Impact of neoadjuvant chemotherapy on physical fitness, physical activity and health-related quality of life of patients with resectable esophageal cancer

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ABSTRACT

Objective: Neoadjuvant chemotherapy (NAC) followed by radical surgery is the standard treatment for patients with resectable esophageal squamous cell carcinoma (ESCC) in Japan. However, some adverse events associated with NAC may result in a decrease in physical fitness that may influence the patient's ability to tolerate surgery. The purpose of this study was to evaluate the impact of NAC on the physical fitness, physical activity and health-related quality of life (HRQOL) of patients with ESCC.

Methods: In this prospective study, we investigated 27 consecutive patients with newly diagnosed resectable ESCC who were scheduled to receive NAC followed by surgery between January 2009 and November 2010. Primary endpoints were change from baseline in physical fitness (knee-extensor muscle strength and six-minute walking distance) and physical activity after NAC. A secondary endpoint was change from baseline in HRQOL.

Results: Physical fitness and physical activity level after NAC did not differ significantly from those before NAC. With regard to HRQOL, only social functioning was significantly different (P = 0.04). The change in physical activity demonstrated a significant correlation with the change in 6-minute walking distance (r = 0.45, P = 0.02).

Conclusions: NAC had no impact on physical fitness and physical activity in patients with ESCC. This result indicated that there was no need for a physiotherapy intervention during NAC to prevent a decline in these parameters.

Key words: esophageal cancer, HRQOL, neoadjuvant chemotherapy, physical activity, physical fitness

<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.[1] Despite optimal treatment, median survival for advanced disease remains less than 1 year. Even in patients with resectable disease, the prognosis is relatively poor after surgery alone.[2-4] This fact has prompted many investigators to explore perioperative systemic treatment, such as chemotherapy or chemoradiotherapy, to improve survival. In Japan, on the basis of the results of several studies, such as JCOG 9204 and JCOG 9907, neoadjuvant chemotherapy (NAC) with cisplatin combined with 5-fluorouracil (5-FU) followed by radical surgery has become the standard treatment strategy for resectable esophageal squamous cell carcinoma (ESCC).[5, 6]

Although NAC is a well-established treatment for improving the outcomes of surgery, several side effects may result in the deterioration of physical fitness, physical activity, and health-related quality of life (HRQOL). Recently, several studies reported the impact of neoadjuvant treatment (chemotherapy or chemoradiotherapy) on HRQOL.[7-9] However, there are no reports on the impact of NAC on physical fitness or physical activity. It is important to clarify whether these parameters will be decreased by NAC, because the compromise of physical fitness by NAC may negatively influence the tolerability and outcome of surgery. In addition, the results of this study will be useful to determine whether a physiotherapy intervention is necessary during the neoadjuvant treatment period to improve these parameters.

The objectives of this study were to evaluate the impact of NAC on physical fitness, physical activity and HRQOL in patients with ESCC and to determine whether physiotherapy is needed during the NAC period.

<Materials and Methods>

Study Design and Subjects

This was a single-center, prospective study conducted to evaluate the impact of NAC on the physical fitness, physical activity and HRQOL of patients with resectable ESCC. The Institutional Review Board of Kyoto University Graduate School of Medicine approved the protocol and consent form for this study, and written informed consent was obtained from all patients. Between January 2009 and November 2010, patients with newly diagnosed ESCC who were scheduled to receive NAC followed by surgery were asked to participate in this study. All patients who were scheduled to receive NAC followed by surgery were eligible. Patients with gait disturbances or cognitive impairment were excluded. Preoperative chemotherapy consisted of two cycles of cisplatin (80 mg/m^2, intravenously) on day 1 and 5-FU (800 mg/m^2 per day in a continuous infusion) on days 1 through 5 at 3-week intervals. Primary outcomes were physical fitness (knee-extensor muscle strength and six-minute walking distance) and physical activity. The secondary outcome was HRQOL. We assessed these outcomes before the initiation of NAC (pre-NAC) and after the completion of NAC (post-NAC).

Demographic and Treatment Information

Information regarding age, gender, weight, clinical stage, histologic tumor type, and side effects was obtained from electronic medical records. Side effects were assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (NCI-CTCAE v3.0). The NCI-CTCAE measure toxicities as grades 1 through 5 (1 is mild, 2 is moderate, 3 is severe, 4 is life-threatening or disabling, and 5 is death associated with the adverse event).

Physical Fitness

To assess physical fitness, we tested knee-extensor muscle strength and 6-minute walking distance. Knee-extensor muscle strength was assessed with an isometric knee-extensor muscle strength machine (IsoForce GT-330, OG GIKEN, Japan). The subject was in the sitting position, and the hip and knee were kept at 90° angles. The maximal isometric strength was measured after adequate premeasurement trials. The 6-minute walking distance was measured with the 6-minute Walk Test, as described by the American Thoracic Society.[10] Subjects walked as far and as fast as they could for 6 minutes. (Subjects were allowed to rest if and as necessary during the 6-minute period.) These tests were conducted by physiotherapists who had been trained in the proper techniques for conducting them.

Physical Activity

Physical activity status was assessed using the last 7-days short version of the International Physical Activity Questionnaire (IPAQ) Japanese version.[11, 12] This measure assessed total vigorous intensity physical activity, total moderate intensity physical activity, total time walking, and time spent sitting during the last 7 days. Each activity type and intensity score is provided 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 daily physical activity (METs･mins/day).

Health-Related Quality of Life

HRQOL was measured with the European Organization for the Research and Treatment of Cancer Quality of Life Core Questionnaire with 30 items (EORTC QLQ-C30).[13] This QOL scale includes a global health status/QOL scale, five functional scales (physical, role, emotional, cognitive, and social functioning), and symptom scales (fatigue, nausea-vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems). Calculation of scores was carried out according to the EORTC QLQ-C30 manual. A difference of ≥10 points in each scale indicates a clinically important change.[14]

Sample Size Calculation and Statistical Analysis

Sample size calculation was based on the difference in the 6-minute Walk Test; primary outcome in this study. Since the walking distance of 54 meters (standard deviation = 93) was thought to be clinically important difference[15-18], the estimated sample sizes required to achieve a power of the test of 80% and a two-sided level of significance of 5% were calculated as 27 patients.

Demographic and treatment variables were described using means and standard deviations, medians and ranges and percentages, where appropriate. All variables were tested for distribution normality using the Shapiro-Wilks normality test. Differences over the course of NAC (pre to post-treatment) were analyzed using paired-sample t-test for continuous variables with normal distribution (weight, knee-extensor muscle strength, and 6-minute walking distance) and the Wilcoxon signed-rank test for non-normally distributed variables (IPAQ score and HRQOL scores). Spearman's rank correlation coefficient was used to evaluate the relationship between changes in physical activity and changes in physical fitness. All statistical analyses were performed with the R statistical package (www.r-project.org). All hypothesis testing was two-tailed, and *P* values of less than 0.05 were considered to indicate statistical significance.

<Results>

During the study period, 33 patients with ESCC underwent NAC before surgery. Among them, 6 were excluded because of gait disturbances (n = 2), cognitive impairment (n = 1), and declined participation (n = 3), so the remaining 27 patients were properly registered and underwent NAC. Patient demographic and treatment data are presented in Table 1. The mean age was 63 years, and 81% were men. The baseline clinical stage (UICC-TNM stage 6th edition) at enrollment was IIA in 11 (41%) patients, IIB in 10 (37%) patients, III in 5 (18%) patients, and IVA in 1 (4%) patient. The histologic type was squamous cell carcinoma in all patients. The occurrence of side effects was as follows: Grade 1 in 23 (85%) patients, Grade 2 in 16 (59%) patients, Grade 3 in 3 (11%) patients, and Grade 4 in 1 (4%) patient. The Grade 3 chemotherapy-related toxicities were mucositis, abdominal pain, and thrombocytopenia. The Grade 4 chemotherapy-related toxicity was hyponatremia. Most patients underwent two cycles of preoperative chemotherapy, although 5 (19%) patients underwent only one cycle because of severe adverse events (n = 2) and progression of disease (n = 3).

Table 2 shows changes in weight, physical fitness data, and physical activity over the course of NAC. Post-NAC variables did not differ significantly from pre-NAC variables. With regard to the global health status/QOL scale, functional scales, and symptom scales, there was a statistically significant difference only in terms of social functioning ($P = 0.04$; Table 3).

Results of the correlational analysis are presented in Figure 1A and 1B. The change in physical activity demonstrated a significant correlation with the change in 6-minute walking distance ($r = 0.45$, $P = 0.02$), but not with the change in knee-extensor muscle strength ($r = -0.01$, $P = 0.95$).

<Discussion>

This is the first report regarding the impact of NAC on physical fitness and physical activity. Results of this prospective study suggested that NAC had no impact on physical fitness, physical activity, and HRQOL in patients with ESCC. We hypothesized that physical activity would decrease because of adverse events, leading to a deterioration in physical fitness. Several studies have reported that treatment (surgery and/or chemotherapy and/or radiation) had a significant negative effect on physical activity.[19, 20] In our study, however, physical fitness and physical activity levels did not decrease over the course of NAC. In addition, the change in physical activity demonstrated a significant positive correlation with the change in 6-minute walking distance. These results indicated that patients who maintained their pretreatment physical activity levels could maintain physical fitness, especially the 6-minute walking distance. Although most patients in this study experienced some kind of adverse event, the severity of these adverse events was relatively mild. This seemed to be one of the reasons that most patients could maintain their physical activity levels. Similarly, HRQOL scores did not deteriorate significantly over the course of NAC, except for social functioning. Our findings are similar to previous work by Safieddine and colleagues, who reported that the impact of NAC on HRQOL in patients with operable esophageal cancer was transient because HRQOL scores returned to baseline levels before surgical intervention.[7]

It was important to understand the impact of NAC on physical fitness, physical activity, and HRQOL in patients with ESCC to determine the need for a physiotherapy intervention to improve these parameters during NAC. The results of the present study indicated that there was no need for a physiotherapy intervention during NAC. However, Nagamatsu and colleagues reported that esophagectomy can be safely performed in patients with a $\dot{V}o^{2}max/m^{2}$ of at least 800 ml/ m^{2}.[21] Thus, physiotherapy may be important before surgery to reduce the risk of postoperative cardiopulmonary complications. Further studies are needed to examine the role of physiotherapy in the treatment of ESCC comprehensively.

This study has some limitations. First, our study was conducted with small sample size, which might not have had enough power to detect significant differences in outcomes. It was possible that each outcome might reach statistical significance with more patients. However, even so, they might not be clinically significant; such as 1 kg weight loss, minimal difference in knee strength, or 2% difference in walk distance. Although only the 17% difference in IPAQ might be clinically significant difference with more patients, the conclusion of this study might not be changed, because IPAQ was the secondary outcome. In addition, the small sample size precluded subgroup analyses stratified by the demographic and treatment characteristics of the patients. Second, we evaluated the impact of chemotherapy alone as a neoadjuvant treatment, because NAC followed by surgery is the standard treatment for the patients with resectable disease in Japan. However, the standard neoadjuvant treatment for the esophageal cancer in Western countries; such as in US or in Europe, is chemotherapy with more strong combination regimen or chemoradiotherapy. Although it might be possible that inclusion of patients who received neoadjuvant chemoradiotherapy or different regimen of NAC might have changed the results of this study, we could not discuss about it from the results of this study. Third, the frequency of the excluded patients (6 patients [18.2%]) was relatively high in this study with the small sample size. Moreover, among them, 2 patients were excluded because of gait disturbances. This might introduce a potential of selection bias, because the finally analyzed patients were limited to the patients with relatively better condition. The fourth limitation was the assessment of physical activity. The Japanese short version of IPAQ is validated and reliable. However, it is not a direct assessment tool of real physical activity, such as daily walking steps.[22, 23] Thus, it should be noted that the IPAQ data alone were probably insufficient to draw definitive conclusions that patients maintained their physical activity levels during NAC.

In conclusion, NAC had no impact on physical fitness, physical activity, and HRQOL in patients with ESCC. The results of this study indicated that there was no need to implement a physiotherapy intervention during NAC to prevent a decline in these parameters. Since the number of patients was rather small, and the assessment tool used was insufficient, further study of a larger number of cases with more quantitative assessment tools is required to confirm the impact of NAC on physical fitness, physical activity, and HRQOL.

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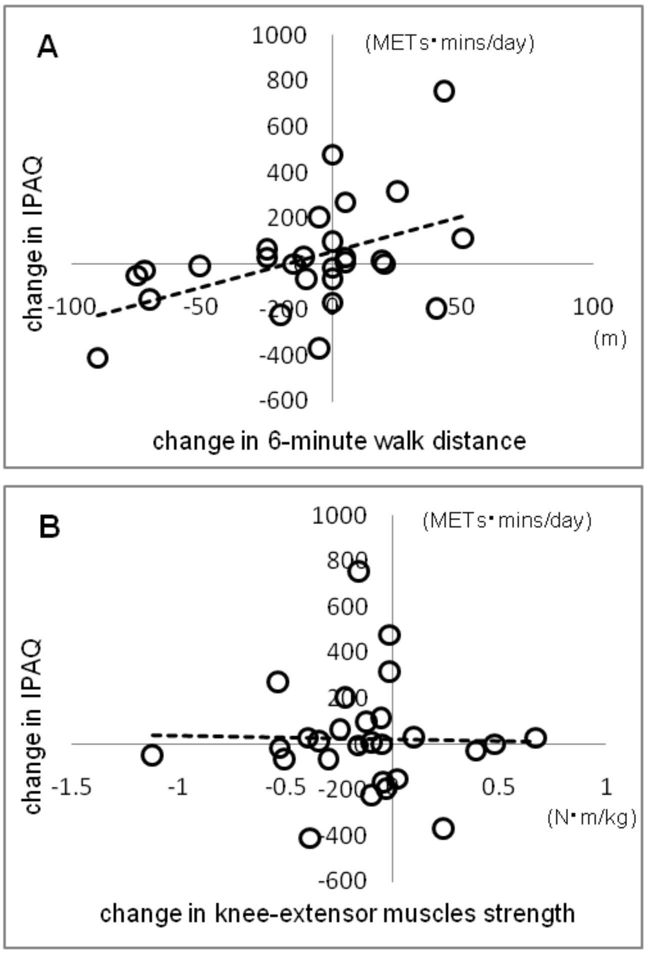

Fig 1. Relationship between changes in physical activity and changes in physical fitness. The change in 6-minute walking distance was correlated positively with the change in IPAQ (r = 0.45, P = 0.02; A), whereas the change in knee-extensor muscle strength had no correlation (r = -0.01, P = 0.95; B).

Table 1. Characteristics of subjects	N = 27 (%)
Age (Mean ± SD)	63.4±6.8
Gender	
Male	22 (81%)
Female	5 (19%)
Clinical stage	
ⅡA	11 (48%)
ⅡB	10 (37%)
Ⅲ	5 (18%)
ⅣA	1 (4%)
Histologic tumor type	
Adenocarcinoma	0 (0%)
Squamous cell carcinoma	27 (100%)
Side effects	
Grade 1	23 (85%)
Grade 2	16 (59%)
Grade 3	3 (11%)
Grade 4	1 (4%)
Grade 5	0 (0%)

Table 2. Changes in weight, physical fitness data and physical activity over the course of NAC treatment

	pre-NAC	post-NAC	p value
Weight (kg)	57.5±11.8	56.5±11.6	NS
Physical fitness			
Knee-extensor muscles strength (N･m/kg)	2.5 ± 0.6	2.4 ± 0.5	NS
6-minute walk distance (m)	574.9 ± 77.8	565.1 ± 75.3	NS
Physical activity			
IPAQ (METs･mins/day)	119.1 (0.0-605.6)	99.0 (0.0-819.0)	NS

NS, not significant.

Weight and physical fitness values expressed as Mean ± SD

IPAQ values expressed as Median (range)

Table 3. Changes in EORTC QLQ-C30 over the course of NAC treatment			
	pre-NAC	post-NAC	p value
global health status (QOL score)	66.7 (16.7-100.0)	66.7 (16.7-91.7)	NS
Functional scales			
Physical	93.3 (66.7-100)	93.3 (60.0-100)	NS
Role	100 (33.3-100)	100 (33.3-100)	NS
Emotional	75.0 (41.7-100)	83.3 (50.0-100)	NS
Cognitive	83.3 (50.0-100)	83.3 (33.3-100)	NS
Social	100 (33.3-100)	83.3 (0-100)	0.04
Symptom Scales			
Fatigue	22.2 (0-55.6)	22.2 (0-66.7)	NS
Nausea and vomiting	0 (0-33.3)	0 (0-66.7)	NS
Pain	0 (0-50)	0 (0-33.3)	NS
Dyspnoea	0 (0-66.7)	0 (0-33.3)	NS
Insomnia	0 (0-66.7)	0 (0-66.7)	NS
Appetite loss	0 (0-66.7)	0 (0-100)	NS
Constipation	0 (0-100)	0 (0-100)	NS
Diarrhoea	0 (0-33.3)	0 (0-33.3)	NS
Financial difficulties	0 (0-100)	0 (0-100)	NS

NS, not significant.

Scores range from 0 to 100 (higher score is higher level of functioning, higher score is greater degree of symptoms).

Values expressed as Median (range)