RESEARCH ARTICLE

Clinical Determinants of Weight Loss in Patients with Esophageal Carcinoma During Radiotherapy: a Prospective Longitudinal View

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Abstract

Purpose: The prevalence of weight loss in esophageal carcinoma patients is high and associated with impairment of physical function, increased psychological distress and low quality of life. It is not known which factors may contribute to weight loss in patients with esophageal carcinoma during radiotherapy in China. The objective of this study was to identify the associated demographic and clinical factors influencing weight loss. Methods: We evaluated 159 esophageal carcinoma patients between August 2010 and August 2013 in a cross-sectional, descriptive study. Patient characteristics, tumor and treatment details, psychological status, adverse effects, and dietary intake were evaluated at baseline and during radiotherapy. A multivariate logistic regression analyss was performed to identify the potential factors leading to weight loss. Results: 64 (40.3%) patients had weight loss ≥5% during radiotherapy. According to logistic regression analysis, depression, esophagitis, and loss of appetite were adverse factors linked to weight loss. Dietary counseling, early stage disease and total energy intake ≥1441.3 (kcal/d) were protective factors. Conclusions It was found that dietary counseling, TNM stage, total energy intake, depression, esophagitis, and loss of appetite were the most important factors for weight loss. The results underline the importance of maintaining energy intake and providing dietary advice in EC patients during RT. At the same time, by identifying associated factors, medical staff can provide appropriate medical care to reduce weight loss. Further studies should determine the effect of these factors on weight loss and propose a predictive model.

Keywords: Esophageal carcinoma - weight loss - radiotherapy - energy intake - adverse effects

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Introduction

In 2008, an estimated 482, 000 cases of esophageal carcinoma (EC) were diagnosed in the world and approximately 407, 000 people died of the disease (Jemal et al., 2008). EC retains its status of top 4th leading cause of cancer deaths and the fifth most common diagnosed cancer in China in 2009 (Chen et al., 2013). The crude incidence rate for EC was 22.1/100, 000 in 2009, accounting for 7.7% of overall new cancer cases (Chen et al., 2013). Surgical treatment played a central role to cure early stage and locally advanced cancer. However, EC was often diagnosed at an advanced stage, and curative surgery could only be considered in 30% to 40% of patients (Schneider and Urba, 2007). The 5-year survival rate was only 35-45% for all patients with EC (Thompson et al., 2008). Radiotherapy (RT) is a valuable curative treatment for non-operable patients or with a non-resectable tumor (Bedenne et al., 2007). According to the survey, about 71.4% of EC patients were treated by RT in China. However, RT could induce side effects like dysphagia, esophagitis, diminished appetite, nausea, vomit, diarrhea, malabsorption and depression which could be in relation with weight loss (Hill et al., 2011).

In patients with EC, weight loss is common at presentation and a frequent cause of patient concern. At the time of initial treatment, prevalence of weight loss in EC patients has been reported to range from 32% to 70%, with 13%-16% of body weight (Khalid et al., 2007; Hill et al., 2011). This body weight alteration was the result of an imbalance between energy intake and energy expenditure and could be explained by a reduced food intake due to tumor obstruction itself, treatment-induced toxicities, cachexia associating hypercatabolism or secretion of proinflammatory cytokines (Laviano et al, 2003). Weight loss has been associated with impairment of physical function, increased psychological distress and low quality of life (Marín Caro et al., 2007; Payne et al., 2012).

However, to our knowledge, it is not known which factors may contribute to weight loss in patients with EC during RT in China, Therefore, the objective of this study was to identify the associated demographic and clinical factors influenced weight loss in EC patients during RT.

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Materials and Methods

Study population

We evaluated 159 consecutive patients diagnosed with EC between August 2010 and August 2013 at RT department of Tianjin Medical University Cancer Hospital, the biggest Cancer Hospital in Tianjin. All patients were treated by RT. The other eligibility criteria were as follows: (1) histologically or cytologically confirmed EC, (2) age of ≥ 18 years, (3) Karnofsky performance score (KPS) ≥ 60, (4) adequate bone marrow (white blood cell count of 4, 000/μl or more and 12, 000/μl or less; neutrophil count of 2, 000/μl or more; platelet count of 100, 000/μlor more; and hemoglobin level of 10.0 g/dl or more), (4) normal renal function (creatinine of <1.5 mg/dl and creatinine clearance of >60 ml/min), and (5) normal hepatic function (total bilirubin of <1.5 mg/dl, serum aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels <twice the upper limit of the normal range). Exclusion criteria included (1) a history of other cancers, (2) psychiatric disorders, and (3) active concomitant malignancy. Written informed consent was obtained from each of the patients prior to their entry into the study. This study was approved by the Ethics Committee of Tianjin Medical University Cancer Hospital

Data Collection

The study nurses weighed the patients at the baseline visit and at the end of RT. They calculated the percentage weight loss compared with the patient's weight assessed at the baseline. For those patients who experienced unintended weight loss ≥5% during RT, analyses were carried out to evaluate influencing factors associated with its incidence.

Before the beginning of RT, a structured general questionnaire was administrated to evaluate the patients' characteristics, including their age, gender, smoking, alcohol drinking, baseline weight, BMI, half year weight loss prior to RT, baseline dysphagia, KPS, prealbumin, and albumin.

The radiation oncologists provided detailed information on the primary tumor: site, pathology classification, the clinical TNM stage, and radiation dose. They assessed weekly from beginning to the end of RT the presence of acute adverse effects including fatigue, insomnia, fever, constipation, diarrhea, loss of appetite, nausea, vomiting, esophagitis, and dermatitis according to the Radiotherapy Oncology Group Acute Radiation Morbidity Scoring Criteria (Cox et al., 1995) and National Cancer Institute Common Terminology Criteria of Adverse Events (version 3.0).

The degree of anxiety was measured by the Chinese version of the Zung self-rating anxiety scale. The SAS is a 20-item, four-point Likert scale self-report instrument that assesses the presence and severity of affective symptoms and somatic components of anxiety. The test–retest reliability of the SAS is 0.9 (Xie and Dai, 2006). Internal consistency studies have demonstrated an α-coefficient of 0.9 for the test items in the Chinese version (Xie and Dai, 2006). The degree of depression was measured by the Chinese version of the Zung self-rating depression scale. The SDS is a 20-item four-point Likert scale self-report instrument that assesses depression. The test–retest reliability of the SDS is 0.9 (Lin et al., 2003). Internal consistency studies have demonstrated an α-coefficient of 0.8 for the test items (Lin et al., 2003). Each participant completed these two scales regarding his or her feeling at baseline and at the end of RT. The patients were considered as suffering from anxiety when their SAS standard scores were higher than 50, and as suffering from depression when their SDS standard scores were higher than 53.

A semi quantitative, 128-item Chinese food frequency questionnaire (FFQ), based on a previously validated instrument (Zhang et al., 2005), was administered at the beginning and at the end of RT. The FFQ assessed the dietary intake respectively over the year preceding treatment for the first questionnaire and during RT for the second. Food photographs were used to help patients quantify the portions consumed. We used the Chinese food composition table to calculate nutrient intakes (e.g., total energy intake, protein, fat, carbohydrates) from FFQ. The

Table 1. Patient Characteristics (n=159)

Characteristic	Number	Percentage	Mean±SD	Min	Max
Age (years)	159		57.6±9.7	44	78
Gender					
Male	122	76.7			
Female	37	23.3			
Weight prior to RT (kg)	159		58.7±7.5	44	89
Smoking					
Yes	125	78.6			
No	34	21.4			
Alcohol drinking					
Yes	109	68.6			
No	50	31.4			
Baseline dysphagia					
Yes	141	88.7			
No	18	11.3			
BMI					
<18.5	37	23.3			
≥18.5	122	76.7			
Half year weight loss prior to RT (%)					
<10	123	77.4			
≥10	36	22.6			
KPS	159		78.9±13.5	60	90
Tumor site					
Upper	58	36.5			
Middle	63	39.6			
Low	38	23.9			
Pathology classification					
Squamous carcinoma	130	81.8			
Adenocarcinoma	29	18.2			
TNM clinical stage					
I/II	42	26.4			
III/IV	117	73.6			
RT dose (Gray)	159		57.6±8.7	50	70
Duration of RT (week)	159		6±1.1	5	7
Prealbumin (g/dl)	159		0.3±0.1	0.04	1.2
<0.2	40	25.2			
≥0.2	119	74.8			
Albumin (g/dl)	159		4.4±0.5	2.4	5.2
<3.0	10	6.3			
3.0-5.5	149	93.7			

BMI, body mass index; KPS, karnofsky performance score; RT, radiotherapy

Table 2. Univariate Analysis the Factors for Weight Loss (n=159)

Variables	Category	Weight loss		χ^2 value	*p*
		≥5%	<5%		
Age[a]	<60	38 (42.7%)	51 (57.3%)	0.5	0.5
	≥60	26 (37.1%)	44 (62.9%)		
Gender	Male	45 (36.9%)	77 (63.1%)	2.5	0.1
	Female	19 (51.4%)	18 (48.6%)		
Smoking	Yes	50 (40.0%)	75 (60.0%)	0.02	0.9
	No	14 (41.2%)	20 (58.8%)		
Alcohol drinking	Yes	46 (42.2%)	63 (57.8%)	0.5	0.4
	No	18 (36.0%)	32 (64.0%)		
Baseline dysphagia	Yes	59 (41.8%)	82 (58.2%)	1.3	0.3
	No	5 (27.8%)	13 (72.2%)		
Weight prior to RT[a] (kg)	<60.5	23 (33.3%)	46 (66.7%)	2.4	0.1
	≥60.5	41 (45.6%)	49 (54.4%)		
BMI	<18.5	19 (51.4%)	18 (48.6%)	2.4	0.1
	≥18.5	45 (36.9%)	77 (63.1%)		
Half year weight loss prior to RT (%)	<10	45 (36.6%)	78 (63.4%)	3	0.08
	≥10	19 (52.8%)	17 (47.2%)		
KPS[a]	<80	29 (33.7%)	57 (66.3%)	3.3	0.06
	≥80	35 (47.9%)	38 (52.1%)		
Histology	Squamous carcinoma	55 (42.3%)	75 (57.7%)	1.3	0.3
	Adenocarcinoma	9 (31.0%)	20 (69.0%)		
Tumor site	Upper	24 (41.4%)	34 (58.6%)	1.7	0.4
	Middle	28 (44.4%)	35 (55.6%)		
	Low	12 (31.6%)	26 (68.4%)		
TNM clinical stage	I/II	12 (28.6%)	30 (71.4%)	3.2	0.07
	III/IV	52 (44.4%)	65 (55.6%)		
Baseline dysphagia	Yes	59 (41.8%)	82 (58.2%)	1.3	0.2
	No	5 (27.8%)	13 (72.2%)		
Treatment breaks	Yes	16 (57.1%)	12 (42.9%)	4	0.04
	No	48 (36.6%)	83 (63.4%)		
Dietary counseling	Yes	32 (33.7%)	63 (66.3%)	4.2	0.04
	No	32 (50.0%)	32 (50.0%)		
RT dose[a] (Gray)	<60	28 (36.8%)	48 (63.2%)	0.7	0.4
	≥60	36 (43.4%)	47 (56.6%)		
Duration of RT[a] (week)	<6	23 (33.3%)	46 (66.7%)	2.4	0.1
	≥6	41 (45.6%)	49 (54.4%)		
Prealbumin (g/dl)	<0.2	21 (52.5%)	19 (47.5%)	3.3	0.07
	≥0.2	43 (36.1%)	76 (63.9%)		
Albumin (g/dl)	<3.0	6 (60.0%)	4 (40.0%)	1.7	0.2
	3.0~5.5	58 (38.9%)	91 (61.1%)		
Depression	Yes	40 (46.5%)	46 (5.35%)	3.1	0.08
	No	24 (32.9%)	49 (67.1%)		
Anxiety	Yes	39 (48.1%)	42 (51.9%)	4.3	0.04
	No	25 (32.1%)	53 (67.9%)		
Fatigue	Grade 0	33 (32.7%)	68 (67.3%)	6.6	0.01
	Grade≥1	31 (53.4%)	27 (46.6%)		
insomnia	Grade 0	24 (34.3%)	46 (65.7%)	1.8	0.2
	Grade≥1	40 (44.9%)	49 (55.1%)		
Fever	Grade 0	54 (40.9%)	78 (59.1%)	0.1	0.8
	Grade≥1	10 (37.0%)	17 (63.0%)		
Constipation	Grade 0	29 (43.9%)	37 (56.1%)	0.7	0.4
	Grade≥1	35 (37.6%)	58 (62.4%)		
Diarrhea	Grade 0	52 (37.7%)	86 (62.3%)	3	0.09
	Grade≥1	12 (57.1%)	9 (42.9%)		
Loss of appetite	Grade 0	13 26.5 (%)	36 (73.5%)	5.5	0.02
	Grade≥1	51 (46.4%)	59 (53.6%)		
Nausea	Grade 0	47 (37.6%)	78 (62.4%)	1.7	0.2
	Grade≥1	17 (50.0%)	17 (50.0%)		
Vomiting	Grade 0	55 (38.7%)	87 (61.3%)	1.3	0.2
	Grade≥1	9 (52.9%)	8 (47.1%)		
Esophagitis	Grade 0	18 (29.0%)	44 (71.0%)	5.3	0.02
	Grade≥1	46 (47.4%)	51 (52.6%)		
Dermatitis	Grade 0	29 (39.2%)	45 (60.8%)	0.1	0.8
	Grade≥1	35 (41.2%)	50 (58.8%)		

[a]Variables were categorized according to the median; Values are the number and percentage of patients; BMI, body mass index; KPS, karnofsky performance score; RT, radiotherapy

Table 3. Associations Between Weight Loss and Food Intake During RT (n=159)

Variables	Category	Weight loss		χ^2 value	*p*
		≥5%	<5%		
Total energy intake (kcal/d)	<1441.3	24 (31.2%)	53 (68.8%)	5.1	0.02
	≥1441.3	40 (48.8%)	42 (51.2%)		
Protein (g/d)	<61.6	33 (44.6%)	41 (55.4%)	1.1	0.3
	≥61.6	31 (36.5%)	54 (63.5%)		
Fat (g/d)	<57.3	30 (36.1%)	53 (63.9%)	1.2	0.3
	≥57.3	34 (44.7%)	42 (55.3%)		
Carbohydrate (g/d)	<227.1	24 (34.3%)	46 (65.7%)	1.8	0.2
	≥227.1	40 (44.9%)	49 (55.1%)		

Variables were categorized according to the median; Values are the number and percentage of patients

Table 4. Multivariate Analysis of the Factors for Weight Loss (n=159)

Risk factor	Category	β	OR	95% CI	*p*-value
Dietary counseling	No vs yes	1.2	3.4	1.6~7.4	<0.05
TNM stage	III/IV vs I/II	1	2.8	1.1~6.8	<0.05
Total energy intake (kcal/d)	<1441.3 vs ≥1441.3	1.3	3.6	1.7 ~7.7	<0.05
Depression	Yes vs no	1.2	3.2	1.5~7.0	<0.05
Esophagitis	Grade≥1vs Grade 0	1	2.6	1.2~5.5	<0.05
Loss of appetite	Grade≥1vs Grade 0	1	2.7	1.2~6.2	<0.05

OR odds ratio, CI confidence interval

value of dietary intake (including energy, protein, fat, and carbohydrate) analyzed in the results refers to the average of the initial and the last evaluation.

Statistical analyses

For descriptive purposes, continuous variables were summarized as arithmetic means and standard deviation (SD). Categorical variables were summarized as relative frequencies and proportions. The variables were examined for their association with weight loss by univariate analysis with the χ^2 test or Fisher's exact test. A multivariate logistic regression analysis was performed to identify the potential factors leading to weight loss. Predictive variables with p values less than 0.1 for the univariate analysis were considered for inclusion in a multivariate model. The significant independent variables contributing to weight loss in patients with EC were extracted using stepwise selection methods. For each factor, the odds ratio and 95 % confidence interval were calculated, and criteria for inclusion in the final model were values of *p* less than 0.05. All of the statistical analyses were performed using SPSS software package version 17.0.

Results

Participant characteristics

A description of the study population is shown in Table 1. 141 (88.7%) patients presented an obstructive tumor and had baseline dysphagia. 95 (59.7%) received dietary counseling during RT. There was no patients performed nasojejunal feeding, jejunostomy or gastrostomy during RT in this study. 64 (40.3%) patients experienced weight loss ≥5% during RT. 28 (17.6%) patients had treatment break. Based on univariate analysis, weight loss was significantly associated with half year weight loss prior to RT, KPS, TNM clinical stage, treatment break, dietary counseling, prealbumin, depression, anxiety, fatigue, diarrhea, loss of appetite, esophagitis, and total energy intake (p<0.1, Table 2 and 3).

According to logistic regression analysis, dietary counseling (odds ratio, 3.4; p<0.05), TNM stage (odds ratio, 2.8; p<0.05), total energy intake (odds ratio, 3.6; p<0.05), depression (odds ratio, 3.2; p<0.05), esophagitis (odds ratio, 2.6 p<0.05), loss of appetite (odds ratio, 2.7; p<0.05) retained as significant influencing factors that contribute to weight loss during RT (Table 4).

Discussion

Weight loss can be a significant problem in EC patients during RT, but its influencing factors remain largely unknown. In this study, several factors were explored to identify factors that could explain weight loss during RT. The results indicated that six factors were associated with the occurrence of weight loss during RT in EC: dietary counseling, the stage of the disease, the total energy intake, depression, the occurrence of esophagitis, and the presence of loss of appetite during RT.

In this study, 40.3% patients had weight loss ≥5% during RT, much higher than the 19% reported by Jager-Wittenaar et al in head and neck cancer patients (Jager-Wittenaar et al., 2007). The results indicated that the incidence of weight loss was higher in EC patients during RT. More attention should be put into screening and intervention. An early risk screening of weight loss and longer period of nutritional intervention may result in effective weight gain and a more positive effect on quality of life, treatment-related morbidity and mortality (Jager-Wittenaar et al., 2007; Khoshnevis et al., 2012). Smoking and alcohol drinking did not appear as factors influencing weight loss in the univariate analysis. This may be because the majority of Chinese patients did smoking or alcohol drinking before the diagnosis and most of them quitted doing it during anti-tumor therapy.

Stage of disease was identified as an important determinant of weight loss on multivariate logistic regression. Patients with III/IV stage benefited in terms of developing weight loss ≥ 5% compared with patients who were in stage I/II. The present result was similar with the findings of Deans et al (Deans et al., 2009). The patients with advanced stage had a more aggressive tumor biological behavior which contained a variety of metabolic and endocrine changes such as higher metabolic demands of the tumor and increased resting energy expenditure (Hopkinson et al., 2006). A sustained and long hyper metabolism could largely lead to negative energy balance. Besides, patients in advanced stage experienced more side effects and diminished quality of life, which affected food consumption (Shahmoradi et al., 2009; Hill et al., 2011).

Our date showed that 54.1% of patients had depression during RT. This finding was higher than 25% reported by previous study in cancer patients (Mitchell et al., 2011). We also found that depression was associated with a 3.2-fold greater incidence of weight loss ≥ 5% ($p<0.05$). It was commonly recognized that psychological factors may add to the extent of body weight loss. As reported by Tian, depressed patients experienced more serious appetite loss and weight loss than the patients with no depression (Tian et al., 2001). Zhang et al. (2013) reported that appropriate comprehensive supportive care interventions might help to improve the psychological state of EC patients. Therefore, we recommended special programs which provided information and training in coping depression and relaxation were needed to develop in the future study.

Esophagitis was the predominant toxicity during RT in patient with EC, which decreased individuals' quality of life. The incidence of esophagitis was 61%, lower than the 89% reported by Seung et al (Seung et al., 2004). The data from this study provided strong evidence to support that the presence of esophagitis was an adverse factor of weight loss. Patients with esophagitis had pain and difficulties in swallowing. Treatment for esophagitis could relieve pain and reduce difficulty in eating, and then improve patients' nutritional status.

In this study, there were 110 (69.2%) patients with loss of appetite during RT, much higher than the 38% reported by Khalid et al study (Khalid et al., 2007). In the multivariate analysis, patients with loss of appetite (OR, 2.7; $p<0.05$) had a higher risk of weight loss during RT. Long-term loss of appetite can cause patient dehydration, electrolyte imbalance and malnutrition; affect the patient's quality of life and well-being (McCreery et al., 2013). It would be benefit to assess digestive symptoms and provide effective interventions to improve appetite during RT.

The total energy intake ≥1441.3 (kcal/d) was a protective factor for weight loss in EC during RT. Energy intake was served as a mediator that several of the identified predictors (e.g., TNM stage, esophagitis, appetite loss and depression) caused a decrease in calorie intake, which then in turn, caused the weight loss. The energy intake was the only variable which can be modified by the clinician; hence the ability to maintain energy intake in EC patients during RT was most important for controlling weight loss. Langius et al. (2013) reported that dietary counseling and interventions can improve patients' energy intake. The data from this study found that patient who had dietary counseling during RT had a lower risk of developing weight loss≥5% than patients with no dietary counseling. Previous studies have been proved that dietary counseling could improve nutritional intake and status in colorectal and breast cancer (Ravasco et al., 2005; Yavuzsen et al., 2012). Dietary counseling should be proposed to all patients received anti-cancer therapy as soon as possible (Senesse et al., 2008). In cases of severely malnourished patients or if the dietary counseling suffers a setback, artificial nutrition should then be proposed (Kato et al., 2013). Dietary interventions should be timely, with the first signs of symptoms, to prevent further nutritional depletion. A high-protein, moderate-fat diet consumed in small, frequent meals can be benefit to improve tolerance to diet. What's more, nutritional therapy could be provided via orally intake, enteral feeding tubes or parenteral means (Orrevall et al., 2009).

This study had some limitations. (1) The sample of this study was from a single hospital with a relatively small number of patients. A multicenter study will be needed in the future. (2) 37 (23.3%) patients in our study were female, so attempts should be made to over sample women in the further study. Despite these limitations, we believe that this study contained valuable predictive value for weight loss in patients with EC during RT.

In conclusion: This study clarified the influencing factors associated with weight loss during RT for EC patients. Depression, esophagitis, and loss of appetite were adverse factors linked to weight loss. Dietary counseling, the early stage disease, and energy intake ≥1441.3 (kcal/d) were protective factors. The results underline the importance of maintaining energy intake and providing dietary intake in EC cancer patients during RT. Meanwhile, by identifying these associated factors, medical staff can provide appropriate medical care to reduce the weight loss. Further studies can investigate the effect of these factors on weight loss and propose a predictive model in patient with EC.

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