Integrative cancer treatment may have a survival benefit in patients with lung cancer
A retrospective cohort study from an integrative cancer center in Korea

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Abstract

Integrative oncology is being increasingly adopted in mainstream cancer care to strengthen anticancer effects and to control cancer-related symptoms.

The objective of this study is to identify the characteristics of patients with lung cancer treated at an integrative cancer center in Korea and to determine the effects of integrative cancer treatment (ICT) on survival outcome in traditional Korean medicine (TKM).

We reviewed medical records for lung cancer patients who visited a single integrative clinical setting, East-West Cancer Center, between January 2014 and December 2015. We classified the patients into groups according to their ICT and whether or not they underwent anticancer traditional Korean Medicine treatment with a multiherbal formula containing *Panax notoginseng Radix*, *Cordyceps militaris*, *P ginseng* C.A.Mey., and *Boswellia carterii BIRDWOOD* (HangAmDan-B), with a herbal formula containing *Rhus verniciflua Stoke*, or with cultivated wild ginseng pharmacopuncture. A descriptive analysis of the characteristics and a survival analysis using the Kaplan-Meier curves with log rank test and a Cox proportional hazard model were performed.

A total of 91 patients were included, and the majority had advanced-stage cancer. Of those patients, 45.1% were in the mono-TKM group and 39.6% were integrative group. Patients with advanced stage had significantly higher mortality than patients with early stage (crude hazard ratio [HR]: 4.41, 95% confidence interval [CI]: 1.56–12.5; adjusted HR: 6.31, 95% CI: 1.24–32.1). In the unadjusted model, for patients in the integrative group, the mortality rate was reduced by 50% compared to mono-TKM group with statistical significance. After adjusting confounders, the mortality rate of integrative group was reduced by 6% compared to mono-TKM group, suggesting positive effect on survival probability of integrative group.

The results suggest that integration of TKM and conventional cancer treatment may have survival benefits in patients with lung cancer. Even though this study has limitations including heterogeneity between treatment groups, the study results suggest that ICT has positive effect on survival probability. To clarify the impacts of ICT for lung cancer and other cancers on survival outcome, further prospective study with a rigorous study design is required in multiclinical setting.

Abbreviations: ACTKMT = anticancer traditional Korean medicine treatment, CAM = complementary and alternative medicine, CCT = conventional cancer treatment, DKMHDU = Dunsan Korean Medicine Hospital of Daejeon University, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, EMR = electronic medical record, EWCC = East-West Cancer Center, ICT = integrative cancer treatment, MST = median survival time, NSCLC = non–small cell lung cancer, OS = overall survival, PD-1, programmed death-1, PD-L1 = programmed death ligand-1, SCLC = small cell lung carcinoma, SD = standard deviation, TKI = tyrosine kinase inhibitor, TKM = traditional Korean medicine, WBCT = Wheel balance cancer therapy.

Keywords: complementary therapies, herbal medicine, integrative medicine, lung neoplasms, pharmacopuncture, survival

1. Introduction

Lung cancer is the most frequently diagnosed cancer, with the highest incident rates occurring in Central and Eastern Europe and in Eastern Asia.[1] Although the mortality rates for patients with lung cancer continue to decline due to reductions in smoking, early diagnosis, and advances in treatment,[2] in Korea, lung cancer was still the leading cause of cancer death in both men and women in 2014, with 5-year relative survival rates of 21.9% for men and 32.4% for women.[3,4]

Various cancer therapies, especially those used for patients with advanced and metastatic cancers, are coordinated and mainly focus on stabilizing the disease and managing cancer-related symptoms.[5] As advanced supportive care, complementary and alternative medicine (CAM) therapies are recommended to intensify holistic and tailored approached by integrating them with conventional cancer treatments (CCTs).[6] In this respect, CAM has increasingly been added to the therapeutic modalities used to treat patients with lung cancer in the hope of enhancing the body's ability to fight the cancer and promoting the patient's wellness.[7,8] Therefore, integrative oncology is expected to be increasingly adopted so as to strengthen anticancer effects and control symptoms.

Wheel balance cancer therapy (WBCT) is an integrative holistic cancer treatment program, which has been implemented at the East-West Cancer Center (EWCC), Dunsan Korean Medicine Hospital of Daejeon University (DKMHDU), Korea, for the past 20 years. The details of WBCT include herbal medicine, metabolism activation (acupuncture, pharmacopuncture, moxibustion, hydrotherapy, and herbal hot-pack therapy), anticancer diets, and mind-body modalities (meditation, controlled breathing, yoga, and qigong). By maximizing patients' natural healing powers, WBCT, either combined with western therapies or administered as a sole therapy, has been reported to have the benefits of decreasing side effects associated with CCT, increasing quality of life, and preventing metastasis.[9,10]

Our previous study of patients with advanced non–small cell lung cancer (NSCLC) showed that WBCT significantly prolonged the survival time for inpatients who had previously received CCT and those who had the Eastern Cooperative Oncology Group (ECOG) performance status <3.[9] However, the characteristics and the survival rates of the patients with lung cancer included in that analysis did not adequately represent those of the usual patients with lung cancer receiving various traditional Korean medicine (TKM) treatments for cancers in different stages and with different progressions. The current level of evidence on the contribution of integrative cancer treatment (ICT) to survival for patients with lung cancer is insufficient. Furthermore, to the best of our knowledge, no previous cohort study based on the population of patients with lung cancer receiving TKM has been reported. Therefore, we designed a retrospective cohort study for the purpose of constructing a retrospective registry for eligible patients with lung cancer, assessing the characteristics of the registry, and investigating the patient survival according to the classification of cancer treatment.

The aim of this study was to describe the characteristics of the retrospective registry for patients with lung cancer who visited the EWCC in Korea and further to investigate the effects on the mortality rate of ICT in TKM or mono-TKM used to treat patients with lung cancer in an actual clinical environment at a single integrative cancer center in Korea. The program of TKM treatments in lung cancer involves herbal medications, acupuncture, moxibustion, heat therapy for activating metabolism, exercise, an anticancer diet, and meditation. We expected this retrospective cohort study to provide insight into both potential ICT for treating patients with lung cancer and the proper rigorous design of future prospective cohort studies.

2. Materials and methods

2.1. Eligibility criteria

A retrospective registry of patients with lung cancer who visited a single integrative clinical setting, the EWCC, was constructed based on electronic medical records (EMRs). At the EWCC, various forms of patients' medical data are routinely recorded on EMR. The eligibility criteria were as follows: diagnosed with lung cancer based on histological or cytological examinations; newly admitted to and had visited the EWCC between January 2014 and December 2015; underwent WBCT at least once in the inpatient/outpatient clinic; agreed to provide personal information. We excluded the patients who had end-stage cancer with a life expectancy of <3 months or ECOG performance status of ≥3 and/or received no WBCT since the medical consultation. All available medical records related to history, examination, diagnosis, progression, treatment, etc were reviewed, with no direct contact with any of the participants, to collect comprehensive information on the eligible patients. This retrospective cohort study was approved by the Institutional Review Board of DKMHDU (approval number: DJDSKH-16-BM-E-1).

2.2. Data collection and patient classification

The demographic and clinical characteristics of the patients in the registry included age, sex, education, type of hospital visit (inpatient/outpatient), occupation, household income, private insurance status, smoking status, past history of cancer, and medical history of lung cancer (date of diagnosis, tumor location, cancer stage, histopathology, metastasis/recurrence, and previous cancer treatment). In particular, we investigated the cancer stage at the time of initial diagnosis, and at the time of enrollment, which is defined as the first day of the patient's visit to the EWCC and the start of WBCT.

WBCT consists of herbal medications, acupuncture, moxibustion, heat therapy for activating metabolism, exercise, an anticancer diet, and meditation.[9,10] Although other treatments lean toward managing symptoms and improving the immune system, the 3 treatments of WBCT the multiherbal formula containing *Panax notoginseng Radix*, *Cordyceps militaris*, *P ginseng C.A.Mey.*, *and Boswellia carterii BIRDWOOD* (Hang-AmDan-B1; HAD-B), the herbal formula containing *Rhus verniciflua Stoke* (Geonchil-jung), and (3) cultivated wild ginseng pharmacopuncture, are prescribed primarily for their anticancer effects. The raw materials of HAD-B, *P notoginseng Radix*, *C militaris, P ginseng C.A.Mey., and B carterii BIRDWOOD* were composed of 1.75: 1.3: 1.3: 1 ratio, and its fluid extract were prescribed as a 486 mg capsule (3 times a day in general). Geonchil-jung contained 500 mg of *R verniciflua Stoke* extract per capsule and 2 capsules were administered at a time (3 times a day in general). The cultivated wild ginseng pharmacopuncture containing 0.36 mg/20 mL of panaxydol, main active ingredient, was prescribed a maximum of 20 mL per day. Preceding studies on the 3 herbal medicines above reported each liquid chromatography data.[11–13] The patients treated with these 3

treatments were considered to have received anticancer traditional Korean medicine treatment (ACTKMT). In the EWCC, the Korean medicine doctors basically prescribe ACTKMT to patients. But, in the case that the patient is reluctant to receive other complementary treatments for cancer in addition to the CCT; the patient only insists on controlling symptoms; oral intake is difficult due to patient's status; or the patient has contraindication of drug administration, ACTKMT is not prescribed. Patients who did not receive ACTKMT were regarded as having been treated for symptom management.

Two independent researchers compiled, integrated, and coded all source data from patients' medical records, which were then double checked. To further describe the characteristics/trends of the cancer treatments used for the patients in the registry, we classified the patients according to the type of treatment into 3 groups: the mono-TKM group, the ICT group (combined TKM and CCT), and the preventive group. The ICT group included patients who were undergoing concurrent CCT for cancer and who had no residual mass but were still undergoing CCT as indicated. The mono-TKM group included those who had refused or decided to discontinue CCT in spite of the recommendation for CCT or whose CCT was withdrawn by the decision of their Western medicine doctor. The preventive group was made up of patients who had received TKM for the purpose of preventing metastasis and recurrence while in complete remission after the completion of CCT.

2.3. Outcome measures and statistical analysis

Demographic and clinical characteristics were presented by using descriptive analyses as means/frequencies and standard deviations (SDs), and the statistical differences between groups were assessed by using either the chi-squared or Fisher exact test for categorical variables and either the 1-way analysis of variance or the Kruskal-Wallis rank sum test for continuous variables. Survival analyses were performed based on data for patients' death provided from the Statistics Korea (KOSTAT) by April 5, 2016, after official request. Survival duration of study patients was calculated from the date of enrollment to date of death or the end of the follow-up. The study patients were considered as right censored if they did not expire at the end of the follow-up. The mortality rates were compared between the treatment groups through a Kaplan-Meier analysis with log rank test. If the proportional hazard assumption held, the hazard ratio (HR) was estimated from the date of enrollment to the date of death through a Cox proportional hazard model. Both crude HR and HR adjusted for clinically significant covariates were presented. The survival analyses were performed according to the cancer stage, treatment group, and treatment details (ACTKMT vs symptom management) by an independent statistician. Statistical analyses were performed using Statistical Analysis Systems (Version 9.3; SAS Institute, Inc, Cary, NC) and R (version 3.4.1).[14] Statistical significance was defined as a P value of <.05. All statistical tests were 2 sided.

3. Results

3.1. Demographic and clinical characteristics

A total of 91 patients met the inclusion criteria and were included in the analysis. The median follow-up was 18 months. Table 1 shows the characteristics of the study participants by treatment group: mono-TKM group (n=41, 45.1%), ICT group (n=36, 39.6%), and preventive group (n=14, 15.4%). The mean (SD) age at baseline was 62.8 (12.6) years. Of the patients in the study, 47.3% were women, which is a larger proportion compared with the 36.8% of women in the prevalent cases of lung cancer in the recent Korean national statistics.[3] All 91 patients were Asian, especially Korean. Statistical differences between groups were observed in age at recruitment, sex, number stage at first diagnosis, number stage at the first visit to the integrative cancer center, experience with previous conventional treatments, and purpose of TKM (Table 1). In terms of histopathology, 45 of the study patients had adenocarcinoma, 14 squamous cell carcinoma (SCC), 9 small cell lung carcinoma (SCLC), and 1 another pathological type of cancer. No patients presented with large cell cancer.

The results demonstrated that the majority of patients with lung cancer who visited the integrative cancer center presented with cancer in an advanced stage (stage IIIB–IV). At the first visit to the EWCC, 12.1% were stage IIIB and 56.6% were stage IV in the number stage system, and 66.67% (n=6) were in an extensive stage in the SCLC Veterans Administration Lung Study Group system stage. Furthermore, among 83 patients (mono-TKM group: 35, ICT group: 34, preventive group: 14) whose data on stages were obtained at both the first diagnosis and the first visit to integrative cancer center, 25.7% (9/35) in the mono-TKM group, 20.6% (7/34) in the ICT group, and no one in the preventive group had the stage change progressively, but none of the differences between the 3 groups was statistically significant (P=.11). In the mono-TKM group, 20 patients had never been treated with CCT. The period from the first diagnosis of lung cancer to the start of TKM was >1 year, with no statistically significant differences being found between the 3 groups (P=.56).

The rates of ACTKMT differed significantly between the 3 groups (P=.003). Among the 3 groups, the mono-TKM group had the largest proportion of patients who had undergone WBCT (38 of 41 patients, 92.7%), followed by the ICT group (28 of 36 patients, 77.8%) and the preventive group (7 of 14 patients, 50.0%). This means that the proportion of patients in the preventive group (7 of 14 patients, 50.0%) who received TKM for symptom management was larger than those in the ICT group (8 of 36 patients, 22.2%) and the mono-TKM group (3 of 41 patients, 7.3%).

3.2. Survival analysis

Of 91 patients, 46 (50.5%) expired during the follow-up. The data of 45 patients were right censored. The median survival time (MST) of the 91 patients was 7.97 months. No comparison of the MST between the groups was performed because in some groups, >50% of the data were right-censored due to the short follow-up. Kaplan-Meier survival curves and P values were presented with crude HR and adjusted HR, along with the number of patients involved. Figure 1 shows a Kaplan-Meier plot of survival time by stage at the first visit to the integrative cancer center. During the study, patients with advanced stage had 441% higher mortality than patients with early stage (crude HR: 4.41, 95% confidence interval [CI]: 1.56–12.48, P=.019 by log-rank test). After adjusting influential covariates including age, sex, previous CCT status, ACTKMT status, and treatment groups, the HR changed to 6.31 (95% CI: 1.24–32.11).

Figures 2 and 3 show Kaplan-Meier curves of patient survival by treatment group for all subjects and for the subjects who

Table 1

General and clinical characteristics by treatment group.

Variables	Total (n=91)	Mono-TKM group (n=41)	ICT group (n=36)	Preventive group (n=14)	P
	N (%)	N (%)	N (%)	N (%)	
Age at recruitment					
Mean ± SD, y	62.8±12.6	66.5±14.5	58.3±8.7	63.8±12.0	.002
Sex					
Male	48 (52.7)	28 (68.3)	14 (38.9)	6 (42.9)	.03
Female	43 (47.3)	13 (31.7)	22 (61.1)	8 (57.1)	
Education					
Elementary school	10 (11.0)	4 (9.8)	3 (8.3)	3 (21.4)	.37
Middle school	7 (7.7)	6 (14.6)	1 (2.8)	0 (0.0)	
High school	16 (17.6)	7 (17.1)	7 (19.4)	2 (14.3)	
College or higher	10 (11.0)	2 (4.9)	6 (16.7)	2 (14.3)	
Unknown	48 (52.7)	22 (53.7)	19 (52.8)	7 (50.0)	
Histopathology					
NSCLC	69 (75.8)	26 (63.4)	31 (86.1)	12 (85.7)	.18
Adenocarcinoma	45 (49.5)	15 (36.6)	23 (63.9)	7 (50.0)	
Squamous cell carcinoma	14 (15.4)	8 (19.5)	3 (8.33)	3 (21.4)	
Large cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Other	1 (1.1)	1 (2.4)	0 (0.0)	0 (0.0)	
Unknown[*]	9 (9.9)	2 (4.9)	5 (13.9)	2 (14.3)	
SCLC	9 (9.9)	6 (14.6)	2 (5.6)	1 (7.1)	
Unknown[†]	13 (14.3)	9 (22.0)	3 (8.3)	1 (7.1)	
Stage at first diagnosis					
Number stage	76	30	33	13	
Stage I	18 (23.7)	4 (13.3)	5 (15.2)	9 (69.2)	.003
Stage II	11 (14.5)	4 (13.3)	6 (18.2)	1 (7.7)	
Stage III	19 (25.0)	8 (26.7)	8 (24.2)	3 (23.1)	
Stage IV	28 (36.8)	14 (46.7)	14 (42.4)	0 (0.0)	
SCLC VALSG system stage	8	5	2	1	
Limited	5 (62.5)	2 (40.0)	2 (100.0)	1 (100.0)	.64
Extensive	3 (37.5)	3 (60.0)	0 (0.0)	0 (0.0)	
Stage at the first visit to integrative cancer center					
Number stage	76	31	32	13	
Stage I	14 (18.4)	2 (6.5)	3 (9.4)	9 (69.2)	<.0001
Stage II	5 (6.6)	1 (3.2)	3 (9.4)	1 (7.7)	
Stage III	14 (18.4)	5 (16.1)	6 (18.8)	3 (23.1)	
Stage IV	43 (56.6)	23 (74.2)	20 (62.5)	0 (0.0)	
SCLC VALSG system stage	9	6	2	1	
Limited	3 (33.3)	1 (16.7)	1 (50.0)	1 (100.0)	.23
Extensive	6 (66.7)	5 (83.3)	1 (50.0)	0 (0.0)	
Previous conventional treatments					
No	25 (27.5)	20 (48.8)	0 (0.0)	5 (35.7)	<.0001
Yes	66 (72.5)	21 (51.2)	36 (100.0)	9 (64.3)	
Surgery	23 (25.3)	7 (17.1)	8 (22.2)	8 (57.1)	.01
Radiotherapy	16 (17.6)	10 (24.4)	4 (11.1)	2 (14.3)	.32
Chemotherapy	42 (46.2)	16 (39.0)	24 (66.7)	2 (14.3)	.002
Targeted therapy	12 (13.2)	5 (12.2)	7 (19.4)	0 (0.0)	.24
Type of hospital visit					
Outpatient	37 (40.7)	17 (41.5)	13 (36.1)	7 (50.0)	.66
Inpatient	54 (59.3)	24 (58.5)	23 (63.9)	7 (50.0)	
Purpose of TKM					
ACTKMT	73 (80.2)	38 (92.7)	28 (77.8)	7 (50.0)	.003
Symptom management	18 (19.8)	3 (7.3)	8 (22.2)	7 (50.0)	
Period from the first diagnosis to TKM start					
Mean ± SD, days	392.1±566.2	340.3±372.5	474.8±692.3	331.6±686.3	.56
Median (IQR)	192.0 (40.5–563.5)	192.0 (22.0–624.0)	247.5 (42.5–610.2)	149.5 (63.0–256.0)	

ACTKMT = anticancer traditional Korean medicine treatment, ICT = integrative cancer treatment, IQR = interquartile range, NSCLC = non–small cell lung cancer, SCLC = small cell lung carcinoma, SD = standard deviation, TKM = traditional Korean medicine, VALSG = Veterans Administration Lung Study Group.

[*] NSCLC, but the medical charts did not contain data on subtypes.

[†] The medical charts contained no data on histological cell types of lung cancer.

underwent ACTKMT, respectively. As shown in Figure 2, the ICT group had an approximately 50% increase in survival with statistical significance compared to the mono-TKM group (crude HR: 0.50, 95% CI: 0.26–0.93, P=.029 by log-rank test). However, the HR changed from 0.50 to 0.94 after adjusting for age, sex, previous CCT status, and ACTKMT status (adjusted
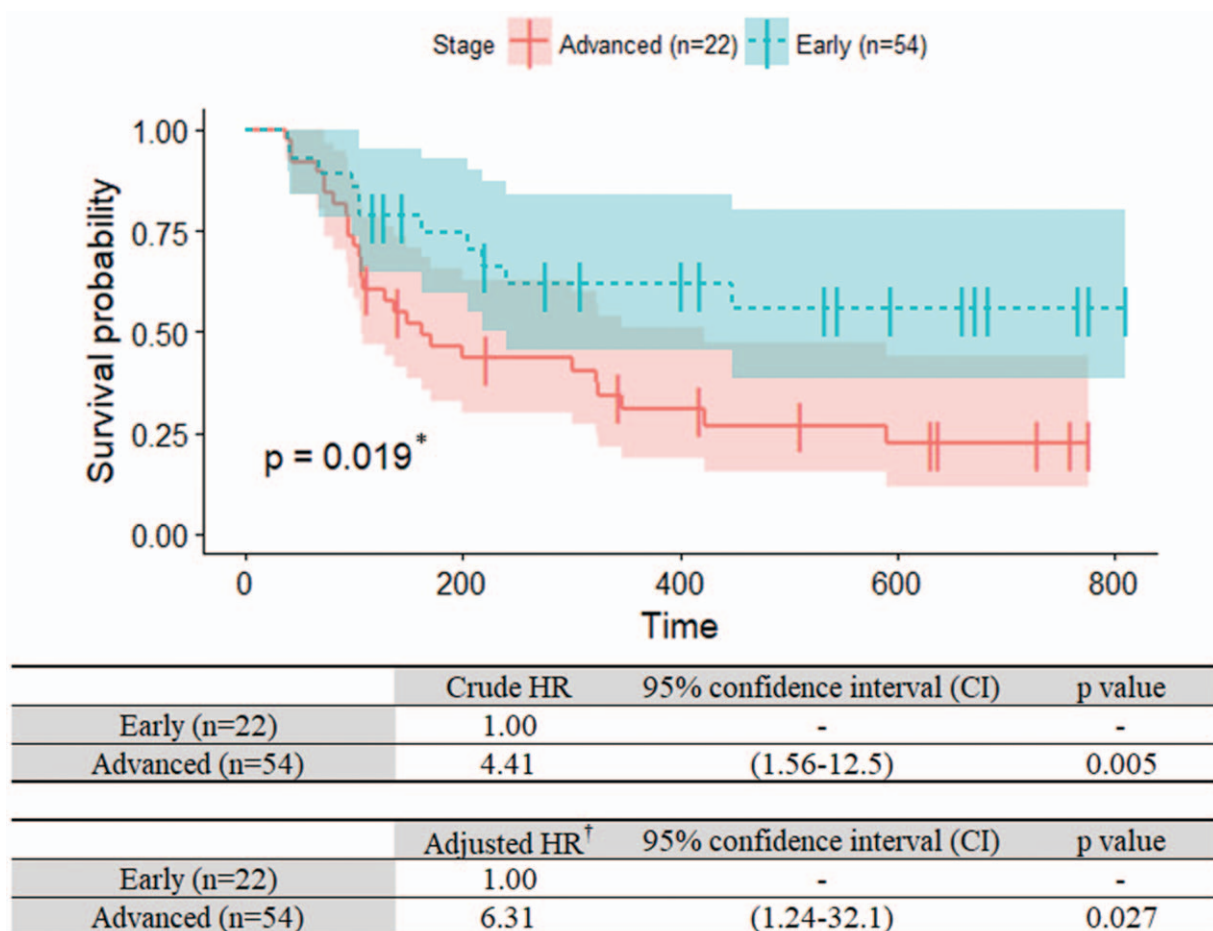
Figure 1. Kaplan-Meier curve of patient survival by stage at the first visit to the integrative cancer center. *Significant difference (P < .05, log rank test). †Adjusted for age, sex, previous conventional cancer treatment (CCT) status, anticancer traditional Korean medicine treatment (ACTKMT) status and treatment groups. HR = hazard ratio.

HR: 0.94, 95% CI: 0.42–2.12). Also, for the subjects who underwent ACTKMT, the ICT group had a 56% lower mortality compared to the mono-TKM group (crude HR: 0.44, 95% CI: 0.22–0.89). Inversely, the ICT group had a 6% higher mortality compared to the mono-TKM group after adjusting influential confounders (age, sex, and previous CCT status) (adjusted HR: 1.06, 95% CI: 0.43–2.57). When referring to the 95% CIs, the current results cannot be interpreted as significant survival decrease by mono-TKM or ICT. That is, the mortality rates of the ICT group and the mono-TKM group were no longer significantly different when the distributions of confounders were balanced.

Figure 4 shows Kaplan-Meier curve of patients who received anticancer TKM treatment in comparison with those who received symptom management. It suggests that receiving symptom management without ACTKMT resulted in a 43% lower mortality compared to ACTKMT (crude HR: 0.57, 95% CI: 0.25–1.28). After adjusting for age, sex, previous CCT status, and different treatment group status, HR changed to 0.78 (95% CI 0.31–1.96).
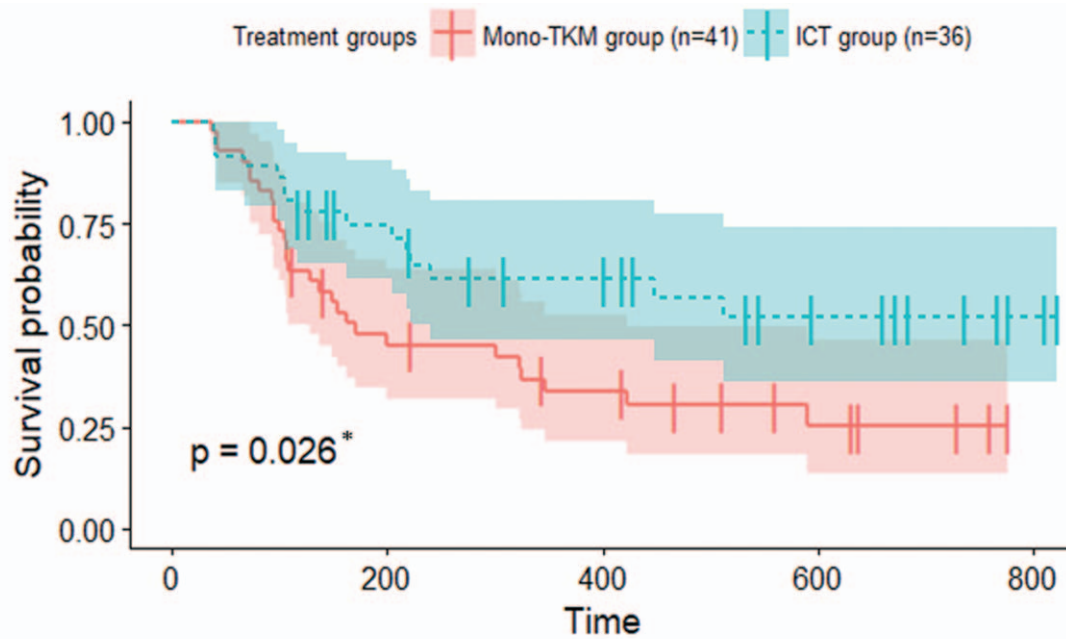
As the Sankey diagram shows in Figure 5, the patients with advanced lung cancer constitute the majority of patients in the integrative cancer center in Korea. Almost half of the mono-TKM group was patients who had never undergone previous

conventional treatment due to either their medical condition not being amenable to any treatment or their refusal. As shown on the right side of this diagram, 92.7% of mono-TKM group received ACTKMT. The only 16.7% of patients who received symptom management belonged to mono-TKM group, whereas 44.4% and 38.9% of patients were ICT group and preventive group, respectively.

4. Discussion

The results of this retrospective cohort study showed that the population who visited the integrative cancer center involved more patients with advanced lung cancer or with progressive disease than patients with early stage of cancer. It also showed that integration of TKM and CCT might have survival benefits in comparison to TKM alone. In the adjusted model, ICT showed positive tendency on survival probability of patients but without statistical significance. The proportion of patients assigned to Mono-TKM group was higher in ACTKMT than in symptom management.

Currently, surgery for patients with cancers in the operable state, chemotherapy, radiation, and chemoradiation are proposed as standard treatments for patients with NSCLC in stages IA to IIIA, whereas surgical resection, chemoradiation, systemic

Figure 2. Kaplan-Meier curve of patient survival by treatment group for all patients. *Significant difference ($P < .05$, log rank test). †Adjusted for age, sex, previous conventional cancer treatment (CCT) status, and anticancer traditional Korean medicine treatment (ACTKMT) status. HR = hazard ratio, ICT = integrative cancer treatment, TKM = traditional Korean medicine.

	Crude HR	95% confidence interval (CI)	p value
Mono-TKM (n=41)	1.00	-	-
ICT (n=36)	0.50	(0.26-0.93)	0.029

	Adjusted HR†	95% confidence interval (CI)	p value
Mono-TKM (n=41)	1.00	-	-
ICT (n=36)	0.94	(0.42-2.12)	0.882

therapy according to the molecular testing, and local therapy are provided to such patients with such cancers in stages IIIB to IVB.[15] For patients with SCLC in limited stages, systemic chemotherapy is an essential component of standard treatment, and surgery, radiotherapy, and individualized treatment, including supportive care, are recommended. Chemotherapy alone is recommended, but radiotherapy may be used as a palliative care, for patients with extensive-stage SCLC.[16]

Many changes in CCT have resulted from molecular discoveries. Targeted agents to inhibit mutations of the epidermal growth factor receptor (EGFR) or the abnormal fusion of anaplastic lymphoma kinase have been developed, and their use to treat patients has led to superior outcomes in comparison to previous systemic treatments.[17] As immunotherapy, programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) blockades can enhance T-cell function to reinforce antitumor activity. Recent evidence suggests that in patients with NSCLC, PD-1/PD-L1 blockades have survival benefit compared to docetaxel.[18] Although new treatment options have shown better efficacy compared to existing CCT,[19] dramatic advances in neither overall survival (OS) nor progression-free survival have been reported.

A number of previous studies showed that the ICT can increase anticancer efficacy in patients with lung cancer. Also, several studies have revealed the clinical benefits, such as an analgesic effect, ease of breathing, relief of anxiety, etc, of integrative therapies for patients with lung cancer.[20–22] A prospective cohort study involving patients with advanced NSCLC revealed that the median survival was prolonged in the group treated with integrated traditional Chinese medicine (TCM) and CCT compared to the CCT-alone group (16.60 vs 13.13 months, $P < .01$).[23] A meta-analysis demonstrated that concurrent administration of TCM herbs plus EGFR tyrosine kinase inhibitor (EGFR-TKI) resulted in a significantly better response rate, as well as 1- and 2-year survival rates, compared to EGFR-TKI alone in patients with advanced NSCLC.[24] In a randomized controlled trial involving patients with stage IIIB and IV NSCLC, intravenous pharmacopuncture (Cinobufacini injection), oral herbal decoction, and acupoint application (mono-TCM treatments) for 21 days were shown to have times to progression and OSs similar to those of patients treated with chemotherapy alone and higher 1-year survival rate (78.1% vs 53.1%, $P = .035$).[25] Several recent meta-analyses demonstrated superior tumor response rates in the ICT group (conventional treatments + intravenous injection of extracts from a single herb or a mixture of herbs) compared with the CCT-alone group.[26–30] Although those studies suggest that patients in the integrative or the mono-
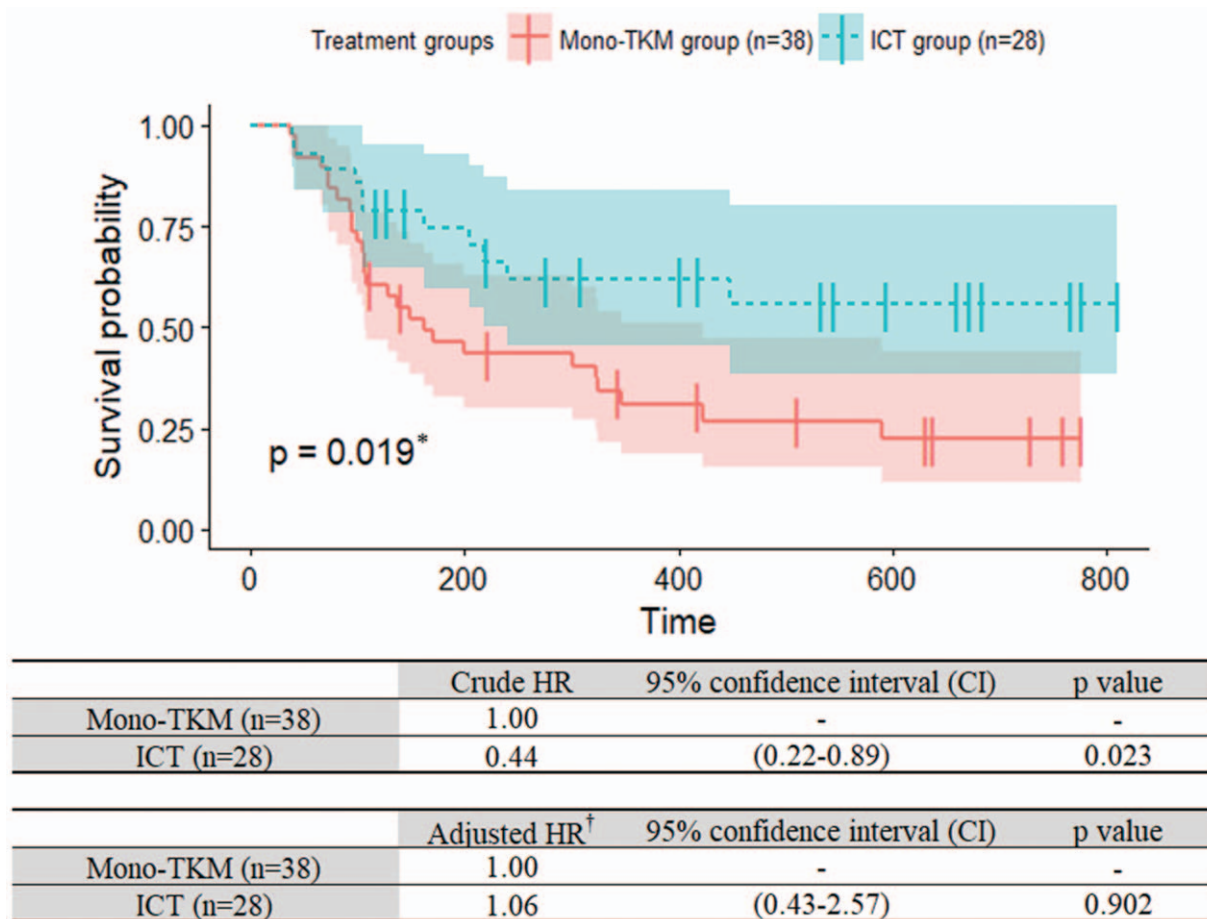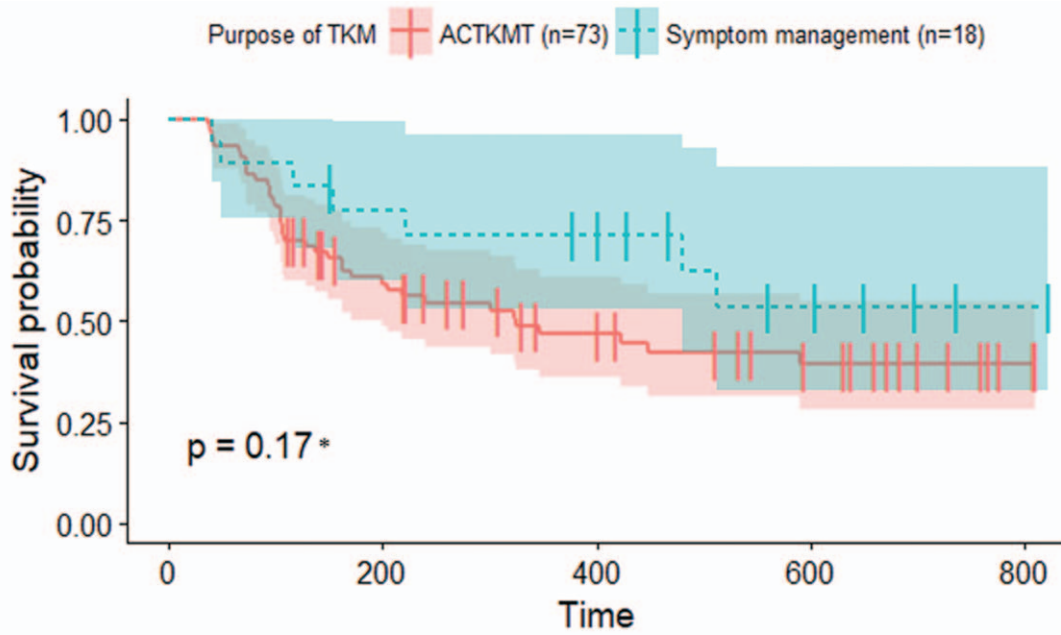
Figure 3. Kaplan-Meier curve of patient survival by treatment group for the patients who underwent anticancer traditional Korean medicine treatment (ACTKMT). *Significant difference (*P* < .05, log rank test). †Adjusted for age, sex, and previous conventional cancer treatment (CCT) status. HR=hazard ratio, ICT=integrative cancer treatment, TKM=traditional Korean medicine.

TKM group exhibited outcome benefits compared to the patients in the CCT-alone group, our study compared the survival benefits of the ICT to those of mono-TKM, not CCT-alone group. Indirectly, MSTs pooled from this study and the results from present studies were compared. MST from the date of enrollment (start of TKM) was 5.59 months in the mono-TKM group consisting mostly of advanced tumor: 13.90 months in patients who had received previous CCT and 4.47 months in patients who had never received CCT. The pooled mean survival was 5.03 months in NSCLC patients without CCT from RCTs mainly involving stage 3 and 4 of NSCLC.[31] In this study, MST in the ICT group was not reached, but could be assumed to be longer than maximum observation period of 27.01 months. A systematic review reported MST ranged from 6.2 to 15.4 months in advanced NSCLC population with squamous disease who received first-line chemotherapy. The MST in NSCLC population with EGFR mutation-positive status ranged from 21.6 to 30.9 months.[32] Other present studies reported MST with CCT: 8.7 months for second-line pemetrexed chemotherapy and 8.5 months for second-line taxanes-based platinum combination in advanced NSCLC[33]; 5.3 months with erlotinib and 5.5 months with docetaxel or pemetrexed chemotherapy in advanced, recurrent, or metastatic NSCLC[34]; 9.2 months with nivolumab versus 6.0 months with docetaxel in advanced SCC.[19] In

summary, integration of TKM and CCT might have survival benefits in comparison to TKM alone and CCT alone.

We addressed 3 particular treatments of all WBCT components, an ICT program offered at the EWCC in Korea as ACTKMT. First, HangAmDan-B is a multiherbal formula containing *P notoginseng Radix*, *C militaris*, *P ginseng C.A. Mey.*, and *B carterii BIRDWOOD*. This formula was demonstrated to inhibit metastasis and recurrence via inhibiting angiogenesis and tumor cell proliferation.[12,35–38] Second, the anticancer activities of *R verniciflua* Stokes through antiangiogenesis, anti-invasion, inhibition of G_1 cell cycle progression, induction of apoptosis, and effects on cell signaling pathways were investigated in a number of experimental studies.[39,40] Third, cultivated wild ginseng (adventitious root culture of *P ginseng*) extracts, which contain ginsenosides (protopanaxadiol and protopanaxatriol type)[41] and flavonoids such as sesquiterpene, quercetin, hesperidin, and anthocyanidin,[42] have been suggested to have anticancer[43,44] and anti-inflammatory[45] effects. Cultivated wild ginseng pharmacopuncture is a new acupuncture technique which injects distilled extract from cultivated wild ginseng into acupuncture points or within a vein[46]; this pharmacopuncture may complement low oral bioavailabilities of ginsenosides and its metabolites.[47] A case series reported that patients with stage III NSCLC who had been

Figure 4. Kaplan-Meier curve of patients who received anticancer TKM treatment in comparison with those who received symptom management only. *Significant difference ($P < .05$, log rank test). †Adjusted for age, sex, previous conventional cancer treatment CCT status and different treatment group status. ACTKMT = anticancer traditional Korean medicine treatment, HR = hazard ratio, TKM = traditional Korean medicine.
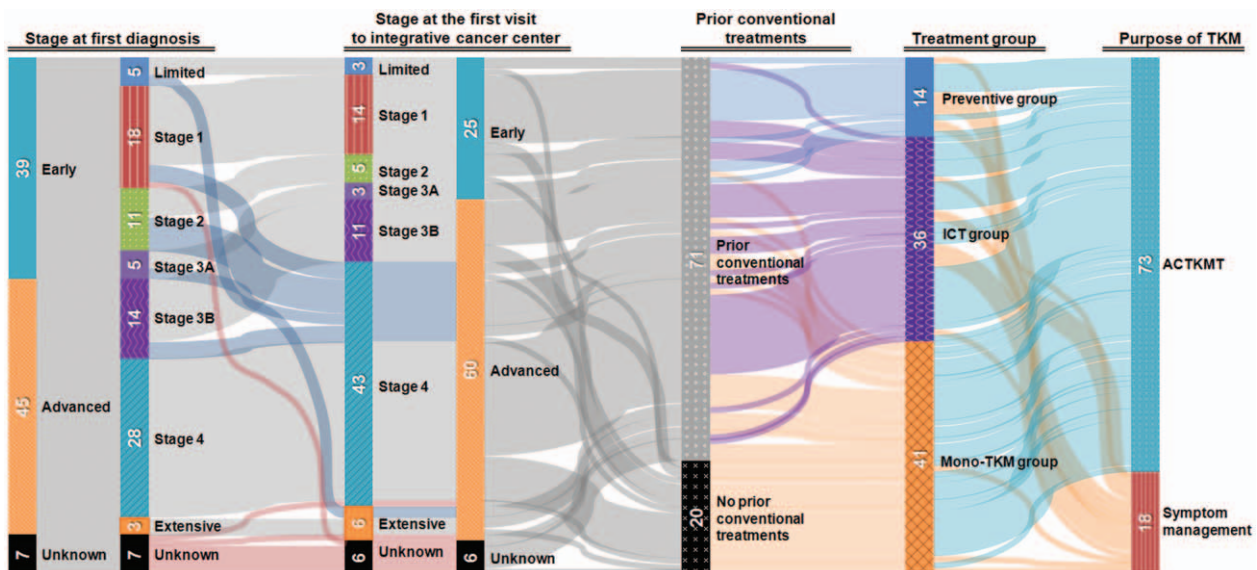

Figure 5. A Sankey diagram visualizing the clinical characteristics between treatment groups in the retrospective cohort study. ACTKMT = anticancer traditional Korean medicine treatment, ICT = integrative cancer treatment, TKM = traditional Korean medicine.

treated with intravenous pharmacopuncture of cultivated wild ginseng had stable disease.[48] These 3 treatments are prescribed to patients in compliance with their disease status, availability of oral administration, and patients' preference.

As we had already found that patients with an advanced stage of lung cancer had worse survival rate than those with an early stage (Fig. 1), in this study, patients with a more advanced stage of patients (53 of 70) were more likely to received ACTKMT than patients with an early stage were (7 of 15) ($P = .03$). Also, a potential bias of a small number of sizes might have been present. In addition, Table 1 and a Sankey diagram (Fig. 5) show heterogeneous characteristics in each treatment group. Therefore, the results of the survival analysis by treatment group must be evaluated cautiously. In addition, survival superiority of the ICT group to the mono-TKM group was not statistically significant in the adjusted model.

Nevertheless, this retrospective cohort study has strengths. To our knowledge, this longitudinal study is the first study to determine the influence of ICT in TKM for cancer treatment in an actual integrative clinical setting in Korea. The analyses suggest that compared to TKM treatment alone, integrative treatments have potential to improve survival in patients with lung cancer. Also, as the results demonstrated prominent clinical heterogeneities between treatment groups, a further prospective cohort study with a study design adjusting for these heterogeneities is required to assess the effects of ACTKMT on survival outcomes in patients with cancer.

5. Conclusions

This retrospective cohort study suggests that, in comparison to patients with lung cancer who undergo TKM alone, those who undergo integrative treatment of TKM and CCT may experience increased survival. These results should, however, be interpreted with caution, considering nonsignificance in the adjusted model, heterogeneity between the treatment groups, and small number of size. In addition, ACTKMT showed decreased survival rate compared to TKM for general symptom management, but the ACTKMT group contained a larger number of patients with advanced cancer. Thus, further cohort studies with a rigorous prospective study design are required.

Author contributions

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