Underweight status predicts a poor prognosis in elderly patients with colorectal cancer

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Abstract. The aim of the present study was to evaluate the effect of underweight status on the survival of elderly patients undergoing surgery for colorectal cancer (CRC). A total of 113 patients aged ≥75 years who underwent curative surgery for CRC were included. In addition to standard perioperative variables, body mass index (BMI) was assessed. The patients were categorized as underweight (BMI<18.5 kg/m^2) or non-underweight (BMI≥18.5 kg/m^2). The 3-year overall survival (OS) and cancer-specific survival (CSS) were analyzed. Of the 113 patients, 24 (21%) were underweight. The two groups were well-balanced regarding all factors evaluated. In the multivariate analysis, underweight status was an independent indicator of lower 3-year OS [hazard ratio (HR)=2.65; 95% confidence interval (CI): 1.08-6.50; P=0.033] and CSS (HR=3.51, 95% CI: 1.16-10.60; P=0.025) rates. Compared with the non-underweight group, the underweight group had significantly worse 3-year OS (66.7 vs. 86.5%, respectively; P=0.017) and CSS (74.1 vs. 90.9%, respectively; P=0.025) rates. Therefore, underweight status was a significant risk factor for poor survival in elderly CRC patients. The development of effective nutritional interventions may improve the prognosis of such patients.

Introduction

Colorectal cancer (CRC) is the third and second most commonly diagnosed cancer in men and women, respectively, with an estimated 1.4 million new cases and nearly 700,000 deaths in 2012 worldwide (1). Approximately 60% of CRC patients are aged >70 years (2). The number of elderly individuals is increasing worldwide due to the increase in the average life span. As a result, the number of middle-old (75-84 years) and oldest-old patients (>85 years) diagnosed with CRC is expected to increase. Although potentially curative resection is not possible in approximately one-fourth of the patients (3), surgery is the most reliable treatment modality. In the preoperative management of elderly patients, cardiovascular risk, respiratory function and the presence of comorbidities are thoroughly assessed. However, nutritional status assessment may be overlooked in routine preoperative evaluation, despite the fact that undernutrition is associated with an increased risk of poor tissue healing and impaired immune function (4), and previous studies reporting that poor nutritional status was associated with worse survival of elderly patients who underwent surgery for lung, ovarian and primary peritoneal cancer (4,5).

Body mass index (BMI) is a useful tool in clinical practice for assessing adult nutritional status, and individuals are considered to be underweight if their BMI is <18.5 kg/m^2. A BMI<18.5 kg/m^2 also indicates undernutrition (6). Several studies conducted among subjects of a broad age range reported that underweight status was a significant predictor of poorer overall survival in CRC (7-13). However, to the best of our knowledge, no study has yet been conducted to investigate the association between underweight status and survival outcome in elderly CRC patients.

The aim of this study was to investigate whether underweight status was associated with a worse survival outcome in elderly patients undergoing curative surgery for CRC.

Materials and methods

Patient population. A total of 113 Japanese patients with pathologically confirmed stage I-III CRC, aged ≥75 years, who underwent curative surgery between January, 2004 and June, 2012 at the Department of Surgery, Omori Red Cross Hospital (Tokyo, Japan) were retrospectively analyzed. The patients were followed up for ≥3 years or until death. Patients with cancer of other organs were excluded. The medical charts of the 113 patients were retrieved from our registry, and clinical, pathological and survival data were collected. The factors included in this study were age, gender, Charlson Comorbidity Index (14), the calculation of which did not include cancer diagnoses, American Society of Anesthesiologists physical status, tumor site, disease stage according to the Union for International Cancer Control (15), histology and BMI at the

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time of diagnosis. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Patients were divided into underweight (BMI<18.5 kg/m^2) and non-underweight (BMI≥18.5 kg/m^2) groups, according to the World Health Organization (WHO) classification (6). The associations between 3-year overall survival (OS) or cancer-specific survival (CSS) and the patients' clinico-pathological data were analyzed. The 3-year OS, CSS and recurrence-free survival (RFS) curves were then estimated for each group using the Kaplan-Meier method. The review board of the hospital approved the study protocol.

Statistical analysis. The associations between BMI and the clinicopathological parameters were assessed using the Pearson's Chi-square or Fisher's exact tests, as appropriate. Cox regression analyses were performed to analyze the survival outcome in univariate and multivariate analyses. Variables that were significant in the univariate analysis were examined in the multivariate analysis. OS, CSS and RFS were determined from the date of surgery to the date of death from any cause, cancer-specific death and recurrence, respectively. The Kaplan-Meier survival curves were compared using the log-rank test. All reported P-values were two-tailed and those <0.05 were considered to indicate statistically significant differences. All data were analyzed using EZR version 1.24 software for Windows (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (16).

Results

Patient characteristics. Of the 113 patients, 20 (17.6%) died within 3 years of surgery: 14 patients succumbed to CRC, whereas the remaining 6 patients died from other causes. The median BMI was 21.3 kg/m^2 (range, 12.6-30.2 kg/m^2), and 1 patient (0.8%) had a BMI of ≥30 kg/m^2. A total of 24 patients (21%) were in the underweight and 89 (79%) in the non-underweight group.

The clinical and pathological characteristics of the patients, stratified by BMI, are listed in Table I. The two groups were well-balanced regarding all factors evaluated, although under-weight patients exhibited a trend toward a higher Charlson Comorbidity Index score compared with patients who were not underweight (P=0.060).

Analysis of OS and CSS. The results of the univariate and multivariate Cox regression analyses for 3-year OS are shown in Table II. In the univariate analysis, the factors significantly associated with poorer 3-year OS were advanced disease stage (P=0.001) and underweight status (P=0.023). The multivariate Cox regression analysis demonstrated that advanced disease stage [hazard ratio (HR)=4.31; 95% confidence interval (CI): 1.76-10.58; P=0.001] and underweight status (HR=2.65; 95% CI: 1.08-6.50; P=0.033) were independently associated with worse 3-year OS.

The results of the univariate and multivariate Cox regression analyses for 3-year CSS are shown in Table III. The factors significantly associated with a poorer 3-year CSS were advanced disease stage (P<0.001), undifferentiated histology (P=0.016) and underweight status (P=0.034). The multivariate Cox regression analysis revealed that advanced disease stage (HR=6.69; 95% CI: 2.08-21.44; P=0.001), undifferentiated histology (HR=4.37; 95% CI: 1.15-16.62; P=0.030), and under-weight status (HR=3.51; 95% CI: 1.16-10.60; P=0.025) were independently associated with a worse 3-year CSS.

Patients in the underweight group had a significantly worse 3-year OS rate compared with those in the non-underweight group (66.7 vs. 86.5%, respectively; P=0.017) and CSS rate (74.1 vs. 90.9%, respectively; P=0.025) (Fig. 1). There was no significant difference in the 3-year RFS rate between the underweight and non-underweight groups (74.3 vs. 77.1%; P=0.74).

Discussion

The association between underweight status and the prognosis of CRC patients has been reported in several studies conducted among patients of all ages, and underweight patients have been shown to have a worse OS (7-13). However, Hines *et al* reported that underweight patients were on average older compared with those in other BMI categories, and more frequently had moderate or severe comorbidities compared with their younger counterparts (10); thus, older age and comorbidities were possible confounding factors when attempting to determine the association between BMI categories and survival outcome in CRC patients (10). In this study, among elderly CRC patients, we found that underweight status, but not the Charlson Comorbidities Index score, was an independent risk factor for all-cause and cancer-specific mortality. Therefore, the worse prognosis of underweight patients was not solely attributed to their older age and more severe comorbidities.

It remains unclear whether underweight status exerts a significant negative effect on CSS or RFS in patients with CRC (7-13). Doria *et al* reported an increased risk of cancer-related death among underweight patients with colon cancer. Two other studies reported that underweight status *per se* was not a significant risk factor for CSS in CRC, and that underweight patients tended to succumb to non-cancer events, which was attributed, at least in part, to an underlying comorbid illness (8,12). In regards to RFS, it has previously been reported that underweight patients have a higher risk of cancer recurrence (12,13). Conversely, other investigators found no association between underweight status and RFS (7,11). In the present study, we observed that underweight patients had a worse CSS but similar RFS with non-underweight patients. One possible explanation for these findings is that underweight status may be associated with more severe comorbidities and a poor performance status, thus preventing effective chemo-therapeutic treatment or surgery when the disease recurs (17). Indeed, underweight patients in this study exhibited a trend toward a higher Charlson Comorbidity Index score and were less likely to receive salvage treatment for recurrent disease compared with patients who were not underweight (16 vs. 75%, respectively; data not shown).

Underweight status in elderly patients may be associated with the loss of muscle and fat mass due to sarcopenia and/or cachexia. Sarcopenia in elderly individuals was defined as the 'progressive loss of muscle mass and strength with a risk

Table I. Baseline characteristics of the CRC patients stratified by BMI.

Characteristics	Non-underweight[a] n (%)	Underweight[b] n (%)	P-value
Age (years)			0.25
<85	73 (82.0)	17 (70.8)	
≥85	16 (18.0)	7 (29.2)	
Gender			0.25
Female	47 (52.8)	16 (66.7)	
Male	42 (47.2)	8 (33.3)	
Charlson comorbidity index			0.060
0, 1	78 (87.6)	17 (70.8)	
≥2	11 (12.4)	7 (29.2)	
ASA physical status			0.19
I, II	63 (70.8)	13 (54.2)	
III, IV	26 (29.2)	11 (45.8)	
Tumor site			0.10
Colon	69 (77.5)	14 (58.3)	
Rectum	20 (22.5)	10 (41.7)	
Stage			0.45
I, II	66 (74.2)	16 (66.7)	
III	23 (25.8)	8 (33.3)	
Histology			0.67
Differentiated	83 (93.3)	22 (91.7)	
Undifferentiated	6 (6.7)	2 (8.3)	

[a]BMI≥18.5 kg/m^2. [b]BMI<18.5 kg/m^2. CRC, colorectal cancer; BMI, body mass index; ASA, American society of anesthesiologists.

Table II. Cox regression analyses of 3-year overall survival.

Variables	Univariate analysis HR	95% CI	P-value	Multivariate analysis HR	95% CI	P-value
Age, years						
≥85 vs. <85	1.76	0.67-4.58	0.24			
Gender						
Male vs. female	1.60	0.66-3.86	0.29			
Charlson comorbidity index						
≥2 vs. 0, 1	1.36	0.45-4.07	0.57			
ASA physical status						
III, IV vs. I, II	1.72	0.71-4.16	0.22			
Tumor site						
Rectum vs. colon	0.86	0.31-2.39	0.78			
Stage						
III vs. I, II	4.47	1.82-10.95	0.001	4.31	1.76-10.58	0.001
Histology						
Undifferentiated vs. differentiated	3.16	0.92-10.80	0.066			
BMI						
Underweight[a] vs. non-underweight[b]	2.82	1.15-6.91	0.023	2.65	1.08-6.50	0.033

[a]BMI<18.5 kg/m^2. [b]BMI≥18.5 kg/m^2. HR, hazard ratio; CI, confidence interval; ASA, American society of anesthesiologists; BMI, body mass index.

Table III. Cox regression analyses of 3-year cancer-specific survival.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age, years						
≥85 vs. <85	1.11	0.30-3.98	0.87			
Gender						
Male vs. female	1.73	0.60-4.99	0.30			
Charlson comorbidity index						
≥2 vs. 0, 1	0.91	0.20-4.07	0.90			
ASA physical status						
III, IV vs. I, II	1.58	0.55-4.57	0.39			
Tumor site						
Rectum vs. colon	1.04	0.32-3.33	0.93			
Stage						
III vs. I, II	7.32	2.29-23.40	<0.001	6.69	2.08-21.44	0.001
Histology						
Undifferentiated vs. differentiated	4.75	1.32-17.07	0.016	4.37	1.15-16.62	0.030
BMI						
Underweight[a] vs. non-underweight[b]	3.13	1.08-9.02	0.034	3.51	1.16-10.60	0.025

[a]BMI <18.5 kg/m². [b]BMI ≥18.5 kg/m². HR, hazard ratio; CI, confidence interval; ASA, American society of anesthesiologists; BMI, body mass index.
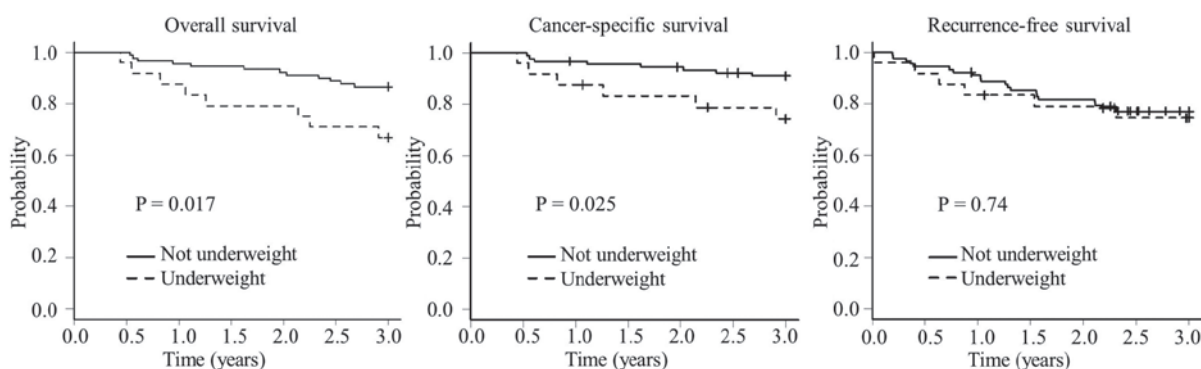

Figure 1. Survival curves of elderly patients who underwent curative surgery for colorectal cancer. Kaplan-Meier estimates of the overall, cancer-specific and recurrence-free survival of patients in the underweight (BMI<18.5 kg/m²; n=24) and non-underweight (BMI≥18.5 kg/m²; n=89) groups. BMI, body mass index.

of adverse outcomes, such as disability, poor quality of life and death' by the Special Interest Group of the European Sarcopenia Working Group in 2010 (18), and it is recognized as a multifactorial geriatric syndrome. The term 'sarcopenia' is used specifically to denote the loss of muscle mass and strength associated with aging, distinct from muscle loss due to other causes, such as immobility or neurological damage. Sarcopenia is independently associated with an increased risk of functional impairment, falls, disability and mortality in the elderly (19). The prevalence of sarcopenia is 50% in individuals aged ≥80 years (18), and several reports demonstrated that sarcopenia is a negative prognostic factor in malignancies, including melanoma (20), hepatocellular carcinoma (21) and diffuse large B-cell lymphoma (22).

Cachexia may be a cause of loss of body fat mass (23). It has been reported that the loss of body fat content late in life is associated with premature death, micronutrient deficiencies, frailty, increased hospital admission, an increased risk of disability from falls and delayed recovery from injury (24-27). In addition, loss of body fat content has been reported to be associated with shorter survival in advanced cancer patients, although the underlying mechanism of this association has not yet been fully elucidated (28,29). One possible explanation is that fat represents the main energy store of the body, and it may be one of the components predicting malnutrition-related risks of mortality and morbidity; thus, body fat confers survival advantages in elderly patients (30).

Although BMI is a simple and useful tool in clinical practice for assessing adult nutritional status, two recent studies revealed that it cannot be used to assess individual components of body weight, such as regional fat distribution or muscle volume; thus, muscular individuals may be incorrectly categorized as overweight or obese (31,32). The authors of those studies also suggested that other parameters denoting body composition, such as fat mass or muscle mass assessed by bioelectrical impedance analyses, dual-energy X-ray absorptiometry and magnetic resonance imaging or computed tomography imaging, would be more useful predictors of survival compared with BMI (31,32). Further studies are required to evaluate the association between BMI and other parameters, and to identify better predictors of appropriate body composition.

The limitations of the present study include its retrospective design, small sample size and lack of data such as physical activity, diet, smoking status and changes in body weight prior to surgery. In regard to the sample size, only 1 (0.8%) of the 113 patients had a BMI of ≥ 30 kg/m^2. However, this reflects the distribution of BMI categories in Japan, where only a relatively small proportion of the middle-old and oldest-old populations have a BMI of ≥ 30 kg/m^2 (33).

In conclusion, the results of the present study indicate that underweight status is an independent poor prognostic factor in elderly CRC patients, which may exert an effect on treatment and post-treatment surveillance. Further studies are required to validate our findings and elucidate the mechanism underlying the negative effect of underweight status on the survival of these patients. The development of effective nutritional interventions may contribute to a better prognosis in such patients.

Acknowledgements

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