RESEARCH ARTICLE

Lack of any Prognostic Value of Body Mass Index for Patients Undergoing Chemoradiotherapy for Esophageal Squamous Cell Carcinoma

Fang Zhang[1], Chuan-Sheng Wang[1], Bo Sun[1], Guang-Bo Tian[1], Fang-Li Cao[2], Yu-Feng Cheng[3]*

Abstract

Background: The relationship between body mass index(BMI) and outcomes after chemoradiotherapy(CRT) has not been systematically addressed. The purpose of this study was to evaluate the effect of BMI on survival in patients with esophageal squamous cell carcinoma (ESCC). Materials and Methods: Sixty ESCC cases were retrospectively reviewed in this study. Patient overall survival(OS) and disease-free survival (DFS) were compared between two groups (BMI<24.00 kg/m^2 and BMI≥24.00 kg/m^2). Results: There were 41 patients in the low/normal BMI group (BMI<24.00 kg/m^2) and 19 in the high BMI group (BMI≥24.00 kg/m^2). No significant differences were observed in patient characteristics between these. We found no difference in 2-year OS and DFS associated with BMI (p=0.763 for OS; p=0.818 for DFS) using the Kaplan-Meier method. Univariate analysis revealed that higher clinical stage was prognostic for worse 2-year OS and DFS, metastasis for 2-year OS, lymph node status for 2-year DFS, while age, gender, smoking, drinking, tumor location and BMI were not prognostic. There were no differences in the 2-year OS (hazard ratio=1.117; p=0.789) and DFS(hazard ratio=1.161; p=0.708) between BMI groups in multivariate analysis, whereas we found statistical differences in the 2-year OS and DFS associated with clinical stage, gender and tumor infiltration (p<0.04), independent of age, smoking, drinking, tumor location, the status of lymph node metastases and BMI. Conclusions: BMI was not associated with survival in patients with ESCC treated with CRT as primary therapy. BMI should not be considered a prognostic factor for patients undergoing CRT for ESCC.

Keywords: Squamous cell carcinoma - esophageal neoplasms - survival - body mass index - chemoradiotherapy

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Introduction

Esophageal cancers are among the most prevalent malignancies worldwide, with high rates of incidence and mortality (Ferlay et al., 2010; Spechler et al., 2011). There are two major histological types of esophageal carcinoma: esophageal squamous cell carcinoma (ESCC) and adenocarcinoma with considerably varied epidemiological features. ESCC continues to be the major type of esophageal cancer in Asia, whereas esophageal adenocarcinoma predominately affects the whites (Ferlay et al., 2010). In China, the ratio of obesity is increasing. In some studies increased the body mass index (BMI) has been shown to correlate with increased risk for breast, pancreatic, colorectal, and esophageal cancers (Renehan et al., 2008). Carmichael A.R showed that obesity was associated with worse prognosis in both pre- and post-menopausal women with breast cancer (Carmichael, 2006). Among 4288 colon cancer patients, a BMI greater than 35.0 kg/m^2 at diagnosis was associated with an increased risk for recurrence of and death from colon cancer (Dignam et al., 2006). Pelucchi et al. (2014) found that a BMI greater than 25.0 kg/m^2 at diagnosis was associated with reduced survival after pancreatic cancer. However, others have shown that the body mass index was not of prognostic value. Hayashi et al. (2010) have shown that the better 5-year overall survival (OS) and disease-free survival (DFS) noted in patients with a high BMI compared with those with a normal/ low BMI is because of the diagnosis of a low baseline clinical stage. Ravi Shridhar et al. (Shridhar et al., 2012) reported that BMI was not associated with survival in patients with esophageal adenocarcinoma treated with chemoradiotherapy (CRT).

The impact of obesity on survival of ESCC has only been minimally addressed. The aim of the present study was to examine whether BMI was of the prognostic value in patients with ESCC who underwent CRT as primary treatment. The end points for this study were 2-year OS and DFS.

*[1]Cancer Centre, the First Hospital of Zibo, Zibo, [2]Cancer Centre, Liaocheng People's Hospital, Liaocheng, [3]Department of Radiotherapy, Cancer Centre, Qilu Hospital, Shandong University, Jinan, Shandong, China *For correspondence: qilucyf@126.com*

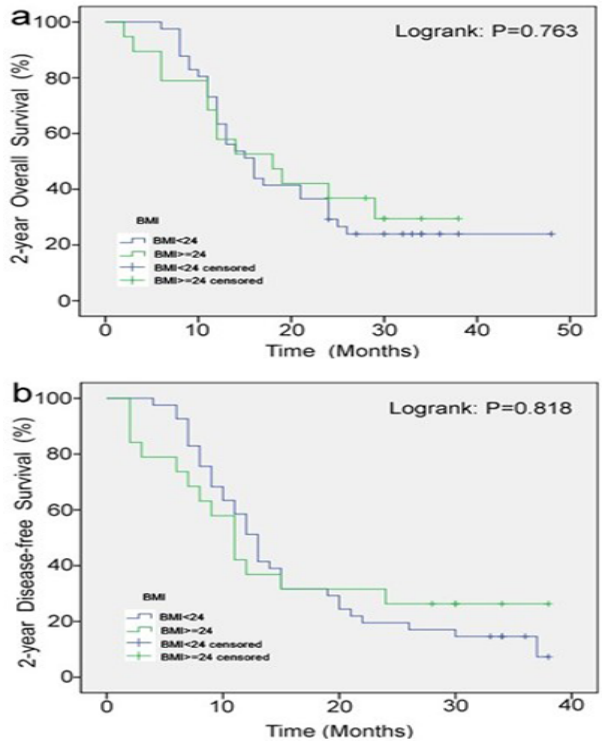

Figure 1. Kaplan-Meier Curves for Survival of 60 Patients with Esophageal Squamous Cell Carcinoma (BMI<24.00 kg/m^2 and BMI≥24.00 kg/m^2). Both 2-year overall survival **a)** and disease-free survival **b)** between two groups remained no statistically significant

Materials and Methods

Patients

Between January 2009 and December 2010, 60 patients who underwent CRT as initial treatment were included in our study at the Qilu Hospital of Shandong University in Jinan and the first hospital of Zibo city in Zibo (China). All patients included in our study underwent standard clinical staging with physical examination, air contrast barium esophagography, upper gastrointestinal esophagoscopy with histological biopsies and computed tomography scans of the cervical, chest and abdomen. Storedinformation regarding alcohol consumption, smoking and other parameters such as tumor recurrences and mortality were captured and analyzed. The exclusion criteria comprised the non-squamous cell subtype, surgical patients and uncooperative patients unable to answer questions or who could not be contacted. All patients had intended CRT as primary therapy according to the practice.

Data collection

Patients' height and weight before initial treatment were recorded and the BMI was calculated according to a standardized definition as weight in kilograms divided by height in meters squared and was classified according to the China specific criteria (underweight/normal weight: BMI <24.00 kg/m^2; overweight/obesity: BMI ≥24.00 kg/m^2) (WHO Expert Consultation, 2004). We stratified patients into two groups. Patient, tumor, and treatment characteristics were retrieved from the Medical Records Room.

Table 1. Patient Characteristics

		BMI<24.00 kg/m^2 (N=41)	BMI≥24.00 kg/m^2(N=19)	*p* value
Age median		69 (38-87)	63 (40-84)	0.222
Male : Female		33:8	17:2	0.480
Smoking	No	16	9	0.542
	Yes	25	10	
Drinking	No	20	11	0.511
	Yes	21	8	
tumor location	Cervical	7	2	0.765
	Upper	7	5	
	Middle	22	9	
	Low	5	3	
Clinical stage	I	3	2	0.904
	II	12	6	
	III	19	7	
	IV	7	4	
T-stage	T1	3	3	0.713
	T2	11	4	
	T3	18	7	
	T4	9	5	
N status	N0	16	7	0.872
	N1	25	12	
M	M0	34	15	0.730
	M1	7	4	

*BMI, body mass index; T-stage, tumor infiltration; N status, the status of Lymph node; M, metastasis

Follow up

Follow-up data were collected until death or January 2013. All patients had a regular follow-up schedule including a complete history and physical examination every 3 months during the first 2 years , every 6 months during the first 3-5 years and every year thereafter. Routine radiological examinations were performed when necessary.

Statistical analysis

All data were analyzed using statistical package SPSS version 17.0 (SPSS Inc., Chicago, IL). The differences between the groups were assessed using the Student's t-test for continuous variables and the x^2 test or Fisher's exact test for categorical variables. The Kaplan-Meier method and log-rank test were used for analysis and comparison of survival curves. For the analysis of 2-year OS, events were defined as death from any cause. For the analysis of 2-year DFS, events were defined as first loco-regional or distant tumor relapse or death from any cause. The Cox proportional hazards model was used to determine the hazard ratio (HR) of variables on 2-year OS and DFS in univariate and multivariate analysis. The results are given as HRs with their 95% confidence interval (CI). All statistical tests performed were two-sided and declared at the 5% significance level.

Results

Patients characteristics

A total of 60 patients (50 men and 10 women) were included in this study. There were 41 patients in the low/normal BMI (BMI<24.00 kg/m^2) and 19 patients in the high BMI (BMI≥24.00 kg/m^2). The median age was 69

Table 2. Cox Univariate Analysis for 2-Year Survival in 60 Patients

		2-Yr Overall Survival			2-Yr Disease-Free Survival		
		HR	95%CI	*p* value	HR	95%CI	*p* value
BMI	BMI<24.00 kg/m^2	1.000	Ref.	-	1.000	Ref.	-
	BMI≥24.00 kg/m^2	1.101	0.576-2.107	0.770	0.932	0.502-1.732	0.824
Age		1.121	0.585-2.146	0.731	0.757	0.421-1.362	0.353
Gender	Male	1.000	Ref.	-	1.000	Ref.	-
	Female	1.792	0.849-3.782	0.126	1.453	0.701-3.012	0.315
Smoking	No	1.000	Ref.	-	1.000	Ref.	-
	Yes	0.829	0.456-1.506	0.538	1.010	0.572-1.782	0.972
Drinking	No	1.000	Ref.	-	1.000	Ref.	-
	Yes	1.050	0.581-1.899	0.871	1.102	0.632-1.921	0.732
tumor location	Cervical	1.000	Ref.	-	1.000	Ref.	-
	Upper	1.001	0.372-2.693	0.998	0.967	0.380-2.457	0.944
	Middle	0.887	0.377-2.087	0.783	0.924	0.416-2.054	0.846
	Low	1.302	0.457-3.714	0.621	0.987	0.358-2.726	0.980
Clinical stage	I	1.000	Ref.	-	1.000	Ref.	-
	II	6.467	0.850-49.206	0.071	8.430	1.112-63.912	0.039
	III	6.382	0.846-48.143	0.072	8.603	1.151-64.308	0.036
	IV	13.454	1.716-105.568	0.013	16.852	2.143-132.520	0.007
T-stage	T1	1.000	Ref.	-	1.000	Ref.	-
	T2	2.363	0.664-8.415	0.185	2.601	0.737-9.183	0.138
	T3	1.839	0.538-6.288	0.331	2.539	0.755-8.543	0.132
	T4	3.927	1.098-14.041	0.035	4.394	1.235-15.629	0.022
N status	N0	1.000	Ref.	-	1.000	Ref.	-
	N1	1.544	0.833-2.861	0.168	1.884	1.044-3.401	0.035
	M			0.012			0.824
	M0	1.000	Ref.	-	1.000	Ref.	-
	M1	2.496	1.220-5.109	0.012	0.932	0.502-1.732	0.824

BMI, body mass index; T-stage, tumor infiltration; N status, the status of Lymph node; M, metastasis

Table 3. Cox Multivariate Analysis for 3-Year Survival in 60 patients

	2-Yr Overall Survival		
	HR	95%CI	*p* value
Drinking			0.005
No	1.000	Ref.	-
Yes	2.139	0.904-5.060	0.083
Gender			0.002
Male	1.000	Ref.	-
Female	7.141	2.096-24.335	0.002
tumor location			0.072
Cervical	1.000	Ref.	-
Upper	0.389	0.116-1.307	0.127
Middle	0.265	0.091-0.767	0.011
Low	0.885	0.236-3.318	0.856
Clinical stage			0.001
I	1.000	Ref.	-
II	17.714	1.664-188.583	0.017
III	5.433	0.300-98.501	0.252
IV	26.866	1.877-384.605	0.015
T-stage			0.005
T1	1.000	Ref.	-
T2	0.218	0.042-1.144	0.072
T3	0.369	0.066-2.069	0.257
T4	1.788	0.248-12.900	0.564
N status			0.056
N0	1.000	Ref.	-
N1	2.539	0.978-6.594	0.056

T-stage, tumor infiltration; N status, the status of Lymph node

(range, 38-87) years in the low/normal BMI group and 63 (range, 40-84) years in the high BMI group at the date diagnosed. No significant differences were observed in patient characteristics between groups. Characteristics of patients are shown in Table 1.

Survival

Figure 1 displays comparisons of 2-year OS and DFS of the patients stratified by BMI<24.00 kg/m^2 versus BMI≥24.00 kg/m^2. We found no statistically significant difference in 2-year OS and DFS associated with BMI (p=0.763 for OS; p=0.818 for DFS) using the Kaplan-Meier method. The median and 2- year OS for patients in the low/normal BMI group were 16 months and 24.4%, 18 months and 31.6% in the high BMI group, respectively (Figure 1a). The median and 2- year DFS for patients in the low/normal BMI group were 13 months and 12.2%, 11 months and 26.3% in the high BMI group, respectively (Figure 1b).

Univariate and multivariate analysis

Univariate analysis of the factors are shown in Table 2. There were no statistical differences in the 2-year OS (HR=1.101; p=0.770)and DFS (HR=0.932; p=0.824) between BMI groups in Univariate analysis. In the Cox univariate model, clinical stage were significantly related to 2-year OS (p=0.009) and DFS (p=0.003). The HR for metastasis for OS was 2.496 (95%CI 1.220-5.109; p=0.012), The HR for the status of Lymph node for DFS was 1.884 (95%CI 1.044-3.401; p=0.035). Univariate analysis revealed that higher clinical stage was prognostic for worse 2-year OS and DFS, metastasis for 2-year OS, the status of Lymph node for 2-year DFS, while age, gender, smoking, drinking, tumor location, tumor infiltration (T-stage) and BMI were not prognostic for 2-year OS and DFS.

Covariates entered in the multivariate Cox regression analyses on 2-year OS included drinking, gender, tumor

Table 4. Cox Multivariate Analysis for 3-Year Survival in 60 patients

	2-Yr Disease-Free Survival		
	HR	95%CI	*p* value
Gender			0.038
Male	1.000	Ref.	-
Female	2.473	1.050-5.823	0.038
Clinical stage			0.002
I	1.000	Ref.	-
II	8.564	0.866-82.773	0.064
III	3.126	0.230-42.434	0.392
IV	14.507	1.186-177.431	0.036
T-stage			0.032
T1	1.000	Ref.	-
T2	0.584	0.133-2.566	0.476
T3	0.981	0.212-4.553	0.981
T4	3.359	0.562-20.094	0.184
N status			0.075
N0	1.000	Ref.	-
N1	1.916	0.936-3.923	0.075

T-stage, tumor infiltration; N status, the status of Lymph node

infiltration, the status of lymph node, tumor location and the clinical stage. The outcomes are shown in Table 3. Covariates entered in the multivariate Cox regression analyses on 2-year DFS included tumor infiltration, the status of lymph node, gender and clinical stage. The outcomes are shown in Table 4. In a multivariate analysis, we found statistical differences in the 2-year OS and DFS associated with clinical stage, gender and tumor infiltration (p<0.04), independent of age, smoking, drinking, tumor location, the status of Lymph node, metastases and BMI. Age, smoking, drinking, tumor location, the status of Lymph node, metastases and BMI were not prognostic for either 2-year OS or DFS. however, there was a trend towards worse 2-year OS and DFS in patients with the status of Lymph node, The HRs for the status of Lymph node of 2-year OS and DFS were 2.539 (95%CI 0.978-6.594; p=0.056) and 1.916 (95%CI 0.936-3.923; p=0.075), respectively.

Discussion

In the present study, we examined the relationship between BMI and outcomes after CRT for ESCC. We found that no statistically significant difference in 2-year OS and DFS associated with BMI using the Kaplan-Meier method. Moreover, there were no statistical differences in 2-year OS and DFS between BMI groups in univariate and multivariate analysis. Our data fail to demonstrate a link with BMI and outcome in ESCC.

Some authors have also found that BMI is not a predictive factor of survival in patients with esophageal carcinoma (Grotenhuis et al., 2010; Shridhar et al., 2012; Wang et al., 2014). In a series of 405 patients with non-metastatic esophageal carcinoma at MD Anderson Cancer Center treated with either definitive or neoadjuvant CRT, there was no significant difference in OS, locoregional control, or metastasis-free survival between BMI≥25kg/m^2 and BMI<25kg/m^2 patients on multivariate analysis (Wang et al., 2014). Similarly, Ravi Shridhar et al. (2012) analyzed the outcome of 303 patients with esophageal adenocarcinoma and showed that BMI was not a prognostic factor for survival in patients treated with CRT. Again, BMI is not of prognostic value with regard to short-term and long-term outcome in 556 patients with esophageal cancer (Grotenhuis et al., 2010). However, several studies have confirmed that BMI is a prognostic factor with esophageal cancer (Trivers et al., 2005; Smith et al., 2008). A population-based case-control study of 1142 cases showed that prediagnosis BMI between 25 and 29.9 kg/m^2 was associated with longer survival for esophageal adenocarcinoma than BMI <25 kg/m^2 (Trivers et al., 2005). In a prospective study of 220 000 men in China, Smith et al. (2008) found that the high BMI was a protective factor of esophageal cancer.

Recent studies have detected the correlation between BMI and other cancers. A study in head and neck cancer suggests that patients underwent CRT with BMI>25 kg/m^2 have longer time to disease recurrence and better survival than similar patients with BMI≤25 kg/m^2 (McRackan et al., 2008). In the study of 152 patients, The median OS was 39 months vs. 18 months and median DFS was 27 months *vs* 13 months in the overweight and normal-weight groups respectively (p<0.01), OS, DFS and long-term survival were better in overweight than normal-weight patients in patients with gastric cancer undergoing adjuvant treatment (Eroglu et al., 2013). In a pooled analysis of eight population-based prospective cohorts studies in Japan, Matsuo et al. (2012) found a significant positive association between BMI and colorectal cancer risk in female and stronger association in male, and Morrison et al. (2013) found that Increasing BMI was associated with increased hazards of death from colorectal cancer. Kizer et al. (2011) analyzed the outcome of 404 patients with locally advanced cervical carcinoma and showed that the 5-year OS rate was 33%, 60%, and 68% for a BMI <18.5 kg/m^2, a BMI from 18.5 kg/m^2 to 24.9 kg/m^2, and a BMI >24.9 kg/m^2, respectively and underweight patients (BMI <18.5 kg/m^2) had diminished OS. Kaviani et al. (2013) reported that obesity was associated with poorer survival in 646 patients with breast cancer. These researches showed that BMI is a prognostic factor of survival, but others found that BMI is not a predictive factor of survival in cancer (Felden and Figueiredo, 2011; Gaudet et al., 2012). A prospective cohort found that there was no association between BMI and head and neck cancer incidence, although BMI was inversely associated with head and neck cancer mortality in smokers (Gaudet et al., 2012). In a case-control study in the South of Brazil, no association was found between the BMI with the occurrence of breast cancer (Felden and Figueiredo, 2011).

Many prognostic factors have been found for ESCC, such as TNM stage, tumor location, tumor infiltration, and the status of Lymph node. All these factors have been included in our analysis. In the study, we found that higher clinical stage was prognostic for worse 2-year OS and DFS, metastasis for OS, the status of Lymph node for DFS, while age, gender, smoking, drinking, tumor location and BMI were not prognostic for 2-year OS and DFS in univariate analysis. Moreover, we found that clinical stage, gender and tumor infiltration were also independent prognostic factors in multivariate analysis. Our results

were similar to those of previous studies (Samadi et al., 2007; Kandaz et al., 2012; Schoppmann et al., 2013; Zhang et al., 2013).

In conclusion, in our study, there is no statistically significant difference in 2-year OS and DFS associated with BMI in patients underwent CRT as primary treatment for ESCC. BMI is not a predictive factor of survival in patients with ESCC. Data regarding the effects of BMI on survival of esophageal cancer patients have so far provided inconsistent results. Many hypotheses were studied to explore the relationship between BMI and cancer. All of these studies required further investigations in different populations to confirm their findings, and had limitations in sample size.

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