

RESEARCH ARTICLE

Patient and Clinical Variables Account for Changes in Health-related Quality of Life and Symptom Burden as Treatment Outcomes in Colorectal Cancer: A Longitudinal Study

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Abstract

Objective: The aim of the current study was to evaluate changes in treatment outcomes in terms of health-related quality of life (HRQoL) and symptom burden at zero, one, three, and six months after an initial diagnosis of colorectal cancer. The demographic and clinical characteristics that account for outcome changes in patients were investigated using a repeated measures framework. **Methods and Materials:** A cohort study was performed of 134 colorectal cancer patients followed from diagnosis to 6 months post-treatment in Central Taiwan. HRQoL and symptoms were assessed at diagnosis and one, three, and six months thereafter. The Functional Assessment of Cancer Therapy-Colon (FACT-C) questionnaire, VAS pain, and the Memorial Symptom Assessment Scale (MSAS) were used for data collection. A generalized estimating equation (GEE) was applied for statistical analysis. **Results:** The majority of the patients were male (55%) and married (91.5%). The mean age was 60.4 years (SD = 11.71). Most were diagnosed stage III and IV colorectal cancer (54.5%). All underwent surgery; some also received chemotherapy (CT) or concurrent chemoradiation therapy (CCRT). The results of the GEE showed that overall, the HRQoL, pain, and symptoms of the patients significantly improved over the treatment period. Patients with stage IV disease who had received surgery and CCRT showed the worst HRQoL. Females, patients with comorbidity, and stage IV patients had higher pain scores over time. Female and stage IV patients had more severe physical symptoms, whereas stage II and IV patients had worse psychological symptoms over time. **Conclusion:** The patients' HRQoL, pain, and symptoms significantly improved over the 6-month treatment period. Certain patient and clinical variables accounted for changes in treatment outcomes regarding HRQoL and symptom burden in colorectal cancer patients.

Keywords: HRQoL - pain - symptom - outcomes - colorectal cancer - GEE - Taiwan

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Introduction

The incidence of colorectal cancer (CRC) has increased in Western countries (Ferlay et al., 2010). In Taiwan, colorectal cancer is the most diagnosed cancer in both men and women (DOH, 2013) and accounts for over 10,000 new cases annually. Survival after colorectal cancer has increased since the implementation of earlier detection programs in Taiwan. The current treatment regimens for colorectal cancer are extensive and can include surgery and/or chemotherapy and radiation therapy (Cunningham et al., 2010). Disease- and treatment-related adverse effects, such as pain and other symptoms, are very common in patients with colorectal cancer and often result in a reduced overall quality of life (QoL) (Arndt et al., 2006; Burton et al., 2007; Chou et al., 2007; Sun et al., 2012).

Outcome data following the effects of extensive treatments on HRQoL and symptom burden over the first six months in colorectal cancer survivors are limited. Additionally, demographic and clinical factors related to changes in treatment outcomes over time have been rarely studied. Research suggests that the health status of colon cancer survivors improves over time since diagnosis (Schneider et al., 2007; Phipps et al., 2008). However, research with small sample sizes, of a cross-sectional nature, and using non-validated questionnaires necessitates the cautious interpretation of these results.

To better define the changes in HRQoL and symptom burden during the first six months of treatment following initial diagnosis and to examine the effects of demographic and clinical variables on these changes, a multivariate repeated measures framework was applied in the current study.

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Materials and Methods

In this descriptive and longitudinal cohort study, 134 confirmed colorectal cancer patients received surgery, chemotherapy, and/or radiation therapy. The study was conducted from November 2009 to July 2012. Patients were recruited from clinics at three major hospitals in central Taiwan. Patients were enrolled before receiving treatment for colon or rectal cancer in the clinics. The inclusion criteria were the following: (a) 18 years or older; (b) newly diagnosed primary colorectal cancer and scheduled to receive treatment; (c) no other cancers; and (d) ability to communicate in Mandarin or Taiwanese. In general, once patients were diagnosed with colorectal cancer, they were scheduled for surgery within a week. Surgical patients were given 2-3 weeks for recuperation prior to cycles of chemotherapy or CCRT. Within six months, the patients had completed all treatments as expected.

This study was approved by the institutional review boards of the university and hospitals (no: S09125) located in central Taiwan. Eligible patients were invited to participate. Information related to the study and consent forms were signed prior to data collection. HRQoL and symptom burden were assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) standard questionnaire and the Memorial Symptom Assessment Scale (MSAS). Pain was measured with a Visual Analog Scale of pain (VAS pain).

The Functional Assessment of Cancer Therapy-Colon (FACT-C) questionnaire was employed to measure health-related quality of life in the colorectal cancer patients (Cella et al., 1993). The FACT-C consists of 36 items (Ward et al., 1999). Participants rated these items on a five-point scale for each of the following subscales: physical (7 items), social/family (7 items), emotional (6 items), functional well-being (7 items) and colon-specific symptoms (9 items). Each subscale score was calculated by taking the sum of the item scores and dividing by the number of items answered. The subscale scores were added to derive a FACT-C total score. Higher scores indicate a better QoL. The FACT-C has been well tested in cancer survivors and found to be reliable, valid and responsive (Ward et al., 1999). The Cronbach α of FACT-C is 0.81, and the individual subscale reliabilities of this study ranged from 0.70 to 0.82.

The visual analog scale of pain (VAS pain) is used for measuring pain intensity. To indicate pain intensity, the VAS consists of a 100-mm straight-line continuum with anchors at each end, representing no pain at the lower end of the scale and the severest possible pain at the upper end of the scale. Patients were asked to indicate the intensity of pain by moving an adjustable marker along the scale. Reliability and validity have been demonstrated satisfactorily for VAS pain (Grossman et al., 1992).

The Memorial Symptom Assessment Scale (MSAS) (Portenoy et al., 1994) was used to quantify the symptom experiences of the cancer patients. The MSAS is a self-rating tool comprised of 32 four-point Likert-type items that capture frequency (1: rarely to 4: almost constant) on physical and psychological subscales. The MSAS is

frequently applied to cancer patients, and its psychometric properties have been established by the developer. The physical symptom subscale and psychological subscale had a reliability coefficient estimate from 0.86 to 0.90 in this study.

The generalized estimating equation (GEE) method with an exchangeable structure for repeated data measures was used to examine the factors associated with changes in HRQoL, pain, and symptoms (at diagnosis, 1, 3, 6 months). We used the GEE approach to consider within-person variability and account for the correlated data resulting from repeated measurements across different time points and multiple observations of the same individual (Zeger & Liang, 1986). Its main advantage is its robustness against the working correlation structure, which must be assumed to be correct for within-subject correlations. The scores of health-related quality of life, symptoms, and pain scores at four-point follow-ups were used as dependent variables. The age, marital status, education level, and gender of the patients were used as explanatory variables in addition to the type of treatment (OP, OP+CT, OP+CCRT), cancer stage, location of cancer, comorbidity, and time. The data were analyzed using SPSS (version 19.0 for Windows, Chicago, IL).

Results

Table 1 shows the demographic and clinical characteristics of the patients. The majority of the patients were male (55%), married (91.5%), and had an education level of high school or less (59%). The mean age was 60.39 years (SD = 11.71). Among the patients, 55% were diagnosed at the third or fourth stage of colorectal cancer (54.5%). Patients received surgery (35.5%) or a combination of surgery and chemotherapy (46.3%).

Figure 1 plots the mean scores of the outcome variables at the time of diagnosis and at 1, 3 and 6 months following treatment. For all treatment outcomes, patients deteriorated at 1 month during surgery and/or

Table 1. Demographic and Clinical Characteristics of Colorectal Cancer Patients

Variable	n	%
Age (mean±SD)	60.39	12.6
Gender	Male	53.7
	Female	46.3
Married	Yes	91
	No	9
Education level	No education	20.9
	High & less	59
	Academic (³ college)	20.1
Comorbidity	Yes	37.3
	No	62.7
Cancer location	Colon	54.5
	Rectum	45.5
Stage of cancer (TNM)	I	13.4
	II	29.9
	III	49.3
	IV	7.5
Treatment	OP	35.5
	OP+CT	46.3
	OP+CCRT	17.9

Table 2. Demographic and Clinical Variables Account for HRQoL, Pain, and Symptoms in Patients with Colorectal Cancer using Generalized Estimating Equations

Variable	HRQoL B/SE	Pain B/SE	Physical symptoms B/SE	Psychological B/SE
Gender (male vs. female)	-4.05 (2.73)	7.04 (9.53)**	0.12 (0.06)*	-0.12(0.09)
Edu (academic vs. no edu)	7.41 (4.30)	-2.93 (4.00)	-0.12 (0.08)	-0.01(0.13)
(high & less vs. no edu)	4.55 (3.58)	-3.07 (3.10)	-0.07 (0.07)	0.13(0.11)
Married (yes vs. no)	-2.58 (4.44)	3.85 (4.46)	0.13 (0.07)	0.14(0.13)
Comorbidity (yes vs. no)	-0.84 (2.69)	-5.79 (2.75)*	-0.03 (0.05)	-0.01(0.08)
Location (colon vs. rectal)	-4.25 (2.86)	3.60 (3.00)	0.04 (0.05)	0.10(0.08)
Cancer stage (IV vs. I)	-15.16 (7.34)*	17.23 (5.70)***	0.50 (0.17)**	0.66(0.20)***
(III vs. I)	1.10 (4.31)	-1.56 (4.51)	0.04 (0.08)	0.17(0.13)
(II vs. I)	-0.44 (4.02)	0.98 (3.91)	0.10 (0.07)	0.26(0.12)*
Treatment (OP+CCRT vs. OP)	-7.89 (3.86)*	6.68 (4.14)	0.01 (0.08)	-0.09(0.11)
(OP+CT vs. OP)	-6.78 (3.88)	1.74 (3.81)	0.08 (0.09)	0.02(0.15)
Time 4 vs. 1	-4.32 (1.57)***	1.16 (2.49)	0.13 (0.05)**	0.06(0.07)
Time 3 vs. 1	-10.43 (1.70)***	8.06 (2.56)**	0.18 (0.05)***	0.07(0.07)
Time 2 vs. 1	-11.30 (1.80)***	16.05 (2.54)***	0.23 (0.04)***	0.24(0.08)***
Age	-0.04 (0.12)	-0.18 (0.12)	0.01 (0.01)	-0.01(0.01)
Constant	92.44 (9.52)***	28.27 (9.53)**	0.31 (0.20)	0.44(0.32)

* $p < .05$; ** $p < .01$; *** $p < .001$

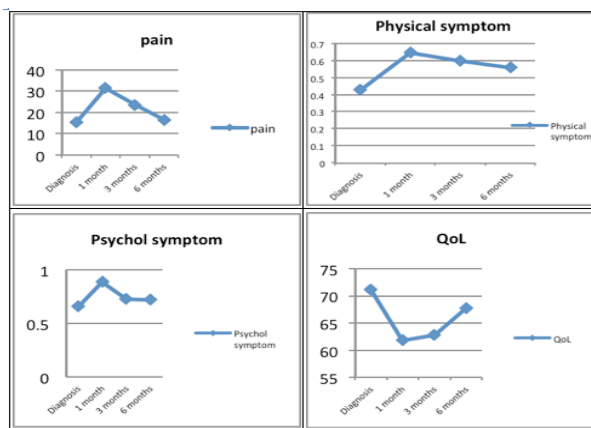


Figure 1. Mean Scores of Treatment Outcomes at Diagnosis, during Treatment (1- month, 3-months) and after Recovery (6-months)

chemotherapy but improved at 6 months. However, these outcomes did not reach the level that was observed at the time of diagnosis.

The results of the GEE (Table 2) showed that the HRQoL of the patients at 1, 3, 6 months was generally significantly worse than at diagnosis, and their physical symptoms significantly improved over time ($p < 0.001$). Patients had higher pain scores at 1-month and 3-months compared to that at diagnosis, and the pain score at 6-months were not significantly different from that at the time of diagnosis. The type of cancer treatment received had no effect on the pain score. Patients had more psychological symptoms at 1-month of treatment than at diagnosis, but those symptoms were not different between diagnosis, 3-months and 6- months.

Relationships were identified between certain demographic and clinical variables and treatment outcomes over time. The results of the GEEs demonstrated that females, patients with comorbidity and stage IV patients experienced more pain over time. Female and stage IV patients showed worse physical symptoms, and stage IV and II patients had worse psychological

symptoms over time. Patients with stage IV disease who received surgery and CCRT had the worst health-related quality of life during the study period.

Discussion

In the current study, GEEs were used to identify the characteristic demographic and clinical factors that affect patient treatment outcomes over time with respect to HRQoL, pain, and symptoms. The results showed that the patients' HRQoL, pain, and symptoms were generally compromised at 1-month and 3-months (during treatment) but improved at 6-months after treatment.

The improvement of HRQoL over time in patients with colorectal cancer was also shown in a previous study (Bouvier et al., 2008; Hulbert-Williams et al., 2012; Sun et al., 2012). Our results also demonstrated that colorectal cancer patients show deterioration in HRQoL during the treatment period. One possible explanation for this is the more severe side effects experienced during treatment. However, Bouvier (2008) documented that adjuvant chemotherapy for colon cancer has no long-term negative impact on the QoL of elderly patients. The increased deterioration in HRQoL during treatment and improvement in the longer-term need to be documented in future population-based studies.

Health-related quality of life (HRQoL) is now considered to be an important outcome of cancer management. Our study found that patients with stage IV disease who received surgery and CCRT had the worst HRQoL over time. Recent studies reported that colorectal cancer patients in stage IV were associated with a lower HRQoL (Färkkilä et al., 2013; Nuhu et al., 2013). Patients with advanced colorectal cancer often receive more aggressive cancer therapies that could have more side effects, thereby potentially having a negative impact on the perceived HRQoL. Cancer survivors experience numerous disease and treatment-related adverse outcomes and a poorer health-related quality of life (HRQoL). Exercise

interventions are recommended to alleviate these adverse outcomes and might have beneficial effects on the HRQoL of cancer patients (Mishra et al., 2012).

Approximately 70% of cancer patients experience pain (Nuhu et al., 2013). Our study verified that patients had higher pain scores during the treatment period, and this pain decreased to near the baseline level at the end of therapy. This finding is consistent with studies of pain trajectories during chemotherapy in outpatients with colorectal cancer, in which pain deteriorated during the initial period of treatment and further decreased after each treatment cycle (Brant et al., 2011; Green et al., 2010). Cancer pain is associated with cancer or its treatment and significantly decreases health and quality of life. Cancer pain assessment and adequate pain treatment to minimize suffering are essential in cancer care. Moreover, we found that females, patients with comorbidity and stage IV patients had higher pain scores over time. Interestingly, the type of cancer treatment received had no effect on the pain scores over time.

Our study documented that patients had significantly worse physical symptoms after 1-month, 3-months, and 6-months of treatment than at the time of initial diagnosis. This finding is consistent with a limited number of studies on physical symptoms (Reyes-Gibby et al., 2007; Brant et al., 2011). One possible explanation for the increase in severity of symptoms is the severe side effects that result from cancer treatments, including surgery, chemotherapy or CCRT. Furthermore, female and stage IV patients showed worse physical symptoms. One explanation for this could be that the women and stage IV patients are more concerned about the effects of the disease and the treatments thus showing more physical symptoms than other patients. This finding suggests that some patients beginning cancer treatment may require supportive care early in the disease/treatment process.

Clinical psychological symptoms (mainly anxiety and depression) are apparent in one-third of cancer patients (Maguire, 2000; Nuhu et al., 2013) and can remain problematic for many years (Sukantarat, 2004). We found that patients at one month after initial diagnosis showed more symptoms and that those symptoms gradually decreased at 6-months, as treatment became completed. Those results are consistent with recent studies (Stommel et al., 2004; Hulbert-Williams et al., 2012). However, anxiety and depression incidence was low in our study, indicating a relatively psychologically stable sample at recruitment.

Our study revealed that stage II and IV patients showed worse psychological symptoms than stage I patients over time. We found no relationship between cancer treatment types and psychological symptoms. Nonetheless, a recent study reported that patients who received surgery and chemotherapy or surgery plus CCRT showed higher levels of depression and anxiety when compared with patients receiving surgery alone (Graça Pereira et al., 2012). However, there is a shortage of evidence of the effects of disease variables on psychological well-being in this population. Regardless, this study highlights the importance of providing psychological intervention for cancer patients, particularly those in stage II and IV and

who have received cancer treatment, as they are more at risk.

The results of this study should be interpreted with consideration of the following limitations. The small number of participants might limit the generalization of these results to other settings, as these patients may not be representative of all colorectal patients in Taiwan. Moreover, patients were followed only for 6 months from the initial diagnosis, which does not include the long-term effects of cancer treatments. We suggest that studies with longer follow-up periods and more detailed data on demographic and socio-economic characteristics are necessary to explain HRQoL, pain and symptoms in these patients more precisely and to inform decision-making in cancer treatment.

In summary, although patients had worsened levels of pain, symptom burden, and HRQoL at 1-month and 3-months of cancer treatment, those levels gradually improved in the recovery phase at 6-months but were still worse than at diagnosis. This finding implies that the cancer itself and the treatment regimens compromised the patients' health-related quality of life and increased the symptom burden. Patients with stage IV cancer who received surgery and CCRT had the worst HRQoL than patients at other stages. Females, patients with comorbidity, and stage IV patients had higher pain scores. Female and stage IV patients had more severe physical symptoms; stage II and IV patients had worse psychological symptoms over time.

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References

- Arndt V, Merx H, Stegmaier C, et al (2006). Restrictions in quality of life in colorectal cancer patients over three years after diagnosis: a population based study. *Eur J Cancer*, **42**, 1848-57.
- Bouvier AM, Jooste V, Bonnetain F, et al (2008). Adjuvant treatments do not alter the quality of life in elderly patients with colorectal cancer: a population-based study. *Cancer*, **13**, 879-86.
- Brant JM, Beck SL, Dudley WN, et al (2011). Symptom trajectories during chemotherapy in outpatients with lung cancer, colorectal cancer, or lymphoma. *Eur J Oncol Nurs*, **15**, 470-7.
- Burton AW, Fanciullo GJ, Beasley RD, et al (2007). Chronic pain in the cancer survivor: a new frontier. *Pain Med*, **8**, 189-98.
- Cella DF, Tulsky DS, Gray G, et al (1993). The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*, **11**, 570-9.
- Chou FY, Dodd M, Abrams D, et al (2007). Symptoms, self-care, and quality of life of Chinese American patients with cancer. *Oncol Nurs Forum*, **34**, 1162-7.
- Cunningham D, Atkin W, Lenz HJ, et al (2010). Colorectal cancer. *Lancet*, **375**, 1030-47.

- Department of Health Taiwan (2013). http://www.doh.gov.tw/cht2006/DM/DM2_p01.aspx?class_no=25&now_fod_list_no=11574&level_no=2&doc_no=79122
- Färkkilä N, Sintonen H, Saarto T, et al (2013). Health-related quality of life in colorectal cancer. *Colorectal Dis*. doi: 10.1111/codi.12143.
- Ferlay J, Parkin DM, Steliarova-Foucher E (2010). Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer*, **46**, 765-81.
- Graça Pereira M, Figueiredo AP, Fincham FD (2012). Anxiety, depression, traumatic stress and quality of life in colorectal cancer after different treatments: A study with Portuguese patients and their partners. *Eur J Oncol Nurs*. **16**, 227-32.
- Green CR, Hart-Johnson T (2010). Cancer Pain: An Age-Based Analysis. *Pain Med*, **11**, 1525-36.
- Grossman SA, Sheidler VR, McGuire DB, et al (1992). A comparison of the Hopkins pain rating instrument with standard visual analogue and verbal descriptor scales in patients with cancer pain. *J Pain Symptom Manage*, **7**, 196-203.
- Hulbert-Williams N, Neal R, Morrison V, et al (2012). Anxiety, depression and quality of life after cancer diagnosis: what psychosocial variables best predict how patients adjust? *Psycho Oncol*, **21**, 857-67.
- Maguire P (2000). Managing psychological morbidity in cancer patients. *Eur J Cancer*, **36**, 556-8.
- Mishra SI, Scherer RW, Geigle PM, et al (2012). Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev*, **8**, CD007566.
- Nuhu FT, Adebayo KO, Adejumo O (2013). Quality of life of subjects with cancers in Ibadan, Nigeria. *J Ment Health*. [Epub ahead of print]
- Phipps E, Braitman LE, Stites S, et al (2008). Quality of life and symptom attribution in long-term colon cancer survivors. *J Eval Clin Pract*, **14**, 254-8.
- Portenoy RK, Thaler HT, Kornblith AB, et al (1994). The Memorial Symptom Assessment Scale: An instrument for the evaluation of symptom prevalence, characteristics, and distress. *Eur J Cancer*, **30A**, 1326-36.
- Reyes-Gibby C, Chan W, Abbruzzese J, et al (2007). Patterns of self-reported symptoms in pancreatic cancer in patients receiving chemoradiation. *J Pain Symptom Manage*, **34**, 244-52.
- Schneider EC, Malin JL, Kahn KL, et al (2007). Surviving colorectal cancer: patient-reported symptoms 4 years after diagnosis. *Cancer*, **110**, 2075-82.
- Stommel M, Kurtz ME, Kurtz JC, et al (2004). A longitudinal analysis of the course of depressive symptomatology in geriatric patients with cancer of the breast, colon, lung, or prostate. *Health Psychol*, **23**, 564-73.
- Sukantarat K, Greer S, Brett S, et al (2004). Physical and psychological sequelae of critical illness. *Br J Health Psychol*, **12**, 65-74.
- Sun V, Borneman T, Koczywas M, et al (2012). Quality of life and barriers to symptom management in colon cancer. *Eur J Oncol Nurs*, **16**, 276-80.
- Ward WL, Hahn EA, Mo F, et al (1999). Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. *Qual Life Res*, **8**, 181-95.
- Zeger SL, Liang KY (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*, **42**, 121-30.