


Survival Analysis of Advanced Non–Small Cell Lung Cancer Patients Treated by Using Wheel Balance Cancer Therapy

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Abstract

Objective. To investigate the clinical effect and the overall survival (OS) rate of patients with advanced non–small cell lung cancer (NSCLC) who have undergone Wheel Balance Cancer Therapy (WBCT). **Methods.** The cases of 33 patients with advanced NSCLC who were treated with WBCT at the East West Cancer Center (EWCC) between October 4, 2004, and October 3, 2013, without undergoing concurrent conventional treatment were analyzed. The Kaplan-Meier method was used to estimate the OS of the cases, and the median OS was calculated according to age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), conventional-treatment history, WBCT treatment duration, and histological tumor type. **Results.** The median OS of all patients was 31.1 (95% confidence interval [CI] = 3.5-58.7) months; the OS rates were 63.6% and 24.2% at years 1 and 2, respectively. The median OS rates of patients under and over 65 years were 45.2 (95% CI = 13.5-76.9) and 19.5 (95% CI = 7.1-31.8) months, respectively ($P = .189$). The median OS rates of patients who received WBCT for >14 days but <28 days and those who received WBCT for ≥ 28 days were 16.2 (95% CI = 13.3-19.2) and 45.2 (95% CI = 14.4-76.0) months, respectively ($P = .437$). The median OS rates of patients who had undergone prior conventional treatment and those who had not were 45.2 (95% CI = 9.1-81.3) and 3.9 (95% CI = unable to calculate) months, respectively ($P = .000$). The median OS rates of patients with squamous cell carcinoma (SCC) and non-SCC lung cancer were 5.6 (95% CI = unable to calculate) and 45.2 (95% CI = 9.1-81.3) months, respectively ($P = .262$). The median OS rate of patients with ECOG PS ≥ 3 was 14.3 (95% CI = 8.8-19.8) months; that of patients ECOG PS <3 could not be calculated. However, the mean OS rates of patients with ECOG PS <3 and with ECOG PS ≥ 3 were 85.7 (95% CI = 58.4-113.0) and 12.7 (95% CI = 8.5-16.9) months, respectively ($P = .000$). No severe adverse events were encountered. **Conclusions.** Our study indicates that WBCT might be effective to prolong the length of survival for patients with advanced NSCLC who have previously undergone conventional treatment and have an ECOG PS <3.

Keywords

advanced non–small cell lung cancer, Wheel Balance Cancer Therapy, integrative cancer treatment, overall survival, quality of life, herbal medication

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Introduction

According to the 2015 cancer statistics of the American Cancer Society, lung cancer is the most common cancer in the United States of America in terms of mortality among both males (28%) and females (26%).¹ In Korea, lung cancer is also the most common cancer in terms of mortality among both males (26%) and females (16%).² Lung cancer treatment is outlined in the National Comprehensive Cancer Network (NCCN) Guidelines.^{3,4} In the United States, 20% of the patients with advanced non–small cell lung cancer

(NSCLC) receive chemotherapy alone, 17% receive radiation therapy alone, and 35% receive a combination of the 2 regimens. Among chemotherapy recipients, targeted therapy

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with bevacizumab is used in 16.5% of the cases; erlotinib, cetuximab, and crizotinib may also be used to treat the advanced stage of the disease.⁵

Although anticancer treatment is important for cancer therapy, symptom management is also necessary. Palliative care, including symptom management, prolongs the survival time of advanced NSCLC patients.⁶ Integrative treatment is generally used to increase the quality of life and alleviate symptoms. However, in the treatment of advanced NSCLC, integrative treatment is also able to enhance the immune system and prolong the survival time^{7,8} and can be used as maintenance therapy.⁹ The American College of Chest Physicians has published evidence-based clinical practice guidelines (3rd edition) for the diagnosis and management of lung cancer in complementary and integrative medicine.¹⁰

The theories of traditional Korean medicine (KM) view human physiology as a network of interdependent organ systems; thus, health is defined as a stable balance among these networks where the metabolism of each organ system is in harmony with that of the other systems. KM therapies focus on restoring homeostasis by synchronizing the networks of the metabolic pathways, thus creating favorable physical environments in which the immune system can function properly. Recently, scientific evidence supporting the efficacy of KM has been found in both preliminary and clinical studies on cancer care. Based on the results of those studies, KM is useful in the management of cancer symptoms and can increase survival. In addition, KM treatment can be effectively integrated into conventional therapy.¹¹

Wheel Balance Cancer Therapy (WBCT), which is based on KM, is an integrative cancer treatment program at the East West Cancer Center (EWCC), which is one of the major integrative cancer centers in Korea. Conventional modes of cancer treatments mostly target tumors whereas WBCT is an indirect approach that targets the physiological environment to induce cancer regression and tumor dormancy.

WBCT can be administered either as inpatient or outpatient care. However, in this study, we needed to evaluate the implementation of WBCT, so we investigated only patients who had been treated on an inpatient basis. WBCT includes an anticancer diet, metabolism activation, anti-angiogenic and immune-enhancing herbal therapy, meditation, and exercise.¹² For the anticancer diet, patients are given a personal diet plan and are advised to consume green vegetables and fruit juice twice a day, which is served at the EWCC. For metabolism activation, patients received acupuncture, moxibustion, hydrotherapy (herbal steam baths), herbal hot pack therapy, and pharmacopuncture (herbal acupuncture) treatments. For antiangiogenic agents and immunotherapy, antiangiogenic and immune-system-stimulating agents, including anticancer capsules (HangAm-Plus [HAP])¹³⁻¹⁵ and immune-enhancing capsules (MyunYuk-Plus [MYP]),^{16,17} are orally administered daily. HAP and MYP, which were developed at the EWCC and consist of herbal

medicines, have been used for about 20 years at the EWCC for the treatment of patients with solid tumors. Under a physician's supervision, patients are given advice on improving the conditions of their minds and bodies through meditation, controlled breathing, yoga, and qi-gong. WBCT is usually, but not always, given concurrently with conventional therapy at the EWCC.

Although WBCT is an integrative cancer intervention used at the EWCC of Daejeon University, Korea, no studies have been done to identify its possible benefits as a sole therapy. The aim of this study was to investigate the possibilities of using the WBCT of the EWCC as an alternative approach to the treatment of patients with advanced NSCLC.

Patients and Methods

Eligibility and Chart Review

This study was approved by the Research Ethics Committee, EWCC (IRB No. DJUMC 14-08). From October 4, 2004, to October 3, 2013, patients were enrolled in the study at their first visit to the EWCC. The eligibility criteria were as follows: (1) diagnosis of lung cancer; (2) treatment with only WBCT without ongoing conventional therapy in the hospital; (3) presence of historically confirmed NSCLC; (4) treatment with WBCT for more than 14 days; (5) Eastern Cooperative Oncology Group (ECOG) performance status (PS)¹⁸ Score of 0 to 3.

During this period, 713 patients who had a diagnosis of lung cancer visited the EWCC. Because the purpose of this research was to investigate the effectiveness of WBCT alone, without any other treatment, 664 patients who underwent simultaneous conventional therapy or who had no record concerning use of conventional therapy were excluded. Because this research had NSCLC as its focus, patients with SCLC or no record of tumor classification were excluded.

WBCT is a holistic total cancer care program that is composed of herbal medications, an anticancer diet, exercise, acupuncture, moxibustion, and so on. In our opinion, WBCT should be continued for at least 14 days if it is to have an effect on the cancer patients, so we analyzed only patients who underwent WBCT without ongoing conventional therapy in the hospital for more than 14 days. Thus, 4 patients who underwent WBCT for fewer than 14 days and 2 patients who took no WBCT were excluded. We also excluded 4 patients who had ECOG PS scores of 4 and one patient whose diagnosis date was uncertain. Finally, 33 patients were included in this research (Figure 1).

Treatment: Wheel Balance Cancer Therapy

A physician completes a physical examination of each patient during treatment. A physical examination includes

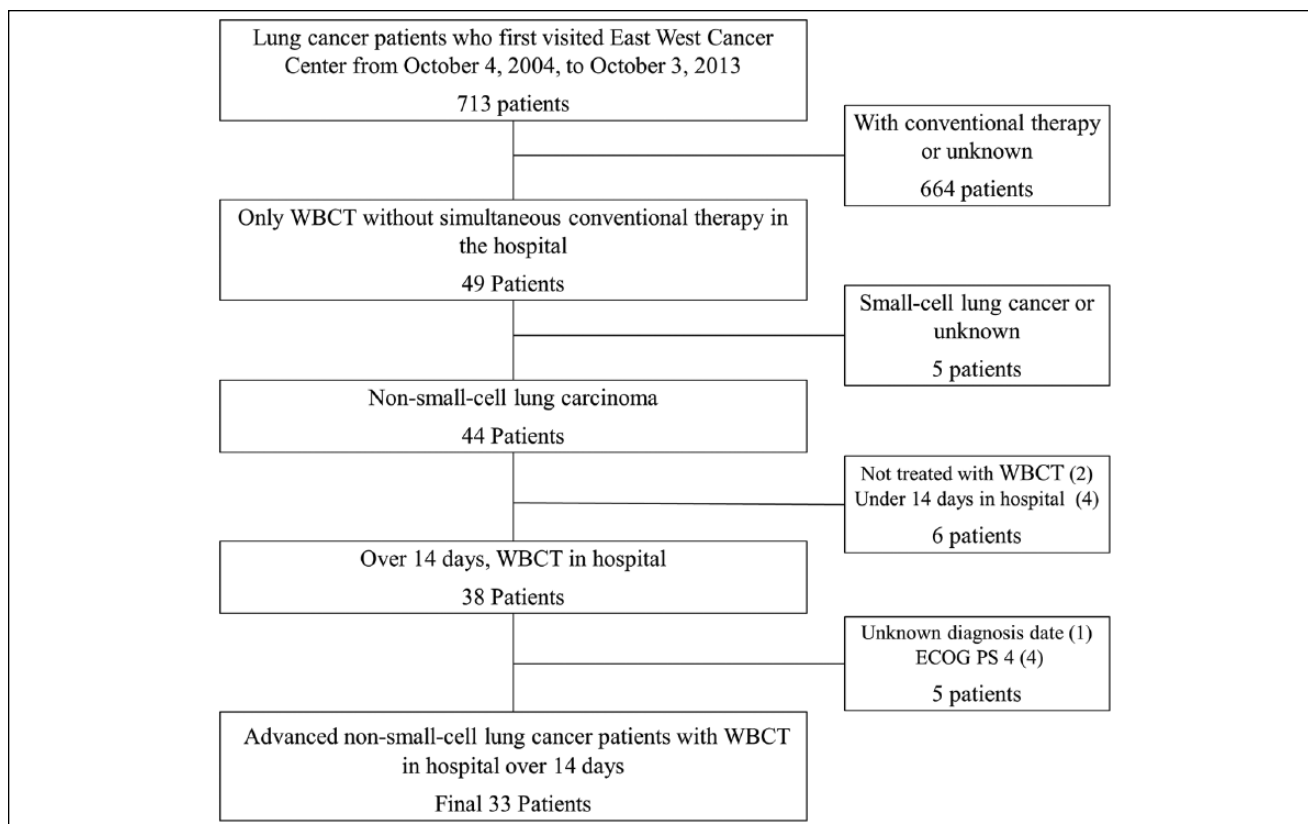


Figure 1. Patient eligibility.

an electrocardiogram, laboratory studies (common blood count and differential blood count, as well as liver and renal function tests), and radiology tests. Based on the results, all patients in the study received only WBCT in the hospital for more than 14 days.

When a patient visits the EWCC, an oncologist examines the patient and teaches him or her how to eat, exercise, and meditate; prescribes herbal medicine; and develops an intervention plan for that patient. A nurse and a specialist helps the patient exercise and implement the intervention plan in the hospital.¹² The details of the WBCT program are presented in Table 1.

We suggest that patients continue to be treated with WBCT after hospital discharge and teach them to care for themselves through diet, exercise, and meditation. Some continue to follow the regimen, but for personal reasons, some do not. Although we do not have data, one of the reasons for their not continuing with the regimen outside the hospital might be an economic one, that is, the lack of coverage by medical insurance. In this study, we investigated only inpatient WBCT.

Evaluation and Statistical Analysis

Evaluation and statistical analyses were performed as follows: basic characteristics that were investigated included

gender, age, ECOG PS, histopathology, whether the patient underwent conventional treatment and if so, treatment duration (≥ 14 days but < 28 days or ≥ 28 days), lines of chemotherapy, cancer stage, and metastases. The overall survival (OS) rate and the hazard ratio (HR) were calculated from the date of diagnosis to the date of death as recorded on the chart or the date of the last follow-up of a patient who was expected to expire within a month according to an expert's opinion. We used the Kaplan-Meier method to estimate the OS and the median OS according to age, ECOG PS, previous conventional treatment, WBCT treatment duration, and histological tumor type. The analysis of the median survival was performed by using PASW Statistics version 17.0 (SPSS, Chicago, IL). For safety and assessment of toxicity, we measured the liver function and the renal function through a blood test. Adverse events were assessed by using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.¹⁹

Results

Patient Characteristics

In total, of the 713 lung cancer patients who visited EWCC, 33 met our eligibility criteria and were selected (Table 2).

Table I. Daily Intervention Contents of the Inpatient Wheel Balance Cancer Therapy Program.

Time	Therapy	Manager	Reference
6:30	Wake-up		
6:30-7:00	Controlled breathing, green vegetables juice	Patient, nurse	At first, oncologist teaches patient and patients do by themselves
7:30-8:00	Breakfast	Nutritionist	Anticancer diet
8:30	Herbal medicine	Oncologist	Anti-angiogenic and immune-system-stimulating agents
8:30-9:00	Herbal hot pack therapy	Nurse	Metabolism activation
9:00-10:00	Acupuncture	Oncologist	Metabolism activation
10:30-12:00	Moxibustion, physiotherapy	Oncologist	Metabolism activation
12:00-12:30	Lunch	Nutritionist	Anticancer diet
13:00	Herbal medicine	Oncologist	Anti-angiogenic and immune-system-stimulating agents
13:30-15:30	Exercise (hiking)	Oncologist or nurse	Patients walk around the mountain with a doctor or nurse
15:30-17:00	Hydrotherapy (herbal steam baths)	Nurse	Metabolism activation
16:00-17:00	Pharmacopuncture (herbal acupuncture) treatments	Oncologist	Metabolism activation
16:00-17:00	Yoga	Yoga specialist	Once a week
17:30-18:00	Dinner	Nutritionist	Anticancer diet
18:30	Herbal medicine	Oncologist	Anti-angiogenic and immune-system-stimulating agents
19:00-19:30	Herbal hot pack therapy	Nurse	Metabolism activation
20:30-21:00	Mind and body through meditation	Patient	At first, oncologist teaches patient and patient does it by himself or herself

The mean age was 63.2 years (range = 25-83 years). Eight patients (24.2%) had received a surgical resection of the tumor, 18 (54.5%) patients had received prior chemotherapy, 15 patients (45.5%) had received radiotherapy, and 5 patients (15.2%) never received any conventional treatment. Histological examination confirmed an adenocarcinoma in 24 patients (72.7%) and a squamous cell carcinoma (SCC) in 7 patients (21.2%). Tumors had metastasized to the bone in 13 patients, the liver in 9 patients, the other lung in 8 patients, and the brain in 7 patients. Three patients had no metastasis in different organs, but because of their age and physical condition, they had not undergone conventional therapy.

Treatment Outcomes

We investigated the survival rate according to age, duration of WBCT, history of prior chemotherapy, histopathology, and ECOG PS. For the analyses of the OS, we used the Kaplan-Meier method,²⁰ and correlations among the 2 groups were established by using the HR (Table 3).

We used the aforementioned method to determine statistically the median OS rate, the 1-year survival rate, and the 2-year survival rate for all patients. The median survival of all patients was 31.1 (95% confidence interval [CI] = 3.5-58.7) months, and the OS rates were 63.6% and 24.2% at the ends of years 1 and 2, respectively (Figure 2).

We analyzed the median OS rate according to the age of the patient. For that, we divided the patients into 2 groups,

one younger than 65 years of age (N = 15) and the other 65 years of age or older (N = 18). The median OS rates of the patients in the former and the latter groups were 45.2 (95% CI = 13.5-76.9) and 19.5 (95% CI = 7.1-31.8) months, respectively. However, the survival outcomes of the 2 groups were not significantly different by the log-rank test ($P = .189$; Figure 3).

We also analyzed the median OS rate according to the duration of WBCT treatment for the 2 groups, one that underwent WBCT for 14 days or longer but less than 28 days (N = 16) and the other that underwent WBCT for 28 days or longer (N = 17). The median OS rates of the patients in the former and the latter groups were 16.2 (95% CI = 13.3-19.2) and 45.2 (95% CI = 14.4-76.0) months, respectively. However, the survival outcomes of the 2 groups were not significantly different by the log-rank test ($P = .437$; Figure 4).

Furthermore, we analyzed the median OS rate according to whether or not conventional treatment had been received, so we divided the patients into 2 groups, one that had undergone prior conventional treatment (N = 28) and one that had not (N = 5). The median OS rates of the patients in the former and the latter groups were 45.2 (95% CI = 9.1-81.3) and 3.9 (95% CI = unable to calculate because of the data having been censored) months, respectively. The survival outcomes of the 2 groups were significantly different by the log-rank test ($P = .000$; Figure 5).

We also analyzed the median OS according to the histological type of the tumor. For that, we divided the patients

Table 2. Patient Characteristics (N = 33).

Characteristics	Number of Patients (%)
Gender	
Male	23 (69.7)
Female	10 (30.3)
Age (years)	
Mean (range)	63.2 (25-83)
ECOG PS	
1	4 (12.1)
2	16 (48.5)
3	13 (39.4)
Previous conventional treatment	
Surgery	8 (24.2)
Chemotherapy	18 (54.5)
Radiation	15 (45.5)
None	4 (12.1)
Number of prior chemotherapy regimens	
0	5 (15.2)
1	6 (18.2)
2	9 (27.3)
≥3	13 (39.4)
Histopathology	
Adenocarcinoma	24 (72.7)
Squamous cell carcinoma	7 (21.2)
Large cell carcinoma	0 (0)
Others	2 (6.1)
Duration of WBCT	
≥14 days, <28 days	16 (48.5)
≥28 days	17 (51.5)
Stage	
IIIb	3 (9.1)
IV	30 (90.9)
Sites of metastases (overlap)	
Liver	9 (27.3)
Lung	8 (24.2)
Bone	13 (39.4)
Brain	7 (21.2)
Others	10 (30.3)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; WBCT, Wheel Balance Cancer Therapy.

into 2 groups, one with SCC lung cancer (N = 7) and the other with non-SCC lung cancer (N = 24). The median OS rates of the SCC patients and the non-SCC patients were 5.6 (95% CI = unable to calculate because of the data having been censored) and 45.2 (95% CI = 9.1-81.3) months, respectively. However, the survival outcomes of the 2 groups were not significantly different by the log-rank test ($P = .262$; Figure 6).

To analyze the median OS rate according to ECOG PS, we divided the patients into 2 groups, one with ECOG PS ≥3 (N = 20) and the other with ECOG PS <3 (N = 13). The median OS rate of the patients with ECOG PS ≥3 was 14.3 (95% CI = 8.8-19.8) months, and that of the patients with

ECOG PS <3 could not be calculated because too many of the data had been censored; however, the mean OS rate for that group was 85.7 (95% CI = 58.4-113.0) months while the mean OS rate for the group with ECOG PS <3 was 17.2 (95% CI = 8.5-16.9) months. The survival outcomes of the 2 groups were significantly different by the log-rank test ($P = .000$; Figure 7).

Safety

We did blood tests when the patients were first admitted to hospital, when they were discharged, and when adverse events occurred. In the blood tests, we checked neutrophil count, liver function, and renal function, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ -glutamyl transferase (GGT), and creatinine (Cr). We also evaluated the outcomes by using CTCAE.¹⁹

The adverse events encountered during this research are listed in Table 4. The 4 patients who had elevated ALP also showed bone metastases; however, during the stay in the hospital, the ALP levels of those patients did not increase further. Five patients had elevated GGT levels when they entered the hospital, and those levels did not increase further while the patients remained hospitalized. One patient had an elevated Cr level, which did not increase further while the patient remained hospitalized. No severe adverse events were encountered.

Discussion

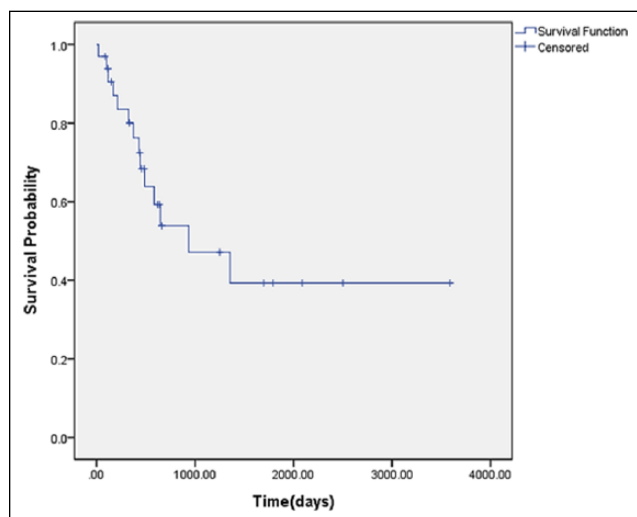
Recently, various integrative cancer therapies have been tried. As WBCT is also one of those therapies, the effectiveness of WBCT compared with conventional therapy for NSCLC patients,²¹ case reports on WBCT,¹² and survival outcomes after WBCT intervention¹³⁻¹⁷ have been investigated. This research is the first to investigate and report the results of the survival times of patients with advanced NSCLC who were treated only with WBCT without any other concurrent treatment.

For this research, we reviewed the records of 773 patients who visited the EWCC during a 10-year period and selected 33 patients who had advanced NSCLC and who had been treated with WBCT without concurrent conventional therapy. WBCT includes interventions that inhibit the growth of cancer cells, reduce the patient's stress, alleviate the patient's symptoms, and enhance the patient's body condition. The combined effect of these interventions is thought to help the patients themselves to overcome the cancer. Thus, WBCT is a total care system, not one treatment. Many studies have investigated individual complementary treatment methods, but this study of WBCT investigated the effect of integrative therapy that included a variety of complementary and alternative treatments.

Table 3. Analysis of the Association Between Survival Rate and Clinical Factors.

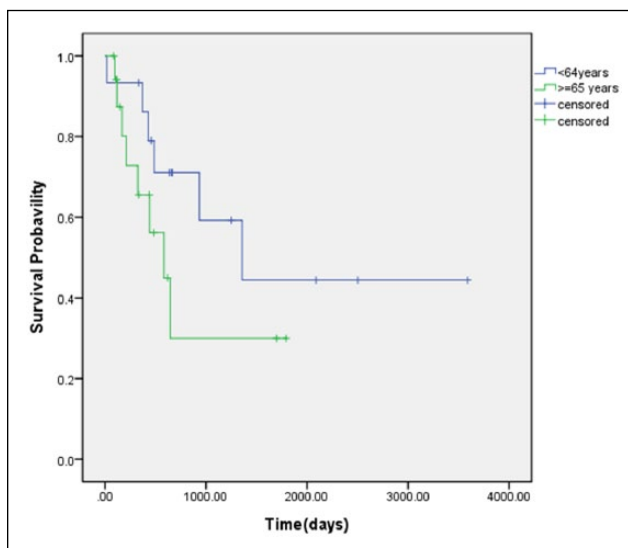
Clinical Factor (n)	Survival Rate			
	Median (Months)	P	HR	P
Age (years)				
<64 (15)	45.2	.189	1.156	.828
≥65 (18)	19.5			
Duration of WBCT				
≥14 days to <28 days (16)	16.2	.437	0.459	.257
≥28 days (17)	45.2			
No. of prior chemotherapy regimens				
0 (5)	3.9	.000**	0.000	.943
≥1 (28)	45.2			
Histopathology				
Non-squamous cell (24)	45.2	.262	2.028	.551
Squamous cell (7)	5.6			
ECOG PS				
<3 (20)	—	.000**	11.480	.004**
≥3 (13)	14.3			

Abbreviations: HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group Performance Status; WBCT, Wheel Balance Cancer Therapy.
** $P < .05$.

**Figure 2.** Overall survival rate of all patients.

The median survival of all patients was 31.1 (95% CI = 3.5-58.7) months, and the overall survival rates, obtained by using the Kaplan-Meier method, were 63.6% and 24.2% at the ends of years 1 and 2, respectively.

We used the NCCN guidelines to compare our results obtained using WBCT with those obtained using conventional therapy.³ In conventional therapy, a curative surgical resection is the optimal treatment, but the use of this procedure is impossible in patients with advanced or metastatic NSCLC because the surrounding tissues are involved and distant metastases are present. Instead, such patients receive systemic therapy to prolong their survival time. Two hospitals in the United Kingdom investigated

**Figure 3.** Overall survival according to age.

Overall survival was longer in the group of patients younger than 65 years of age than it was in the group of patients 65 years of age or older, but the difference was not statistically significant.

(during a 2-year period) patients with advanced NSCLC who had received multiple lines of systemic therapy. After the first-line systemic therapy, 50 out of 110 patients received the second-line systemic therapy, of which 10 patients received the third-line and 2 patients received the fourth-line systemic therapy.²² Thus, approximately 45% of the patients who received the first-line therapy subsequently received therapy again because of recurrent or progressive NSCLC.

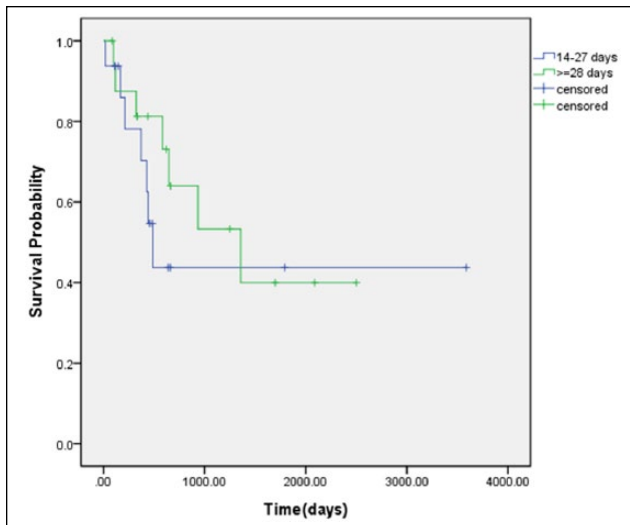


Figure 4. Overall survival according to duration of treatment. The survival probability of patients who underwent WBCT for 14 days or longer, but less than 28 days, was longer than it was for patients who underwent WBCT for 28 days or longer, but the difference was not statistically significant.

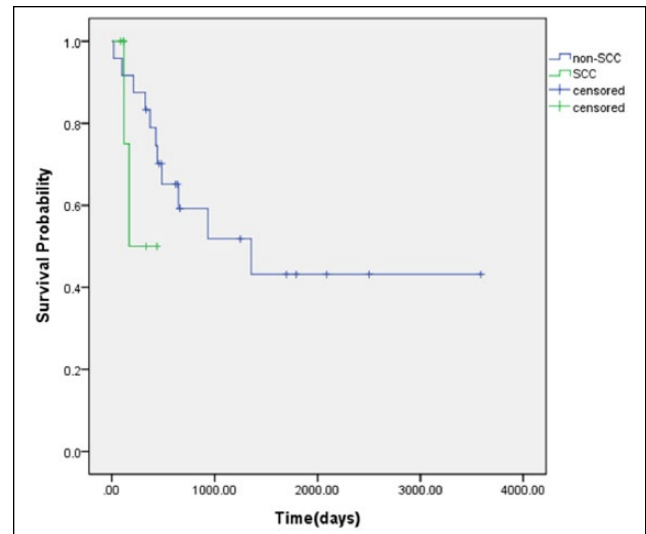


Figure 6. Overall survival according to histological type. Overall survival was longer in the group with non-SCC lung cancer than it was in the group with SCC, but the difference was not statistically significant.

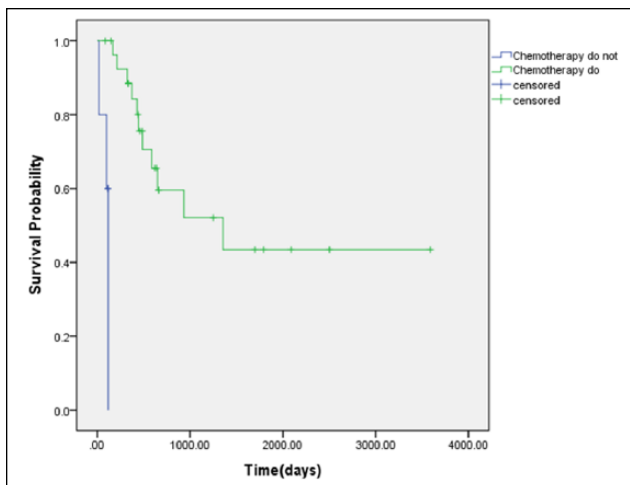


Figure 5. Overall survival according to having undergone conventional treatment. Overall survival was significantly longer in the group that underwent prior conventional treatment than it was in the group that did not.

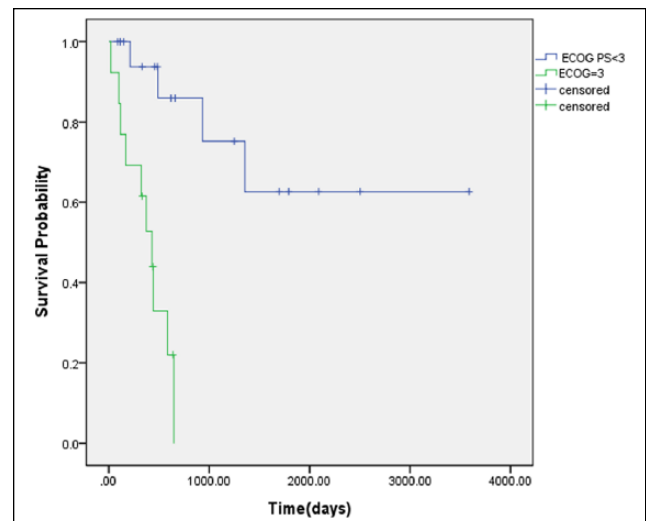


Figure 7. Overall survival according to ECOG PS. The median OS rate of patients with ECOG PS <3 could not be calculated because too many were censored. Thus, we also analyzed the mean OS rate of patients with ECOG PS <3 and with ECOG PS \geq 3 and found a significant difference between the 2 groups.

According to the NCCN guidelines, the standard first-line therapy is platinum-based doublet chemotherapy, which may be combined with etoposide, docetaxel, gemcitabine, vinblastine, pemetrexed, or vinorelbine.^{23,24} After the failure of the first- and the second-line therapies, a new target agent, such as nivolumab, ramucirumab, erlotinib, afatinib, or crizotinib, is selected with a chemotherapy combination.³ Patients with ECOG PS 0 to 2 have options for subsequent therapy; those options include docetaxel, pemetrexed, erlotinib, gemcitabine, ramucirumab plus docetaxel, or nivolumab.³

In several phase III studies of cytotoxic agents for the second-line therapy, the reported values for the median OS rate with docetaxel treatment were 30.7 weeks,²⁵ 7.0 months,²⁶ 5.7 months,²⁷ 7.9 months,²⁸ and 8.0 months,²⁹ and those for pemetrexed treatment were 8.3 months²⁸ and 10.1 months.³⁰ In a recent phase III study of ramucirumab plus docetaxel, the median OS rate was 10.5 months.³¹ In another phase III study of nivolumab for advanced SCC-NSCLC patients, the median OS rate was 9.2 months.³² If an epidermal growth factor receptor (EGFR) mutation is sensitized

Table 4. Adverse Events During the Entire Treatment.

	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	≥ Grade 3 (%)
Hematological				
Neutropenia	0	0	0	0
Liver function				
AST increased	0	0	0	0
ALT increased	0	0	0	0
ALP increased	15.2	0	0	0
GGT increased	3.0	12.1	0	12.1
Renal function				
Cr increased	3.0	0	0	0

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ -glutamyl transferase; Cr, creatinine.

Table 5. Studies About Agents of Conventional Systemic Therapy for Advanced Non–Small Cell Lung Cancer.

Study	Intervention	Versus	Number	Median OS
Ramlau et al ²⁵	Docetaxel 75 mg/m ²	Topotecan	415	30.7 weeks
Shepherd et al ²⁶	Docetaxel 100 mg/m ² or 75 mg/m ²	BSC	104	7 months
Fossella et al ²⁷	Docetaxel 100 mg/m ² or 75 mg/m ²	Vinorelbine/ifosfamide	250	5.7 months
Hanna et al ²⁸	Docetaxel 75 mg/m ²	Pemetrexed	288	7.9 months
Kim et al ²⁹	Docetaxel 75 mg/m ²	Gefitinib	710	8.0 months
Hanna et al ²⁸	Pemetrexed 500 mg/m ²	Docetaxel	283	8.3 months
Karampeazis et al ³⁰	Pemetrexed 500 mg/m ²	Erlotinib	166	10.1 months
Garon et al ³¹	Ramucirumab 10 mg/kg + docetaxel 75 mg/m ²	Placebo + docetaxel	628	10.5 months
Brahmer et al ³²	Nivolumab 3 mg/kg	Docetaxel		9.2 months
Karampeazis et al ³⁰	Erlotinib 150 mg/day	Pemetrexed	166	8.2 months
Shepherd et al ³³	Erlotinib 150 mg/day	Placebo	488	7.9 months
Shaw et al ³⁵	Crizotinib 500 mg/day	Pemetrexed/docetaxel	173	20.3 months
Ohyanagi et al ³⁶	Bevacizumab 15 mg/kg + docetaxel 60 mg/m ²	None	27	21.6 months
Fujimoto et al ³⁷	Cisplatin 60 mg/m ² + docetaxel 60 mg/m ² + irinotecan 50 mg/m ²	None	25	14.3 months
This study	Wheel Balance Cancer Therapy	None	33	31.1 months

Abbreviations: OS, overall survival; BSC, best supportive care.

positive, patients may receive EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib or afatinib. In 2 different second-line therapy phase III studies of EGFR TKIs, the median OS rates with erlotinib treatment were 8.2 months³⁰ and 7.9 months.³³ For anaplastic lymphoma kinase–positive patients, crizotinib is superior for chemotherapy.³⁴ The median OS rate with crizotinib treatment was 20.3 months.³⁵ In a phase II study of docetaxel plus bevacizumab combination therapy, the median OS rate was 21.6 months.³⁶ In a study of recurrent or advanced NSCLC patients who received the triplet cisplatin, docetaxel, and irinotecan, the median OS rate was 14.3 months, but this combination has been proven to be too toxic to be used for patient treatment (Table 5).³⁷

In a study conducted in China, treatment of advanced NSCLC in dementia patients with traditional Chinese medicine (TCM) alone was found to be superior to chemotherapy alone in elevating the quality of life and prolonging survival time.³⁸ Another study³⁹ investigated the effect of

another TCM therapy, Guben Xiaoliu Capsule (GCX), in treating patients with advanced NSCLC. In terms of the immediate effect, the integrative group (chemotherapy plus GCX, 16.7%) was apparently superior to the TCM alone group (GCX only). However, the median OS rate was 15 months in the TCM alone group, 12 months in the integrative group, and 9 months in the chemotherapy alone group. The TCM alone group also showed reduced toxicity.

Furthermore, in the United States, 193 patients with colon cancer were treated at a clinic of Chinese medicine and by using conventional therapy. They were treated with herbal medicine as Chinese medicine or Pan-Asian medicine plus vitamins, both of which were combined with conventional therapy and integrative treatment including diet and exercise. The combined treatment reduced the risk of death for patients with stage 4 colon cancer by 75% compared with that for patients with stage 4 colon cancer treated with conventional therapy alone.⁴⁰

A Korean study investigated the survival of patients with NSCLC stages over IIIb treated with HAP, which contains anti-angiogenic agents derived from Korean herbal medicine and is included in WBCT as an anticancer treatment. In that clinical study, the 1-year survival rate was 62.1%, the 2-year survival rate was 34.9%, and the median survival time was 17.0 months.²¹ HAP suppresses inflammatory responses by inhibiting Syk/NF- κ B and JNK/ATF-2 pathways.¹³ It also inhibits the activities of the matrix metalloproteinases (MMP)-2 and MMP-9 and upregulates the expressions of the tissue inhibitors of metalloproteinases (TIMP)-1 and TIMP-2, which inhibits the motility and the invasiveness of NCI-H460 cells.¹⁵

This study investigated the impact of using WBCT for the treatment of patients with advanced NSCLC. The median OS rate of all patients was 31.1 (95% CI = 3.5-58.7) months, and the OS rates were 63.6% and 24.2% at the ends of years 1 and 2, respectively, indicating that the treatment was safe.

Because prior chemotherapy had failed for 28 of the 33 patients included in this research, they visited the EWCC for WBCT treatment. Four of these patients were over 70 years of age, and 1 patient had a private reason for visiting the EWCC. Thirteen patients could not receive additional conventional therapy because of an ECOG PS = 3. We treated these advanced NSCLC patients with WBCT. The survival time was longer for patients under the age of 65 than it was for patients 65 years of age or older (HR = 1.156, $P = .828$) and for patients with ECOG PS 0 to 2 than it was for patients with ECOG PS = 3 (HR = 11.480, $P = .004$). Thus, younger patients (<65 years of age) and patients with ECOG PS 0 to 2 treated with WBCT had longer median OS than the more elderly patients (≥ 65 years of age) and those with ECOG PS = 3. However, the difference in the median OS rate according to age was not statistically significant.

Of the 28 patients who had undergone prior chemotherapy, 22 patients received more than the third line of therapy (maximum = seventh line). The chemotherapy regimens included cisplatin, docetaxel, gemcitabine, vinorelbine, paclitaxel, and carboplatin. The median OS rate of the patients who underwent conventional treatment including systemic therapy was 45.2 months as compared with 3.9 months for patients who had undergone no conventional treatment. Of the 5 patients who had never undergone conventional therapy, 4 patients had ECOG PS 3 and were over 70 years of age; their general condition was poor, and treatment was limited, so their survival time was shorter than that of the other patients.

In the aforementioned studies, the median OS rate for chemotherapy with cytotoxic agents was 7.0 to 10.1 months. The median OS with combination therapy with a target agent was up to 21.6 months, whereas it was 15.0 to 17.0 months with TCM alone or combination therapy with KM. The median OS of patients with advanced NSCLC treated

with WBCT was 31.1 months, that is, longer than in the previously mentioned cases.

WBCT is an integrative cancer treatment program at the EWCC. While the exact metabolic pathway of WBCT has not yet been identified, WBCT is thought to suppress cancer by inhibiting angiogenesis and enhancing immunity¹³⁻¹⁷ and to alleviate clinical symptoms by using KM therapy such as herbal medication, acupuncture, moxibustion, and so on. The median OS rate of patients who had undergone prior chemotherapy was 45.2 months; WBCT is thought to be a tumor-dormancy-inducing therapy for patients who resist conventional regimens.⁴¹ Tumor dormancy is known to contribute to homeostatic controls, such as anti-angiogenesis, despite active proliferation and immunological conditions.⁴²

For patients with advanced NSCLC, because of old age, the adverse effects of chemotherapy, the lack of tolerance to chemotherapy regimens, the failure of many lines of therapy, and private reasons, some cancer patients cannot undergo conventional systemic therapy. Cytotoxic therapy is important for reducing tumor size, but adverse events can affect the patients' condition and survival. In addition to survival, alleviating symptoms and elevating quality of life are important to patients.^{6,43} Our study suggests that WBCT may be a good alternative therapeutic approach for treating patients with advanced NSCLC. Blood tests, including neutrophil count, liver function, and renal function, revealed no severe adverse events.

However, this study has several limitations. WBCT was practiced only at the EWCC and only for a limited time period. The period from 2004 to 2013, from which the cancer patients were selected, was too long, and the records that were available had many limitations. Thus, many patients were excluded. Of the 713 patients with lung cancer that were initially evaluated from this time period, only 33 met the eligibility criteria and were included in this study. In addition, because of the retrospective observational nature of this study, not all the dates of death were known exactly, so some statistical analyses were based on the last follow-up. Because the assumption that all censored survival times occurred immediately after their censoring times may not be reasonable, the survival estimates may be somewhat biased. This study included patients who had been treated at various times over a 10-year period, during which time standard therapy and survival times changed for the better. Thus, selecting patients with exactly the same conditions from all the patients in that 10-year period was difficult. The records for the safety assessment were limited because of the long period of time from which patients were selected.

In the future, we need to investigate advanced conventional therapy and the impact of wealth. Conventional therapy is improving, and newly developed agents are being added. We will continue our analysis by comparing the

results achieved with WBCT against those achieved by using the new agents. Furthermore, we know that the efficacy of WBCT treatment depends on the duration of the treatment and that some patients might not continue the treatment for financial reasons, such as the lack of money or the lack of coverage by medical insurance. Thus, further studies addressing the impacts of economic status, medical insurance coverage, the duration of treatment, and other biases are needed if the efficacy of WBCT is to be firmly established.

Conclusion

When advanced NSCLC patients were treated with WBCT, this therapy significantly prolonged the survival time for those who had previously undergone conventional treatment and those who had ECOG PS <3. In the future, more controlled clinical trials with larger samples and with comparisons to other treatments are needed.

Declaration of Conflicting Interests

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