Master's Thesis of Science

The Feasibility of Prehabilitation for Presurgical Patients with Endometrial Cancer: A Multi-Center Study

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The Feasibility of Prehabilitation for Presurgical Patients with Endometrial Cancer: A Multi-Center Study

By
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Abstract

Objective: The primary objective of this study is to develop a prehabilitation exercise program and evaluate the feasibility of the prehabilitation exercise program for new patients diagnosed with endometrial cancer who were scheduled for gynecological surgery. The secondary aim was to determine the impact of the prehabilitation exercise program on the health-related fitness and psychological stress outcomes of the patients.

Methods: The exercise program was developed to improve preoperative physical and psychological health status in patients with endometrial cancer. Women with endometrial cancer patients were recruited from 4 oncology outpatient clinics in Seoul, Korea. All patients received an individual exercise program known as CORE (Challenge, Overcome, Resolve, Enhance), which consists of 60 minutes of moderate resistance, aerobic, and core stability exercises. This was performed 5 times supervised for 2 weeks before surgery. The feasibility was determined by program adherence, adverse events, and safety.

Results: Over the course of 12.5 days before surgery, 17 patients followed the CORE program and results were recorded for 5 training sessions. Adherence to the CORE exercise program was high; 88.9% of the scheduled CORE program attended, and no adverse events occurred. Patients who completed this program significantly improved their health-related fitness (cardiorespiratory function; p =.006, grip strength; p =.017, curl-up; p =.007, flexibility; p =.001), waist circumstance p=.004, but there was no significantly difference between pre and post measurements in BMI; p = 0.89, and FEV1 and FE6 was no changed. As the impact of exercise intervention on emotional distress,

there were significant improvements in EORTC-QOL-C30 (global QOL, p =.001), (functional scale, p =.001), (symptoms scale, p =.004). Also, there was significant improvement in Hospital Anxiety (p =.049), Depression (p =.006) and M. D. There was no difference for M. D. Anderson symptom inventory (p = .05).

Conclusion: The prehabilitation CORE program is feasible and safe for patients with endometrial cancer who are scheduled for endometrial cancer surgery. It shows benefits for health-related fitness and psychological health status of patients. This program will provide the basis for implementation of exercise participation in patients with endometrial cancer before surgery. There is still insufficient evidence to support any robust conclusions regarding the ideal characteristics of an exercise prehabilitation intervention and the impact, it may have on clinical and post-operative outcomes.

Keywords:

Endometrial Cancer, Prehabilitation, Preoperative, Exercise, Physical activity, Quality of Life

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Contents

Table

Figure

I. Introduction

1. Significance of the Study

While the number of cancer patients has been decreasing excluding thyroid cancer since 2012 (National Cancer Information Center, 2014), the incidence of endometrial cancer has been gradually increasing, and it will be the most common form of gynecological cancer in the South Korea with 1,616 new cases being diagnosed in 2010 alone (Lim et al., 2013). Endometrial cancer has a very good prognosis, with a 5-year survival rate of 96% (American Cancer Society, 2011). Subsequently, health-related fitness and quality of life are now recognized as an important outcome for endometrial cancer survivors.

Primary treatment of endometrial cancer includes surgery with or without adjuvant chemotherapy or radiation. These treatments are generally associated with physiological and psychological impairments such as cardiovascular, musculoskeletal weakness, depression and longer term physical limitation after treatment (Cairu Li, Samsioe, & Iosif, 1999; Kornblith et al., 2007; Prue, Allen, Gracey, Rankin, & Cramp, 2010). Besides the type of surgery, these risk factors are determined by the patient's preoperative health status. In addition, several studies suggested that preoperative function, age and comorbid disease are important predictor of postoperative outcomes (Arozullah, Khuri, Henderson, & Daley, 2001; Fukuse, Satoda, Hijiya, & Fujinaga, 2005; Dronkers, Chorus, Meeteren, & Hopman-Rock, 2013; Lingard, Katz, Wright, & Sledge, 2004). Functional limitation and physical inactivity levels are associated with poorer outcomes, which emphasizes the importance of preoperative health status in patients waiting for cancer surgery (Arozullah et al., 2001; Fukuse et al., 2005; Dronkers et al., 2013; Lingard et al., 2004; Saxton & Velanovich, 2011); Saxton A et

al., 2011).

Prehabilitation defined as a procedure to enhance functional capacity and improve psychological stress before scheduled surgery, has received remarkable recognition in field of oncology (Silver, 2015). Improved preoperative physical performance and psychological stress may lead a patient in a better position to withstand postoperative stress (Courtney et al., 2012; Topp, Ditmyer, King, Doherty, & Hornyak III, 2002; Dronkers et al., 2013; Hulzebos et al., 2006). However, most prehabilitation exercise programs are limited to major cancers such as colon, prostate, and lung cancer (Singh, Newton, Galvão, Spry, & Baker, 2013). In addition, these follow international guideline including frequency, intensity, duration and mode of exercise program such as exercise guidance of cancer patients, ACSM (Schmitz et al., 2010). Thus, it is unclear whether the programs are suitable for cancer patients in Korea. Furthermore, it has not yet been established on prehabilitaion exercise program for endometrial cancer patients in Korea and international study. To the best our knowledge, and individualized exercise program has not yet evaluated.

Therefore, the aim of this study was to introduce the feasibility study of protocol evaluating the prehabilitation exercise program in management of endometrial cancer patients who were scheduled for endometrial cancer surgery to improve their health-related fitness and quality of life outcomes.

2. The purpose of the study

The aim of this study was to investigate the feasibility study of protocol evaluating the prehabilitation exercise program in management of endometrial cancer patients who were scheduled for endometrial cancer surgery to improve their health-related fitness and quality of life outcomes for 2 weeks before surgery

3. Research Hypothesis

There are couples of hypothesis after flowing this sentence.

a. Patients with endometrial cancer may be able to perform preoperative exercise intervention without any adverse event.

b. Prehabilitation exercise intervention will improve health-related fitness in endometrial cancer patients.

c. Prehabilitation exercise intervention will have a positive effect on psychological health improvement in endometrial cancer patients.

4. Limitations

This study is limited in the following manners:

a. There was no control group to compare the outcome before and after CORE program.

b. The patients could not be controlled for daily intake and physical activity.

c. The sample size was not enough even though multi-centers study.

II. Literature review

1. Endometrial Cancer

Gynecological cancer is classified into endometrial cancer, cervical cancer, and ovarian cancer that emerges from tissue of the uterus. According to National Cancer Center in 2012, the prevalence of age-standardization of endometrial cancer was 36.1% per 100,000 population, which was 2.3% of female cancer cases in Korea. (Ministry of Health and Welfare, 2012). The incidence rate of standardization was 5.4 persons per 100,000 people in 2010, which shown a tendency to increase comparing with 2.4 persons in 1999. However, the incidence of endometrial cancer is very low in 2008, compared with western counties such as United States (16.5 persons per 100,000) and United Kingdom (13.1 persons per 10,000). Additionally, in case of only endometrial cancer, the incidence of age standardization increased from 1999 (2.4%) to 2010(4.6 %). This has been increased 6.9% per year (Lim et al., 2013). According to WHO statistics, 249 women who died of cancer due to cancer of the uterus in 2010 have increased by 6.7% annually since 1993 (Lee et al., 2014). According to World Health Organization, the number of death from endometrial cancer was 249 among women who death from cancer in 2010. It has been increased by 6.7% annually since 1993. The relative survivor rate was 86.2% in endometrial cancer from 2006 to 2010. This was increased 4.7% comparing with 1993 to 1995. As in the west countries, considering that endometrial cancer accounts for the majority of uterine cancer, and uterine sarcoma is a rare form of carcinoma, the burden of disease caused by the endometrial cancer is likely to increase in Koreas as well. This increasing of endometrial cancer incidence in Korea seems to be due to the westernization of the diet and lifestyle change.

Table. 1 Endometrial cancer standardization age (Lim et al., 2013)

Year	Overall	Cervical	Endometrium	Ovary
1999	23.7	16.3	2.4	5.0
2000	22.1	15.0	2.3	4.8
2001	23.2	15.8	2.6	4.8
2002	22.7	4.8	2.8	5.0
2003	22.5	14.1	3.2	5.1
2004	21.3	13.0	3.1	5.1
2005	21.3	12.3	3.5	5.4
2006	21.2	12.1	3.6	5.4
2007	20.8	11.0	3.9	5.9
2008	21.3	11.4	4.3	5.5
2009	20.6	10.5	4.7	5.3
2010	21.0	10.6	4.6	5.7
APC	-1.1	-4.3	6.9	1.5
95% CI	-1.53 to -0.70	-4.92 to -3.63	6.05 to 7.66	0.82 to 2.23
p-value	<0.001	<0.001	<0.001	<0.001

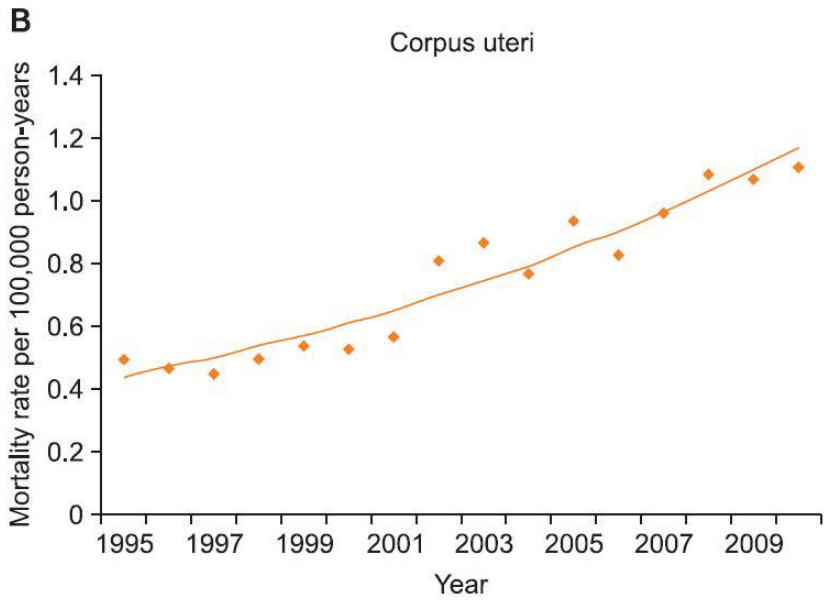


Figure. 1 Mortality of Endometrial cancer standardization age (Lee et al., 2014)

2. Exercise & Cancer

For a long time, many studies reported that exercise can improve complications and quality of life for cancer patients after treatments. Several studies examining the role of exercise with cancer patients have related to the increased level of physical activity during and after treatment with positive benefits on decreasing rates of fatigue, enhancing physical performance, and improving quality of life. (Stricker, Drake, Hoyer, & Mock, 2004). The lack of physical activity is occurred naturally for cancer patients. Many studies shown that exercise regime may have positive effects on cancer patient's quality of life in a variety of ways, including physical, functional, psychological, and emotional well-being from exercise training (Courneya, Mackey, & Jones, 2000). Also other study reported that exercise is meaningful benefit as non-pharmacologic therapy base on strong evidence to improve cancer-related fatigue (Dimeo, 2001).

3. Exercise & Endometrial Cancer

The most important risk factors for endometrial cancer are postmenopausal unopposed estrogen therapy, obesity, and nulliparity. In contrast, physical activity represents an important modifiable preventive factor for endometrial cancer. Plausible biologic mechanisms linking increased physical activity to decreased endometrial cancer risk include decreased levels of sex steroids, insulin resistance, and chronic inflammation. Physical activity may be directly involved in these biologic pathways or indirectly by reducing obesity. Keum reported that physical activity in relation to risk of endometrial cancer (Keum et al., 2014). In the same

way studies suggest that physical activities associated with reduced risk of developing endometrial cancer (Moore, Gierach, Schatzkin, & Matthews, 2010). Thus, physical activity may reduce the risk of endometrial cancer by 32 to 46% (NCI, Endometrial Cancer Treatment et al., 2014). Many studies have examined the relationship between physical activity and the risk of endometrial cancer then few endometrial cancer survivors meet the health recommendations for physical activity (Vivian E Von Gruenigen et al., 2011). In a meta-analysis of 33 studies, the average endometrial cancer risk reduction associated with high versus low physical activity 20% (Schmid et al., 2015).

4. Prehabilitation Exercise

Preoperative status is a process of buffering and improving potentially harmful physical and mental stress on patients. (Carli & Zavorsky, 2005). The setting of surgery, pre-operative physical (eg, exercise and diet) and / or psychological conditioning (eg, stress management and education) aims to increase physical and mental reserves to prevent the decreased function and well-being that expected surgery-related to surgery Figure 2 (Carli & Zavorsky, 2005).

Treatment of cancer is known to cure or alleviate many physical illnesses. However, it shows the major stress that causes adverse effects that are related with purpose of treatment. These adverse events harmfully affect the ability to perform daily activities, ultimately lowering the quality of life, and affecting post-operative recovery (Phillips-Bute et al., 2006). For example, Litwin & Shpall found that 30% and 36% of men who underwent radical prostatectomy for prostate cancer returned to baseline body function

and energy levels for three months after surgery(Litwin, McGuigan, Shpall, & Dhanani, 1999). Similarly, patients with major surgical treatment experienced physical fatigue, decreased concentration and sleep disturbances for up to 9 weeks after discharge (Salmon & Hall, 1997).

A study of modifiable risk factors found that preoperative physical examination, physical activity and nutritional status were predictors of surgical complications and recovery (Gillis et al., 2014; Santa Mina, Scheede-Bergdahl, Gillis, & Carli, 2015). Conversely, pre-operative worsening is associated with surgical complications and requirements for intensive care that may be aggravated by long-term postoperative rest and adverse nutritional intake (Mayo et al., 2011). These findings highlighted strategies for preventing the weakening in physical function and overall health status associated with treatment.

An important question to increase post-operative recovery is to present recovery optimization behavior at the most suitable time. Owing to the concerns associated with troubling the curing process, the post-operative duration may not be ideal for introducing new and positive health behaviors. Rather, the preoperative period can be (i) a more physically or emotionally significant time to intervene in the patient (as compared to the post-operative period) by better exploiting the patient's physical condition; (b) an opportunity to effectively use surgery waiting time; (c) a "teachable moment" for a patient with a reflection on the need for a major surgery, and on the surface, the period before surgery, is a modifiable risk, such as exercise and dieting, that protects physiological preservation in the face of surgical insults. It may be the best time to invest in factors. In fact, clinicians and researchers are testing pre-operative lifestyle interventions to improve clinically relevant outcomes with surgery experience.

This strategy is commonly referred to as prehabilitation: physical (eg, exercise and diet) and / or psychological adjustment (eg, stroke management and education) before surgery in the surgical environment, the goal is to increase physical and mental protection areas to prevent surgery-related reductions in function and health (Santa Mina et al., 2015).

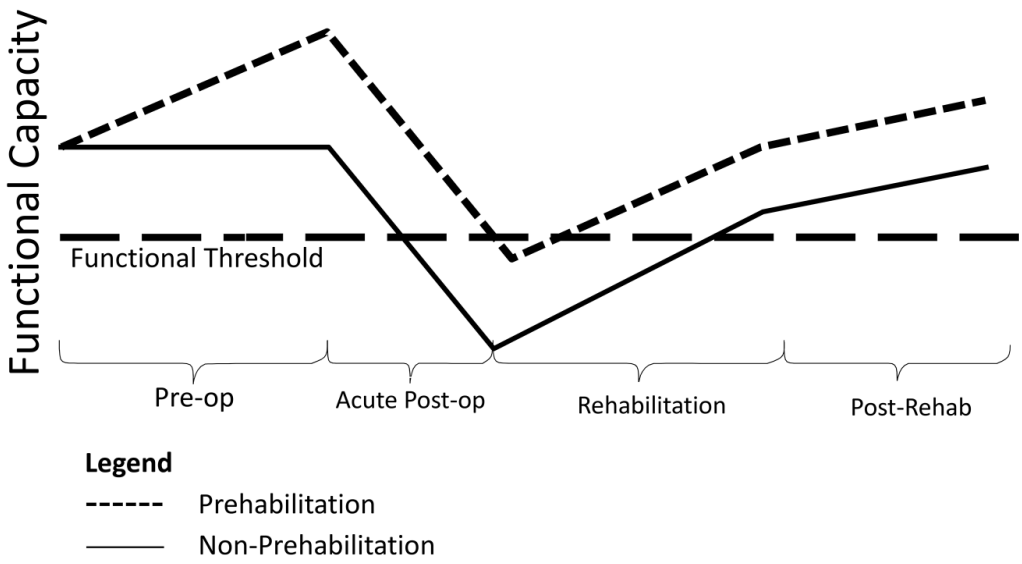


Figure. 2 Conceptual model of prehabilitation compared rehabilitation (Santa Mina et al., 2015)

III. Research Methods

1. Patients and Study design

This study is a single-arm, multi-center, prospective feasibility study to evaluate the effect of CORE program (Challenge, Overcome, Resolve, and Enhance). The patients newly diagnosed with endometrial cancer, scheduled oncological surgery were recruited between July 2016 and July 2017 from the Obstetrics and Gynecology at S University, K (An-arm, Guro), and Gangnam-Cha hospital in Seoul, Korea. After the outpatient consult, 19 patients underwent the health status measurements, of which 17 completed in the exercise program. The main reasons for drop out in the program were related to the surgery adjustment (n = 2).

At baseline participants were diagnosed with endometrial cancer, visited, and completed a laboratory assessment involving assessment of anthropometrics, health-related fitness, and completion of self-reported questionnaires, followed by 2 weeks CORE program. This assessment routine was repeated before intervention and surgery. Prehabilitation exercises were controlled by using the resilience elastic band from the weight bearing method using the whole body strength and core. Intensity of exercise and physical activity were monitored using a wearable device (Fitbit charge HR). Ethnical approval for this study was received from the Seoul National University, in Seoul, Korea. Patients were invited to measure health status and were asked to eligible participants were checked if patients were eligible to participate in the study. Eligible patients includes: (1) 20 years of age or older, (2) patient newly diagnosed with endometrial cancer, (3) able to use smart application, (4) Willingness to participate in the study for 2 weeks before surgery, (5) Understanding, consent and sign the study.

The study design is as follows figure 2.

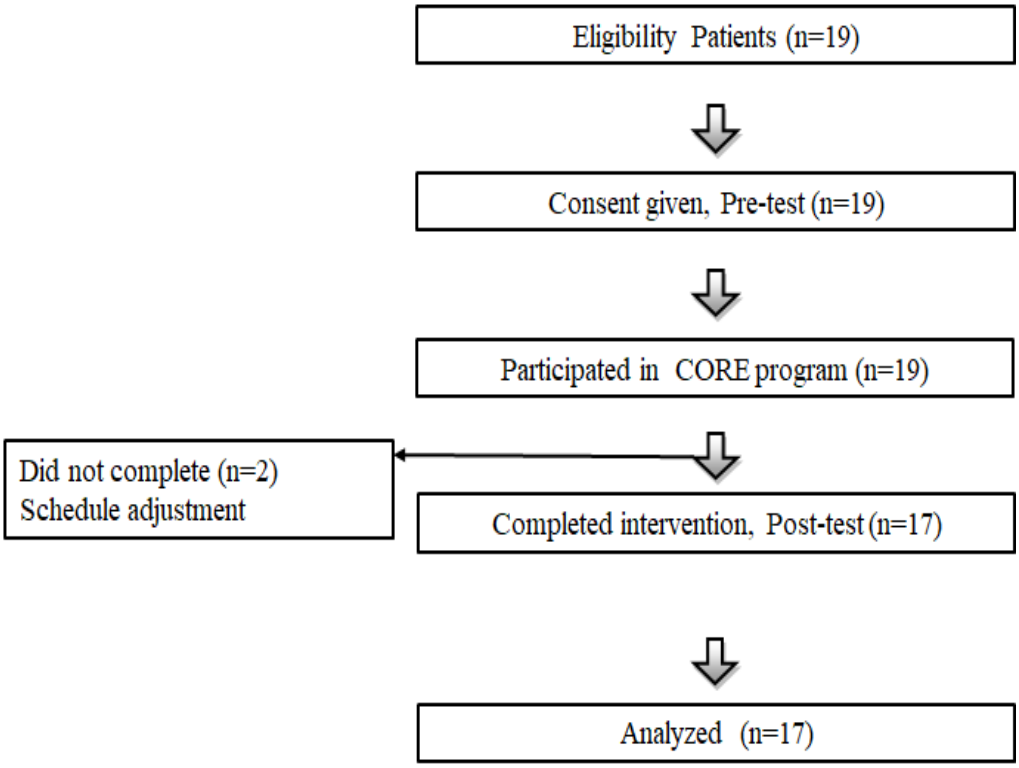


Figure. 3 Study design

2. Exercise Intervention

Table. 2 Exercise protocol

Dynamic Warm-up (5 min)							
	Resistance exercise	Part	Intensity		Core exercise	Part	Intensity
1	Push Up	Chest	12reps	1	Hip Flx/Ext.	Core	12reps
2	Squat	Low limb	12reps	2	Crunch	Core	12reps
3	Bent Over Row	Back	12reps	3	Bird	Core	30sec
4	Lunge	Low limb	12reps	4	Plank	Core	30sec
5	Lateral Raise	Shoulder	12reps	5	Side Plank	Core	30sec
6	Calf Raise	Low limb	12reps	6	Bridge	Core	12reps
7	Arm Curl	Arm	12reps	7	Hip Adduction	Core	12reps
8	Rest		120sec	8	Rest		120sec
Cool down & Stretching (5 min)							

2-1. Exercise

All patients were participated in an individualized exercise program named CORE (**C**hallenge, **O**vercome, **R**esolve, and **E**nhance). The CORE program consisted of 60-minutes; a 5-minute dynamic warm-up, 20-minute of resistance training for total body (targeted 7 major muscle groups performed at an intensity of 12 repetitions maximum, 3 set, weight bearing and elastic-band), 20-minute core stability training (7 motions performed, 30 second tolerable with 3 set), and a 10-minute dynamic with breathing exercise cool-down. For aerobic exercise, it was recommended to subjects to walk 10,000 steps per day. Each patient was instructed 5 times with supervised

individualized exercise 2 weeks prior to surgery. The exercise was implemented at moderate-intensity, 60% of the maximal heart rate of the subjects being monitored by the Fitbit charge HR. When not meeting with the supervisor, patients were encouraged to walk 10,000 steps, and perform the CORE program at home with the provided exercise instructions, elastic-band, and Fitbit charge HR monitoring the intensity of exercise and daily steps. The program begins with meeting an exercise specialist, who tells subjects about how to empower muscle movement and gradually increasing in repetitions if tolerable. Also communication with the patients via phone or text was done to ensure program compliance, support appropriate progression, and address any barriers to exercise that may prevent ongoing participation.

The participants underwent measurements of an exercise checklist for each exercise motion, and walking in each meeting with the exercise specialist. The exercise checklist consisted of two types of events. One is resistance training which consisted of two concepts of total body exercise (push-up, squat, bent-over-row, lunge, lateral raise, calf raise, arm curl) and core exercise (hip-flexor, crunch, bird, plank, side plank, bridge, hip adduction) training. The other one is aerobic exercise which consisted of walking 10,000 steps per day.

3. Measurements

Assessments of anthropometrics, health-related fitness, balance, respiratory function, physical activity (GPAQ), quality of life (EORTC QOL-C30), and anxiety & depression (HADS), physical symptoms (MDACC Sx invention) were conducted at baseline, and after intervention.

Table. 3 Measurements

Measurements	Method	Model & Manufactory
Feasibility	Adherence Adverse events	Engaged in baseline to end-point Side effect
Body Composition	Inbody-720	Biospace, Korea
Health-related fitness	Cardiovascular function Strength (grip strength) Endurance strength Flexibility Legs strength Balance (closed eyes)	Åstrand rhyming-test My-5402, TAKEI, JAPAN Curl-up Sit and reach Sit to stand Single leg stand
Body function	FVE1 FVE6	COPD-6
Quality of Life	EORTC-QOL-C30 Anxiety & Depression Cancer-related Symptoms	Euro Qol Research Foundation Hospital Anxiety & Depression Scale MDACC Sx invention
Physical Activity	GPAQ	Global Physical Activity Questionnaire

3-1. The Primary outcome: Feasibility

Given the novelty of this type of trial, it was not clear whether there would be recruitment, adherence or attrition challenges across study arms. Accordingly, feasibility was assessed for a full-scale trial in the following ways:

Feasibility was measured by adherence to complete 5 times supervised exercise program. Adherence to participate in the five times supervised one on one CORE program was administered by the average of exercise sessions and mean of missed exercise session during the intervention. The safety was assessed through the charting of adverse events related to the intervention. Adverse events were classified using the National cancer Institute's Common Terminology Criteria for Adverse Events Version 4.0 (National Institute of Health, National cancer Institute, 2010).

3-2. Secondary outcomes: Health-related fitness and Psychological

Patients completed health-related physical fitness, and psychological self-reported questionnaires measurements at baseline and the end point of intervention.

4. Physical assessments

Health-related physical fitness is composed of five contents, which are cardio-respiratory, strength, endurance strength, flexibility, and body composition, and assessed, leading to the developments of exercise intervention. During the cycling, heart rate was measured using a fitbit (Fitbit charge HR).

4-1. Body Composition

Body weight, percentage of body fat, fat mass, BMI and WHR were measured using Inbody 720 (Biospace, Korea). The patients rested for 10 minutes after arrival at the laboratory, and the subjects were prohibited excessive physical activity 24 hours before and were informed no drink or no food before measurements.

4-2. Cardiovascular Function

The CRF (Cardiorespiratory fitness) test was performed on electronically break cycle ergometers (Lode Corival 9069, Lode BV, Groningen, Netherlands). The Åstrand

submaximal cycle ergometer 6 minute test, offering an indirect estimation of the maximal oxygen consumption ($VO_{2\,max}$), which can be taken as an indicator for aerobic capacity (Noonan & Dean, 2000). Prior to each test, heart rate, blood pressure and saturation at rest were measured. Patients started pedaling on the ergometer for 6 min with a frequency of 50 rounds per minute. The workload (Watt) was determined by the exercise specialist based on an estimated fitness level of the patient. Following the warm-up, if exercise heart rate was between 120 and 170 bpm, the work rate remained constant for an additional 3 min. If exercise heart rate was below 120 bpm after the 2-min warm-up, workload was increased. Heart rate was recorded every minute. The highest heart rate between 5 and 6 min was considered the mean steady state value and used to estimate VO_{2max} (ml/kg/min) using the Åstrand nomogram (Åstrand & Ryhming, 1954).

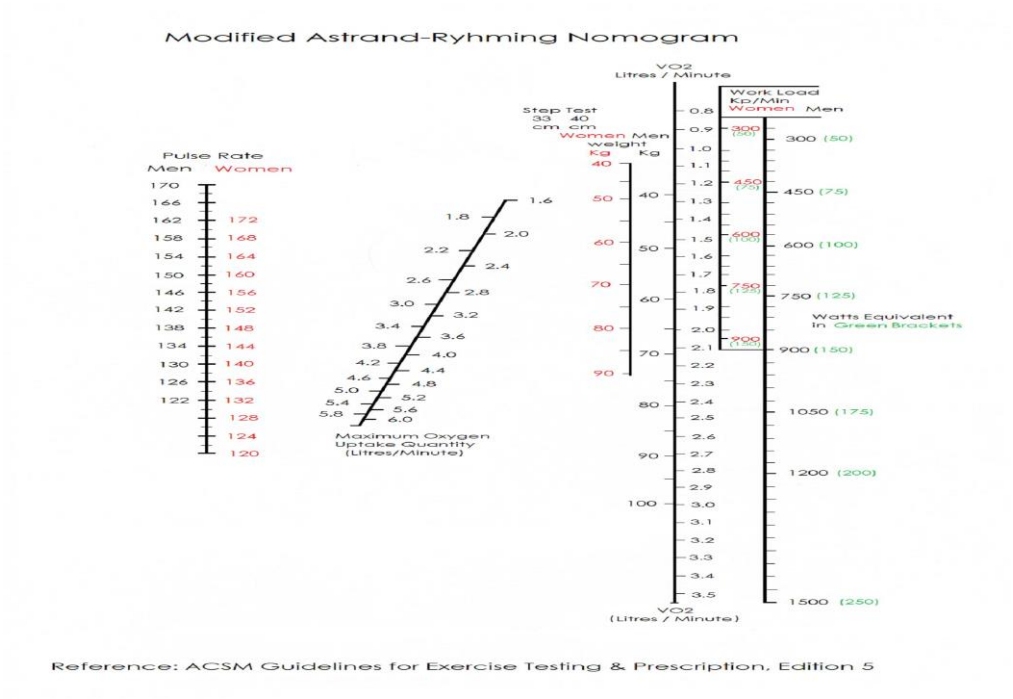


Figure. 4 Modified Åstrand Rhyming Nomogram

4-3. Strength (Grip Strength)

For the strength, upper-limb was assessed using a hand-grip dynamometer (My-5402, TAKEI, JAPAN). The patients held the dynamometer parallel to their side with the dial facing away from the boy and performed twice trials with each hand. Testing was perfumed with the patient alternating between the right and left hand, allowing at least 1 minute of rest between trials. The average score was used as the measure of static strength (Nordenskiöld & Grimby, 1993).

4-4. Curl-up (Endurance Strength)

The participant assumed a supine position on a mat with knee at 90°. The arms were at the side, with fingers touching a piece of tape. A second piece of tape was place 10-cm beyond the first piece of tape. A metronome was used to establish a rate of 20 crunches per minute.

Participants performed crunches until they could no longer touch the line or could not maintain the repetition rate, or until they reached volitional fatigue. The participant had to lift the shoulder blades off the (trunk makes a 30° angle with the mat) with fingers touching the second piece of tape. The low back should be flattened before curling up. The participant must touch both pieces of tape (the start and the finish tape).

4-5. Flexibility (Sit and Reach)

Flexibility was measured using sit and reach of the hamstrings and low back, participants sat on the floor with shoulders, head and legs straight in front. A 30-cm ruler on the mat between their legs was placed against the soles of the feet with the zero end of the measuring device toward the participants. Participants maintained head and shoulder contact with the wall while holding arms straight in front of the body to establish the starting position. Bending forward at the waist and marinating straight legs, participants twice trials sliding their fingertips along the top of the measuring device. The best of the twice trials was used as the final score.

4-6. Sit to stand

Lower-limb strength was measured using sit-to-stand, the test measures how many times the patient manage to stand up and sit down from a chair in 30 seconds (C. J. Jones, Rikli, & Beam, 1999). The patients is seated in the middle of the chair, back straight; feet approximately shoulder width apart and placed on the floor at an angle slightly back from the knees, with one foot slightly in front of the other to help maintain balance. Arms are crossed at the wrists and against the chest. Demonstrate the task both slowly and quickly. Have the patients practice a repetition or 2 before completing the test. The patients is encouraged to complete as many full stands as possible within 30 seconds. The patients is instructed to fully sit between each stand. The 30 second chair stand involves recording the number of stands a person can complete in 30 seconds rather than the amount of time it takes to complete a pre-determined number of repetitions.

4-7. Balance Test

The balance test was assessed by single leg stand, measured the time that patients balanced on single leg up slightly while keeping their eyes closed. Patients was performed on a single leg without shoes or socks on the foot and with the hands place on the hips in order to prevent use of arms for balance. Patients were stopped if the legs touch each other, if the weight-bearing foot moves on the floor, if the non-weight bearing foot touches the floor or if the hands are removed from the waist (Chrints et al, 1991). Patients performed twice with closed eyes and the best time of twice trials used.

4-8. Pulmonary Function

To measure pulmonary function, a portable automatic COPD-6 was used and measured using a mouthpiece. Placed a clip on patient's nose to keep both nostrils closed. Also placed mouthpiece. Patients tried three times. After a brief breathing, it was able to breath with maximum effort as quickly and completely as possible.

5. Self-reported Questionnaires

Self-reported questionnaire were completed at all before and after exercise intervention using tools previously validated among patients with cancer.

5-1. GPAQ (Global Physical Activity Questionnaire)

GPAQ (Global Physical Activity Questionnaire), Korean version (Jeon, 2013) used, and covers several components of physical activity, such as intensity, duration, and frequency, and it assesses three domains in which physical activity is performed (occupational physical activity, transport-related physical activity, and physical activity, and physical activity during discretionary or leisure time) to quantify the intensity, and time of physical activity volume within last 7 days (Cleland et al., 2014).

5-2. EORTC (European Organization for Research and Treatment of Cancer)

The health-related quality of life was measured using EORTC QLO-C30 questionnaire of the "European Organization for Research and Treatment of Cancer", including 5 function (physical, role, emotional, cognitive social function) scale, 13 symptoms (fatigue, nausea & vomiting, pain, insomnia, appetite loss, constipation, diarrhea, financial difficulties) scale (Greimel et al., 2006).

5-3. HADS (Hospital Anxiety-Depression Scale)

The Korean version (오세만, 민경준, & 박두병, 1999), HADS (Hospital Anxiety-Depression Scale) developed by Zigmond and Snaith is to find out the depression, anxiety of emotional disorder and management in patients under examination and treatment for a variety of clinical problems. HADS is 14-item scale to detect anxiety

and depression, each item scored 0 to 3. Data generated is ordinal. 0-7, normal, 8-10 borderline/mild, >10 clinical case (Zigmond & Snaith, 1983).

5-4. MDASI (MD Anderson Inventory)

MD Anderson Inventory (MDASI), Korean version, used to measure experienced symptoms, and discomfort in daily function by cancer patients, cancer treatment. The 19 questionnaire for Multi symptoms experience and interference Korean version (Yun et al., 2006), symptoms and interference of cancer, MD Anderson Inventory (Cleeland et al., 2000).

6. Statistical Analysis

Baseline subject characteristics, including demographic, health-related fitness, and psychological score on all exercise and functional tests, were reported using descriptive data (mean ± SD). Test compared pre-intervention and post-intervention data, with statistical significance set at p <.05. Pre and post Paired t-test determined differences between baseline assessments and post-assessment.

IV. Results

1. Participant Characteristics

Baseline characteristics of the participants are summarized in Table. 4 The mean age of the participants was 46.9 ± 12.3 years, with the mean of body mass index of participants being 27.0 ± 5.3 kg/m^2 with approximately two-thirds of participants being overweight or obese. 89% of patients were I/IA, IB stage of cancer (15). There were no stage II subjects, one subject at the stage III, none at stage, and two subjects at the hormone therapy stage. Most patients were significantly inactive at baseline, meaning that they were either completely sedentary or physical inactive but no reaching the 150 min-wk-American College of Sports Medicine Guideline. 15 patients were surgery and 2 patients were surgery with chemotherapy. 2 patients did not complete the exercise intervention because of surgery schedule adjustment.

Table. 4 Subjects characteristics (N = 17)

Characteristic	M (SD)	Min-max	N (%)
Age (year)	46.9 (12.3)	27-71	17 (100)
Height	158.6 (6.0)	148-170.6	17 (100)
Weight (kg)	67.7 (11.9)	50-93	17 (100)
Body mass index (kg/m^2)	27.0 (5.3)	19-36	17 (100)
Cancer Stage, n			
I / IA, IB			15 (88)
II			-
III			1 (6)
IV			-
Unknown			1 (6)
Treatment type			
Only surgery			13 (68)
Surgery & Chemotherapy			2 (10)
Hormonal therapy			-
Unknown			2(10)

Data are presented as mean (SD).

2. Feasibility

2.1. Adherence

All patients (n=19) scheduled with endometrial cancer surgery were invited between July 2016 and July 2017. After the outpatient consulting, 19 patients underwent the health status measurements, of those 17 completed in the pre and post measurements and engaged in the CORE intervention. The main reasons for drop out in the CORE program were related to schedule adjustment (n = 2). 17 subjects attended, resulting in an overall 89.4% of intervention adherence.

2.2. Checklist of Exercise Intervention

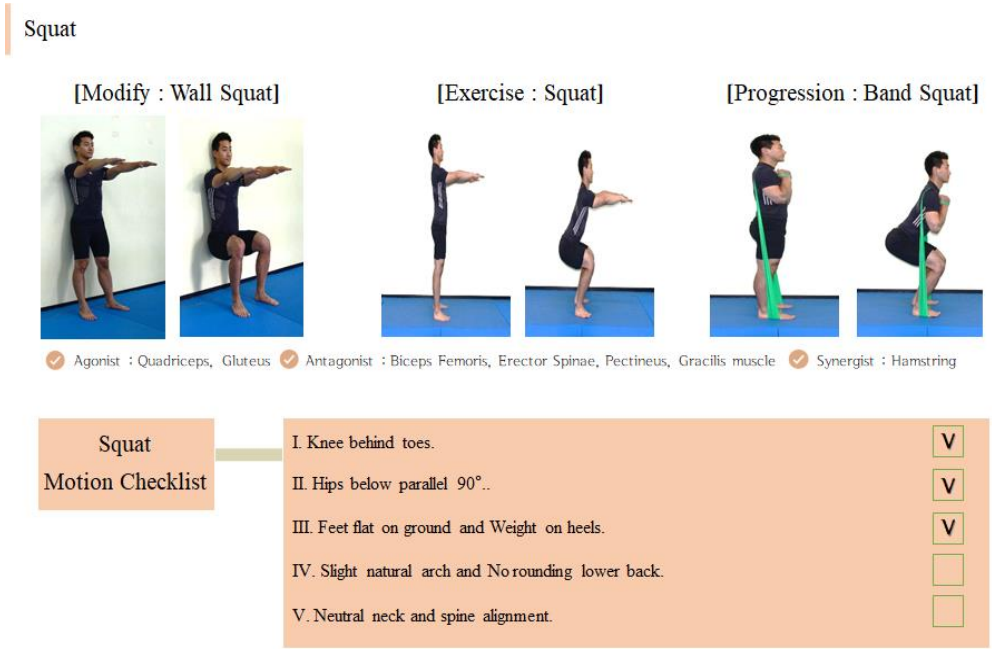


Figure. 5 Ex. checklist for resistance training

The participants underwent measurements of exercise checklist for each exercise motions, and walking every meeting. The exercise checklist consisted of two type of event. One is resistance training which consisted of two concepts of exercise total body (push-up, squat, bent-over-row, lunge, lateral raise, calf raise, and arm curl) and core exercise (hip-flexor, crunch, bird, plank, side plank, bridge, hip adduction). The other one is aerobic exercise which consisted of walking 10,000 step per day before surgery. For the resistance exercise, there is a checklist which shows how to complete each motion perfectly Figure 5.

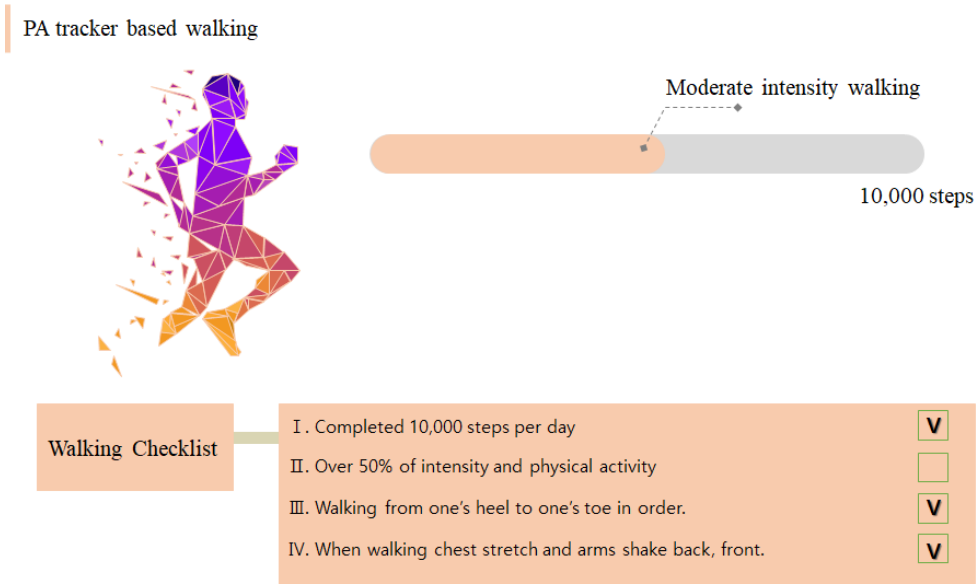


Figure. 6 Ex. Checklist aerobic training

Also aerobic exercise has a checklist too Figure. 6. For resistance (total body & core) exercise program, an average of one day needed for perfecting each movement (lateral raise, calf raise, arm-curl / hip flexion/extension, plank, bridge, hip adduction), and an average of two days to perfect other movements (push-up, squat, bent-over-low, lunge

/ crunch, bird and side plank). Side plank of core training took an average of three days Table 5.

Table. 5 Day of exercise completion (Resistance training)

Total body	1st	2nd	3 th	4 th	5th	Core
Lateral raise Calf raise Arm-curl	1st	2nd	3 th	4 th	5th	Hip flx/ext. Plank Bridge Hip adduction
Push-up Bent-over-row Squat Lunge	1st	2nd	3 th	4 th	5th	Crunch Bird
	1st	2nd	3 th	4 th	5th	Side plank

The walking for aerobic exercise was recommended per 10.000 steps per day. 89.4% of patients achieved. The least amount of stems achieve was 7.671 and the most amount of steps achieve was 15.019.

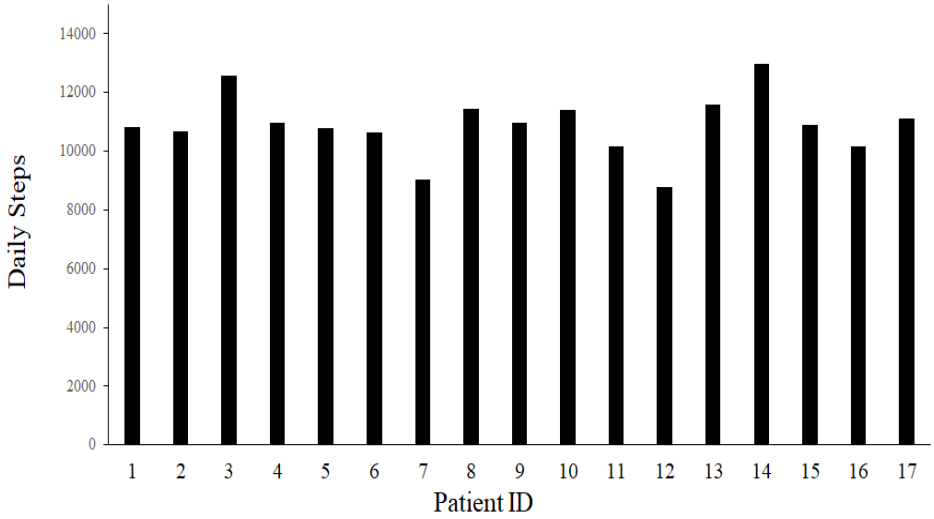
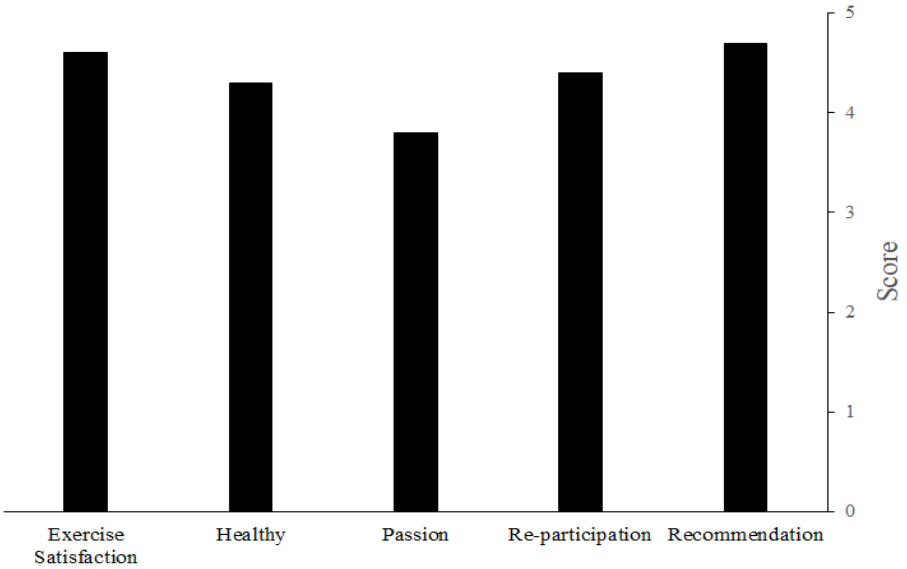


Figure. 7 Mean of individual steps data collected from physical activity monitoring (Fitbit charge HR) before surgery.

2.3. Adverse Events & Satisfaction

The comprehensive CORE program was safe and there were no adverse events related to the exercise intervention. Additionally, no injuries or adverse events occurred during fitness testing at any time point (baseline and follow-up). Figure. 8 is presents the satisfaction of the comprehensive CORE program taken by a questionnaire which consisted of 5 questions, each question score ranging from 0 to 5. Satisfaction score was 4.6, health improvement 4.3, passion for exercise 3.8, considering follow-up exercise program 4.3, and recommendation this program to other people 4.6. The comprehensive CORE program satisfaction was 4.3.



Abbreviation: EPS; exercise satisfaction, Re-P; re-participation, Reco; recommendation

Figure. 8 Satisfaction of CORE program

3. Health-related Fitness Outcomes

17 participants completed baseline and end point assessments of health-related fitness. The results are presented in Table. 6. Patients who completed this program significantly improved their health-related fitness. There was significantly between pre and post measurement in cardiorespiratory function p = .006), there was significant improvements in grip strength (p = .017), there was significantly increased between pre and post measurement in curl-up (p = .007), there was significantly improvements in

flexibility (p = .001) but there was no significant difference between pre and post measurement in BMI (p = 0.89), FEV1 and FE6 was not significantly change.

3-1. Health-related fitness

Table. 6 Health-related fitness before and after exercise intervention

Health-related Fitness	Pre	Post	p-value
CRF (ml/kg/min)	25.3 (4.6)	27.6 (4.8)	0.006*
Hand Grip (kg)	26.8 (4.2)	27.8 (3.6)	0.017*
Curl-ups (times/min)	2.4 (3.4)	6.5 (6.9)	0.007*
Flexibility	7.0 (10.5)	10.1 (10.5)	< 0.001**
BMI	27.0 (5.3)	26.6 (5.0)	0.89
Balance (sec)	10.3 (7.5)	18.1 (14.1)	0.021*
Leg strength (times/30sec)	23.7 (4.7)	29.6 (4.2)	< 0.001**
FEV1(L)	1.9 (0.4)	2.0 (0.5)	0.43
FEV6(L)	2.6 (0.6)	2.6 (0.6)	0.87

Abbreviation: CRF = Cardiovascular Function; BMI = Body Mass Index; Values are presented as mean (SD) between pre and post difference, * p<.05, ** p<.01

3-2. Cardiovascular function

Table. 7 Cardiovascular function

There was significantly improvements in cardiorespiratory function p =.006.

Health-related Fitness	Pre	Post	p=value
CFR(ml/kg/min)	25.3 (4.6)	27.6 (4.8)	0.006*

Values are presented as mean (SD) between pre and post difference, * p<.05.

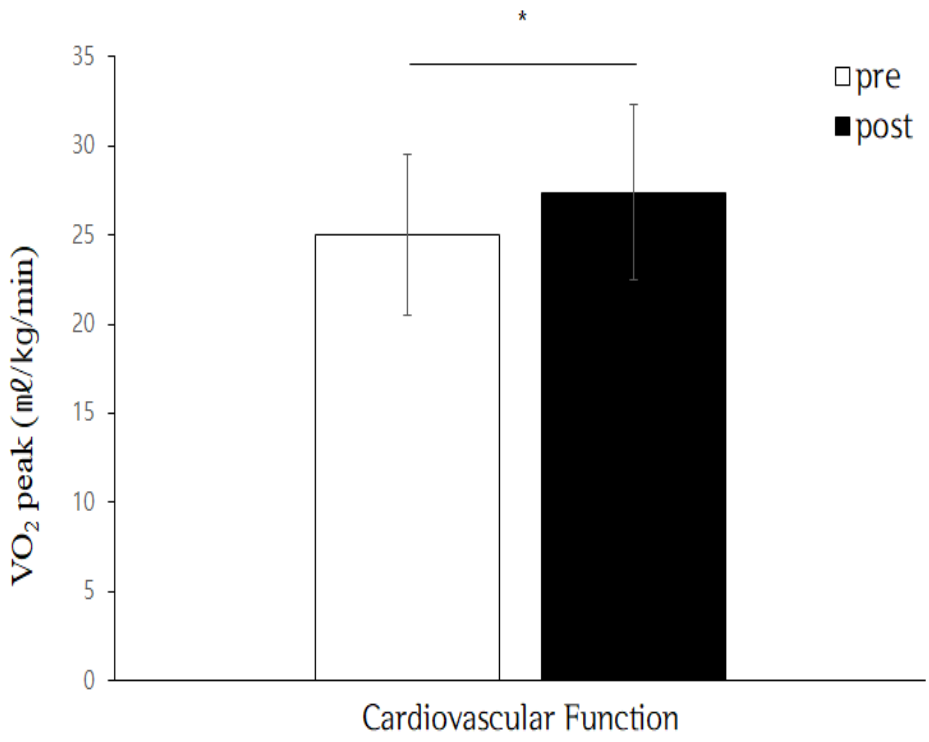


Figure. 9 Cardiovascular function

3-3. Strength

Table. 8 Grip strength

There was significantly improvements in grip strength p = .017.

Health-related Fitness	Pre	Post	p=value
Hand Grip (kg)	26.8 (4.2)	27.8 (3.6)	0.017*

Values are presented as mean (SD) between pre and post difference, * p<.05.

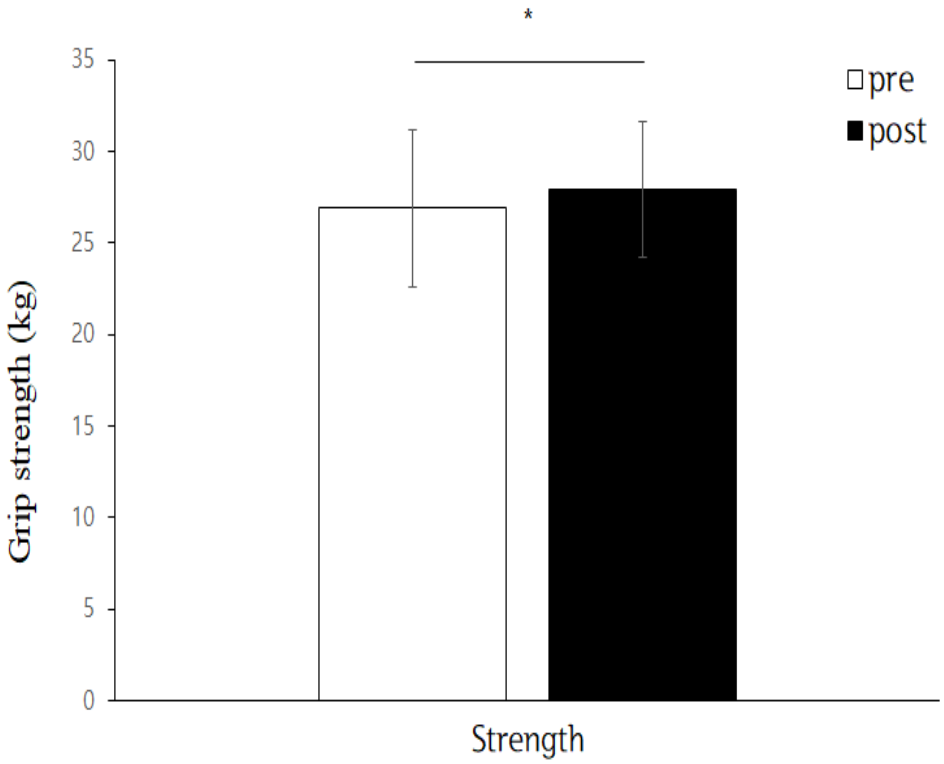


Figure. 10 Grip strength

3-4. Endurance strength

Table. 9 Curl-up

There was significantly improvements in curl-up p =.007.

Health-related Fitness	Pre	Post	p=value
Curl-ups (times/min)	2.4 (3.4)	6.5 (6.9)	0.007*

Values are presented as mean (SD) between pre and post difference, * p<.05.

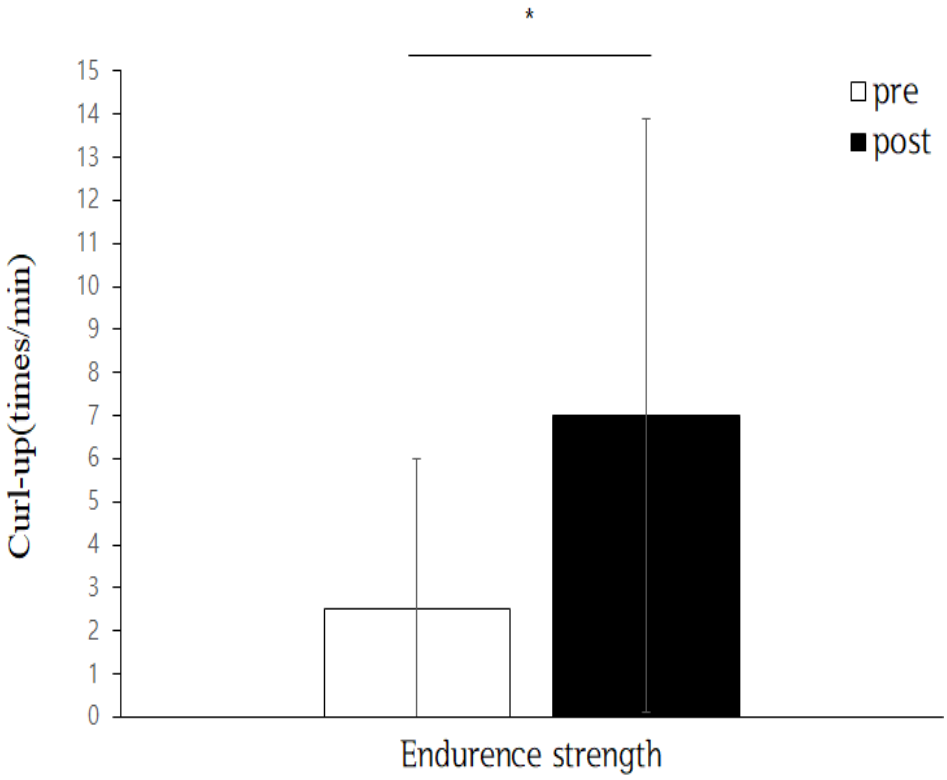


Figure. 11 Curl-up

3-5. Flexibility

Table. 10 Sit and reach

There was significantly improvements in sit and reach p =.001.

Health-related Fitness	Pre	Post	p=value
Flexibility (Dronkers et al.)	7.0 (10.5)	10.1 (10.5)	< 0.001**

Values are presented as mean (SD) between pre and post difference, ** $p < 0.001$

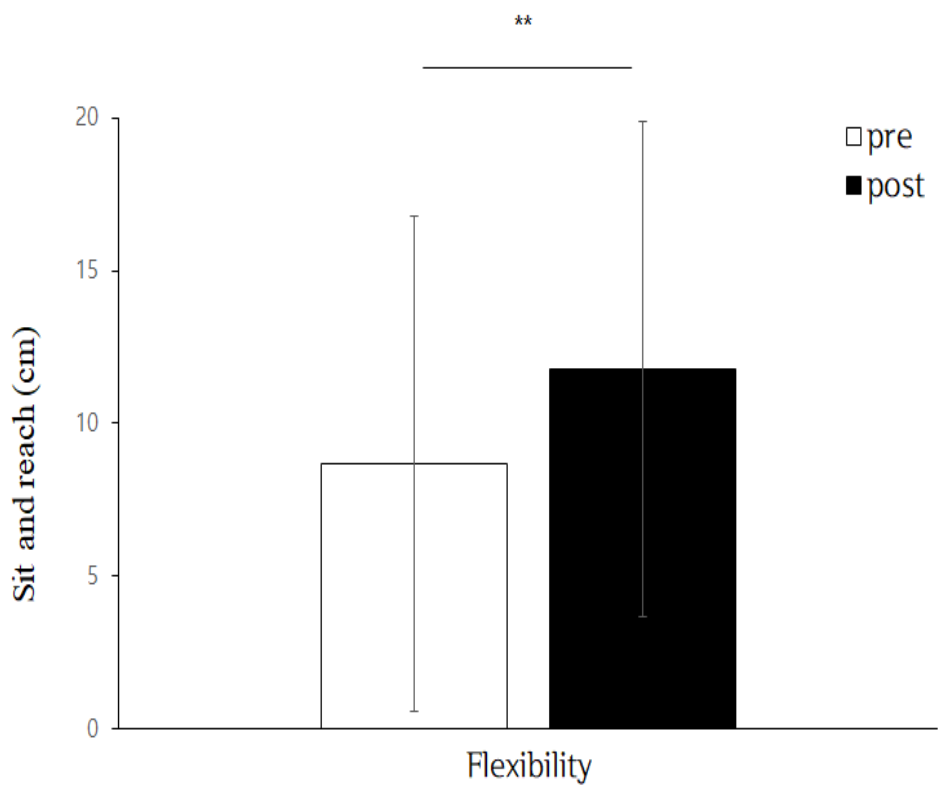


Figure. 12 Sit and reach

3-6. Body Composition

Table. 11 Body composition

There were no significantly difference in body composition p =.89.

Health-related Fitness	Pre	Post	p=value
BMI (body mass index kg/m^2)	27.0 (5.3)	26.6 (5.0)	0.89

Values are presented as mean (SD) between pre and post difference, ∗ p<.05.

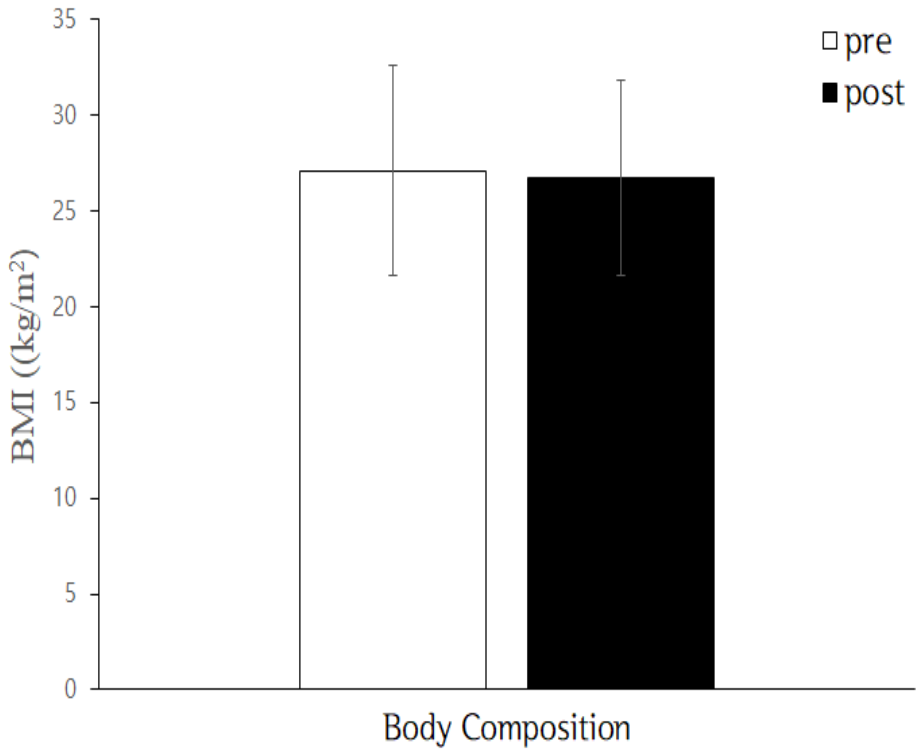


Figure. 13 Body Composition

3-7. Balance

Table. 12 Single leg stand

There was significantly improvements in single leg test p =.021.

Physical Function	Pre	Post	p=value
Balance (sec)	10.3 (7.5)	18.1 (14.1)	0.021*

Values are presented as mean (SD) between pre and post difference, * p<.05.

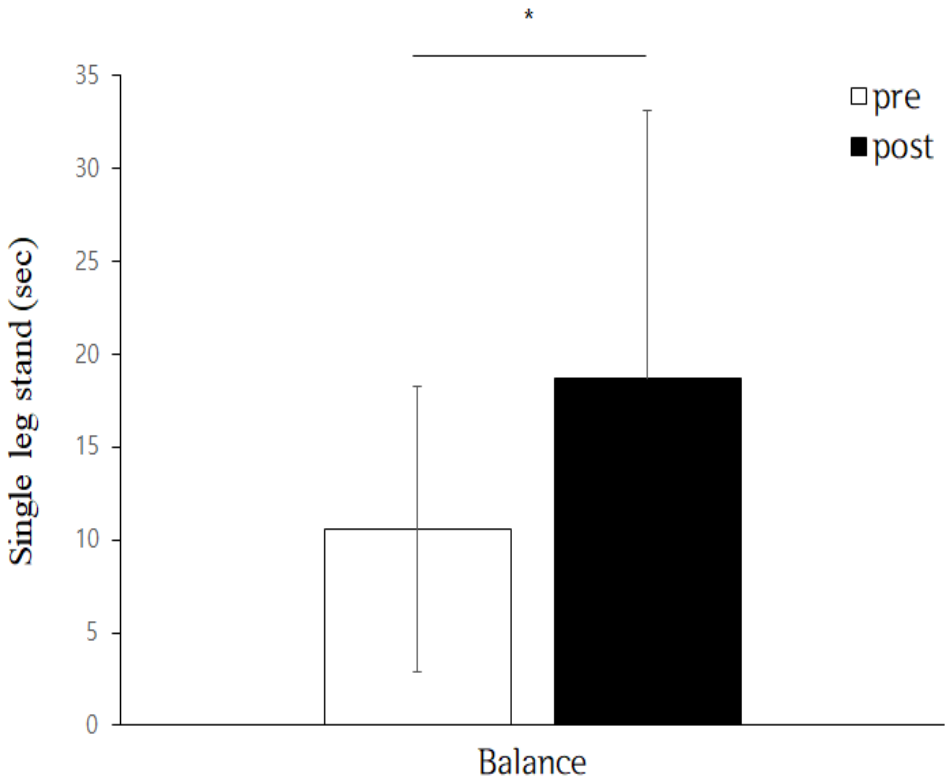


Figure. 14 Balance

3-8. Leg strength

Table. 13 Sit to stand

There was significantly improvement in sit to stand p =.001.

Physical Function	Pre	Post	p=value
Leg strength (times/30sec)	23.7 (4.7)	29.6 (4.2)	< 0.001**

Values are presented as mean (SD) between pre and post difference, ** p<.001.

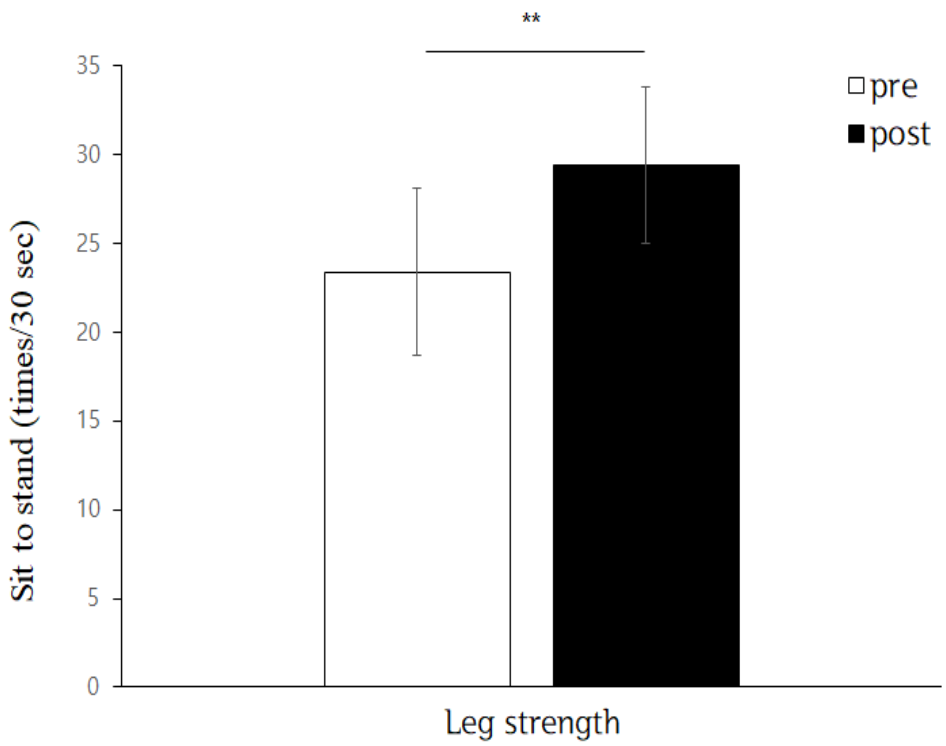


Figure. 15 Leg strength

3-9. Pulmonary Function

Table 14. Pulmonary Function

There were no significantly difference in FEV1 (p = 0.43) and FEV6 (p = 0.87).

Breathing capacity	Pre	Post	p=value
FEV1(L)	1.9 (0.4)	2.0 (0.5)	0.43
FEV6(L)	2.6 (0.6)	2.6 (0.6)	0.87

Values are presented as mean (SD) between pre and post difference, * p<.05.

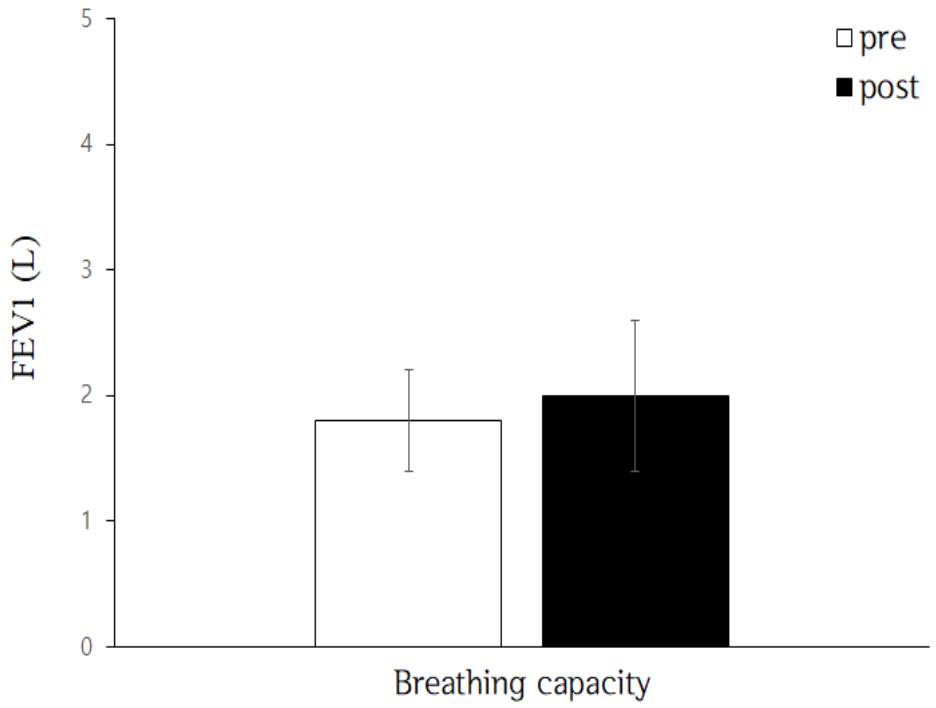


Figure. 16 FEV1

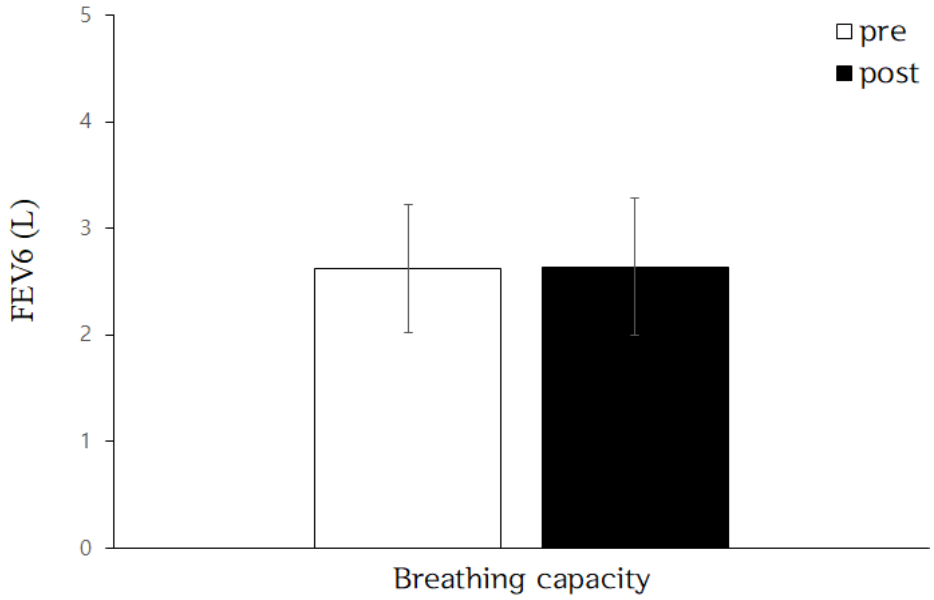


Figure. 17 FEV6

4. Questionnaires Outcomes

The impact of exercise intervention on emotional distress is presented in table 15. There were significant improvements in EORTC-QOL-C30 (global QOL, p = .001), (functional scale, p = .002), (symptoms scale, p = .007). Also there were significant improvements in hospital anxiety (p = .036) and depression (p = .001). There were no significant different for M. D. Anderson symptom inventory (p = .05).

Table. 15 Questionnaires outcomes

Characteristic	Pre	Post	*p*=value
EORTC-QOL-C30			
Global health status	54.9 (22.6)	76.4 (16.4)	< 0.001**
Functional scales	82.3 (7.3)	89.2 (7.0)	<0.001**
Symptom scales	19.9 (12.6)	12.1 (7.1)	0.004*
Hospital Anxiety Depression			
Anxiety	4.6 (2.7)	3.5 (2.2)	0.049*
Depression	6.1 (2.9)	3.5 (2.2)	0.006*
M.D.Anderson symptom inventory	21.7 (15.2)	14.7 (15.4)	0.05

Values are presented as mean (SD) between pre and post difference, * p<.05, ** p<.001; QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; Hospital Anxiety & Depression Scale statistically significant; M.D.Anderson symptom inventory.

Table. 16 HRQOL

There were significantly improvements in EORTC-QOL-C30 (global QOL, p =.001), (functional scale, p =.001), (symptoms scale, p =.004).

Characteristic	Pre	Post	p=value
EORTC-QOL-C30			
Global health status	54.9 (22.6)	76.4 (16.4)	< 0.001**
Functional scales	82.3 (7.3)	89.2 (7.0)	<0.001**
Symptom scales	19.9 (12.6)	12.1 (7.1)	0.004*

Values are presented as mean (SD) between pre and post difference, * p<.05, ** p<.01; QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire;

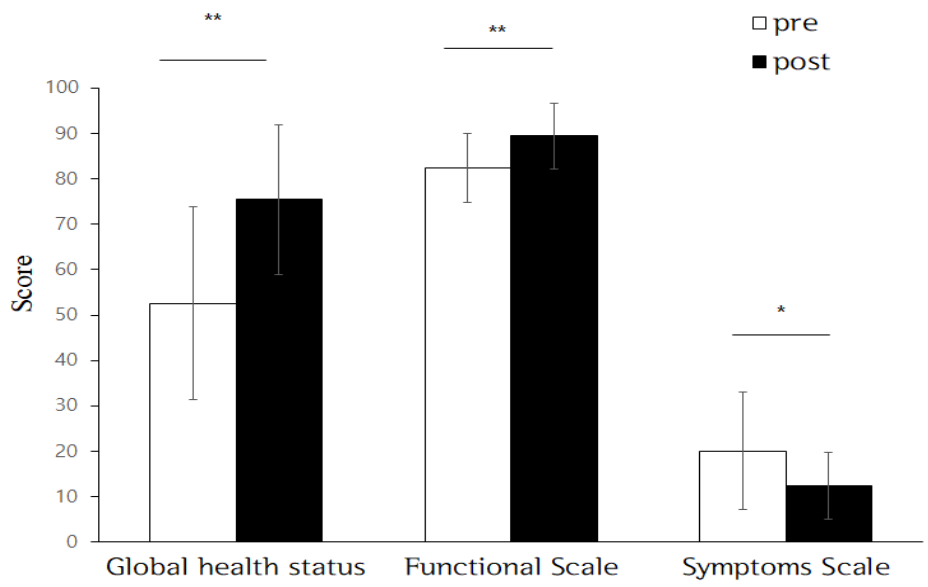


Figure. 18 HRQOL

Table. 17 Hospital Anxiety & Depression Scale

There were significantly improvements in Hospital Anxiety (p =.036) and Depression (p =.001).

Hospital Anxiety Depression	Pre	Post	p=value
Anxiety	4.6 (2.7)	3.5 (2.2)	0.049*
Depression	6.1 (2.9)	3.5 (2.2)	0.006*

Values are presented as mean (SD) between pre and post difference, * p<.05, ** p<.01;

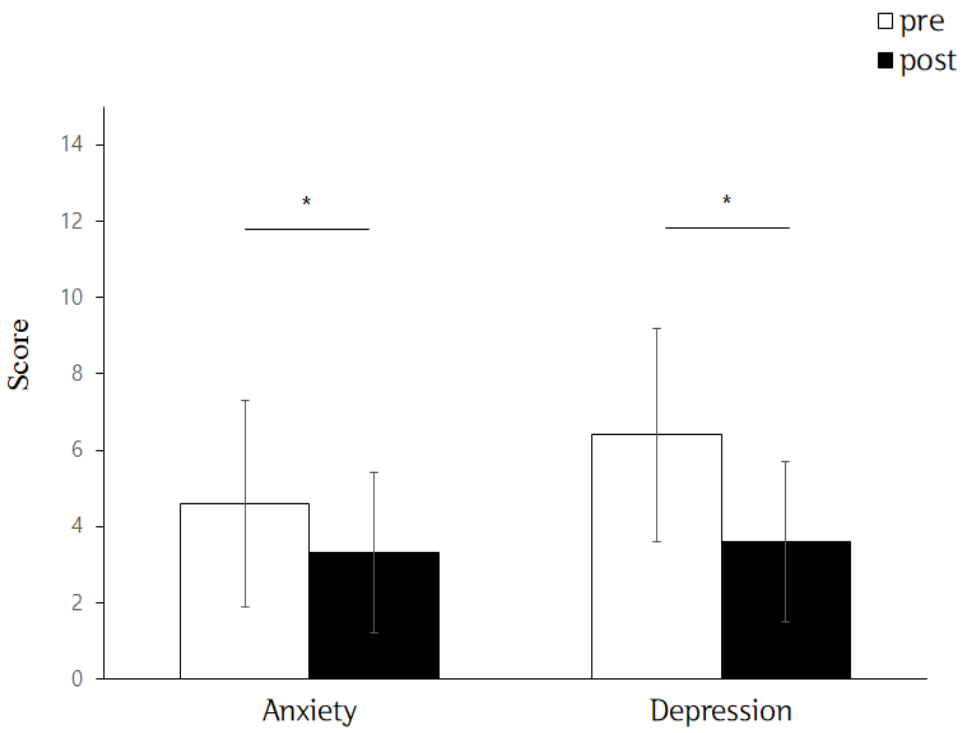


Figure. 19 Hospital Anxiety & Depression Scale

Table. 18 M.D.Anderson symptom inventory

There were no significantly different for M. D. Anderson symptom inventory (p =.05).

M.D.Anderson symptom inventory	Pre	Post	p=value
	21.7 (15.2)	14.7 (15.4)	0.05

Values are presented as mean (SD) between pre and post difference, * p<.05; M.D.Anderson symptom inventory.

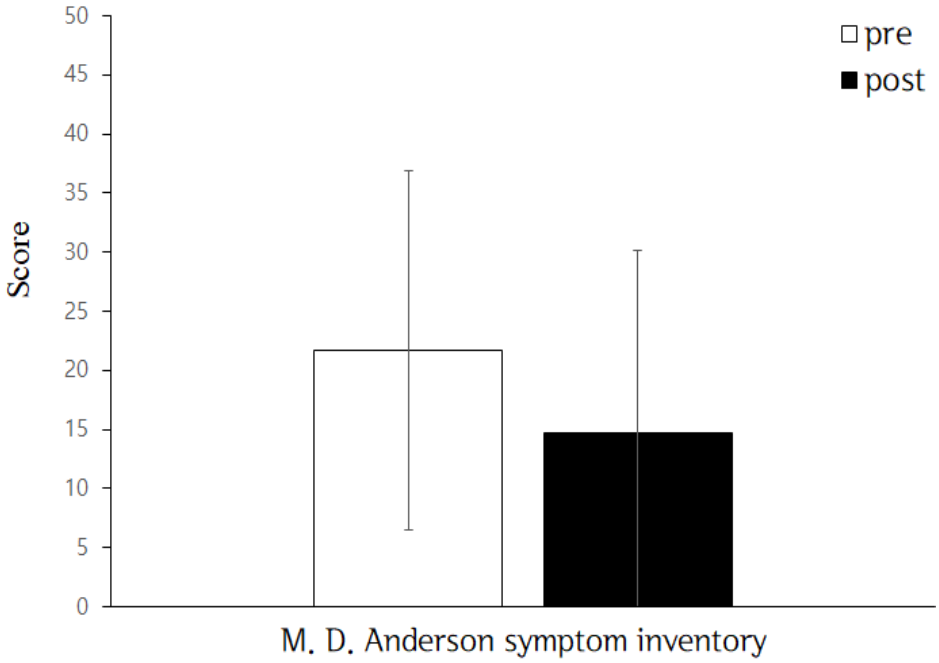


Figure. 20 M.D.Anderson symptom inventory

V. DISCUSSION

This is the first study to investigate the feasibility of the CORE prehabilitation exercise program and its effects on preoperative health-related fitness and psychological health status in patients awaiting endometrial oncological surgery. The primary discovering of this study was that short and moderate intensity supervised exercise programs are feasible and safe. In addition, adherence to the CORE exercise program was high and no adverse events occurred during the program. Second, patients who completed the intervention had improvements in health-related fitness and psychological health although the duration of exercise intervention was short due to the process of treatment.

1. Feasibility of exercise program

This study has shown that the CORE program is highly feasible in terms of adherence to the intervention sessions and the intervention itself. The majority of participants (n=17/19, 89%) completed CORE program and no adverse event during and after the intervention. This is in the line with revenues from a recent other types of studies (Valkenet et al., 2016), (Coats et al., 2013). The level of adherence and no occurrence of adverse events validated in among the CORE program participants may be attributed to the following factors.

High level of adherence to the exercise program before surgery extensively linked to the recovery of cancer patients after surgery thus adherence to the intervention may be predictable factors impacting health-related fitness, and quality of life. Furthermore, it

has been hypothesized that prehabilitation exercise program may protects from negative impact of complications on decreasing physical fitness for cancer patients after surgery.

The CORE program consists of 5 individualized (one-to-one) training sessions with an exercise specialist before surgery at the health and exercise science laboratory in Seoul National University, Korea. The components of the exercise were based on national and cancer-related recommendations of the American Cancer Association, the American College of Sports Medicine, and evidence from the literature (Schmitz et al., 2010; Bull et al., 2010; American Cancer Society et al., 2016). Physical activity or exercise recommended during and after cancer treatment is safe, the exercise prescription should be tailored, and encouraged according to the patients (Schmitz et al., 2010; Ligibel & Denlinger, 2013; L. W. Jones, 2011; American Cancer Society, 2016). Therefore, the CORE program will be tailored to the individual patients taking into account patients' present health status, level of physical activity, comorbidities and medical history though a pre-exercise medical assessment according to ACSM recommendations (Schmitz et al., 2010). Additionally, most popular of gynecology cancer patients were preferred for individual exercise (Tyrrell, Keats, & Blanchard, 2014).

Unfortunately, there are no recommendations for exercise intervention in endometrial cancer prior to surgery because it has not been yet studied. Accordingly, the CORE program was followed common recommendation for cancer patient when developing the program including aerobic, resistance, and core exercise (Schmitz et al., 2010; Beesley, Eakin, Janda, & Battistutta, 2008; Courneya et al., 2005; Galvão, Taaffe, Spry, Joseph, & Newton, 2011; Thayer, Yamamoto, & Brosschot, 2010). The duration (2

weeks) and frequency (5 times before surgery) of the CORE program were based on surgery schedule from endometrial cancer treatment as there are few literature reviews of concrete guidance on essential attributes and components of exercise program with endometrial cancer patients (Smits et al., 2015; V. E. von Gruenigen et al., 2008).

Second, minimizing barriers may be significant during the prehabilitation period that exercise is adapted as well as the early maintenance stage (Rogers, Courneya, Shah, Dunnington, & Hopkins-Price, 2007). To reduce the barriers participated in CORE program, this study provided two areas of exercise and allowed the patients to exercise time at the desired time. The exercise checklist was developed considering the short duration of intervention. In particular, most patients are not used to exercising and had lower physical function. Thus the checklist was used to subdivide the correct motion to allow accurate stimulation to the target site, which provided feedback to the patients who might be highly motivated to the CORE. Consequently, the patients were satisfied and appreciated the exercise sessions about the comprehensive CORE program. The above reasons show that the CORE program may validate feasibility and safety in patients with endometrial cancer before surgery.

2. Health-related fitness & Psychological effects of CORE Program

This is the first study to show the data significant improvements in health-related fitness and psychological status for patients with endometrial cancer before gynecological surgery as a prehabilitation exercise program. This study indicated that there are significant improvements in muscular strength, cardiovascular function, flexibility, and balance of endometrial cancer patients. Health-related fitness is

associated with cancer and cancer patients. In particular, cardiorespiratory function is a vital independent predictor of all-cause mortality in cancer patients (L. W. Jones et al., 2012; Peel et al., 2015). The cause of death in endometrial cancer patients is cardiovascular disease which is more rapidly increasing than the risk from endometrial cancer 5 years after diagnosis (Ward et al., 2012). More importantly, (Peel et al., 2015) it has been reported that CRF shown lower and higher blood pressure in morbidly obese with endometrial cancer patients compared to obese control. The present study found that short-term of intervention before surgery improved CRF at baseline (P = 0.006) that patients followed on 5 times supervised CORE program sessions and home-based unsupervised sessions with guidance book. Most patients walked over 10,000 steps daily recommended to be completed exercise during the intervention. This improvement is likely to be important to endometrial cancer patients comorbidity with obesity who rarely meet the health recommendation (Vivian E Von Gruenigen et al., 2011) that all cancer patients avoid physical inactivity, and participate in 150 min of moderate-intensity, or 75 min of vigorous-intensity, as they may aid to reduce postoperative adverse events (Schmitz et al., 2010). Li found that feasibility pilot study, patients engaged in the prehabilitation program, compared with traditional rehabilitation, demonstrated significantly higher compliance and functional walking capacity throughout the perioperative period (Chao Li et al., 2013).

Furthermore, The CORE program led to improvement of psychological benefits in EORTC QLQ C-30, and HADS (Hospital Anxiety Depression Scale). These improvements were similar with previous studies of exercise in patients with cancer (Mishra, Scherer, Snyder, Geigle, & Gotay, 2014). The preoperative patients of lower functional status were associated with postoperative morbidity and mortality with

poorer score being linked to increased risk in colon cancer patients undergoing surgery (Anthony et al., 2003; Saxton & Velanovich, 2011; Ihemelandu et al., 2013). In gynecologic cancer patients, poorer pre-operative QoL score is significantly related with post-operative morbidity and hospital readmission (Doll et al., 2014). Therefore, the fact that the CORE program improved QoL score of endometrial cancer patients may benefit post-operative reduction of Qol after surgery.

The strength of the CORE program is supervised individual intervention, one-to-one sessions in private places (laboratory, local gym) and the preferred moderate intensity of exercise was monitored during the intervention with Fitbit charge HR (Karvinen et al., 2006). It has been reported that feasible aim and individualized prescription are able to improve adherence and compliance to an intervention (Bourke et al., 2013). In addition, Travel distance is importance to participate in the CORE program

Limitation to the current study include: 1) no control group, 2) no data after surgery, and not enough patients. First, there is no control group compared outcomes of exercise group with non-exercise group with. Second, there is no data after surgery due to this study being designed to evaluate the effect of CORE program (Challenge, Overcome, Resolve, and Enhance) for patients newly diagnosed with endometrial cancer before oncological surgery.

Future study, therefore, should include a control group. In additional, it is necessary to investigate the effect of prehabilitation on the physical fitness and psychological status of endometrial cancer patients after treatment. Furthermore, a recent study by Bozuk and Martin indicated that postponing treatment until 48 days after diagnosis did not seem to have any effect on survival. Thus, to improve cardiovascular fitness of

some patients with the aim of reducing postoperative complications, it may be advantage to extend preoperative period (Bozcuk & Martin, 2001).

In conclusion, the prehabilitation CORE program is feasible and safe for patients with endometrial cancer who were scheduled for endometrial cancer surgery and benefits health-related fitness and psychological health status. This program will provide the basis for implementation of exercise participation in patients with endometrial cancer before surgery. However, there is still insufficient evidence to support any robust conclusions regarding the ideal characteristics of an exercise prehabilitation intervention and the impact, it may have on clinical and post-operative outcomes.

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오세만, 민경준, & 박두병. (1999). 병원 불안-우울 척도에 관한 표준화 연구. *J Korean Neuropsychiatr Assoc, 38*(2).

국 문 초 록

자궁내막암 환자의 수술 전 예방적 재활운동의 타당성: 다 기관 연구

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체 육 교 육 과

본 연구는 자궁내막암 신환자를 대상으로 수술 전 재활운동 프로그램을 개발하기 위한 연구로써, 근거 기반 운동 프로그램의 타당성 및 안전성 확인을 목적으로 한다. 또한 개발된 재활 운동 프로그램이 자궁내막암 환자의 건강체력 및 정신건강에 미치는 영향을 알아보기 위한 연구이다.

연구 대상자는 총 17명으로, 서울시 S, G, A, Ch병원에서 자궁내막암 진단을 받고 수술 대기 중인 환자 중 본 연구의 기준에 포함된 환자들로 진행되었다. 운동 프로그램 (CORE; **C**hallenge, **O**vercome, **R**esolve, **E**nhance)은

저항운동, 유산소, 코어 운동 프로그램으로 구성되었다. 2주간의 supervised 운동은 수술 전까지 총 5회 1:1 그리고 60분 동안 진행 되었다. 운동 전문가와 만나지 않은 날은 home-based 운동을 하도록 하였으며, 운동 안내책자를 제공 하였다. 대상자 관리를 위해 대상자 스스로의 운동일지 작성과 연구자가 전화를 하고 문자 메시지를 전송하여 운동 참여를 독려하였다. 본 연구에서 개발된 예방적 재활운동 프로그램의 타당도 및 효과 검증은 운동 중재 동안 5번의 supervised 운동 순응도와 운동 중재 중 발생하는 부작용, 그리고 운동 동작 수행 가능성 평가 및 예방적 재활운동 프로그램 만족도 평가를 통해 결정 하였으며, 운동 중재 전 후에 건강체력과 신체활동량, 삶의 질, 신체 증상, 그리고 우울증 설문 등을 측정 하였다. 예방적 재활운동의 순응도는 88.9% 였으며, 운동 중재 중 부작용은 발생 하지 않았고, 운동 동작 수행 능력은 평균 두 번째 운동 세션에서 모든 동작을 완벽히 수행하였다. 대응표본t검정 분석결과 건강체력 (심폐체력; p = .006, 악력; p = .017, 근지구력; p = .007, 유연성; p = .001) 과, 허리둘레 (p=.004)가 유의하게 계선 되었다. 그러나 BMI; p = .89, FEV1 및 FE6는 유의미한 변화가 없었다. EORTC QLQLQ-C30 (global QOL, p =.001), (functional scale, p =.001), (symptoms scale, p =.004)는 유의하게

증가하였으며, 병원 불안-우울 증상 Hospital Anxiety (p = .049) 및 Depression (p = .006)도 유의하게 증가하였다. MDACC Sx inventory (암 환자가 앓고 있는 질병 및 치료 과정에서 느끼는 증상)에서는 유의한 변화가 없었다.

따라서, 자궁내막암 신환자를 대상으로 수술 전 약 2주간의 예방적 재활운동 (CORE) 은 실행 가능하며, 안전할 뿐 아니라 자궁내막암 환자의 수술 전 신체적, 정신적 상태를 개선시킬 수 있다. 또한 이 연구는 수술 전 자궁내막암 환자에게 운동 참여의 기틀을 마련해 줄 수 있으며, 운동을 통한 신체기능의 향상, 신체활동량의 증가는 자궁내막암 환자에게 건강하고 활력 있는 삶을 제공할 수 있을 것이라 사료된다.

주요어 : 자궁내막암, Prehabilitation, 수술 전 재활, 운동, 신체활동, 삶의 질

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