

## RESEARCH ARTICLE

# Longitudinal Study of Cancer-Related Fatigue in Patients with Colorectal Cancer

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### Abstract

**Background:** Dynamic changes of cancer-related fatigue (CRF) among hospitalized patients with colorectal cancer were determined. **Materials and Methods:** This longitudinal, descriptive study involved 96 hospitalized patients with colorectal cancer, all recruited from a tertiary general hospital in Guangzhou, China. Patients completed questionnaires three times to assess the degree of fatigue, and measurement points were within one week of admission, at 2 to 3 days after surgery and 3 weeks after surgery. **Results:** Significant differences among the three measurement points ( $p < 0.01$ ) were observed. The scores of fatigue in the second survey were the highest, followed by the third and first surveys. Colon cancer patient scores were higher than those of rectal cancer patients with a significant difference ( $p < 0.05$ ). Colorectal patients experienced different degrees of fatigue at different periods during hospitalization. **Conclusions:** This study highlights the importance of interventions that are carefully tailored to patients based on the characteristics at different periods to alleviate fatigue.

**Keywords:** Colon cancer - rectal cancer - cancer-related fatigue - longitudinal study

*Asian Pac J Cancer Prev*, 15 (7), 3029-3033

### Introduction

Colorectal cancer is the fourth leading cause of advanced cancer in males and the third in females in the world (Center et al., 2009). A rising incidence of colorectal cancer has been observed in China in recent years, especially in large and medium-size cities, among which Guangzhou ranked first in 31 cancer registration points ([http://gzdaily.dayoo.com/html/2012-09/14/content\\_1895518.htm](http://gzdaily.dayoo.com/html/2012-09/14/content_1895518.htm)). Therefore, symptom care has become an important goal for nursing. Studies reported that the physical and psychological status were significantly improved by telephone counseling services (TCS). A survey recently conducted to explore the content of the TCS for colorectal cancer patients (Lin et al., 2014). Heidarnia et al. (2013) found that social determinants have significant effects in 5-year survival of cancers in terms of job, city region residency and having parents during childhood.

The current treatment regimens for colorectal cancer are extensive and may include surgery, chemotherapy, and radiation therapy. Cancer and treatment-related toxicities, such as fatigue, pain, sleep disturbance, and lack of appetite, are common in colorectal cancer patients and may affect the overall quality of life (Arndt et al., 2006).

Fatigue has been reported as the most prevalent symptom associated with cancer and cancer treatments (Curt et al., 2000; Lesage and Portenoy, 2002; Ahlberg et al., 2003). Cancer-related fatigue is defined as "a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual

functioning" by the National Comprehensive Cancer Network (Mock et al., 2000; National Comprehensive Cancer Network, 2003). Fatigue occurs at diagnosis and becomes increasingly prevalent with advanced cancer. It is also distressing and disruptive to disease-free survivors (Servaes et al., 2007). Fatigue occurs over a continuum, which range from tiredness to exhaustion. However, patients are often reluctant to report their fatigue for various reasons, including poor understanding of fatigue, belief that fatigue is inevitable and untreatable, and fear of distracting doctors from treatment of cancer (Stone et al., 2000; Ancoli-Israel et al., 2001; de Jong et al., 2002; Nail, 2002a; Payne, 2002; National Institutes of Health, 2011). The causes of fatigue are not well understood, but both cancer and the secondary effects of treatments contribute to fatigue. Anemia and poor nutrition frequently occur with colorectal cancer and anti-cancer treatments, but anemia is considered as the most important cause of fatigue (Dicato, 2003; Respini et al., 2013). Previous studies have demonstrated a significant association between fatigue severity and haematocrit (Lind et al., 2002; Prue et al., 2006; Kitano et al., 2007). Malnutrition, as a consequence of colorectal cancer, may cause anemia and affect functional status (Mustian et al., 2007). Capuano et al. reported that weight loss independently affected fatigue and quality of life (Capuano, 2008). Ravasco et al. (2005) observed low fatigue in colorectal cancer patients receiving intensive nutritional support and undergoing radiotherapy. Many studies have been conducted to seek alternative therapies to improve fatigue including physical

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trainings, psychological inventions, cognitive inventions and so on. He et al. (2013) retrospectively analysed the effect of acupuncture and moxibustion for fatigue.

Quality of life is an important concern for cancer patients. However, evidence have indicated that high degrees of fatigue during treatment can significantly reduce physical function and well-being (Jacobsen et al., 1999; Given et al., 2001; Mock et al., 2002; Nail et al., 2002b). To alleviate fatigue and further establish nursing interventions for colorectal cancer patients, the present study was conducted to explore the dynamic changes of fatigue in hospitalized patients. This study evaluates fatigue at varying periods during treatment and highlights the importance of interventions that are carefully tailored to patients based on the characteristics at different periods to alleviate fatigue.

## Materials and Methods

### Subjects

A total of 96 patients (56.25% with colon cancer and 43.75% with rectum cancer) participated in the study. All patients were recruited in over eight months in a tertiary general hospital in Guangzhou, China. The patients were eligible to participate if they were suffering from colon or rectum cancer and have been recently scheduled for surgery. The patients were 18 years old or older, possessed basic Chinese reading and writing skills, had known about their diagnosis, and had voluntarily participated in the study. The patients were excluded if they had known nothing of their disease, were reluctant to complete the questionnaires, had finished preoperative chemotherapy, were suffering from a combination of primary cancer and other serious illnesses, and had cognitive impairment that prevented data collection. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Guangzhou First Municipal People's Hospital. Written informed consent was obtained from all participants.

### Data collection

In this longitudinal study, data were collected within one week of admission and on 2 d to 3 d and 3 w after surgery. The time frame of the first measurement was chosen after considering the fact that patients are usually hospitalized for one or two weeks before surgery for preoperative examination. The patients were expected to experience the highest level of fatigue after surgery, and after considering if patients' physical condition can allow questionnaire completion, the second measurement was performed 2 d to 3 d after surgery. The study focused on the dynamic changes of fatigue in hospitalized patients; thus, we chose to perform the third measurement 3 w after surgery. Before data collection, the investigators explained the study by using unified guidance and obtained patients' written informed consent. In our polling circles, questionnaires were considered invalid if patients died, given up treatment, or refused to continue their participation in the study. Valid questionnaires of each polling circle were automatically scrolled to the next cycle for continuative investigation.

### Variables and measurement

The participants completed a demographic questionnaire at the first measurement, and the following data were collected: gender, age, education, marital status, and occupation. Clinical data included the type of cancer, type of chemotherapy, chemotherapy regimen, and histologic type.

Fatigue was assessed using the Cancer Fatigue Scale (CFS) within 1 w of admission, at 2 d to 3 d after surgery, and 3 w of surgery. The CFS has 15 items and three subscales, namely, physical fatigue, affective fatigue, and cognitive fatigue. A self-reported, five-point, and Likert-type scale (1=no to 5=very much) was used. The reliability coefficients of the CFS in two studies ranged from 0.84 to 0.88 for the total scale and from 0.76 to 0.89 for the subscales (Okuyama et al., 2000a, 2000b). Higher scores indicate higher levels of fatigue.

### Statistical analysis

Data were analyzed using IBM SPSS Statistics version 16.0. Descriptive statistics and frequencies were generated for demographic data and fatigue. Chi-square test was used to analyze the comparability of demographic data between two groups (colon cancer patients and rectum cancer patients). A general linear model was used to examine the dynamic changes of fatigue and between-subjects effects. Differences of fatigue between groups were analyzed using an independent-sample t test.

## Results

### Patients' characteristics

A total of 165 patients completed the questionnaires within one week of admission. At 2 d to 3 d and 3 w after surgery, 128 and 96 valid questionnaires were collected, respectively. The characteristics of the two groups are summarized in Table 1.

Demographic and clinical characteristics were not significantly different between the two groups ( $p>0.05$ ), and colon cancer patients and rectum cancer patients were comparable for fatigue symptoms.

### General linear model

A general linear model was used to determine the dynamic changes of fatigue. In the model, the dependent variable was fatigue, and the constant variables were time (the three measurement points) and group (54 colon cancer patients and 42 rectum cancer patients). The results showed that the time ( $F=214.604, p=0.000$ ) and the group effects ( $F=33.517, p=0.000$ ) were both significant. Figure 1 illustrates how the fatigue scores from the two groups of patients changed over the three measurement points. The mean fatigue scores of colon cancer patients were higher than those of rectum cancer patients. Two parallel curves indicated that the interaction between time and group effects was not significant.

### Fatigue over time

The means and standard deviations (SDs) of fatigue scores were 14.88 (SD=5.179) within one week of admission (N=96), 26.79 (SD=3.896) at 2 d to 3 d after

**Table 1. Demographic and Clinical Characteristics of two Groups**

Characteristics	Colon cancer (n=54)	Rectum cancer (n=42)	$\chi^2$	P
Gender				
Male	37(68.5%)	21(50%)	3.388	0.066
Female	17(31.5%)	21(50%)		
Age (rang), years				
<40	5(9.3%)	3(7.1%)	2.959	0.228
41~60	13(24%)	17(40.5%)		
>60	36(66.7%)	22(52.4%)		
Education				
Elementary	11(20.4%)	13(31%)	2.148	0.542
High	24(44.4%)	19(45.2%)		
Senior High	16(29.6%)	8(19%)		
College	3(5.6%)	2(4.8%)		
Marital status				
Married	52(96.3%)	39(92.9%)	0.566	0.452
Widowed	2(3.7%)	3(7.1%)		
Occupation				
Blue collar workers	13(24.1%)	14(33.3%)	2.468	0.481
Retired	29(53.7%)	23(54.8%)		
White collar workers	9(16.7%)	3(7.1%)		
Others	3(5.6%)	2(4.8%)		
Type of chemotherapy				
None	7(13%)	1(2.4%)	3.463	0.063
Intraoperative or postoperative chemotherapy	47(87%)	41(97.6%)		
Chemotherapy regimen				
None	7(13%)	1(2.4%)	6.558	0.161
Tegafur 1g	15(27.8%)	9(21.4%)		
Fluorouracil 0.5g	3(5.6%)	6(14.3%)		
Fluorouracil 1g	4(7.4%)	6(14.3%)		
Fluorouracil 1.25g	25(46.3%)	20(47.6%)		
Histologic types				
Low differentiated adenocarcinoma	8(14.8%)	5(11.9%)	2.319	0.509
Middle differentiated adenocarcinoma	43(79.6%)	31(73.8%)		
High differentiated adenocarcinoma	1(1.9%)	2(4.8%)		
Type adenomatous polyp and nasal endoscopy	2(3.7%)	4(9.5%)		

**Table 2. Significant Change in Fatigue Over Time: One-Way ANOVA tests (n=96)**

	Within one week of admission (1 <sup>st</sup> measurement)	Days 2~3 of surgery (2 <sup>nd</sup> measurement)	3 weeks of surgery (3 <sup>rd</sup> measurement)	F	P
Minimum	4	19	14		
Maximum	28	38	29		
Mean	14.88	26.79	20.44	192.627	0
SD	5.179	3.896	3.34		

**Table 3. Dynamic Change in Fatigue of Two Groups (n=96)**

Time	Group	n	Mean	SD	t	p
Within one week of admission	Colon cancer	54	16.65	5.166	4.1e09	0
	Rectum cancer	42	12.6	4.266		
Days 2~3 of surgery	Colon cancer	54	28	3.938	3.664	0
	Rectum cancer	42	25.24	3.275		
3 weeks of surgery	Colon cancer	54	21.06	3.483	2.092	0.039
	Rectum cancer	42	19.64	3.003		

between groups of colon cancer patients versus rectum cancer patients based on the analysis of independent-samples t test (Table 3).

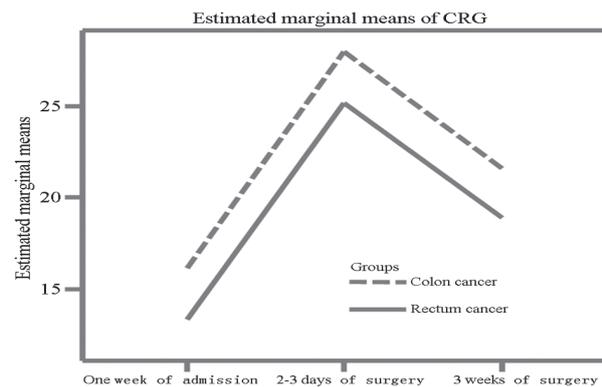
## Discussion

The results showed that colorectal cancer patients displayed different degrees of fatigue during hospitalization. Fatigue affects patients at different treatment periods and requires a dynamic and continual intervention tailored for patients.

The results of the present study are consistent with those of previous studies showing that patients experience different degrees of fatigue within treatments during hospitalization. The patients showed a mild level of fatigue one week before surgery as a consequence of cancer-related anemia. Anemia is a prevalent symptom among colorectal cancer patients. Digestive hemorrhage caused by the disease itself, hemolysis, and increased concentrations of cytokines are potential causes of impaired iron use that contribute to anemia. Tel et al. (2011) reported that patients with lower hemoglobin experienced higher level of fatigue. This finding suggests that anemia treatment may show beneficial effects on fatigue.

These results may be caused by the sample composition, which is mostly comprised of older patients. Age may have a particular negative effect on fatigue; thus, fatigue level is statistically higher 3 w after surgery than 1 w before surgery. Fatigue can affect disease-free survivors from months to years after completion of treatment. The results of a study conducted in 1957 comprising survivors of breast cancer showed that up to 30% of the patients reported persistent fatigue 3 yr after diagnosis (Bower et al., 2000).

Colorectal patients displayed higher fatigue severity after surgery possibly because colorectal cancer often requires invasive treatments that affect physical and psychological well-being and body image. On one

**Figure 1. Profile Plots**

surgery, and 20.44 (SD=3.34) at 3 w of surgery (Table 2). One-way ANOVA tests revealed a significant difference in fatigue scores among the three measurement points (F=192.627, p=0.000) (Table 2). The mean fatigue scores 2 d to 3 d after surgery were highest, followed by those 3 w after surgery. The lowest mean fatigue scores were obtained within one week of surgery. High scores indicated a higher level of fatigue.

### Fatigue in the two groups

Significant differences were observed in fatigue

hand, fatigue usually occurs after surgery when energy expenditure is reduced. On the other hand, loss of nutrients can contribute to the development of fatigue because of fasting and hypermetabolism that occur after surgery. Several prospective studies have determined the effect of improvements in nutritional state on the level of fatigue (Ahlberg et al., 2003). The findings of such studies suggest that fatigue increases when patients undergo radiation therapy, chemotherapy, and treatment with biological response modifiers. Fatigue has been reported by up to 80% of individuals treated with cytotoxic chemotherapy (Hofman et al., 2007). Deficiency of food intake is caused by side effects of chemotherapy, such as anorexia, nausea, vomiting, and hypogeusia, which contribute to the increase in malnutrition, thereby inducing the development of fatigue.

A significant difference was found in fatigue severity between the group of patients with colon cancer versus patients with rectum cancer ( $p < 0.05$ ). The surface of tumor differs from the normal appearance of the large intestine, such that bleeding can easily occur with the friction created by the movement of the stool over the tumor. Stool is always formed as a solid in the low colon; thus, hematochezia is the most prevalent symptom in patients with left hemi-colon carcinoma and rectum cancer. The stool in the right hemi-colon is still semi-fluid; thus, less bleeding occurs. Moreover, the color change caused by a low amount of blood mixed in the stool is imperceptible to patients. Moreover, the sample was composed of many older individuals who can hardly detect hematochezia because of decreased reaction and sensitivity. Further bleeding may be evident in dark red to black stool because patients have presented anemic symptoms. Published studies have revealed that anemia was more prevalent in patients with right hemi-colon cancer. Fatigue is a well-recognized symptom of anemia. The mean score of fatigue in colon cancer patients was higher than that in rectum cancer patients.

Several limitations in this study are as follows. The generalization of the results is limited by the small number of patients, who were all recruited in only one hospital, and the use of a convenience sample. Additionally, ethical considerations ruled out recruitment of patients who felt too sick or tired after surgery. Considering that this sample was composed of patients with colorectal cancer in a hospital, an attrition rate of 53% for nearly one month was expected. Elisabeth et al. reported a similar loss (49%) for nearly two weeks (Spichiger et al., 2012). The high attrition rate, however, must be considered as a risk factor when interpreting the changes over time.

Further studies should determine the potential correlation between fatigue in patients and colorectal cancer at each stage of hospitalization and if malnutrition is a dependent predictor of fatigue. Finally, the side effects of anti-cancer treatments on the occurrence of fatigue among patients must be studied.

This work is the first longitudinal study that investigates fatigue in colorectal cancer patients during hospitalization in a tertiary general hospital by using a general linear model for data analysis. Different degrees of fatigue at different periods of treatment can interfere with quality of

life such that psychiatric symptoms may occur. Moreover, the ability to cope with treatment side effects, physical functions, and confidence of overcoming illness are lower. A greater understanding of colorectal cancer-specific factors that may predict fatigue can lead to better clinical interventions.

Informing patients of the risk factors that may induce fatigue is important. Hospitals should provide effective interventions to help patients understand fatigue and deal with fatigue through the treatment stages. Nursing interventions should be specifically tailored to patients at different periods of hospital stays, especially to those who underwent surgery or chemotherapy.

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