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Impact of preoperative cachexia on postoperative length of stay in elderly patients with gastrointestinal cancer

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ABSTRACT

Objectives: The aim of the present study was to investigate the impact of preoperative cachexia on postoperative length of stay (LOS) in elderly patients with gastrointestinal cancer.
Methods: This prospective cohort study enrolled 98 patients (≥60 y of age) with gastric or colorectal cancer who were scheduled to undergo curative surgery and were categorized as either having cachexia or as being in a non-cachexia group. The definition of cachexia was patients with >5% loss of stable body weight over the previous 6 mo, a body mass index (BMI) <20 kg/m^2 and ongoing weight loss >2%, or sarcopenia and ongoing weight loss >2%. Multivariable Poisson regression analysis was performed with postoperative LOS as the dependent variable and the presence of cachexia as the independent variable, and age, sex, Eastern Cooperative Oncology Group performance status, education, cancer type, clinical stage, surgical approach, and the Charlson Comorbidity Index as confounding variables.
Results: Twenty-two patients (22.4%) were diagnosed with cachexia. Postoperative LOS was 17.1 ± 8.7 d in the non-cachexia group and 20.6 ± 10.8 d in the cachexia group. Multivariable Poisson analysis showed that preoperative cachexia was significantly associated with prolonged postoperative LOS after adjustment (2.41 d; 95% confidence interval, 0.28 to 4.55; $P = 0.027$).
Conclusions: Our results suggested that preoperative cachexia prolongs postoperative LOS in elderly patients with gastrointestinal cancer, implying that cachexia should be assessed and treated before surgery.

Introduction

Gastrointestinal (GI) cancer treatments mainly involve surgery, and enhanced recovery after surgery (ERAS) protocol is required to reduce surgical stress and accelerate recovery in patients. One of the parameters of ERAS is postoperative length of stay (LOS), and prolonged postoperative LOS has been shown to increase readmission rate [1], decrease the rate of overall survival [2], and increase hospitalization costs [3]. Therefore, postoperative LOS is a clinically and socially relevant problem.

The number of elderly patients with cancer is rising in Japan [4], and a previous study has reported that older patients who undergo laparoscopic gastrectomy experience prolonged postoperative LOS, implying that aging is a risk factor for prolonged postoperative LOS [5]. Therefore, it is necessary to identify the risk factors associated with prolonged postoperative LOS in the elderly.

Recently, cachexia has been receiving increasing attention because it potentially can be modifiable [6–10] and can have an effect on adverse outcomes such as postoperative complications [11], diminished physical functioning [12], and decreased survival [13]. Therefore, cachexia also may affect postoperative LOS. Cancer cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment [14]. The prevalence of cachexia among all cancer patients is reportedly 16.6% to 80%, which is high compared with its prevalence in other diseases [11,15]. Furthermore, a previous report, using real-world data from the International Classification of Diseases-9 for the prevalence of cachexia (0.4%), has shown that patients diagnosed with cachexia experienced prolonged LOS compared with non-cachexia patients [16]. However, this rate is

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much lower than that reported in previous studies and thus it is possible that the effect of cachexia on postoperative LOS was underestimated. In contrast, to develop accurate diagnostic criteria, experts in clinical cancer and cachexia research have issued a consensus statement to guide clinical decision making in the management of cachexia [14]. However, few studies have used this cachexia criteria. Furthermore, as the body type of Asians differs from that of Western populations [17], studies in Asian populations with the consensus cachexia criteria are necessary.

Thus, the present study aimed to investigate the impact of preoperative cachexia on postoperative LOS in elderly Japanese patients with GI cancer.

Participants and Methods

Study design and settings

This single-center prospective cohort study was conducted between December 2015 and April 2017 at an urban university hospital. The study was approved by the ethics committee of Kobe University Graduate School Health Science and was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. All patients provided informed consent before participation.

Participants and eligibility criteria

We approached 133 Japanese patients with gastric or colorectal cancer for the study. Patients ≥60 y of age who were scheduled to undergo curative surgery were eligible. The exclusion criteria included the presence of simultaneous cancers or missing data. After excluding, 98 patients were selected.

Data collection and measurements

Data of demographic characteristics, preoperative treatment, and cancer cachexia before surgery were collected. Postoperative LOS and postoperative complications within 30 d after surgery were investigated at discharge.

Demographic data

Demographic data collected include age, sex, the Eastern Cooperative Oncology Group performance status (PS), and education, whereas preoperative treatment data included cancer type, clinical stage, surgical approach, comorbidity, and postoperative complications within 30 d after surgery; these data were collected from the medical records of patients. Comorbidity was assessed using the Charlson Comorbidity Index (CCI) [18], which assigns weight to specific diseases. Thus, comorbid conditions with a weighted score of 1 include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, ulcer disease, mild liver disease, and diabetes mellitus, whereas those with a weighted score of 2 include diabetes mellitus with end-organ damage, any tumor, leukemia, and lymphoma. Moderate or severe liver disease has a weighted score of 3, whereas metastatic solid tumors and AIDS have a weighted score of 6 [19]. The total score is calculated by adding these weighted scores. Patients were classified into three groups based on total scores as 0, 1, and ≥2 [20]. Postoperative complications within 30 d after surgery were defined according to the Clavien–Dindo classification [21], and any postoperative conditions defined as Clavien–Dindo grade ≥II were identified as postoperative complications.

Postoperative LOS

Postoperative LOS was calculated as the duration between the day of surgery and the day of discharge from the GI ward.

Cancer cachexia

The definition of cachexia was patients with >5% loss of stable body weight over the previous 6 mo, a body mass index (BMI) <20 kg/m^2 and ongoing weight loss >2%, or sarcopenia and ongoing weight loss >2% [14]. Sarcopenia was defined as low muscle mass according to the Asian consensus definition [22]. Specifically, low muscle mass was defined as a skeletal muscle mass index (SMI) of <7 kg/m^2 for men and <5.7 kg/m^2 for women. Muscle mass was assessed using multifrequency bioelectrical impedance with eight tactile electrodes (InBody 430; Inbody Japan, Tokyo, Japan).

Statistical analysis

Patient characteristics were compared between those with and without cachexia using Student's *t* test for normalized variables, the Wilcoxon rank-sum test for non-normalized values, and χ^2 tests or Fisher's exact test for categorical values. If the exact count in any cell was <10, Fisher's exact test was applied. Poisson (identity link) regression analyses were performed with postoperative LOS as the dependent variable, and the presence of cachexia or patient characteristics as the independent variable. Covariates were selected on the basis of previous studies on LOS, and included the following variables, namely, age, sex, ECOG PS, education, cancer type, clinical stage, surgical approach, and CCI [23–25]. All statistical analyses were performed using the STATA 14.1 software (Stata Corp, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

Results

Clinical and demographic characteristics were compared between patients with and without cachexia (Table 1). Twenty-two patients (22.4%) were classified as cachexia. No significant relationships were observed between cachexia and patient characteristics. Postoperative LOS was 17.1 ± 8.7 d in the non-cachexia group and 20.6 ± 10.8 d in the cachexia group.

Next, we used Poisson regression models to analyze the association between postoperative LOS and cachexia or patient characteristics (Table 2). Univariate Poisson regression analysis identified cachexia, age, sex, ECOG PS, cancer type, clinical stage, surgical approach, and CCI, as factors that significantly prolonged postoperative LOS. In multivariable Poisson analysis, cachexia significantly affected prolonged postoperative LOS after adjustment for age, sex, ECOG PS, education, clinical stage, surgical approach, and CCI (2.41 d; 95% confidence interval, 0.28 to 4.55; $P = 0.027$).

Discussion

The present study investigated the impact of preoperative cachexia on postoperative LOS in elderly Japanese patients with GI cancer. The results demonstrated that preoperative cachexia is associated with prolonged postoperative LOS.

Although a previous study on various diseases investigated an association between cachexia and LOS in the United States, that study did not use the consensus diagnostic criteria for cachexia [16], and the prevalence of cachexia was reported as 0.4%, which is much lower than that of previous studies [11,15]. It is, therefore,

Table 1
Baseline characteristics

	Non-cachexia (n = 76)	Cachexia (n = 22; 22.4%)	*P*-value
Age (y)†	71.9 ± 7.1	74.8 ± 7.7	0.133
Sex: Male, n (%)	52 (68.4)	18 (81.8)	0.289
ECOG PS, n (%)			0.501
0	64 (84.2)	17 (77.3)	
1	10 (13.2)	5 (22.7)	
2	2 (2.6)	0 (0)	
Education (y)†	12.7 ± 2.7	13.0 ± 3.3	0.533
Cancer type, n (%)			0.789
Gastric	39 (51.3)	12 (54.5)	
Colorectal	37 (48.7)	10 (45.5)	
Clinical stage, n (%)			0.768
0–2	61 (80.3)	17 (77.3)	
3–4	15 (19.7)	5 (22.7)	
Surgical approach, n (%)			0.689
Endoscopic	69 (90.8)	19 (86.4)	
Open	7 (9.2)	3 (13.6)	
CCI, n (%)			0.739
0	34 (44.8)	8 (36.4)	
1	14 (18.4)	5 (22.7)	
≥2	28 (36.8)	9 (40.9)	
Postoperative complication, n (%)	18 (23.7)	6 (27.3)	0.781

CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status.
Data on age and education are expressed as mean (SD), and the others as n (%).
†Statistical analysis used by the Wilcoxon rank-sum test.

Table 2
Poisson regression analysis of the relationship between postoperative LOS and cachexia or patient characteristics

	Univariate		Multivariate	
	Postoperative LOS (95% CI)	*P*-value	Postoperative LOS (95% CI)	*P*-value
Cachexia				
No	Reference		Reference	
Yes	3.53 (1.41 to 5.64)	0.001	2.41 (0.28 to 4.55)	0.027
Age	−0.14 (−0.25 to −0.04)	0.009	−0.16 (−0.28 to −0.04)	0.007
Sex				
Male	Reference		Reference	
Female	−4.15 (−5.91 to −2.39)	<0.001	−1.23 (−3.27 to 0.80)	0.236
ECOG PS				
0	Reference		Reference	
1	4.28 (1.77 to 6.79)	0.001	3.34 (0.78 to 5.91)	0.011
2	0.81 (−5.13 to 6.76)	0.788	0.57 (−5.65 to 6.79)	0.856
Education	0.02 (−0.28 to 0.32)	0.885	−0.17 (−0.46 to 0.12)	0.254
Cancer type				
Gastric	Reference		Reference	
Colorectal	−3.69 (−5.36 to −2.02)	<0.001	−2.83 (−4.77 to −0.88)	0.004
Clinical stage				
0–2	Reference		Reference	
3–4	−2.58 (−4.57 to −0.59)	0.011	−2.17 (−4.35 to 0.01)	0.051
Surgical approach				
Endoscopic	Reference		Reference	
Open	5.28 (2.21 to 8.35)	0.001	2.61 (−0.78 to 5.99)	0.131
CCI				
0	Reference		Reference	
1	7.89 (5.38 to 10.39)	<0.001	7.61 (5.09 to 10.13)	<0.001
≥2	0.99 (−0.80 to 2.79)	0.278	0.88 (−1.12 to 2.88)	0.387

CCI, Charlson Comorbidity Index; ECOG PS, the Eastern Cooperative Oncology Group performance status; LOS, length of stay.

possible that patients with cachexia were actually assigned to the control group, thereby underestimating the impact of cachexia on LOS. As we diagnosed cachexia based on the consensus diagnostic criteria, we believe that our results not only support and expand results of previous studies but also have significant impact.

Delay in wound healing because of cachexia may be one of the reasons for prolonged postoperative LOS. Previous studies have suggested a possible association between cachexia and delayed wound healing as well as malnutrition and inflammation [26,27]. In recent years, data from some intervention studies aimed at improving cancer cachexia have become available. One randomized controlled trial on appetite stimulants reported that a combination of megestrol acetate and thalidomide led to increased body weight and handgrip strength, and improved quality of life [6]. Additionally, other studies have reported that anamorelin, which induces ghrelin, an appetite-stimulating peptide hormone, also increased body weight [7]. High-dose espindolol has been shown to reverse weight loss and improve fat-free mass [8], and exercise training was also efficacious in cachexia because of the diminution of tissue-wasting effects [9]. As cachexia is a multifactorial syndrome, multimodal interventions, including nutrition support, exercise, and drug therapy, may be necessary. A previous randomized phase II feasibility trial reported that multimodal interventions for cachexia resulted in weight gain [10]. Taken together, the results of these previous studies imply that cachexia is potentially manageable and reversible. Therefore, the assessments of and interventions for cachexia before performing surgery are important to shorten postoperative LOS.

Despite demonstrating preoperative cachexia as a risk factor for prolonged postoperative LOS, the present study had a few limitations. First, the findings could not be generalized because this was a single-institutional study; future multicenter studies are necessary to assess the broad applicability of the results of the present study. Second, there is possibility of selection bias as a majority of the patients were relatively healthy, with PS values of 0 or 1 and clinical stage of 0–2, and were healthy enough to participate. Therefore, further study including patients with severe PS and advanced stage should be conducted. Third, the present study considered inadequate data about the difference between colorectal and gastric cancer: patient profile, weight before surgery, depletion, symptoms, and duration between diagnosis and surgery. More research is required with detailed data about patients.

Conclusion

Results from the present study suggested that preoperative cachexia prolongs postoperative LOS in elderly patients with GI cancer. Thus, the assessment of and interventions for cachexia before performing surgery are useful to shorten postoperative LOS.

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References

[1] Honda M, Hiki N, Nunobe S, Ohashi M, Mine S, Watanabe M, et al. Unplanned admission after gastrectomy as a consequence of fast-track surgery: a comparative risk analysis. Gastric Cancer 2016;19:1002–7.
[2] Ma L, Li J, Shao L, Lin D, Xiang J. Prolonged postoperative length of stay is associated with poor overall survival after an esophagectomy for esophageal cancer. J Thorac Di 2015;7:2018–23.
[3] Polverejan E, Gardiner JC, Bradley CJ, Holmes-Rovner M, Rovner D. Estimating mean hospital cost as a function of length of stay and patient characteristics. Health Econ 2003;12:935–47.
[4] Hori M, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H. Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol 2015;45:884–91.
[5] Kim MG, Kim HS, Kim BS, Kwon SJ. The impact of old age on surgical outcomes of totally laparoscopic gastrectomy for gastric cancer. Surg Endosc 2013;27:3990–7.
[6] Wen HS, Li X, Cao YZ, Zhang CC, Yang F, Shi YM, et al. Clinical studies on the treatment of cancer cachexia with megestrol acetate plus thalidomide. Chemotherapy 2012;58:461–7.

[7] Garcia JM, Friend J, Allen S. Therapeutic potential of anamorelin, a novel, oral ghrelin mimetic, in patients with cancer-related cachexia: a multicenter, randomized, double-blind, crossover, pilot study. Support Care Cancer 2013;21:129–37.
[8] Stewart Coats AJ, Ho GF, Probhash K, von Healing S, Tilson J, Brown R, et al. Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). J Cachexia Sarcopenia Muscle 2016;7:355–65.
[9] Battaglini CL, Hackney AC, Goodwin ML. Cancer cachexia: muscle physiology and exercise training. Cancers (Basel) 2012;4:1247–51.
[10] Shlheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase feasibility trial of a multimodel intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle 2017;8:778–88.
[11] Mason MC, Garcia JM, Sansgiry S, Walder A, Berger DH, Anaya DA. Preoperative cancer cachexia and short-term outcomes following surgery. J Surg Res 2016;205:398–406.
[12] Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006;83:1345–50.
[13] Bachmann J, Büchler MW, Friess H, Martignoni ME. Cachexia in patients with chronic pancreatitis and pancreatic cancer: impact on survival and outcome. Nutr Cancer 2013;65:827–33.
[14] Fearon KC, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–95.
[15] Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer 2014;14:754–62.
[16] Arthur ST, Noone JM, Van Doren BA, Roy D, Blanchette CM. One-year prevalence, comorbidities and cost of cachexia-related inpatient admissions in the USA. Drugs Context 2014;3:212265.
[17] Yatsuya H, Li Y, Hilawe EH, Ota A, Wang C, Chiang C, et al. Global trend in overweight and obesity and its association with cardiovascular disease incidence. Circ J 2014;78:2807–18.
[18] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–8. 3.
[19] Frenkel WJ, Jongerius EJ, Mandjes-van Uitert MJ, van Munster BC, de Rooij SE. Validation of the Charlson Comorbidity Index in acutely hospitalized elderly adults: a prospective cohort study. J Am Geriatr Soc 2014;62:342–6.
[20] Potretzke MA, Kim EH, Knight BA, Anderson BG, Park AM, Sherburne Figenshau R, et al. Patient comorbidity predicts hospital length of stay after robot-assisted prostatectomy. J Robot Surg 2016;10:151–6.
[21] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
[22] Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consenseus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 2014;15:95–101.
[23] Wu BW, Yin T, Cao WX, Gu ZD, Wang XJ, Yan M, et al. Clinical application of subjective global assessment in Chinese patients with gastrointestinal cancer. World J Gastroenterol 2009;15:3542–9.
[24] Hendry PO, Hausel J, Nygren J, Lassen K, Dejong CH, Ljungqvist O, et al. Determinants of outcome after colorectal resection within an enhanced recovery programme. Br J Surg 2009;96:197–205.
[25] Leung AM, Gibbons RL, Vu HN. Predictors of length of stay following colorectal resection for neoplasms in 183 Veterans Affairs patients. World J Surg 2009;33:2183–8.
[26] Stechmiller JK. Understanding the role of nutrition and wound healing. Nutr Clin Pract 2010;25:61–8.
[27] Ng MF. Cachexia – an intrinsic factor in wound healing. Int Wound J 2010;7:107–13.