RESEARCH ARTICLE

Association between Physical Activity and Postoperative Complications after Esophagectomy for Cancer: A Prospective Observational Study

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Abstract

Background: Postoperative complications after esophagectomy can lead to considerable patient discomfort and prolonged length of hospital stay. Lack of physical activity can be one of the independent risk factors for postoperative complications because physical activity is closely related to physical function. The objective of this study was to determine whether physical activity among esophageal cancer patients decreases their risk of postoperative complications after esophagectomy. Materials and Methods: We investigated 51 consecutive patients with newly diagnosed resectable esophageal cancer who were scheduled to receive esophagectomy between January 2009 and November 2011. Demographic, clinicopathologic, and treatment information were recorded and physical function was measured. The last 7-days short version of the International Physical Activity Questionnaire was used to assess physical activity before the operation. Stepwise multiple logistic regression analysis was used to determine whether preoperative physical activity is related to the risk of postoperative complications. Results: Male gender [OR 18.6, (95%CIs: 1.2-284.4); P=0.035], 3-field lymph node dissection (OR 9.6, [95%CIs: 1.4-66.6]; P=0.022), low-level physical activity (OR 28.3, [95%CIs: 3.5-227.7]; P=0.002), and preoperative comorbidities [OR 5.9, (95%CIs: 1.1-31.5); P=0.037] were found to be independently associated with postoperative complications. Conclusions: The present study shows that low-level physical activity, preoperative comorbidities, and 3-field lymph node dissection are independent and significant risk factors for postoperative complications after esophagectomy. Although further study is required, maintaining high-level physical activity preoperatively may decrease the risk of postoperative complications.

Keywords: Esophagectomy - physical activity - postoperative complications

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Introduction

Esophageal cancer was the eighth most common malignancy (482,000 cases, 3.8% of all cancers) and the sixth leading cause of cancer death (406,000 deaths, 5.4% of all cancers) worldwide in 2008 (Ferlay et al., 2010). Esophageal cancer often has a poor prognosis. Major surgery, including esophagectomy, can offer a 30% chance of cure (Hulscher et al., 2002; Rouvelas et al., 2005). However, such a procedure carries a high risk of severe complications and has a detrimental impact on health-related quality of life (HRQOL) (McCulloch et al., 2003; de Boer et al., 2004; Reynolds et al., 2006; Djärv et al., 2008).

Esophagectomy is perhaps the most traumatic general surgical procedure. Pulmonary complications are the most common serious morbidity after esophagectomy (Whooley et al., 2001; Bailey et al., 2003; Law et al., 2004) and can lead to considerable patient discomfort and prolonged length of hospital stay (Stéphan et al., 2000; Reeve et al., 2008). Anastomotic leakage and recurrent laryngeal nerve injury are also common complications after esophagectomy, leading to poor HRQOL (Djärv, 2009). Hence, esophagectomy can strongly influence the physical and psychosocial outcomes of patients.

Recently, several studies have suggested that self-reported regular exercise (e.g. ≥9 METs*hour/week, equivalent to brisk walking for 30 minutes/day×5 days/week) is associated with a 15-61% reduction in the risk of cancer-specific death and all-cause mortality after a diagnosis of operable breast (Holmes et al., 2005; Irwin et al., 2008), colorectal (Meyerhardt et al., 2006; 2009), and prostate cancer (Kenfield et al., 2011). Another study has also reported the positive effects of physical activity on postoperative pulmonary complications (Feeney, 2011). Therefore, lack of physical activity could be an independent risk factor for postoperative complications because physical activity is closely related

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to physical function. However, few studies have addressed associations between physical activity and postoperative complications after esophagectomy.

The objective of this study was to determine whether physical activity among esophageal cancer patients decreases their risk of postoperative complications after esophagectomy. We hypothesized that physical activity has a favorable effect on the risk of postoperative complications, such as pulmonary complications and cardiovascular complications.

Materials and Methods

Study design and patients

This was a single-center, prospective study conducted to determine whether preoperative physical activity among Japanese patients with esophageal cancer is related to their risk of postoperative complications. The protocol and consent form for this study were approved by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. Written informed consent was obtained from all patients. Between January 2009 and November 2011, patients with newly diagnosed esophageal cancer who were scheduled to receive either neoadjuvant chemotherapy before surgery or surgery alone were considered eligible and asked to participate in this study. Patients with gait disturbances who required assistive devices were excluded. All patients were admitted in the intensive care unit for the immediate postoperative period. Cervical anastomoses were monitored clinically; patients resumed oral diet on the seventh postoperative day. They also received a physiotherapy intervention perioperatively from a physical therapist. The intervention included deep breathing and coughing exercises, assistance with early ambulation, and resistance training and aerobic exercise.

Measures and procedure

Demographic, clinicopathologic, and treatment information including age, gender, clinical stage, tumor histology, location of tumor, preoperative comorbidities, and neoadjuvant chemotherapy was collected through a review of electronic medical records. Type of operation was recorded: (1) thoracoscopic and laparoscopic esophagectomy; (2) thoracoscopic and laparotomic esophagectomy; (3) thoracotomic and laparoscopic esophagectomy. Other surgical data that were recorded included region of lymph node dissection (≤ 2-field or 3-field), blood loss volume, and duration of surgery; postoperative complications were also documented prospectively. In this study, five preoperative comorbidities were recorded: hyperuricemia, heart disease (history of previous myocardial infarction, coronary artery disease, and diagnosis of congestive heart failure), diabetes mellitus (insulin and non-insulin-dependent), hypertension, and chronic obstructive pulmonary disease. Postoperative complications included pulmonary complications (defined as pneumonia, atelectasis, and respiratory failure), cardiovascular complications (including myocardial infarction, severe arrhythmia, heart failure, and cardiogenic pulmonary edema and pulmonary embolism), anastomotic leakage, chylothorax, and recurrent laryngeal nerve palsy. These postoperative complications were assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (≥grade 2). To assess preoperative physical fitness, we measured body mass index (BMI), forced vital capacity (FVC), forced expiratory volume in one second percent predicted (FEV1%), knee-extensor muscle strength, and 6-minute walking distance. BMI was calculated by dividing weight (kg) by height in meters squared (m^2). A portable micro-medical spirometer (Autospiro-407, MINATO, Japan) was used to measure FEV1% and FVC. Knee-extensor muscle strength was assessed with an isometric knee-extensor muscle strength machine (IsoForce GT-330, OG GIKEN, Japan). The hip and knee were kept at a 90° angle while the subject was sitting. The maximal isometric strength was measured after adequate practice trials. The 6-minute walking distance was measured using the 6-minute Walk Test, according to guidelines of the American Thoracic Society (2002). Subjects walked as far and as fast as they could in 6 minutes (subjects were allowed to rest if necessary during the 6-minute period). These tests were conducted by trained physiotherapists before the patient's operation (usually 2-3 days before surgery).

Physical activity

Physical activity status was assessed using the last 7-days short version of the International Physical Activity Questionnaire (IPAQ) Japanese version (Murase, 2002; Craig et al., 2003). This measure assessed total moderate and vigorous intensity physical activity, total time walking, and time spent sitting during the last 7 days. Each activity type and intensity score is assigned a Metabolic equivalent (MET) value according to the published protocol (e.g., MET for walking=3.3, cycling=6.0, moderate intensity=4.0, vigorous intensity leisure=8.0) (Craig, IPAQ. At a glance: IPAQ Scoring Protocol. http://www.ipaq.ki.se/scoring.htm. Accessed March 20, 2006). According to the published IPAQ scoring protocol, we calculated average weekly physical activity (METs*hours/week).

Statistical analysis

For data analysis, relationships of categorical variables were assessed using Chi-square tests and numerical variables with postoperative complications were assessed using t-tests. For multivariate analysis, stepwise multiple logistic regression analysis was performed, with occurrence of postoperative complications as a dependent variable and other preoperative/intraoperative patient and tumor data as independent variables. The associations between preoperative patient and tumor characteristics and postoperative complications were calculated as odds ratio (OR) with 95% confidence intervals (95%CIs). Type of operation was categorized in two groups: thoracoscopic and laparoscopic esophagectomy were categorized as minimally invasive techniques; thoracotomic and laparotomic esophagectomy were categorized as open surgery. If the patients had at least one comorbidity, they were classified as having at least one comorbidity"; otherwise, they were classified as having no comorbidities.

In the same way, if the patients had at least one complication, they were classified as having at least one complication"; otherwise, they were classified as having no complication. Occurrences within 14 days of surgery were considered as postoperative complications. Physical activity was analyzed as MET-hour per week (<9 METs*h/wk or ≥9 METs*h/wk) on the basis of prior work (Holmes et al., 2005). P values of less than 0.05 were considered as statistically significant. Statistical analysis was performed using SPSS software (version 20.0) for Windows (SPSS Inc., Tokyo, Japan).

Results

During the study period, 55 patients with esophageal cancer underwent esophagectomy. Among them, 4 were excluded because of gait disturbances (n=3) and declined participation (n=1), leaving 51 patients (93%) for the final analysis. Demographic, clinicopathologic, and treatment information of the participants is presented in Table 1. The mean age was 65.0±7.3 years, and 86% of participants were men. The baseline clinical stage (UICC-TNM stage 6th edition) at enrollment was I in 10 (20%) patients, IIA in 14 (27%) patients, IIB in 14 (27%) patients, and III in 13 (26%) patients. The pathological diagnosis was squamous cell carcinoma in all cases. Tumor location was as follows:

Table 1. Characteristics of Patients

	Overall	With complications	Without complications	P value
Number of patients	51	20	31	
Age (years)	65.0±7.3	65.0±7.1	65.0±7.6	n.s
Gender				n.s
Male	44	19	25	
Female	7	1	6	
BMI	21.3±3.0	21.5±2.6	21.1±3.3	n.s
Clinical stage				0.042
0-I	10	1	9	
IIA	14	4	10	
IIB	14	9	5	
III	13	6	7	
Location				n.s
Upper third	14	7	7	
Middle third	18	7	11	
Lower third	19	6	13	
Neoadjuvant chemotherapy				0.026
Yes	34	17	17	
No	17	3	14	
Lymphadenectomy				0.035
≤ 2-field	32	9	23	
3-field	19	11	8	
Operation				n.s
Minimally invasive techniques	46	18	28	
Open surgery	5	2	3	
Operation time	523.9±67.2	543.7±60.1	511.1±69.4	n.s
Blood loss	177.4±238.8	182.4±141.6	174.3±286.9	n.s
Comorbidities				0.003
Hyperuricemia	1	1	0	
Heart disease	2	1	1	
Diabetes mellitus	2	2	0	
Hypertension	7	4	3	
COPD	6	5	1	

*n.s, not significant

Table 2. Preoperative Physical Fitness and Physical Activity

	Overall	With complications	Without complications	P value
FVC	111.50±14.1	112.20±13.4	111.00±14.8	n.s
FEV1	98.50±17.0	96.00±17.8	100.10±16.5	n.s
Muscle strength	2.28±0.67	2.20±0.57	2.33±0.73	n.s
6MD	558.80±74.2	531.80±87.9	576.30±59.0	n.s
PA: <9 METs*h/wk	21	14	7	0.001
≥9 METs*h/wk	30	6	24	

*n.s, not significant; FVC, forced vital capacity; FEV1, forced expiratory volume in one second percent predicted; 6MD, 6-minute walking distance; PA, physical activity

Table 3. Multivariate Analysis of Possible Variables for Postoperative Complications after Esophagectomy

	Odds ratio	95% confidence interval	P value
Male	18.6	1.2-284.4	0.035
3-field lymph node dissection	9.6	1.4-66.6	0.022
Low-level physical activity	28.3	3.5-227.7	0.002
Preoperative comorbidities	5.9	1.1-31.5	0.037

upper third esophagus in 14 (27%), middle third esophagus in 18 (36%), and lower third esophagus in 19 (37%). Neoadjuvant chemotherapy had been given to 67% of the patients. Thoracoscopic and laparoscopic esophagectomy was performed in 46 (90%) patients. The region of lymph node dissection was 2 fields or fewer in 32 (63%) patients and 3 fields in 19 (37%) patients. Out of 51 patients, 20 (39%) had postoperative complications; 3 (6%) had pulmonary complications; 3 (6%) had cardiovascular complications; 8 (16%) had anastomotic leakage; 2 (4%) had chylothorax; and 13 (25%) had recurrent laryngeal nerve palsy. Eighteen (35%) patients had preoperative comorbidities. Preoperative physical fitness and physical activity are presented in Table 2. Thirty (59%) patients had high-level physical activity (≥9 METs*h/wk).

The univariate analysis revealed that postoperative complications occurred more frequently in patients with worse clinical stage (P=0.042), neoadjuvant chemotherapy (P=0.026), 3-field lymph node dissection (P=0.035), low-level physical activity (<9 METs*h/wk) (P=0.001), and preoperative comorbidities (P=0.003) (Table 1 and 2).

Results of the multivariate analysis are presented in Table 3. Male gender [OR 18.6, (95%CIs: 1.2-284.4); P=0.035], 3-field lymph node dissection [OR 9.6, (95%CIs: 1.4-66.6); P=0.022], low-level physical activity [OR 28.3, (95%CIs: 3.5-227.7); P=0.002], and preoperative comorbidities [OR 5.9, (95%CIs: 1.1-31.5); P=0.037] were found to be independently associated with postoperative complications.

Discussion

The current study shows that patients with low-level physical activity, 3-field lymph node dissection, and preoperative comorbidities have a higher risk of postoperative complications. According to some previous studies, advanced age, tumor location, operation duration, 3-field lymph node dissection, and comorbidity were identified as independent risk factors for postoperative

complications (Law et al., 2004; Gockel et al., 2005; Cooke et al., 2009). In our study, 3-field lymph node dissection was identified as an independent risk factor that may led to a higher incidence of recurrent laryngeal nerve palsy— the most frequent postoperative complication in our study (25%).

This is the first report on the physical activity of esophageal cancer patients in relation to postoperative complications after esophagectomy. The indicated possible effect of physical activity can be attributed, at least partially, to its effect on lifestyle-related diseases, such as hypertension and diabetes mellitus. Generally, there is an inverse linear relationship between physical activity level and all-cause mortality; this is commonly because of lifestyle-related disease (Lee and Skerrett, 2001; Ismail-Beigi, 2012). In our study, the incidence of anastomotic leakage was 16%, which is comparable to the incidence reported in other series (Rutegård et al., 2009; Aminian et al., 2011). The most important predisposing factor for anastomotic leakage is ischemia of gastric conduit (Urschel, 1995). One previous study has also reported history of hypertension and diabetes mellitus as independent risk factors for anastomotic leakage, possibly due to reduced microperfusion of tissues (Aminian et al., 2011). In the present study, the patients with high-level physical activity may have had a reduced risk of anastomotic leakage by maintaining a better circulation. The finding that postoperative complications occurred less frequently in patients with high-level physical activity suggests that increasing activity during the preoperative period may be of benefit. Such an intervention could be encouraged in the weeks before surgery— particularly when patients are receiving neoadjuvant therapy.

The rate of pulmonary complications was 6%, which is lower than that reported in a previous study (16%) (Law et al., 2004). The physiotherapy intervention, especially deep breathing and coughing exercises and assistance with early ambulation, may have contributed somewhat to a reduction in the risk of pulmonary complications.

This study has some limitations. First, the relatively small sample size and the single-center design can limit the generalization of the results. Second, this was a prospective observational study. Although higher preoperative physical activity might have contributed to a reduction in the risk of postoperative complications after esophagectomy, we could not directly evaluate the effect from the results of this study. Therefore, further study of a larger number of cases with a controlled intervention is required to elucidate the impact of preoperative physical activity on postoperative complications.

In conclusion, the present study shows that low-level physical activity, preoperative comorbidities, and 3-field lymph node dissection are independent and significant risk factors for postoperative complications after esophagectomy. Although further study is required, maintaining high-level physical activity preoperatively may decrease the risk of postoperative complications.

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