6.43, 10.67)	88.19 ± 3.62	3.01 (-6.08, 12.09)	83.24 ± 3.33	4.25 (-4.13, 12.63)
6-month follow-up	78.00 ± 7.47	-10.45 (-30.50, 9.60)	86.69 ± 7.27	1.50 (-17.83, 20.84)	81.71 ± 7.04	2.72 (-16.20, 21.63)
1-year follow-up	87.56 ± 3.86	-0.88 (-7.94, 6.18)	89.86 ± 4.02	4.68 (-2.32, 11.68)	77.86 ± 3.66	-1.13 (-7.79, 5.54)
EORTC QLQ-C30 symptom						
Baseline	12.05 ± 4.21		20.23 ± 4.44		24.24 ± 4.01	
Post-intervention	11.47 ± 3.43	-0.58 (-11.47, 10.31)	21.02 ± 3.65	0.80 (-10.77, 12.36)	20.12 ± 3.38	-4.12 (-14.78, 6.53)
6-month follow-up	16.64 ± 6.98	4.58 (-13.31, 22.48)	16.39 ± 6.76	-3.84 (-20.72, 13.04)	24.10 ± 6.54	-0.15 (-16.85, 16.56)
1-year follow-up	19.34 ± 5.09	7.29 (-7.15, 21.72)	20.85 ± 5.19	0.62 (-13.10, 14.34)	25.16 ± 4.82	0.91 (-12.70, 14.53)
EORTC QLQ-LC13						
Baseline	10.83 ± 4.00		16.36 ± 4.21		23.48 ± 3.81	
Post-intervention	9.17 ± 4.54	-1.66 (-12.34, 9.02)	23.15 ± 4.83	6.79 (-4.61, 18.19)	26.19 ± 4.46	2.71 (-7.92, 13.34)
6-month follow-up	12.23 ± 5.42	1.40 (-10.91, 13.71)	20.58 ± 5.35	4.22 (-7.40, 15.85)	23.96 ± 5.10	0.47 (-11.03, 11.98)
1-year follow-up	10.91 ± 3.84	0.08 (-7.77, 7.93)	20.33 ± 4.00	3.97 (-4.13, 12.08)	22.64 ± 3.64	-0.85 (-8.29, 6.60)
Timed up and go, seconds						
Baseline	10.10 ± 0.87		9.38 ± 0.91		10.92 ± 0.83	
Post-intervention	7.84 ± 0.63	-2.26 (-4.04, -0.48)	9.16 ± 0.67	-0.21 (-2.10, 1.67)	9.62 ± 0.61	-1.29 (-3.02, 0.44)
6-month follow-up	8.19 ± 1.05	-1.91 (-4.27, 0.45)	9.33 ± 0.99	-0.05 (-2.09, 1.99)	9.51 ± 0.98	-1.41 (-3.57, 0.75)
1-year follow-up	8.49 ± 0.79	-1.61 (-5.91, 2.68)	7.62 ± 0.79	-1.76 (-5.09, 1.57)	9.32 ± 0.74	-1.60 (-5.60, 2.40)

(continued)

Table 2. (continued)

Outcomes	Aerobic exercise group (n = 10)		Tai-chi group (n = 9)		Control group (n = 11)	
	Mean ± SE	Within-group change from baseline (95% CI)	Mean ± SE	Within-group change from baseline (95% CI)	Mean ± SE	Within-group change from baseline (95% CI)
30s sit to stand						
Baseline	10.80 ± 1.06		10.22 ± 1.12		8.45 ± 1.01	
Post-intervention	15.32 ± 1.12	4.52 (2.19, 6.85)	11.40 ± 1.19	1.18 (-1.31, 3.66)	9.67 ± 1.10	1.22 (-1.10, 3.54)
6-month follow-up	15.30 ± 1.63	4.50 (1.37, 7.63)	11.06 ± 1.60	0.84 (-1.85, 3.54)	11.03 ± 1.53	2.57 (-0.29, 5.44)
1-year follow-up	14.26 ± 1.71	3.46 (-0.11, 7.04)	14.33 ± 1.76	4.10 (0.56, 7.65)	10.45 ± 1.60	2.00 (-1.30, 5.29)
6MWT, meter						
Baseline	389.33 ± 25.77		409.03 ± 27.17		389.38 ± 24.57	
Post-intervention	381.62 ± 18.94	-7.71 (-68.26, 52.85)	428.45 ± 20.14	19.42 (-44.83, 83.67)	420.57 ± 18.63	31.19 (-27.86, 90.24)
6-month follow-up	411.31 ± 38.32	21.98 (-60.55, 104.51)	408.13 ± 36.67	-0.91 (-71.39, 69.58)	431.81 ± 35.80	42.43 (-33.14, 117.99)
1-year follow-up	394.72 ± 35.80	5.39 (-59.64, 70.41)	446.38 ± 35.98	37.35 (-20.57, 95.27)	416.36 ± 33.69	26.98 (-32.70, 86.66)
One-leg standing test, seconds						
Baseline	26.88 ± 15.96		80.62 ± 16.82		32.33 ± 15.21	
Post-intervention	40.54 ± 27.89	13.66 (-47.47, 74.79)	108.88 ± 29.63	28.25 (-37.08, 93.58)	22.19 ± 27.31	-10.14 (-71.21, 50.93)
6-month follow-up	38.72 ± 16.75	11.84 (-40.43, 64.10)	55.99 ± 14.95	-24.64 (-72.91, 23.64)	35.77 ± 15.46	3.44 (-45.05, 51.93)
1-year follow-up	32.90 ± 27.10	6.02 (-56.89, 68.93)	113.61 ± 26.93	32.98 (-25.00, 90.97)	30.67 ± 25.33	-1.66 (-59.96, 56.64)
Daily step count (actigraphy)						
Baseline	11115.13 ± 1563.24		11004.59 ± 1647.80		10582.20 ± 1563.24	
Post-intervention	11258.81 ± 1641.47	143.67 (-3132.30, 3419.64)	12373.24 ± 1741.72	1368.64 (-2127.93, 4865.22)	10578.16 ± 1641.47	-4.04 (-3280.01, 3271.92)
6-month follow-up	11447.80 ± 1714.93	332.67 (-2960.241, 3625.574)	10591.52 ± 1725.09	-413.07 (-3552.15, 2726.01)	10970.88 ± 1714.93	388.68 (-2904.23, 3681.59)
1-year follow-up	10990.14 ± 1767.69	-124.99 (-3644.40, 3394.41)	11292.00 ± 1827.02	287.41 (-3278.53, 3853.35)	8518.20 ± 1708.94	-2064.00 (-5353.84, 1225.84)
Total sleep time, minutes (actigraphy)						
Baseline	283.03 ± 25.95		240.46 ± 27.35		295.48 ± 25.95	
Post-intervention	259.49 ± 21.45	-23.54 (-112.48, 65.40)	249.09 ± 24.71	8.64 (-88.87, 106.14)	251.12 ± 21.45	-44.36 (-133.30, 44.57)
6-month follow-up	246.88 ± 39.51	-36.15 (-148.85, 76.54)	323.96 ± 39.88	83.50 (-29.75, 196.76)	307.35 ± 39.51	11.86 (-100.83, 124.55)
1-year follow-up	378.07 ± 48.29	95.04 (-74.07, 264.14)	325.53 ± 47.81	85.08 (-87.95, 258.10)	308.64 ± 42.72	13.16 (-144.93, 171.25)
Sleep efficiency, % (actigraphy)						
Baseline	91.13 ± 1.40		89.69 ± 1.48		90.70 ± 1.40	
Post-intervention	88.29 ± 1.90	-2.84 (-9.51, 3.84)	89.32 ± 2.19	-0.36 (-7.82, 7.09)	90.29 ± 1.90	-0.41 (-7.09, 6.26)
6-month follow-up	92.68 ± 1.59	1.55 (-4.86, 7.96)	93.20 ± 1.63	3.51 (-3.19, 10.22)	93.89 ± 1.59	3.18 (-3.23, 9.59)
1-year follow-up	90.26 ± 2.45	-0.87 (-9.25, 7.51)	90.66 ± 2.43	0.97 (-7.63, 9.57)	92.23 ± 2.17	1.52 (-6.31, 9.36)
Salivary cortisol area under curve						
Baseline	74.23 ± 9.45		64.53 ± 9.96		67.64 ± 9.01	
1-year follow-up	65.18 ± 9.24	-9.06 (-21.88, 3.77)	70.93 ± 9.74	6.40 (-7.12, 19.92)	67.27 ± 8.81	-0.37 (-12.60, 11.86)
Diurnal cortisol slope						
Baseline	-0.000825 ± 0.000270		-0.001300 ± 0.0001369		-0.001450 ± 0.000090	
1-year follow-up	-0.000900 ± 0.000128	-0.000075 (-0.000800, 0.000650)	-0.000775 ± 0.000210	0.000525 (0.000137, 0.000913)	-0.001075 ± 0.000311	0.000375 (-0.000254, 0.001004)

Abbreviations: 6MWT, 6-minute-walk-test; BFI, Brief Fatigue Inventory; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire; EORTC QLQ-LC13, European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire and the corresponding lung cancer-specific module; HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Quality Index; SE, standard error.

self-reported measurements were employed to assess both short-term and long-term effects of interventions comprehensively. Survival rate and circadian rhythms at 1 year appeared similar across the 3 groups. The aerobic exercise group showed trends of larger improvement in some aspects of physical performance (up and go, sit to stand) compared to the tai-chi group, while the tai-chi group showed larger improvement in anxiety, lung cancer-associated symptoms, activity levels, and some aspects of physical performance (6MWT and balance). The control group also reported improvement in anxiety, depression, sleep disturbance, and some aspects of physical performance (up and go, sit to stand). Notably, no changes from baseline were statistically significant except the improvement in physical performance in the aerobic exercise group.

The findings demonstrate that most of the sample in the aerobic exercise and tai-chi groups completed the 12-week interventions (80% and 78%, respectively), with satisfactory adherence rates (supervised sessions: 75% and 89%, respectively; self-practice: 87% and 225%, respectively). The major cause of withdrawal and missing the exercise sessions was progression of disease condition. According to a systematic review published in 2019, the post-intervention completion rates of exercise interventions conducted among patients with advanced cancer ranged from 58% to 90%, with levels of adherence ranging from 44% to 95%.³⁷ Although previous research suggested that advanced lung cancer patients often have difficulty completing structured exercise interventions owing to a high symptom burden,³⁸ our study findings on completion and adherence fall within the higher end of the range reported by previous studies, showing that most patients were willing to participate as long as physically able. This may be explained by the design of our exercise interventions consistent with previous literature on exercise preference of advanced cancer patients (group exercise led by a trained exercise expert).³⁹ Besides, no participants in either intervention group reported significant detriment to their QoL over the intervention period, revealing that advanced lung cancer patients are capable of exercising without compromising their QoL, which is encouraging and warrants further investigation to confirm exercise's benefits in this population.

When the adherence rates of the aerobic exercise and tai-chi interventions are compared, tai-chi yields higher adherence to both supervised (75% vs 89%) and self-practice sessions (87% vs 255%). This is not surprising, because research has suggested that low-to-moderate-intensity exercises such as qigong can achieve similar health improvements in vulnerable populations with better compliance than conventional exercise.⁴⁰ A RCT among fibromyalgia patients also found that participants attended the tai-chi training sessions more often than the aerobic exercise sessions (62% vs 40%).¹⁴ In addition to better compliance, low-intensity exercise also had links with lower injury risk and long-term sustainability,⁴⁰

which our preliminary findings also supported. In the present study, there was no adverse event in the tai-chi group, while in the aerobic exercise group, 1 participant reported lip numbness during the exercise class. Although the diagnosis–hematoma–was not developed due to the exercise intervention, safety should be closely monitored in advanced lung cancer patients while doing moderate-intensity exercise. Regarding sustainability, adherence was assessed at 3 months post-intervention, revealing that both groups had a decrease in adherence at 3 months post-intervention. Yet, the tai-chi group still demonstrated higher adherence than the aerobic exercise group (81% vs 38%). The higher adherence and longer-term sustainability of the tai-chi group may also be explained by the cultural appropriateness of the exercise mode. Tai-chi is a form of qigong, which is a mind-body intervention rooted in a Traditional Chinese medicine concept and is a preferable complementary and alternative medicine for insomnia in the Chinese population.⁴¹ More large-scale RCTs are needed to explore whether tai-chi is more favorable, safe, and sustainable than conventional aerobic exercise in different cultural groups.

Although effect estimates are not the focus of the present feasibility study, the relatively remarkable improvements observed in the aerobic exercise and tai-chi groups are worth attention. Those include (i) agility and lower leg strength in the exercise group and (ii) anxiety, exercise capacity, and balance in the tai-chi group. The 1-year survival rate of the 3 groups appeared similar. A pilot randomized cross-over study revealed that standard endurance and strength training (n=13) was superior to qigong (n=11) in improving sleep, feelings of weakness, and exercise capacity in mixed advanced gastrointestinal and lung cancer patients.¹⁵ Given that both the cross-over study and the present feasibility study have small sample size, the actual intervention effects cannot be determined and what caused the discrepancies in findings between 2 studies are uncertain. In view of the discrepancies in findings between the cross-over study and the present feasibility study, further high-quality, fully-powered RCTs are needed to understand the effects of different modes of exercise training in patients with advanced lung cancer fully. On the other hand, the increase in exercise levels in the control group participants in this study warrants attention. With the written WHO guideline on physical activity, they engaged in substantial aerobic exercise from baseline to post-intervention (119% of the prescribed amount) and from post-intervention to follow-up (109% of the prescribed amount), respectively. Another RCT conducted in inoperable lung cancer patients also demonstrated an increasing trend in time spent in physical activity in the control group participants who received exercise education materials, though in a smaller magnitude than the exercise group.⁴² These may be explained by the possibility that participants who consented to participate in exercise-related research tended to have high motivation to increase exercise behavior. Another plausible

explanation is that readily available printed materials may also be useful in promoting engagement in regular physical activity.^{43,44} If self-management guidelines continue to be found to have similar benefits to the supervised exercise interventions in advanced lung cancer patients in future fully powered studies, further initiatives should focus on ways to implement delivery of print self-management guidelines in clinical settings, as it is less costly and less labor intensive than supervised sessions.

There are limitations to this study. First, this feasibility study lacks statistical power to draw any conclusion on the effect-related outcomes. A fully-powered RCT is warranted to confirm the comparative effects of the 2 exercise interventions. Second, participants were recruited from 1 single clinical site, limiting the generalizability of the findings. Recruitment conducted from multiple sites can reduce the risk of selection bias. Third, our site of recruitment was out-patient clinics and 1 of the inclusion criteria was KPS scores ≥ 80 . Thus, the findings may be limited to advanced lung cancer patients who have relatively good performance status. Fourth, the methods of measuring adherence in the current study are limited to self-reported exercise logs and class attendance.

Conclusions

The findings in this feasibility study indicate that both 12-week aerobic exercise and tai-chi interventions are feasible and acceptable for the advanced lung cancer patients. Tai-chi group patients are more likely to adhere to the prescribed intervention and to continue to practice it beyond the intervention period. A future RCT with a larger sample from multiple sites is proposed, to confirm the comparative effects of the 2 exercise interventions relative to the self-management group and to enhance the generalizability of the findings. Also, the adherence monitoring strategies should be more robust to incorporate objective measurement during each supervised and self-practice exercise session such as heart rate monitors or pedometers.

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Trial Registration

ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT03482323).

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Supplemental Material

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