Factors associated with fatigue one month after surgery in patients with gastrointestinal cancer

Eisuke KOGURE, PT, Ph.D1 and Tsuyoshi HARA, PT, Ph.D2

1) Rehabilitation Progress Center Inc
2) Department of Physical Therapy, School of Health Science, International University of Health and Welfare

ABSTRACT. Objective: The purpose of this study was to examine the factors associated with the occurrence of cancer-related fatigue (CRF) one month after surgery in patients with gastrointestinal cancer. Method: The study included 96 patients with gastrointestinal cancer (50 males and 46 females, mean age 62.7 ± 11.4 years). Data of the Cancer Fatigue Scale (CFS), 6-minute walk distance (6MWD), and hospital anxiety and depression scale (HADS) were obtained before surgery and one month after surgery. The subjects were divided into the following two groups: severe CRF group (CFS score of ≥19 points) and mild CRF group (CFS score of <19 points). Each parameter was compared between the severe and mild CRF groups. The factors associated with CRF were identified by logistic regression analysis involving factors with significant differences between the groups. Result: The CFS score showed a significant interaction, and the CFS score, 6MWD, and HADS score showed significant differences both before and one month after surgery between the two groups. The CFS score was significantly higher in the severe CRF group than in the mild CRF group both before and one month after surgery. Additionally, the 6MWD was significantly lower in the severe CRF group than in the mild CRF group both before and one month after surgery. The factors identified on logistic regression analysis were the preoperative CFS score and preoperative 6MWD. Conclusion: CRF occurring one month after surgery might be affected by preoperative fatigue and preoperative exercise tolerance.

Key words: Patients with gastrointestinal cancer, Cancer-Related Fatigue, Exercise tolerance

Among cancer patients, rehabilitation is widely performed from the prevention period to the palliative period11. Early intervention is important to improve the physical function and quality of life (QOL) after surgery7. However, there are patients whose physical function and QOL decline because of cancer-related symptoms before and after cancer treatment, and fatigue is one of the symptoms8-10. Cancer-related fatigue (CRF) is defined as a distressing, persistent, and subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment, which is not proportional to recent activity and interferes with usual functioning81. CRF is influenced by the side effects of chemotherapy and radiation therapy78, physical function, the mental state90, nutrition, inflammation, and anemia10-121. In physical function, exercise tolerance and CRF are related123, and aerobic exercise is said to be beneficial for CRF124. It has been reported that CRF is associated with anxiety and depression in the psychological aspect125. There are many studies that have reported patients with cancer experiencing CRF before and after chemo and radiation therapy126-128. Perioperative CRF has been found to occur one month after surgery111, and it has been mentioned that some patients with gastrointestinal cancer might experience CRF after surgery12. However, there has been no report involving a comprehensive analysis of factors that cause CRF after surgery, including physical function and psychological aspects, such as anxiety and depression. The investigation of factors that cause CRF after surgery in patients with gastrointestinal cancer might provide useful information for improving QOL with physical therapy.

Therefore, the present study aimed to examine the factors associated with the occurrence of CRF at one month after surgery in patients with gastrointestinal cancer.
Method

1. Subjects

The subjects were 496 patients with gastrointestinal cancer who were admitted to the International Medical Welfare University Mita Hospital for surgery between October 1, 2014, and January 31, 2018, and who were recommended to undergo physical therapy at the Department of Rehabilitation by a gastrointestinal surgeon. The inclusion criteria were no radiation or chemotherapy before surgery, independence with regard to activities of daily living, and discharge home. The exclusion criteria were complications after surgery and missing data. Among the subjects that met the inclusion criteria, 204 provided consent for this study. Among these 204 subjects, 108 were excluded as they met the exclusion criteria. Thus, 96 subjects (50 males and 46 females, mean age 62.7 ± 11.4 years) were finally included in this study. A flow diagram representing the selection of research subjects is shown in Figure 1.

2. Methods

The following data of the subjects were assessed: basic information, surgical information, length of hospital stay, physical therapy intervention time during hospitalization, body mass index (BMI), and laboratory findings at one or more days before surgery and one month after surgery.

The present study was approved by the ethics committee of the International University of Health and Welfare Graduate School (approval number: 15-Ig-43). The subjects signed a consent form after receiving an explanation about the methods, and measurements were performed after obtaining consent.

Basic information evaluated age, sex, and cancer stage. Surgical information evaluated surgical site, surgical procedure, surgical time, and blood loss. Laboratory findings evaluated serum albumin, C-reactive protein, and hemoglobin.

CRF was evaluated using the cancer fatigue scale (CFS)\(^9\), which involves a questionnaire for CRF. Moreover, it is possible to conveniently evaluate CRF using this...
questionnaire. The CFS consists of physical fatigue, mental fatigue, and cognitive fatigue. The total score of the items is considered as the overall score, and a higher score indicates a stronger feeling of fatigue. The questionnaire included 15 questions, and each question had 5 options ranging from a score of 1 to 4 points. A score of 1 point indicated no CRF, whereas a score of 4 points meant severe CRF. The total score ranges from a minimum of 0 points to a maximum of 60 points. The cut-off value is 19 points, and individuals with a score of 19 points or more are considered to have severe fatigue that is an obstacle to ADL.

The 6-minute walk distance (6MWD) was measured for physical function evaluation. The 6MWD was adopted because it has relevance in the evaluation of gait ability after surgery for gastrointestinal cancer and can be assessed as exercise tolerance. The 6MWD was assessed according to the American Thoracic Society Medical Guidelines. A 50-m walkway without a slope was used, and the 6MWD was measured under maximum effort. An examiner followed each subject and used a walking distance measuring device (Sekisui Jushi, SDM-1) to measure the walking distance.

The hospital anxiety and depression scale (HADS) was used to assess anxiety and depression. It included 14 items, 7 for anxiety and 7 for depression, and each item had 4 options, with the score ranging from 0 to 3 points. The total scores for anxiety and depression are summed, and a score of 7 points or less indicates no diagnosis, a score between 8 and 10 points indicates a suspected diagnosis, and a score of 11 points or more indicates a certain diagnosis.

Each parameter was assessed one or more days before surgery (before surgery) and one month after surgery following discharge to home (one month after surgery). In order to examine the factors that influence CRF at one month after surgery, the subjects were divided into the following 2 groups: severe CRF group (those with a CFS total score of 19 points or more at one month after surgery) and mild CRF group (those with a CFS total score of less than 19 points).

3. Physical therapy intervention after surgery

The physical therapy intervention schedule and measurement flow are shown in Figure 2. Physical therapy was performed on the day before surgery to evaluate guidance of sitting up from the supine position, CRF, physical function, and mental condition. Physical therapy after surgery was started on the day after the surgery. After surgery, early ambulation and pulmonary rehabilitation were started in the intensive care unit or general ward. Depending on the condition of the patient, the walking distance was gradually increased, and low-load exercises, including lower limb muscle exercises, such as squats, were started. After stabilization of symptoms and removal of the drain, physical therapy was performed in a rehabilitation room. In the rehabilitation room, pulmonary rehabilitation, trunk and lower limb muscle exercises with low load, and aerobic exercise with an ergometer were performed. Additionally, guidance was provided for self-exercise after discharge.

4. Statistical analysis

The χ² test, unpaired t-test, and Mann-Whitney U test were used to compare basic information, surgical information, length of hospital stay, physical therapy intervention time, BMI, laboratory findings, 6MWD, and HADS score between the study groups. The analysis of the CFS score involved mixed-model two-way ANOVA, and the post-hoc test involved the Mann-Whitney U test. The change and difference in each period between the 2 groups were examined. Furthermore, in multiple logistic regression analysis (forward selection method: likelihood ratio), each parameter with a significant difference was included as an independent variable and CRF severity one month after surgery was included as a dependent variable. In addition, the Hosmer-Lemeshow test was used to determine the degree of conformity in the multiple logistic regression analysis.

All data were analyzed using IBM SPSS Statistics 21.0 for Windows (IBM Corp, Armonk, NY, USA). The significance level was set at 5% for the unpaired t-test and Mann-Whitney U test.

Results

The characteristics of the subjects in the 2 study groups are presented in Table 1. There were no significant differences in basic information, surgical information, length of hospital stay, physical therapy intervention time during hospitalization, BMI, and laboratory findings between the severe CRF and mild CRF groups. The 6MWD was significantly lower in the severe CRF group than in the mild CRF group both before surgery and one month after surgery (p < 0.05). The HADS anxiety and depression scores were significantly higher in the severe CRF group than in the mild CRF group both before surgery and one month after surgery (p < 0.05).

Changes in the CFS score before surgery and one month after surgery are shown in Table 2. There was a significant difference between the CFS score of the severe and mild CRF groups (p < 0.05). The CFS score was higher in the severe CRF group than in the mild CRF group both before surgery and one month after surgery (p < 0.05).

Table 3 shows the details of the logistic regression analysis, in which each parameter, excluding the CFS score one month after surgery, was included. The preoperative CFS score (partial regression coefficient: 0.020, significance probability: 0.001, odds ratio: 1.021, and 95% confidence interval: 1.079-1.282) and preoperative 6MWD (partial regression coefficient: 0.007, significance probability:
Table 1. Patient characteristics before surgery and one month after surgery in the severe and mild CRF groups

|                         | Severe CRF group | Mild CRF group | p-value |
|-------------------------|------------------|----------------|---------|
| Subjects (n)            | 28               | 68             |         |
| Age (years)             | 65.0±11.8        | 61.7±11.2      | n.s     |
| Sex (n)                 |                  |                |         |
| Male                    | 18 (64%)         | 32 (47%)       | n.s     |
| Female                  | 10 (36%)         | 36 (53%)       |         |
| Cancer stage (n)        |                  |                |         |
| I                       | 11 (39%)         | 29 (43%)       | n.s     |
| II                      | 9 (32%)          | 19 (28%)       |         |
| III                     | 4 (14%)          | 19 (28%)       |         |
| IV                      | 4 (14%)          | 1 (1%)         |         |
| Surgical site (n)       |                  |                |         |
| Esophagus               | 1 (4%)           | 2 (3%)         | n.s     |
| Stomach                 | 6 (21%)          | 14 (21%)       |         |
| Liver                   | 0 (0%)           | 4 (6%)         |         |
| Pancreas                | 8 (29%)          | 10 (15%)       |         |
| Colon                   | 8 (29%)          | 28 (41%)       |         |
| Rectum                  | 5 (8%)           | 10 (16%)       |         |
| Surgical procedure (n)  |                  |                |         |
| Laparoscopy             | 18 (64%)         | 47 (69%)       | n.s     |
| Laparotomy              | 10 (36%)         | 21 (31%)       |         |
| Operation time (min)    | 287.6±92.9       | 251.1±89.7     | n.s     |
| Blood loss (mL)         | 224.6±353.7      | 227.2±411.0    | n.s     |
| Length of hospital stay (days) | 17.7±7.3 | 15.2±7.0 | n.s     |
| Physical therapy intervention time during hospitalization (min) | 370.7±199.8 | 323.8±189.0 | n.s     |
| BMI                     |                  |                |         |
| Before surgery          | 23.3±2.9         | 22.2±3.4       | n.s     |
| One month after surgery | 22.3±2.8         | 21.4±3.2       | n.s     |
| Alb (g/dL)              |                  |                |         |
| Before surgery          | 4.4±0.3          | 4.4±0.3        | n.s     |
| One month after surgery | 4.2±0.3          | 4.3±0.3        | n.s     |
| CRP (mg/dL)             |                  |                |         |
| Before surgery          | 0.2±0.3          | 0.3±0.6        | n.s     |
| One month after surgery | 0.5±0.7          | 0.2±0.4        | n.s     |
| Hb (g/dL)               |                  |                |         |
| Before surgery          | 13.5±1.6         | 13.8±1.5       | n.s     |
| One month after surgery | 12.5±1.5         | 12.9±1.4       | n.s     |
| 6MWD (m)*               |                  |                |         |
| Before surgery          | 494.7±89.0       | 570.1±89.8     | p < 0.05|
| One month after surgery | 476.3±86.3       | 562.7±91.8     | p < 0.05|
| HADS depression†        |                  |                |         |
| Before surgery          | 6.5 (3.3, 9.0)   | 4.0 (2.3, 6.8) | p < 0.05|
| One month after surgery | 7.0 (5.0, 8.0)   | 3.0 (1.0, 5.0) | p < 0.05|
| HADS anxiety†           |                  |                |         |
| Before surgery          | 7.0 (6.0, 9.0)   | 3.0 (1.0, 6.0) | p < 0.05|
| One month after surgery | 8.0 (5.3, 9.0)   | 1.0 (1.0, 1.0) | p < 0.05|

The values of age, operation time, blood loss, length of hospital stay, BMI, CRP, Alb, Hb, and 6MWD are shown as mean ± standard deviation.

The values of HADS anxiety and depression are shown as median (25th percentile, 75th percentile).

CRF, cancer-related fatigue; BMI, body mass index; Alb, albumin; CRP, C-reactive protein; Hb, hemoglobin; 6MWD, 6-minute walk distance; HADS, hospital anxiety and depression scale; n.s, not significant

* unpaired t-test
† Mann-Whitney U test

0.001, odds ratio: 0.093, and 95% confidence interval: 0.987-0.999) were detected as independent variables. The model χ² test result was significant at p < 0.01, and the Hosmer-Lemeshow test indicated a good fit (p = 0.315).

Discussion

In this study, we classified subjects into 2 groups according to the severity of CRF at one month after surgery and examined the factors that cause CRF. According to the results of this study, the CRF was significantly higher in the severe CRF group than in the mild CRF group both before surgery and one month after surgery. It was revealed that exercise tolerance was significantly lower in the severe CRF group than in the mild CRF group both before surgery and one month after surgery. The HADS anxiety and depression scores were significantly higher in the severe CRF group than in the mild CRF group both before surgery and one month after surgery.
Factors associated with fatigue

Table 2. Change in the CFS score before surgery and one month after surgery

|                  | Severe CRF group | Mild CRF group | p-value |
|------------------|------------------|----------------|---------|
| CFS score‡†      | Before surgery   | 20.5 (16.8, 27.0) | 12.0 (7.8, 17.3) | p < 0.05 |
| One month after surgery | 22.0 (20.5, 26.0) | 10.0 (5.3, 14.0) | p < 0.05 |

The value of the CFS score is shown as median (25th percentile, 75th percentile).

‡ Mixed-model two-way ANOVA interaction
† Mann-Whitney U test

Table 3. Logistic regression analysis for factors associated with CRF

| Partial regression coefficient | Odds ratio | 95% confidence interval | p-value |
|--------------------------------|------------|-------------------------|---------|
| Preoperative CFS               | 0.020      | 1.021                   | 1.079-1.282 | <0.001 |
| Preoperative 6MWD              | -0.007     | 0.993                   | 0.987-0.999 | <0.001 |

Model χ² test, p < 0.01

Independent variables: Mild CRF 0, Severe CRF 1

Input variables: preoperative CFS, preoperative and postoperative 6MWD, and preoperative and postoperative HADS

CRF, cancer-related fatigue; CFS, cancer fatigue scale; 6MWD, 6-minute walk distance; HADS, hospital anxiety and depression scale

one month after surgery. In multiple logistic regression analysis, preoperative CFS score and preoperative 6MWD were detected as independent variables.

According to previous research, patients with gastrointestinal cancer before the start of treatment who have severe CRF may have significantly lower physical activity and significantly higher anxiety and depression on the Numerical Rating Scale. In addition, it has been reported that CRF and exercise tolerance in perioperative gastrointestinal cancer are negatively correlated both before and one month after surgery.

Those who have a severe CRF prior to surgery have strong anxiety and depressive symptoms and may have reduced exercise tolerance due to decreased physical activity. However, logistic regression analysis showed that the factors related to postoperative CRF were preoperative CRF and preoperative exercise tolerance, not anxiety and depression. Previous studies have reported that patients who underwent colorectal surgery and who have a high fatigue after surgery have been reported to have a high fatigue before surgery. In exercise therapy, aerobic exercise has been shown to improve from 4.3 to 3.5 on the CRF visual analog scale for pancreatic and bile duct cancer patients. In addition, it has been reported that 6MWD of colorectal cancer patients who have undergone exercise therapy from before hospital admission to before surgery has increased walking distance of about 50 m after 4 weeks of surgery compared to the control group. It has been reported that SF36 overall QOL significantly improved from 65 to 77 points by performing preoperative exercise intervention for patients undergoing surgery for colorectal liver metastasis.

As a result, patients with perioperative gastrointestinal cancer who had severe CRF after surgery may have lower exercise tolerance from before surgery. In addition, patients with perioperative gastrointestinal cancer who had severe CRF after surgery may have lower exercise tolerance from before surgery. It is necessary to improve exercise tolerance before hospital admission in order to avoid deterioration of CRF one month after surgery. This might lead to an improvement in CRF before surgery and might reduce CRF one month after surgery.

As a limitation of this study, the cause of CRF due to differences in gastrointestinal cancer sites has not been examined. In the future, it will be necessary to increase the number of cases and examine the factors that cause CRF due to differences in gastrointestinal cancer sites. The exercise approaches for the period before hospital admission to before surgery and the period after discharge to one month after surgery could not be examined. It is necessary to consider the exercise approaches for the period before hospital admission to before surgery. The future task is to examine whether CRF after surgery can be improved by providing guidance on self-exercise with the aim to improve exercise tolerance before hospital admission. It is important to clarify whether exercise tolerance improvement before surgery contributes to CRF improvement not only before surgery but also one month after surgery and contributes to QOL improvement one month after surgery.

Conclusion

Exercise tolerance was lower and CRF was greater both before surgery and after surgery in gastrointestinal cancer patients with severe CRF one month after surgery than in those with mild CRF. The factors associated with CRF one month after surgery were the preoperative CFS...
score and preoperative 6MWD. Thus, CRF occurring one month after surgery might be affected by preoperative fatigue and preoperative exercise tolerance. It is suggested that self-exercise instructions and interventions are important for improving exercise tolerance and CRF before hospital admission.

**Conflict of Interest:** There are no conflicts of interest to be disclosed in this study.

**References**

1) Dietz JH: Rehabilitation of the cancer patient. Med Clin North Am. 1969; 53: 607-624.
2) Cho I, Son Y, et al.: Feasibility and Effects of a Postoperative Recovery Exercise Program Developed Specifically for Gastric Cancer Patients (PREP-GC) Undergoing Minimally Invasive Gastrectomy. J Gastric Cancer. 2018; 18: 118-133.
3) Degner LF and Sloan J: Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last four weeks of life. J Pain Symptom Manage. 1991; 5: 83-93.
4) Vainio A and Auvinen A: Prevalence of symptoms among patients with advanced cancer: an international collaborative study. J Pain Symptom Manage. 1991; 12: 3-10.
5) NCCN Guidelines Version 2 2018 Cancer-Related-Fatigue [Internet]. New York: National Comprehensive Cancer Network (NCCN). [cited 2019 Jun. 1]; Available from: https://oncolife.com.ua/doc/nccn/fatigue.pdf
6) Coyle N, Adelhardt J, et al.: Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last four weeks of life. J Pain Symptom Manage. 1991; 5: 83-93.
7) Prue G, Rankin J, et al.: Cancer-related fatigue: A critical appraisal. Eur J Cancer. 2006; 42: 846-863.
8) de Jong N, Candel MJ, et al.: Prevalence and course of fatigue in breast cancer patients receiving adjuvant chemotherapy. Ann Oncol. 2004; 15: 896-905.
9) Kogure E: Relationship Between changes in fatigue and physical function, anxiety, and depression in patients with gastrointestinal cancer in the perioperative period. Jpn J Rehabil Med. 2017; 54: 536-545.
10) de Raaf PJ, Sleijfer S, et al.: Inflammation and fatigue dimensions in advanced cancer patients and cancer survivors. Cancer. 2012; 118: 6005-6011.
11) Christensen T and Kehlet H: Postoperative fatigue. World J Surg. 1993; 17: 220-225.
12) Jensen MB, Houborg KB, et al.: Postoperative changes in fatigue, physical function and body composition: an analysis of the amalgamated data from five randomized trials on patients undergoing colorectal surgery. Colorectal Dis. 2011; 13: 588-593.
13) Tomruk M, Karadibak D, et al.: Predictors of functional capacity in colorectal cancer patients. Support Care Cancer. 2015; 23: 2747-2754.
14) Kessels E, Husson O, et al.: The effect of exercise on cancer-related fatigue in cancer survivors: a systematic review and meta-analysis. Neuropsychiatr Dis Treat. 2018; 14: 479-494.
15) Richardson A: Fatigue in cancer patients: a review of the literature. Eur J Cancer. 1995; 4: 20-32.
16) Dimeo F, Fetscher S, et al.: Effect of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. Blood. 1997; 90: 3390-3394.
17) Segal R, Evans W, et al.: Structured exercise improves physical functioning in women with stage I and II breast cancer: Results of randomized controlled trial. J Clin Oncol. 2001; 19: 657-665.
18) Mustian KM, Peppone L, et al.: A 4-week home-based aerobic and resistance exercise program during radiation therapy: a pilot randomized clinical trial. J Support Oncol. 2009; 7: 158-167.
19) Okuyama T, Akechi T, et al.: Development and validation of the cancer fatigue scale: a brief, three dimensional, self-rating scale for assessment of fatigue in cancer patients. J Pain Symptom Manage. 2000; 19: 5-14.
20) Okuyama T, Wang XS, et al.: Validation study of the Japanese version of the brief fatigue inventory. J Pain Symptom Manage. 2003; 25: 106-117.
21) Okuyama T, Tanaka K, et al.: Fatigue in ambulatory patients with advanced lung cancer: prevalence, correlated factors, and screening. J Pain Symptom Manage. 2001; 22: 554-564.
22) Moriello C, Mayo NE, et al.: Validating the six minute walk test as a measure of recovery after elective colon resection surgery. Arch Phys Med Rehabil. 2008; 89: 1083-1089.
23) American Thoracic Society: ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002; 166: 111-117.
24) Zigmond AS and Snaith RP: The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983; 67: 361-370.
25) Kugaya A, Akechi T, et al.: Screening for psychological distress in Japanese cancer patients. Japanese Journal of Clinical Oncology. 1998; 28: 333-338.
26) Goedendorp MM, Gielissen MF, et al.: Severe fatigue and related factors in cancer patients before the initiation of treatment. Br J Cancer. 2008; 99: 1408-1414.
27) Yeo TP, Burrell SA, et al.: A progressive postresection walking program significantly improves fatigue and health-related quality of life in pancreas and periampullary cancer patients. J Am Coll Surg. 2012; 214: 463-475.
28) Li C, Carli F, et al.: Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. Surg Endosc. 2013; 27: 1072-1082.
29) Dunne DF, Jack S, et al.: Randomized clinical trial of prehabilitation before planned liver resection. Br J Surg. 2016; 103: 504-512.