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Health-Related Quality of Life and Oncologic Outcomes after Surgery in Older Adults with Colorectal Cancer

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Abstract

Purpose: Data regarding changes in functional status and health-related quality of life (HRQOL) before and after surgery are lacking. We identified colorectal cancer patients from the SEER-Medicare Health Outcomes Survey (MHOS) linked database to evaluate the association between HRQOL and survival.

Methods: HRQOL survey data captured physical/mental health, activities of daily living (ADLs), and medical comorbidities. Patients who underwent surgery with HRQOL surveys prior to cancer diagnosis and ≥1 year after diagnosis were selected. Patient, disease, and HRQOL measures were analyzed in regard to overall survival (OS), disease-specific survival (DSS), and non-DSS.

Results: Of 590 patients included, 55% were female, 75% were Caucasian, and 83% had colonic primary. Disease extent was localized for 52%, regional for 41%, and distant for 7%. Median OS was 83 months. Decreased OS was independently associated with age ≥75 (HR 1.7, $p<0.0001$), male sex (HR 1.4, $p=0.011$), advanced disease (regional: HR 2.0, $p<0.0001$; distant: HR 7.0, $p<0.0001$), and decreased mental HRQOL (HR 1.4, $p=0.005$). Decreased DSS was independently associated with advanced disease (regional: HR 4.1, $p<0.0001$; distant: HR 16.5, $p<0.0001$) and rectal primary (HR 1.6, $p=0.047$). Decreased non-DSS was independently associated with age ≥75 (HR 2.2, $p<0.0001$), male sex (HR 1.4, $p=0.03$), decreased mental HRQOL (HR 1.4, $p=0.02$), and increased comorbidities (HR 1.4, $p=0.04$).

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CONFLICT OF INTEREST

The authors have no conflicts of interest or funding sources to report in relation to this work.

DATA SHARING

All data used in this manuscript were derived from the SEER-MHOS combined dataset, which is subject to data use agreements managed by the National Institutes of Health.

Conclusions: The potential overall survival benefit of oncologic surgery is diminished by declines in physical and mental health. Early identification of older surgical patients at-risk for functional and HRQOL declines may improve survival following colorectal cancer surgery.

Keywords

Quality of life; functional status; geriatric oncology; colorectal cancer

INTRODUCTION

In the United States, the proportion of the population at least 65 years of age has been steadily increasing since 1980 and is expected to approach 20% by the year 2030 [1]. As the population ages, the incidence of cancer is also projected to increase over time [2]. The majority of patients with a cancer diagnosis will undergo surgery as a component of their care, and for many, surgical resection represents the best opportunity for cure. The need for and extent of surgery in treating cancer among older adults is without consensus as evidenced by multiple studies evaluating the use and efficacy of minimally invasive surgery to maximize the benefits of resection while minimizing its attendant morbidity [3, 4].

Multiple considerations must be taken when evaluating older patients' appropriateness for surgical resection, since outcomes of the operation are not just dependent on tumor biology but perhaps equally as much on patient-centered factors, such as health-related quality of life (HRQOL), medical comorbidities, frailty, functional status, and fall risk [5]. Assessment tools of these complementary factors together provide the most complete picture of a patient's well-being. Comorbidities represent significant and often chronic medical conditions, which may represent the patient's ability to recover from an operation since they reflect the patient's physiologic rather than chronologic age [6]. Frailty assessment measures the patient's physiologic reserve and associated vulnerability to stressors such as surgical complications [7]. Functional status evaluates the patient's ability to perform everyday tasks of self-care [8]. A history of falls or increased risk thereof indicates poorer physical and mental health [9, 10]. Each of these constructs independently predicts outcomes following surgery [11–14].

Older surgical patients with cancer represent one of the most vulnerable patient populations. The coexistence of advanced age, comorbidities, frailty, and impaired functional status incurs increased risk of post-operative complications, delayed recovery, and need for additional care [15, 16]. Although the incidence of colorectal cancer is third in the United States, patients over 65 years of age remain an understudied survivorship population [17]. Studies show that colorectal cancer survivors experience declines in physical health and functional status when compared to healthy age-matched controls [13]. Our previous work has shown that gastrointestinal cancer patients report immediate declines in physical function after surgery, with slow recovery and potential for persistent impairment well after the operation [18]. An improved understanding of the relative impact of patient-centered factors on survival following surgery among older adults with colorectal cancer may better identify at-risk patients and potential target areas for perioperative interventions. Using the Surveillance, Epidemiology, and End Results (SEER) program and the Medicare Health

Outcomes Survey (MHOS) linked data resource, we studied functional impairments and HRQOL before and after surgery in older adults (65 years and older) with colorectal cancer and compared changes in outcomes with survival.

METHODS

We applied for and obtained data from a linked resource of the SEER program and the MHOS database. The SEER-MHOS linked data resource is jointly managed by the National Cancer Institute (NCI) and the Centers for Medicare and Medicaid (CMS). The data set links SEER cancer registry data and patient-reported outcomes (PROs) from the MHOS obtained from a nationwide sample of Medicare Advantage Organization enrollees aged 65 years and older. The MHOS has been continuously recruiting yearly cohorts since 1998. The study randomly samples Medicare Advantage enrollees with survey administration by mail or telephone, with follow-up surveys at 2 years [19, 20]. Combined, the SEER-MHOS dataset describes HRQOL outcomes for older cancer patients.

Sample

We identified colorectal cancer survivors who underwent surgery from 15 yearly cohorts (1998-2014) of the SEER-MHOS data resource. Survivors with a first diagnosis of colorectal cancer were included. A subset of survivors who had completed HRQOL surveys both before diagnosis (i.e. baseline) and at least one year after diagnosis (i.e. follow-up) were selected for longitudinal analysis. We chose one year post-diagnosis as sufficient elapsed time to account for treatment around the time of surgery and post-operative recovery, since timing of treatment was not available from the dataset. We did not limit how long before diagnosis the baseline survey could have been completed, leading to the first time interval of median 12 months. The time after diagnosis was specified to be at least one year but again with no time limit, leading to the time interval of median 25 months. Survivors whose responses were from proxy respondents or who had more than one missing ADL response were excluded.

Under the Health Insurance Portability and Accountability Act (HIPAA) of 1996, SEER-MHOS data are exempt from additional informed consent and are considered a limited dataset. All survivors who participated in the MHOS provided informed consent at initial survey. In accordance with HIPAA policies, investigators for this analysis completed signed user agreement forms prior to receiving the data.

Measures

Demographic characteristics obtained through the SEER cancer registry linked cases included age, sex, marital status, race/ethnicity, education level, and income. Comorbidities considered included heart conditions (angina, myocardial infarction, or congestive heart failure), stroke, chronic obstructive pulmonary disease, diabetes, and inflammatory or irritable bowel conditions. Disease-specific characteristics included stage of disease (localized, regional, or distant) and primary tumor location (colon or rectum).

The MHOS evaluates HRQOL using the Medical Outcomes Study 36-item Short Form (SF-36) for HRQOL from 1998-2005, and the VR-12 from 2006 onward [21]. The SF-36

and VR-12 contain items that measure physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, mental health, role limitations due to emotional problems, and social functioning. The measures yield two summary scores: physical component summary (PCS) and mental component summary (MCS) [22]. The SF-36 has been applied and validated in colorectal surgery populations.[23, 24]

The adapted Katz activities of daily living (ADL) index was used to assess functional limitations. The index ranks adequacy of performance by level of difficulty (no difficulty; a little difficulty; a lot of difficulty) in the following six functions: bathing, dressing, toileting, transferring, continence, and feeding. An aggregate score of 6 indicates full function, 3-4 indicates moderate impairment, and 2 or less indicates severe functional impairment [8, 25].

Beginning in 2003, questions from the Centers for Disease Control and Prevention (CDC) Healthy Days Module on the number of days of poor physical and mental health in the past month were added to the MHOS. Previous research shows that the number of unhealthy days questions have been linked to greater hospitalization and mortality.[20] Ranges for this question include 0, 1-13, and 14 days (14 is the threshold considered as frequent mental distress) [26]. Beginning in 2006, questions from the National Committee for Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) on falls and fall risk management were added. These questions include: 1) number of falls in the past 12 months; 2) gait or balance issues; and 3) patient-provider discussion on fall risk management.

The date of death variable (missing if alive at last follow-up) from the original dataset was used to code participant survival as alive or deceased. Together, survival and the SEER cause-specific death classification variables were utilized to classify cause of death into three categories: alive, dead from colorectal cancer, or dead from other cause.

Statistical Analysis

SAS 9.4 (SAS Institute, Cary, NC) was used for analysis. A two-sided p-value <0.05 was considered significant.

Patient demographics and disease characteristics were presented as summary statistics. Categorical variables were reported as percentages and continuous variables as means with standard deviation (SD). The six ADLs were reported as the composite Katz score, dichotomized to moderate/severe or minor/no impairment. Comorbidities were summed. Mental and physical HRQOL scores were dichotomized using the population mean.

Baseline and follow-up data were compared to evaluate changes in the Katz score, total comorbidities, and mental and physical HRQOL. Subset analyses were performed for patients in the SEER-MHOS enrolled as of 2003 and as of 2006 for the number of mental and physical ‘bad days’ and gait and fall issues, respectively. McNemar’s test was used to compare frequencies, and the Generalized Estimation Equations were used for comparison, adjusting for covariates.

Kaplan-Meier method was used to estimate the overall survival functions, and groups were compared by the log-rank test. For overall survival, univariate analysis using Cox regression

was performed to assess the risk factors. Step-wise multivariate analysis was performed by successively including the most significant variable ($p<0.05$) given those significant variables already in the model until no further significant variables could be included. Non-significant variables were then successively removed in a step-wise manner starting from the least significant ($p>0.05$), followed by further testing individually the significance of the non-included variables to obtain a parsimonious multivariate model. The risk factors for disease-specific and non-disease-specific survival were assessed similarly using Fine and Gray proportional sub-distribution hazards models accounting for competing risks.

RESULTS

We identified a total of 1,175 older adults with a primary diagnosis of colorectal cancer from the linked data resource, of whom590 patients (50.2%) were eligible to be included based on our selection criteria. Of the 590 patients included in analysis (Table 1), 55% were female, 75% were Caucasian, 56% were married, 20% completed four years of college, and 53% were diagnosed with colorectal cancer at ≥75 years of age. Overall, 52% had localized disease, whereas 41% had regional lymph node involvement, and 7% had distant disease dissemination. Among 482 patients with income data, 18% reported annual income greater than $50,000.

Comparison of baseline to follow-up PROs

The median time from baseline survey to diagnosis was 12 months, and the median time from baseline survey to follow-up survey was 25 months. Katz ADL composite score was 5.3 (SD ±1.3) at baseline and declined for 17% of patients from baseline to follow-up ($p=0.0005$, adjusted for age, education, and stage). Of 580 patients with complete comorbidity survey data, 27% reported an increase in number of comorbidities ($p<0.0001$, no significant covariates). Physical HRQOL was at or above the population mean for 31% of patients and declined for 54% between baseline and follow-up ($p<0.0001$, adjusted for age and education). Mental HRQOL was at or above the population mean for 68% of patients at baseline, with 44% of patient reporting a decline on follow-up survey ($p=0.083$, adjusted for marital status, race, and education) (Table 2).

Subset analyses showed no significance difference in either the number of days of poor physical health between baseline (5.2±10.1) and follow-up (5.5±9.4; $p=0.29$, adjusted for race, education, and stage), or the number of days of poor mental health (2.5±7.6 at baseline to 2.8±7.6 at follow-up; $p=0.41$, adjusted for income).

Overall survival

Median overall survival was 83 months. On univariate analyses, decreased survival was significantly associated with older age, more advanced disease stage, decline in Katz score, and increase in comorbidities. Patient sex, socioeconomic factors, primary tumor location, and physical HRQOL were not significantly associated with overall survival. Multivariate analysis showed that patient age ≥75 years, Caucasian race, male sex, with advanced disease stage, and a decline in mental HRQOL were independently significantly associated with decreased overall survival (Table 3). Overall survival curves for the population stratified by

change in comorbidities and mental HRQOL are shown (Figures 1A, 1B). Stratification was included in order to visually represent how survival differed between groups based on patient-centered outcomes that were independently associated with survival.

An increase in the number of days with poor physical health was significantly associated with decreased overall survival (HR 1.7, p=0.007), as well as patient age ≥75 (HR 1.6, p=0.011) and regional or distant disease involvement (HR 2.5 and HR 12.8, respectively, p<0.0001; referent: localized). Number of poor mental health days was not associated with survival. A second subset analysis of 268 patients surveyed starting in the year 2006 showed that falls, gait disturbances, and balance issues were not significantly associated with overall survival.

Disease-specific and non-disease-specific survival

Competing-risks analyses were performed to determine factors associated with disease-specific versus non-disease-specific survival (Table 4). Cause-specific mortality analyses found that disease-specific survival was associated with disease factors, i.e. stage, while non-disease-specific survival was associated with patient factors, i.e. mental HRQOL.

DISCUSSION

This study demonstrates that among older adult patients who underwent surgery for colorectal cancer, PROs are significant predictors of post-operative mortality. Overall, patients in this cohort experienced worsening of PROs over time; in particular those of Katz ADL scores, physical HRQOL, and number of comorbidities were associated with poorer outcomes. In terms of survival, mental HRQOL was associated with decreased overall as well as non-disease-specific survival. Increased number of comorbidities was also associated with decreased non-disease-specific survival. Despite significant declines in Katz ADL scores and physical HRQOL, neither PRO was independently associated with overall survival, disease-specific survival, or non-disease-specific survival. Instead, patient factors, namely age, sex, and race, were associated with non-disease-specific survival; meanwhile, the disease factors of advanced stage and site of primary tumor were associated with disease-specific survival.

Patient-reported health-related outcomes are increasingly recognized as important factors associated with outcomes following resection of malignancy [27]. Tumor biology is a critical component in the estimation of expected results of surgery and chance at cure of disease. However, significant decline in another aspect of the patient's overall well-being, such as functional status, frailty, or fall risk, can substantially compromise the anticipated outcome [28]. Peri-operative identification and mitigation of these factors are particularly important to optimize outcomes in vulnerable populations such as older cancer patients. More recently, the burgeoning field of pre-habilitation has emphasized the importance of pre-operative conditioning, including programs to integrate comprehensive geriatric assessment, improve nutrition, increase activity, and establish care with multidisciplinary services such as physical and occupational therapy [29, 30]. Although interest in such initiatives has grown, identification of patients who would most benefit from pre-habilitation programs remains to be fully elucidated. Our study helps better identify who among older

colorectal cancer patients might be at greater risk of experiencing adverse events related to PROs that are amenable to pre-operative and post-operative interventions. Specifically, efforts aimed at integrating perioperative geriatric assessment, preventing neurocognitive decline, and improving emotional well-being may address issues related to mental HRQOL and accumulation of comorbidities, respectively.

The concept of chronological age as a standalone, objective measurement of patients' well-being and fitness is arguably antiquated. However, patient age has been shown to influence how older adult patients are managed, even after having undergone surgery [31]. The body of literature evaluating surgical outcomes among older patients has emphasized other aspects of patients' well-being as better predictors than age alone [32, 33]. The SEER-MHOS database has provided the basis for several such studies for multiple types of malignancy [19, 34]. Currently, the concept of 'aging' is increasingly considered as a complex intersection of a multitude of factors including, but not limited to, validated measurement tools such as ADL scores, frailty indices, comorbidity weighting systems, and fall risk assessments [35].

In this study, we found that the majority (75%) of patients lived at least 5 years after receiving a diagnosis of colorectal cancer, with a substantial minority (30%) living 15 years and beyond, illustrating the potential for long-term survival for older adult colorectal cancer patients. We identified multiple factors, including PROs, which were associated with decreased overall survival. Competing-risks analyses clearly demonstrated that disease-related factors were associated with disease-specific survival and that non-disease-related factors were associated with non-disease-specific survival. Interestingly, we did not identify overlap between the two analyses. These findings further underscore how changes in patients' global health can substantially impact their survival independent of disease-related considerations, consistent with other analyses [11, 14, 15].

Limitations of the SEER-MHOS dataset pertinent to this analysis include the lack of data on timing of surgical resection in relation to the PRO surveys or specifics of administration and sequence of chemotherapy and/or radiation therapy. Although the receipt of surgical intervention is available from the dataset, more granular data on timing and receipt of other therapies would have enhanced the survival analyses in terms of survival from operation and better accounting for the rather different treatment algorithms for colon versus rectal cancer. In addition, our inclusion criterion of a completed PRO survey at least a year following the diagnosis of colorectal cancer potentially skewed our study population to more favorable disease biology and/or better initial functional status than excluded patients. This is reflected by the median survival of 83 months following diagnosis among this older patient population, as well as the median time of 25 months from diagnosis to completion of the follow-up HRQOL survey. Overall this may represent a sample bias. However, even among this cohort of potentially more favorable functional status and/or disease biology, PROs remained independently associated with survival. The relative impact of PROs on survival among a less favorable cohort may be further accentuated. Finally, we recognize that colon and rectal cancers are treated differently, which potentially would have an impact on our HRQOL-related findings. For this analysis, we chose to include both sites in an effort to strive for a more comprehensive presentation of the results.

In summary, PROs such as mental HRQOL are associated with survival following surgery for colorectal cancer among older patients. Patients' comorbidities are also negative predictors of survival. Consideration of multiple facets of patients' well-being, including age, functional status, mental and physical health, and stage of disease, is important in order to optimize outcomes of resection of colorectal cancer.

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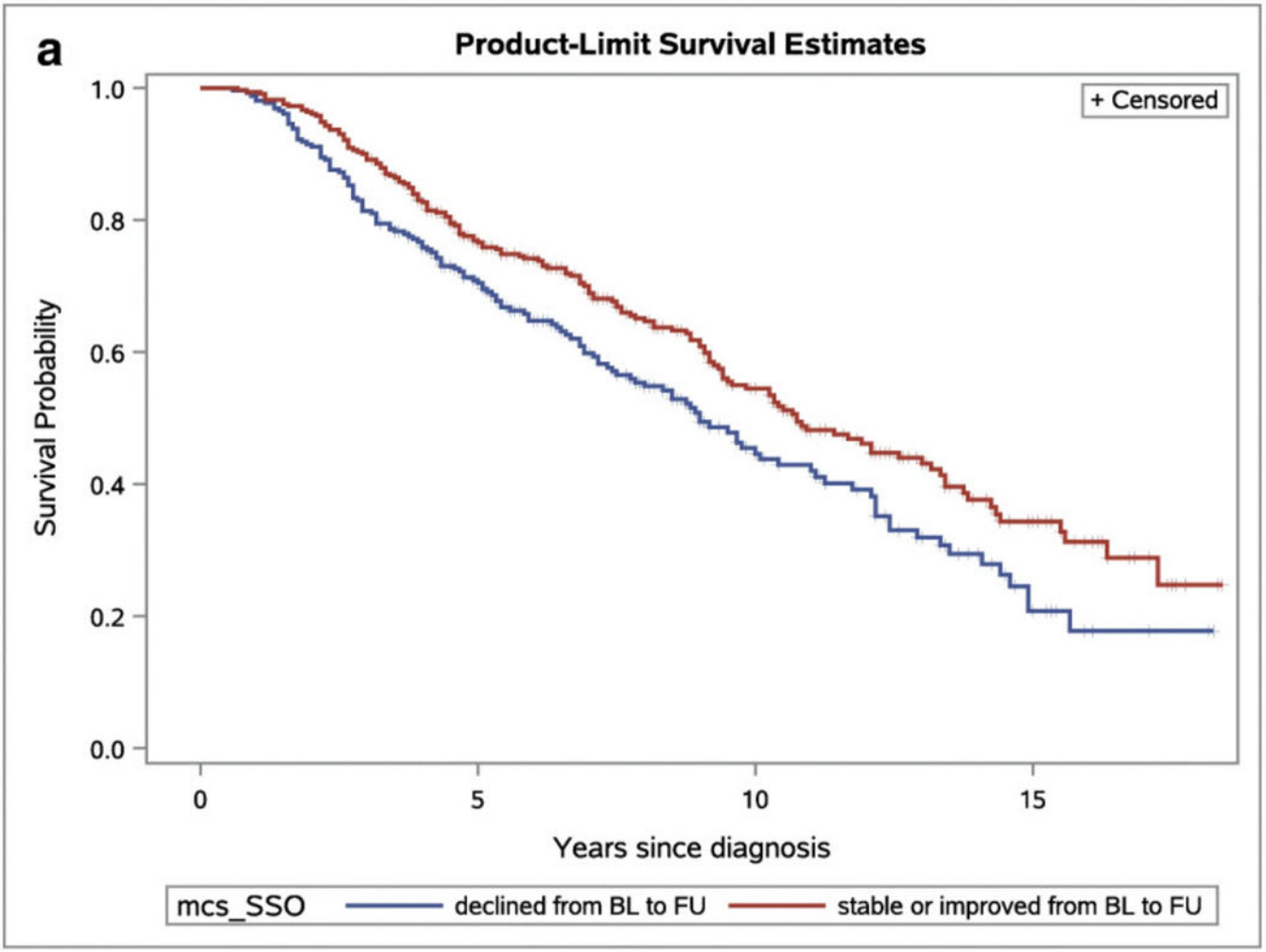
SYNOPSIS

Health-related quality of life was assessed among older colorectal cancer surgical patients in the SEER-MHOS dataset. Early identification of older surgical patients at risk for declines in functional and health-related quality of life may optimize oncologic outcomes.



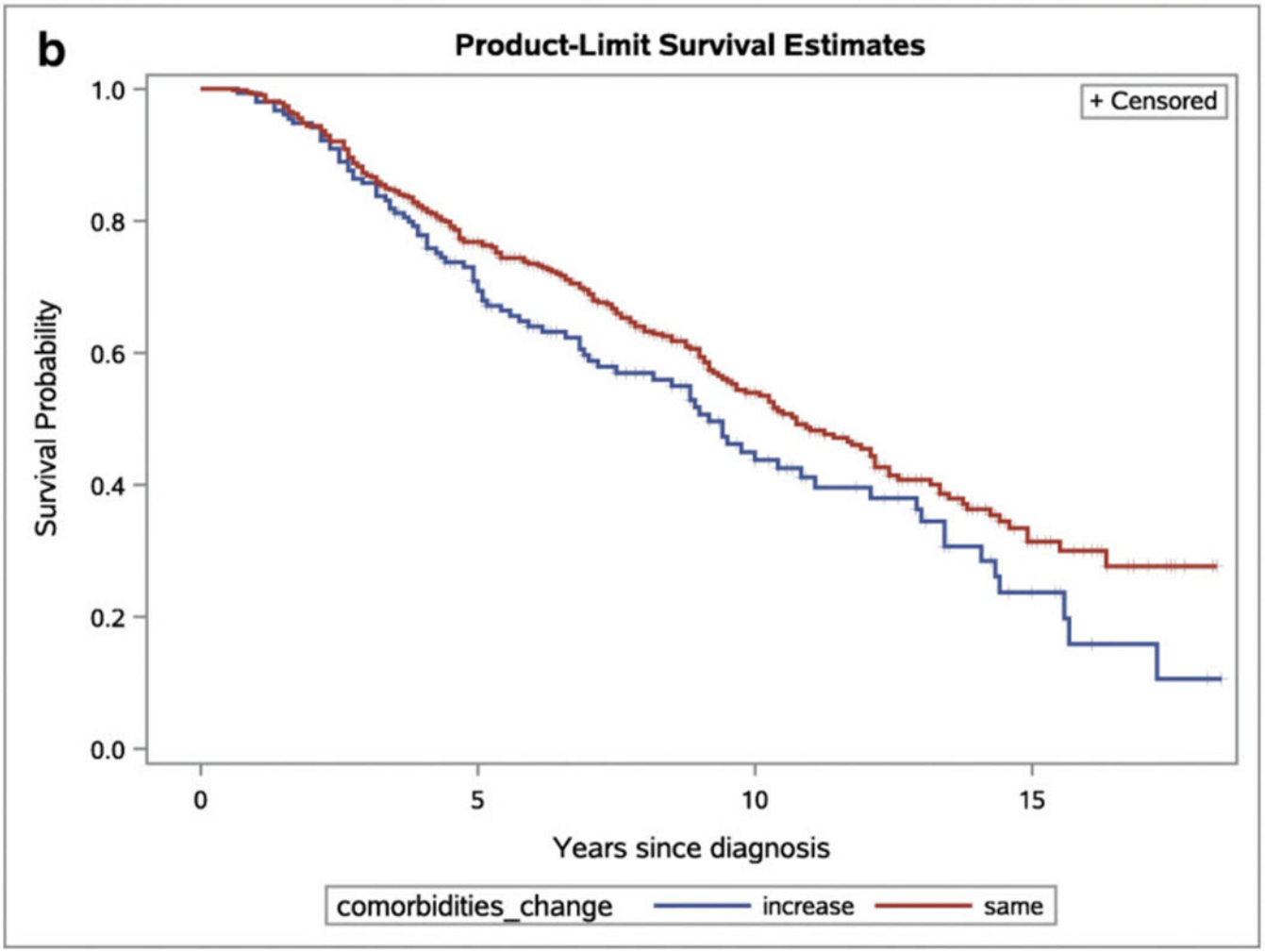


Figure 1.
Kaplan-Meier curves of overall survival stratified by comorbidities (A) and mental health-related quality of life (B)

Table 1:

Patient demographic and clinicopathologic features

Variable		N=590 (%)
Age at first survey, years	65 to 74	320 (54)
	75+	270 (46)
Sex	Male	265 (45)
	Female	325 (55)
Marital status	Married	325 (56)
	Not Married	254 (44)
	Missing	11
Race	Caucasian	445 (75)
	Other	145 (25)
Education level	Up to some college	469 (81)
	4+ years of college	107 (19)
	Missing	14
Income	< $30,000	285 (59)
	$30,000-$49,999	110 (23)
	≥ $50,000	87 (18)
	Missing	108
Comorbidities	0	317 (54)
	1	200 (34)
	>1	73 (12)
Stage of disease	Localized	309 (52)
	Regional	239 (41)
	Distant	42 (7)
Primary disease site	Colon	492 (83)
	Rectum	98 (17)

Table 2:

Change in health-related quality of life, activities of daily living, and comorbidity scores between survey time points

Variable	Change from baseline to follow-up	Number (%)	*p* Value
Katz ADL Score	Stable or improved	490 (83%)	0.0005
	Declined	100 (17%)	
Comorbidities*	Stable	426 (73%)	<0.0001
	Increased	154 (27%)	
Physical HRQOL	Stable or improved	271 (46%)	<0.0001
	Declined	319 (54%)	
Mental HRQOL	Stable or improved	331 (56%)	0.054
	Declined	259 (44%)	

ADL = activity of daily living; HRQOL = health-related quality of life

* = 10 patients did not have appropriate comorbidity-related data on the follow-up survey and were excluded from this analysis

Table 3.

Univariate and multivariate analyses with overall survival as outcome measure

			Univariate Analysis			Multivariate Analysis		
Variable		**N (%)**	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**
Age, years	65-74	320 (54)	Ref	-	-	Ref	-	-
	≥75	270 (46)	1.7	1.38-2.18	**<0.0001**	1.7	1.31-2.10	**<0.0001**
Sex	Female	325 (55)	Ref	-	-	Ref	-	-
	Male	265 (45)	1.1	0.90-1.41	0.31	1.4	1.07-1.71	**0.011**
Marital Status	Married	325 (56)	Ref	-	-			
	Not Married	254 (44)	1.1	0.84-1.34	0.61	-	-	-
	Unknown	11	-	-	-			
Race	Non-White	145 (25)	Ref	-	-	Ref	-	-
	White	445 (75)	1.6	1.21-2.18	**0.0012**	1.4	1.03-1.86	**0.031**
Education	Up to college	469 (81)	Ref	-	-			
	4+ years college	107 (19)	1.0	0.75-1.38	0.93	-	-	-
	Missing	14	-	-	-			
Income	≥ $50,000	87 (18)	Ref	-	-			
	$30,000-49,999	110 (23)	1.0	0.70-1.57	0.84	-	-	-
	< $30,000	285 (59)	1.1	0.76-1.54	0.67			
	Missing	108	-	-	-			
Stage	Localized	309 (52)	Ref	-	-	Ref	-	-
	Regional	239 (41)	2.0	1.54-2.52	**<0.0001**	2.0	1.55-2.54	**<0.0001**
	Distant	42 (7)	7.0	4.87-9.97	**<0.0001**	7.0	4.84-10.1	**<0.0001**
Disease Site	Colon	492 (83)	Ref	-	-	-	-	-
	Rectum	98 (17)	1.0	0.77-1.42	0.76			
Katz ADL Score	Stable/improved	490 (83)	Ref	-	-	-	-	-
	Declined	100 (17)	1.6	1.18-2.07	**0.0018**			
Comorbidities	Stable	426 (73)	Ref	-	-			
	Increased	154 (27)	1.3	1.01-1.67	**0.041**	-	-	-
	Missing	10	-	-	-			
Physical HRQOL	Stable/improved	271 (46)	Ref	-	-	-	-	-
	Declined	319 (54)	1.0	0.81-1.28	0.90			
Mental HRQOL	Stable/improved	331 (56)	Ref	-	-	Ref	-	-
	Declined	259 (44)	1.4	1.08-1.71	**0.0081**	1.4	1.11-1.76	**0.0049**

ADL = activity of daily living; HRQOL = health-related quality of life

Table 4.

Comparison of multivariate analyses of disease-specific versus non-disease-specific survival

			Disease-Specific Survival						Non-Disease-Specific Survival					
			Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis		
Variable		**N (%)**	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**
Age, years	65-74	320 (54)	Ref	-	-	-	-	-	Ref	-	-	Ref	-	-
	≥75	270 (46)	0.94	0.64-1.37	0.73				2.1	1.62-2.85	**<0.0001**	2.2	1.63-2.91	**<0.0001**
Sex	Female	325 (55)	Ref	-	-	-	-	-	Ref	-	-	Ref	-	-
	Male	265 (45)	0.85	0.58-1.25	0.42				1.3	1.00-1.75	**0.047**	1.4	1.04-1.82	**0.026**
Race	Non-White	145 (25)	Ref	-	-	-	-	-	Ref	-	-	-	-	-
	White	445 (75)	1.5	0.94-2.53	0.088				1.5	1.03-2.07	**0.034**			
Stage	Localized	309 (52)	Ref	-	-	Ref	-	-	Ref	-	-			
	Regional	239 (41)	4.0	2.48-6.60	**<0.0001**	4.1	2.49-6.63	**<0.0001**	1.1	0.81-1.45	0.58	-	-	-
	Distant	42 (7)	15.9	8.75-29.0	**<0.0001**	16.5	9.13-29.9	**<0.0001**	0.98	0.55-1.76	0.96			
Disease Site	Colon	492 (83)	Ref	-	-	Ref	-	-	Ref	-	-	-	-	-
	Rectum	98 (17)	1.4	0.91-2.27	0.12	1.6	1.01-2.57	**0.047**	0.8	0.51-1.19	0.25			
Katz ADL Score	Stable/improved	490 (83)	Ref	-	-	-	-	-	Ref	-	-	-	-	-
	Declined	100 (17)	1.4	0.89-2.27	0.14				1.4	0.95-1.94	0.089			
Comorbidities	Stable	426 (73)	Ref	-	-	-	-	-	Ref	-	-	Ref	-	-
	Increased	154 (27)	0.95	0.61-1.48	0.81				1.5	1.09-1.98	**0.013**	1.4	1.01-1.86	**0.042**
Physical HRQOL	Stable/improved	271 (46)	Ref	-	-	-	-	-	Ref	-	-	-	-	-
	Declined	319 (54)	1.1	0.78-1.67	0.50				0.9	0.69-1.21	0.55			
Mental HRQOL	Stable/improved	331 (56)	Ref	-	-	-	-	-	Ref	-	-	Ref	-	-
	Declined	259 (44)	0.97	0.66-1.42	0.88				1.5	1.13-1.97	**0.0048**	1.4	1.08-1.89	**0.015**

ADL = activity of daily living; HRQOL = health-related quality of life