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Research article

The Effects of Preoperative Weight Loss on Nutritional Status and Prognosis for Esophageal Cancer

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Abstract

Objective: The use of neo-adjuvant chemotherapy and the presence of a progressive disease during the preoperative waiting period are associated with nutritional deterioration in patients with esophageal cancer. This study aimed to evaluate the effect of preoperative weight loss on the perioperative nutritional status and postoperative prognosis of patients with esophageal cancer.

Patients and Methods: A total of 119 patients with esophageal cancer were divided into two study groups based on their preoperative and normal body weights. One group comprised patients with ≥5% weight loss (WL group) and the other group comprised those with <5% weight loss (weight maintenance; WM group) in the preoperative phase. Furthermore, we conducted a multivariate analysis using a Cox proportional hazards model to estimate postoperative prognosis factors in patients with esophageal cancer.

Results: The WL group had a significantly higher risk of dysphagia, esophageal obstruction, and a deteriorated nutritional status, than the WM group. Furthermore, oral intake was significantly lower in the WL group than that in the WM group ($p < 0.05$). Additionally, the WL group had both an inferior postoperative nutritional status and lower survival rate than the WM group ($p = 0.049$). Multivariate analysis identified only disease stage as preoperative independent predictors of mortality. In a multivariate analysis of preoperative weight loss as a potential independent variable, after excluding disease stage, the hazard ratio (95% confidence interval) of preoperative weigh loss was 3.17 (0.83–12.07).

Conclusion: Preoperative weight loss was associated with compromised preoperative and postoperative nutritional statuses. Moreover, preoperative weight loss was associated with poor postoperative prognosis in patients with esophageal cancer. Our study data indicated the importance of positive nutritional support before esophagectomy.

Keywords: Nutrition; Esophageal Cancer; Preoperative Weight Loss; Prognosis

Introduction

Esophagectomy is among the most invasive surgeries performed in patients with esophageal cancer; in addition to the tumor dissection, this surgery involves a wide operative field that includes the neck, chest, and abdomen, as well as lymph node dissection. Because the esophagus acutely affects metabolic, neuroendocrine, and immune systems, postoperative patients experience significant deterioration of nutritional status because of hypermetabolism and digestion-absorption disorders [1-5]. In early stages, esophageal cancer is often asymptomatic and difficult to detect; accordingly, symptomatic patients often present with progressive disease. In recent years, a comparative study of the timing of perioperative therapy yielded better results with neo-adjuvant chemotherapy than with adjuvant chemotherapy [6]. However, patients receiving neo-adjuvant chemotherapy experienced the same postoperative stresses as patients who underwent surgery alone, including malnutrition and weight loss associated with diarrhea and anorexia resulting from renal dysfunction, bone marrow suppression and digestive toxicity caused by preoperative chemotherapy. Weight loss is a well-known occurrence after esophagectomy, with a reported weight loss of 10% during the first postoperative year. Moreover, other study reported that an early recovery of postoperative nutrient status is difficult for patients after esophagectomy [7,8]. This study aimed to investigate the influence of preoperative nutritional status on postoperative nutritional status and prognosis.

Materials and Methods

1. Subjects

A total of 119 patients at Osaka City University were enrolled in this study between April 1, 2009 and January 31, 2011. All patients were diagnosed with esophageal cancer and underwent esophagectomy (thoracoscopic laparotomy or thoracolaparotomy) and enterostomy. Patients were surveyed preoperatively and 1 month, 3 months, and 6 months postoperatively. All patients signed informed consent to participate in the study, and the study received the approval of the Ethics Committee at Osaka City University Medical School.

2. Neoadjuvant therapy and complications

Details regarding neoadjuvant therapy and complications were collected from medical charts.

3. Anthropometry

Each patient's height, preoperative weight, arm circumference (AC), triceps skinfold (TSF), and grip strength were measured during the nutritional status evaluation. The body mass index (BMI), arm muscle circumference (AMC), and arm muscle area (AMA) were subsequently calculated. . To consider the age and sex related differences, AC, TSF, grip strength, AMC, and AMA were dicided by each age and sex median in accordance with the Japanese Anthropometric Reference Data 2001 (JARD2001) and the Physical Strength Athletic Capability Incestigation of Japan 2008, and these were shown as percentages. The usual body weight (UBW), defined as the patient's weight 6 months before surgery, was recalled. InBody 430 (InBody Co., Ltd., Seoul, Korea) was used to perform body composition analysis, and the data were divided by each age and sex for the machine data (muscle, fat, and mineral). The %UBW was measured in a ration of the preoperative and postoperative weight to the the recalled weight. The %PRE was measured as a ratio of the postoperative weight to preoperative weight.

4. Laboratory data and nutritional status assessment

To evaluate the nutritional status, data were collected for the following parameters: white blood cell (WBC) count, total lymphocyte count (TLC), C-reactive protein (CRP), albumin (Alb), cholinesterase (ChE), triglyceride (TG), total cholesterol (T-Chol), high-density lipoprotein cholesterol (HDL-Chol), low-density lipoprotein cholesterol (LDL-Chol), free fatty acid (FFA), transthyretin (TTR), retinol-binding protein (RBP), zinc (Zn), copper (Cu), and iron (Fe). To assess the nutritional status, the prognostic nutritional index (PNI) 3), nutritional risk index (NRI), and controlling nutritional status (CONUT) 9) were determined. PNI and NRI were calculated using the following formulas: PNI = 10 × Alb + 0.005 × TLC; NRI = 10.7 × Alb + 0.00039 × TLC + 0.11 × Zn – 0.44 × Age

CONUT was calculated using Table 1 and the following formulas: CONUT score = (Alb score) + (TLC score) + (T-Chol score)

Table 1. Assessment using the CONUT score

Alb	≧ 3.50	3.00 - 3.49	2.50 - 2.99	< 2.50
Score	0	2	4	6
TLC	≧ 1600	1200 - 1599	800 - 1199	< 800
Score	0	1	2	3
T-Cho	≧ 180	140 - 179	100 - 139	< 100
Score	0	1	2	3

5. Nutritional intake during the hospital stay

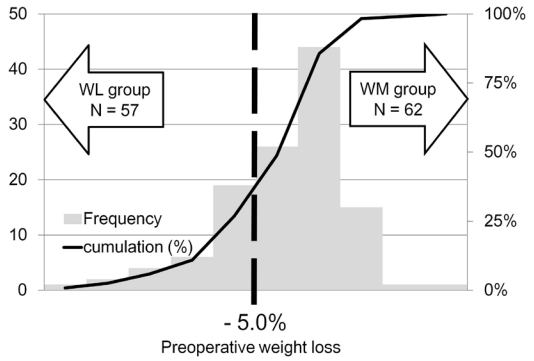
To evaluate the nutritional status during hospital stays, information about the daily oral intake (only hospital diet), enteral diet, and intravenous diet during the 1-week preoperative period was collected. These data were used to calculate the average energy, protein, fat, and salt content values.

6. Classification according to the rate of preoperative weight loss

The %Pre distribution is shown in Figure 1. For this study, patients were classified into the following groups according to a median %Pre of 4.7%: %Pre ≥ 95.0%, Weight Maintenance

group (WM group) and %Pre < 95.0%, Weight Loss group (WL group). We compared the two groups to determine the effect of preoperative weight loss.

Figure 1. Subjects distribution using rate of preoperative weight loss.



7. Statistical Analysis

The outcomes are presented as means ± standard deviations (SDs), numbers of patients, or percentages. The Mann–Whitney U and chi-square tests were used to compare data. Survival data were analyzed using the Kaplan–Meier survival model and were calculated from the date of surgery to the date of death or the most recent follow-up. The log-rank test was used to determine statistical differences between the two groups. For the multivariate analysis, a Cox proportional hazards model was used to determine the independent prognostic factors. Analytical factor included preoperative weight loss (WM group vs. WL group), sex (M vs. F), age (<65 vs. ≥65 years), stage (Stage 0–II vs. III–V), neoadjuvant therapy (yes vs. no), BMI (<18.5 vs. ≥18.5), and PNI (<45 vs. ≥45).

Dr. SPSS II statistical software for Windows, version 11.01 J (SPSS Inc., Chicago, IL, USA) was used for analytical comparisons of the two groups. SAS 9.4 software (SAS Institute, Inc., Cary, NC, USA) was used for the univariate and multivariate analyses. A p value <0.05 was considered statistically significant.

Results

1. Preoperative characteristics and nutritional statuses of the patients

The patients' preoperative characteristics and nutritional status details are listed in Tables 2, 3 and 4. Height and preoperative body weight did not differ significantly between the groups. However, the UBW was significantly higher in the WL group (WM vs. WL: 57.9 ± 8.5 kg vs. 62.7 ± 10.7 kg, p = 0.021). The WL group had significantly higher rates of radiotherapy and complications of dysphagia and obstruction. On the other hand, the groups did not differ significantly with regard to sex, age, tumor stage, or chemotherapy use.

Table 2. Subjects characteristics.

	n	
Sex (Male/Female)	119	90/29
Age (years)	119	64.1 ± 8.0
Tumor Stage (0/I/IIa/IIb/III/IVa/IVb/V)	119	13/25/24/14/25/15/3
Height (cm)	119	163.5 ± 7.7
Weight (kg)	119	56.1 ± 8.9
BMI (kg/m^2)	119	20.9 ± 2.7
UBW (kg)	119	60.2 ± 9.9
% UBW	119	93.5 ± 7.5
Preoperative chemotherapy (Yes/No)	119	47/72
Preoperative radiotherapy (Yes/No)	115	17/98
Manification disorder (Yes/No)	118	10/108
Dysphagia (Yes/No)	117	10/107
Obstruction (Yes/No)	117	43/74

Data are expressed as mean±SD or as number of patients.

Table 3. Subjects characterisitcs between WM group and WL group.

	WM group	WL group	P value
Sex (Male/Female)	48/14	42/15	0.637
Age (years)	64.9 ± 8.3	63.1 ± 7.7	0.223
Tumor Stage (0/I/IIa/IIb/III/IVa/IVb/V)	8/17/9/10/11/6/1	5/8/15/4/1 4/9/2	0.082
Height (cm)	163.3 ± 7.6	163.6 ± 6.9	0.850
Weight (kg)	57.2 ± 8.3	54.8 ± 9.4	0.073
BMI (kg/m^2)	21.4 ± 2.5	20.4 ± 2.9	0.025
UBW (kg)	57.9 ± 8.5	62.7 ± 10.7	0.021
Preoperative chemotherapy (Yes/No)	26/36	21/36	0.572
Preoperative radiotherapy (Yes/No)	5/57	13/44	0.026
Manification disorder (Yes/No)	7/54	3/54	0.228
Dysphagia (Yes/No)	2/59	8/48	0.034
Obstruction (Yes/No)	14/47	29/27	0.001
Postoperative hospitalization days (days)	32.6 ± 15.4	39.7 ± 34.1	0.790

Data are expressed as mean±SD or as number of patients.
Differences between the two groups were analyzed using the chi-squared test and the Mann-whitney U test.
P values less than 0.05 were considered significant.

Compared with the WM group, the WL group had significantly lower AC, TSF, and %Fat values in anthropometry analysis. Regarding laboratory data, the WL group had a significantly higher CRP and poorer nutrient assessment index values (PNI, NRI, and CONUT) relative to the WM group.

Table 4. Anthropometric assessments and laboratory evaluation between WM group and WL group

	WM group	WL group	WM : WL	P value
% UBW	99.0 ± 2.9	87.6 ± 6.4	62 : 57	< 0.001
% AC	97.6 ± 7.1	94.1 ± 9.7	62 : 57	0.036
% TSF	102.3 ± 35.1	88.7 ± 38.5	62 : 57	0.022
% AMC	98.7 ± 8.3	96.9 ± 7.8	62 : 57	0.100
% AMA	98.1 ± 16.1	94.5 ± 15.1	62 : 57	0.100
% Hand grip strength	77.5 ± 16.5	76.7 ± 18.2	62 : 57	0.644
% Skeltal muscle	91.9 ± 7.1	89.6 ± 8.2	61 : 56	0.181
% Body fat	126.3 ± 47.5	109.3 ± 50.5	61 : 56	0.029
% Mineral	90.0 ± 6.4	88.9 ± 8.7	61 : 56	0.468
TLC (cells/mm^3)	1660 ± 556	1596 ± 581	62 : 57	0.509
CRP (mg/dL)	0.25 ± 0.60	1.06 ± 1.88	62 : 57	< 0.001
Alb (g/dL)	4.12 ± 0.32	3.95 ± 0.33	62 : 57	0.002
ChE (IU/L)	312 ± 64	271 ± 63	61 : 57	< 0.001
TG (mg/dL)	155 ± 98	127 ± 63	62 : 57	0.297
T-chol (mg/dL)	205 ± 35	187 ± 45	61 : 57	0.006
HDL-chol (mg/dL)	53 ± 14	47 ± 16	49 : 41	0.032
LDL-chol (mg/dL)	120 ± 33	108 ± 29	50 : 41	0.031
FFA (mEq/L)	0.39 ± 0.28	0.41 ± 0.29	49 : 40	0.704
TTR (mg/dL)	28.6 ± 6.9	23.6 ± 7.3	52 : 43	< 0.001
RBP (mg/dL)	4.3 ± 1.1	3.9 ± 2.9	48 : 41	0.001
Zn (μg/dL)	67 ± 13	67 ± 14	54 : 47	0.889
Cu (μg/dL)	110 ± 18	133 ± 30	53 : 47	< 0.001
Fe (μg/dL)	97 ± 34	72 ± 38	55 : 48	< 0.001
PNI	49.5 ± 4.2	47.5 ± 4.9	62 : 57	0.024
NRI	54.9 ± 4.6	52.8 ± 5.3	54 : 47	0.035
CONUT	1.0 ± 1.3	1.6 ± 1.6	61 : 57	0.022

Data are expressed as mean±SD or as number of patients.
Differences between the two groups were analyzed using the Mann-whitney U test.
P values less than 0.05 were considered significant.

Preoperative dietary data are shown in Table 5. The totals of each nutrient, regardless of nutrient route, did not differ significantly among the groups. However, the WL group had significantly lower and higher nutrient intakes via the oral and intravenous routes, respectively, when compared with the WM group. The groups did not differ significantly with respect to enteral nutrition.

2. Postoperative nutritional statuses of patients

The nutritional statuses at 1, 3, and 6 months postoperation are shown in Tables 6, 7, and 8. Although weight did not significantly differ between the groups at any survey point, the %UBW in the WL group remained significantly lower than that of the WM group until 6 months postoperatively (WM vs. WL: 86.3 ± 6.1% vs. 81.7±7.3%, p = 0.001). Regarding anthropometric data, the %AMC and %AMA were significantly lower in the WL group than that in the WM group at the 6-month postoperative time point. In the body composition analysis, the %Fat value was significantly lower in the WL group than that in the WM group at the 1-month postoperative survey, although these values did not significantly differ thereafter. Of the laboratory data and nutritional index data, the ChE and PNI at 1 and 3 months postoperatively were significantly lower and the CRP at 6 months postoperatively was significantly higher in the WL group, compared with the than WM group.

Table 5. Nutritional intake for the duration of preoperative one week

	WM group	WL group	WM : WL	P value
Oral intake + Enteral nutrition + Intravenous nutrition				
Energy (kcal/day)	1508 ± 346	1589 ± 333	62 : 57	0.130
Protein (g/day)	60.5 ± 14.8	60.1 ± 14.4	62 : 57	0.836
Fat (g/day)	36.8 ± 16.1	32.1 ± 13.8	62 : 57	0.167
Salt (g/day)	7.5 ± 1.8	7.0 ± 1.7	62 : 57	0.189
Percentage of Oral intake				
Energy (%)	78.8 ± 23.7	62.8 ± 34.0	62 : 57	0.007
Protein (%)	80.1 ± 24.0	64.2 ± 34.5	62 : 57	0.008
Fat (%)	90.3 ± 26.4	78.9 ± 36.8	62 : 57	0.046
Salt (%)	79.1 ± 22.0	62.6 ± 34.2	62 : 57	0.008
Percentage of Enteral nutrition				
Energy (%)	3.5 ± 12.7	4.7 ± 16.6	62 : 57	0.673
Protein (%)	3.6 ± 12.9	4.9 ± 17.5	62 : 57	0.673
Fat (%)	4.5 ± 15.3	5.9 ± 19.8	62 : 57	0.673
Salt (%)	2.1 ± 8.2	3.5 ± 14.1	62 : 57	0.658
Percentage of Intravenous nutrition				
Energy (%)	17.7 ± 21.0	32.4 ± 33.1	62 : 57	0.026
Protein (%)	16.3 ± 21.3	30.9 ± 33.4	62 : 57	0.028
Fat (%)	0.3 ± 2.7	9.9 ± 27.3	62 : 57	0.019
Salt (%)	18.8 ± 20.8	33.8 ± 33.0	62 : 57	0.014

Data are expressed as mean±SD or as number of patients.
Differences between the two groups were analyzed using the Mann-whitney U test.
P values less than 0.05 were considered significant.

3. Long term outcomes after esophagectomy

The postoperative survival rates in both groups are shown in Figure 2. The WL group had a significantly lower postoperative survival rate, compared with the WM group (p = 0.049). The results of univariate and multivariate analyses of various factors are shown in Table 9. The univariate analysis identified preoperative predictors of mortality, including preoperative weight loss, sex, age, stage, neoadjuvant therapy, BMI, and PNI, which were then subjected to a multivariate analysis. However, the only preoperative independent predictor of mortality was disease stage, which had the highest hazard ratio of 8.57 (95%

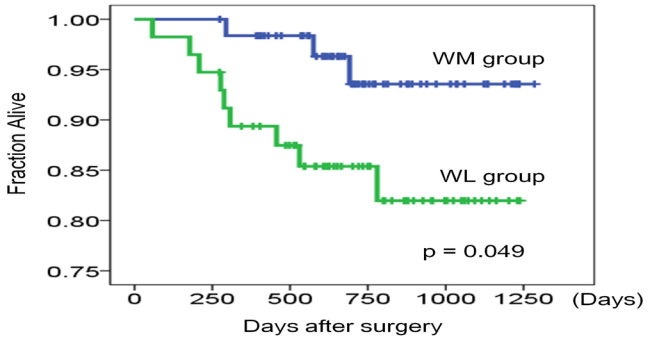
confidence interval: 1.84–40.02). We then conducted a multivariate analysis wherein the disease stage was excluded to investigate the potential prognostic factors among the variables, and identified preoperative weight loss as a potential independent variable (Table 10). Compared with sex [hazard ratio = 4.35 (0.50–38.04)], the hazard ratio of preoperative weight loss was 3.17 (0.83–12.07). Moreover, another multivariate analysis evaluated only stage III–V patients (Table 11). No factors were statistically related, and preoperative weight loss had the highest hazard ratio [3.00 (0.61–14.81)].

Table 6. Postoperative 1 month.

	WM group	WL group	WM : WL	P value
Weight (kg)	54.1 ± 7.6	52.5 ± 8.7	54 : 52	0.164
% UBW	94.3 ± 4.2	84.4 ± 7.0	54 : 52	< 0.001
% PRE	94.3 ± 4.0	96.7 ± 3.8	54 : 52	0.001
% AC	93.6 ± 7.2	91.2 ± 9.4	55 : 53	0.198
% TSF	91.0 ± 31.8	82.5 ± 31.2	55 : 53	0.176
% AMC	95.6 ± 7.9	94.2 ± 7.7	55 : 53	0.284
% AMA	92.1 ± 15.2	89.3 ± 14.5	55 : 53	0.286
% Hand grip strength	70.0 ± 16.7	69.1 ± 18.9	55 : 53	0.638
% Skeltal muscle	87.5 ± 8.9	86.9 ± 8.9	53 : 49	0.955
% Body fat	114.2 ± 43.8	97.8 ± 46.8	53 : 49	0.046
% Mineral	89.3 ± 8.5	90.5 ± 10.5	53 : 49	0.630
BMI (kg/m^2)	20.3 ± 2.3	19.7 ± 2.8	54 : 52	0.119
TLC ($cells/mm^3$)	1490 ± 760	1271 ± 479	58 : 51	0.215
CRP (mg/dL)	1.75 ± 3.03	2.55 ± 3.92	60 : 56	0.200
Alb (g/dL)	3.42 ± 0.47	3.31 ± 0.50	60 : 56	0.256
ChE (IU/L)	214 ± 72	188 ± 56	48 : 41	0.037
TG (mg/dL)	116 ± 74	103 ± 39	50 : 45	0.272
T-chol (mg/dL)	161 ± 37	163 ± 34	49 : 45	0.677
TTR (mg/dL)	19.1 ± 6.4	15.6 ± 5.6	41 : 32	0.011
RBP (mg/dL)	2.91 ± 0.89	2.64 ± 1.28	39 : 30	0.095
PNI	41.4 ± 6.4	38.9 ± 5.6	57 : 50	0.025
CONUT	3.7 ± 2.6	4.3 ± 2.6	47 : 42	0.176

Data are expressed as mean±SD or as number of patients.
Differences between the two groups were analyzed using the Mann-whitney U test.
P values less than 0.05 were considered significant.

Figure 2. The survival curve for patients after esophagectomy between WM group and WL group.



The survival rates were calculated using the Kaplan-Meier method.
Difference between two groups were analyzed using the log rank test.
P value less than 0.05 were considered significant.

Table 7. Postoperative 3month

	WM group	WL group	WM : WL	P value
Weight (kg)	52.3 ± 7.7	51.3 ± 8.6	47 : 46	0.420
% UBW	88.7 ± 4.1	82.2 ± 6.2	47 : 46	< 0.001
% PRE	89.6 ± 3.9	93.7 ± 4.8	47 : 46	< 0.001
% AC	90.6 ± 6.5	88.1 ± 8.8	47 : 44	0.161
% TSF	83.2 ± 31.1	78.8 ± 35.4	47 : 44	0.382
% AMC	93.5 ± 6.8	91.4 ± 7.0	47 : 44	0.118
% AMA	87.8 ± 12.7	84.0 ± 12.9	47 : 44	0.118
% Hand grip strength	69.6 ± 15.8	69.1 ± 17.8	47 : 46	0.935
% Skeltal muscle	85.6 ± 8.7	84.3 ± 10.0	47 : 44	0.413
% Body fat	95.1 ± 37.1	92.1 ± 47.3	47 : 44	0.600
% Mineral	90.0 ± 20.7	85.6 ± 10.9	47 : 44	0.193
BMI (kg/m^2)	19.5 ± 2.1	19.1 ± 2.7	47 : 46	0.345
TLC ($cells/mm^3$)	1602 ± 588	1417 ± 695	57 : 51	0.113
CRP (mg/dL)	0.47 ± 0.77	0.84 ± 1.73	57 : 52	0.474
Alb (g/dL)	3.90 ± 0.33	3.72 ± 0.30	57 : 53	< 0.001
ChE (IU/L)	263 ± 85	224 ± 65	41 : 41	0.026
TG (mg/dL)	101 ± 40	103 ± 41	51 : 43	0.967
T-chol (mg/dL)	186 ± 33	182 ± 36	53 : 43	0.553
PNI	47.0 ± 5.2	44.1 ± 5.2	57 : 50	0.004
CONUT	1.51 ± 1.48	2.19 ± 1.84	53 : 42	0.076

Data are expressed as mean±SD or as number of patients.
Differences between the two groups were analyzed using the Mann-whitney U test.
P values less than 0.05 were considered significant.

Table 8. Postoperative 6month

	WM group	WL group	WM : WL	P value
Weight (kg)	51.7 ± 6.5	50.6 ± 9.1	41 : 34	0.322
% UBW	86.3 ± 6.1	81.7 ± 7.3	41 : 34	0.001
% PRE	89.6 ± 7.1	92.8 ± 7.9	41 : 34	0.012
% AC	90.0 ± 5.9	87.0 ± 9.0	39 : 34	0.087
% TSF	76.2 ± 29.0	75.2 ± 34.3	39 : 34	0.686
% AMC	93.5 ± 5.3	90.6 ± 7.2	39 : 34	0.029
% AMA	87.7 ± 10.0	82.6 ± 13.3	39 : 34	0.028
% Hand grip strength	74.4 ± 13.3	73.6 ± 19.4	41 : 34	0.523
% Skeltal muscle	87.0 ± 6.2	87.2 ± 9.6	40 : 33	0.588
% Body fat	84.0 ± 27.7	78.9 ± 42.1	40 : 33	0.224
% Mineral	87.9 ± 7.6	85.6 ± 8.3	40 : 33	0.533
BMI (kg/m^2)	19.1 ± 1.9	18.9 ± 2.7	41 : 34	0.419
TLC ($cells/mm^3$)	1637 ± 647	1564 ± 693	52 : 45	0.452
CRP (mg/dL)	0.31 ± 0.81	0.78 ± 1.79	50 : 46	0.016
Alb (g/dL)	4.00 ± 0.24	3.96 ± 0.38	51 : 46	0.191
ChE (IU/L)	248 ± 48	250 ± 77	48 : 40	0.140
TG (mg/dL)	81 ± 36	92 ± 41	48 : 40	0.524
T-chol (mg/dL)	185 ± 26	187 ± 35	47 : 41	0.474
PNI	48.1 ± 4.3	47.2 ± 6.0	51 : 45	0.208
CONUT	1.23 ± 1.15	1.83 ± 1.82	46 : 41	0.057

Data are expressed as mean±SD or as number of patients.
Differences between the two groups were analyzed using the Mann-whitney U test.
P values less than 0.05 were considered significant.

Table 9. Multivariate Cox analysis for survival in overall

			Alive n=107	Dead n=12	Univariate Hazard Ration	p value	Multivariate Hazard Ration	p value
Preoperative weight loss	0	WM：%PRE≧95%	59	3	1		1	
	1	WL：%PRE< 95%	48	9	3.43 (0.93-12.69)	0.065	2.56 (0.65-10.04)	0.177
Sex	1	Female	28	1	1		1	
	0	Male	79	11	3.47 (0.45-26.92)	0.234	3.91 (0.45-33.67)	0.215
Age	0	< 65	59	6	1		1	
	1	≧65	48	6	1.26 (0.41-3.90)	0.691	1.29 (0.37-4.49)	0.685
Stage	0	Stage 0 ~ II	74	2	1		1	
	1	StageIII ~ V	33	10	9.96 (2.18-45.51)	0.003	8.57 (1.84-40.02)	0.006
Neoadjuvant therapy	0	yes	54	4	1		1	
	1	no	53	8	2.25 (0.67-7.55)	0.188	1.50 (0.42-5.42)	0.536
BMI	0	≧18.5	90	9	1		1	
	1	＜18.5	17	3	1.59 (0.43-5.87)	0.487	1.27 (0.33-4.92)	0.726
PNI	0	≧45	86	8	1		1	
	1	＜45	21	4	1.93 (0.58-6.43)	0.282	1.47 (0.39-5.57)	0.575

Analysis was performed using the Cox proportion hazard model. P value less than 0.05 were considered significant

Table 10. Multivariate Cox analysis for survival excluding Stage

			Alive n=107	Dead n=12	Univariate Hazard Ration	p value	Multivariate Hazard Ration	p value
Preoperative weight loss	0	WM：%PRE≧95%	59	3	1		1	
	1	WL：%PRE< 95%	48	9	3.43 (0.93-12.69)	0.065	3.17 (0.83-12.07)	0.091
Sex	1	Female	28	1	1		1	
	0	Male	79	11	3.47 (0.45-26.92)	0.234	4.35 (0.50-38.04)	0.184
Age	0	< 65	59	6	1		1	
	1	≧65	48	6	1.26 (0.41-3.90)	0.691	1.08 (0.33-3.55)	0.906
Neoadjuvant therapy	0	yes	54	4	1		1	
	1	no	53	8	2.25 (0.67-7.55)	0.188	1.66 (0.46-6.04)	0.440
BMI	0	≧18.5	90	9	1		1	
	1	＜18.5	17	3	1.59 (0.43-5.87)	0.487	1.75 (0.45-6.84)	0.420
PNI	0	≧45	86	8	1		1	
	1	＜45	21	4	1.93 (0.58-6.43)	0.282	1.52 (0.41-5.59)	0.532

Analysis was performed using the Cox proportion hazard model.
P value less than 0.05 were considered significant.

Table 11. Multivariate Cox analysis for survival in patients with stageIII-V

			Alive n=33	Dead n=10	Univariate Hazard Ration	p value	Multivariate Hazard Ration	p value
Preoperative weight loss	0	WM：%Pre≧95%	16	2	1		1	
	1	WL：%Pre<95%	17	8	3.11 (0.66-14.70)	0.152	3.00 (0.61-14.81)	0.178
Sex	1	Female	15	3	1		1	
	0	Male	18	7	2.02 (0.51-7.95)	0.316	2.38 (0.58-9.69)	0.226
BMI	0	≧18.5	27	7	1		1	
	1	＜18.5	6	3	1.50 (0.39-5.80)	0.557	1.23 (0.31-4.84)	0.765
PNI	0	≧45	26	6	1		1	
	1	＜45	7	4	2.32 (0.65-8.24)	0.195	1.75 (0.47-6.48)	0.401

Analysis was performed using the Cox proportion hazard model. P value less than 0.05 were considered significant.

Discussion

Postoperative weight recovery is known to be difficult for patients with esophageal cancer who experience perioperative weight loss [7,8]. We hypothesized that better preoperative nutritional status maintenance would help to prevent deterioration in the postoperative nutritional status of patients with esophageal cancer. This study therefore investigated the inflence of preoperative weight loss on the perioperative nutritional status and postoperative prognosis. This study included more than 100 patients treated at a single facility and by the same practitioner. Moreover, as the relatively short study period allowed all patients to undergo surgery according to the same operative and perioperative management procedures, we consider this study to provide a high quality analysis of patients undergoing esophagectomy.

Regardless of tumor stage, the preoperative nutritional status was worse in the WL group than in the WM group. The relevance of preoperative weight loss and the tumor stage was not obvious, as a previous study reported that patients with a BMI ≥25 tended to have a lower tumor stage at the time of esophageal cancer diagnosis, compared to patients with a BMI < 25 [10]. However, the Japanese esophageal cancer patients in this study had BMI values within the normal range, and there were no report adapting this study. In addition, cancer patients tend to be malnourished, regardless of the tumor size [11]. The mere existence of a tumor is associated with deterioration in the nutritional status.

The total nutrient intake during the preoperative hospital stay did not differ significantly between the groups; however, the WL group had a significantly lower oral nutrition intake and higher intravenous nutrition intake than the WM group. Furthermore, the WL group included significantly more patients who underwent radiotherapy and experienced dysphagia and obstruction, compared with the WM group. Deterioration of the nutritional status in response to a decrease in intake is known to correlate with esophageal stricture and fibrogenesis, and heartburn is a known side effect of radiotherapy for patients with esophageal cancer [12]. In previous reports, patients undergoing neoadjuvant therapy with radiotherapy for esophageal cancer had a 2-fold increase in the risk of malnutrition [13]; the present study also suggested an association between radiotherapy and deterioration inthe nutritional status. The TSF and %Fat, which are related to body fat, were significantly lower in the WL group than in the WM group, whereas the %Muscle, which is related to body protein, did not differ significantly between the groups. In both groups, the %Muscle values were lower than the reference value calculated by the body composition analyzer. In other words, regardless of the degree of weight loss, all patients with esophageal cancer might experience a decrease in body protein; therefore, the difference in weight loss between the two groups might result from a difference in body fat loss. The Alb, ChE, and TTR values, which are related to internal organ proteins, were within normal limits in both groups, indicating the maintenance of proteins in these organs.

The WL group had a significantly poorer postoperative survival prognosis than did the WM group. Dewys reported that patients with >5% weight loss before chemotherapy had a significantly poorer prognosis than did patients with a <5% weight loss [14], which was similar to the results observed

in our study. A study of patients undergoing thoracoscopic esophageal cancer surgery found that those with a ≥10% weight loss during the first postoperative year had a significantly poorer prognosis, compared with those who experienced a <10% during the same period [15]. Our multivariate analyses suggested the disease stage was the only independent preoperative predictors of mortality, although preoperative weight loss was a potential independent variable. Although this study did not investigate local tumor growth (T) or region lymph node spread (N), which are components of the TMN classification, these factors are known to be independent prognostic predictors in patients with esophageal cancer [16-18]. This study defined preoperative weight loss as a >5% weight loss. Ikeda et al. stated that disease clinical TMN stage (III and IV), CRP (≥0.5 mg/dL), and body weight loss (>2%) were independent negative prognostic predictors in patients with esophageal cancer, and reported a hazard ratio for >2%weight loss of 1.64 (95% confidence interval: 1.09–2.46) [19]. In patients, significant body weight loss might therefore correlate strongly with the development of cancer-related cachexia [20]. In addition to disease progression, patients often exhibit a reduced nutritional status and decreased immunologic function because dysphagia and obstruction decrease oral intake [2-5,21]. This study indicates that intake disorders resulting from progressive cancer have an adverse impact on prognosis. Walsh et al. reported that neoadjuvant therapy confers a significant long-term survival advantage [22], and a meta-analysis reported a similar long-term advantage [23]. However, our study did not find this factor to be significant.

Our results suggest that weight loss adversely affects the postoperative survival rate. Patients with esophageal cancer tend to have a poor nutritional status throughout the preoperative and postoperative periods; however, the postoperative nutritional status and long-term survival would benefit from better maintenance of the preoperative nutritional status. Moreover, preoperative weight loss is thought to associate with a worse postoperative prognosis in patients with esophageal cancer. Data from the present study therefore indicate the importance of positive nutritional support prior to esophagectomy. Regardless of the primary lesion, patients with postoperative malnutrition are known to experience delayed wound healing and increased mortality and complication rates [24]. We believe that minimizing preoperative weight losses and preventing malnutrition will reduce the risk of perioperative complications and improve the survival rate.

We also considered potential limitations of this study. First, our study had a retrospective design, relatively small sample size, and short follow-up period. A prospective study with a large sample size is warranted in the future. Second, our study did not investigate nutrient intake from diagnosis to preoperative hospital admission, and therefore we could not identify an association between preoperative nutrient intake and the nutritional status. These issues will be addressed in a future study.

Conclusion

In patients treated surgically for esophageal cancer, preoperative weight loss was associated with postoperative nutritional status. The prevention of preoperative weight loss not only helped to maintain a better preoperative nutritional status, but also helped to mitigate and recover from postoperative weight loss.

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