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The Effect of Cachexia On Survival In Metastatic Gastric Cancer Patients Treated With Best Supportive Care

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ABSTRACT

In this retrospective study, we aimed to investigate the effect of cachexia on survival in metastatic gastric cancer (GC) patients treated with best supportive care (BSC) using real-life data.

From 2015 to 2019, metastatic GC patients who were treated with BSC were included in this study. The study enrolled 53 metastatic GC patients, 36 (67.9%) were male and 17 (32.1%) were female. The median age of the patients was 66 years. The patients were assigned into two groups, according to body mass index (BMI): BMI <18kg/m^2 or BMI ≥18 kg/m^2. A total of 18 patients (33.9%) were in the BMI <18kg/m^2 group and 35 patients (66.1%) were in the BMI ≥18 kg/m^2 group. There was a statistically significant difference between the two BMI groups with a median overall survival (mOS) of 1 month in the BMI <18kg/m^2 group and 3 months in the BMI ≥18 kg/m^2 group (p<0.001). In the multivariate analyses, age (hazard ratio [HR], 0.97), chronic obstructive pulmonary (HR, 6.53), BMI <18kg/m^2 (HR, 2.31), liver metastasis (HR, 3.53), and peritoneum metastasis (HR, 2.31) were associated with OS.

In this study, we found that presence of cachexia at the time of diagnosis in metastatic GC patients treated with BSC was associated with shorter survival in comparison to non-cachectic patients.

Key Words: Cachexia; Gastric Cancer; Best Supportive Care; Body Mass Index

Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed type of cancer and the third leading cause of cancer death, worldwide. Approximately 50% of GC patients have locoregional disease at the time of diagnosis. Although treatment modalities have been developed, only half of those patients can undergo potentially curative surgery (1, 2).

Surgical resection is the main treatment for early GC. Advanced or metastatic GC patients are treated with systemic chemotherapy. Cachexia is one sign of advanced GC (2, 3).

Cachexia is observed in many chronic diseases, especially in cancer patients. The European Palliative Care Research Collaborative has recommended three criteria to determine the presence of cachexia: weight loss over a 6-month period, and either diagnosis of sarcopenia or low body mass index (BMI) in cancer patients. Ultimately, cancer-related cachexia leads to a decrease in daily life activities due to skeletal muscle loss (4-7).

Cachexia-associated metabolic disorders can decrease tolerance for continuation of treatment in GC patients. Previous studies have shown that patients with cachexia have a lower quality of life and poor survival in patients with solid tumors including, GC patients who are treated with chemotherapy (8-10). A recent study conducted by Fukahori et al. showed that weight loss during chemotherapy is related to adverse events and reduced survival in patients with GC (11).

However, there is limited data regarding cachexia in GC patients treated with best supportive care (BSC). In this retrospective study, we aimed to investigate the effect of cachexia on survival in metastatic GC patients treated with BSC, using real-life data.

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Materials and Methods

Study Population: A total of 53 metastatic GC patients, who were treated and followed-up from 2015 through 2019 at Van Yüzüncü Yıl University Hospital, were retrospectively enrolled in this study. Of those GC patients, 36 (67.9%) were male and 17 (32.1%) were female. The median age of the patients was 66 years (range, 22–92). The following inclusion criteria were used: patients older than 18 who were treated with BSC for stage IV GC. Patients equal to or under the age of 18, non-metastatic patients, patients who were treated with chemotherapy, and those with missing data were excluded from the study. This study was approved by the Ethics Review Committee of Yüzüncü Yıl University Hospital.

Data Collection: The patients' age, gender, presence of diabetes mellitus, hypertension, chronic ischemic heart disease, congestive heart failure, and chronic obstructive pulmonary disease, smoking status, height, weight, BMI, histologic subtypes (adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma), tumor grade, metastasis localization at the time of diagnosis, Eastern Cooperative Oncology Group performance scale (ECOG PS), and final status (dead or alive) were obtained from the archive files. BMI was calculated by dividing the weight into the height squared (kg/m^2). The patients were classified into two study groups, based on BMI: BMI <18.5 kg/m^2 and BMI ≥18.5 kg/m^2. Overall survival (OS) was calculated as the time from diagnosis to the date of death.

Statistical Analysis: Statistical Package for Social Sciences 22.0 for Windows (IBM Corp, Armonk, NY, USA) was used for the statistical analysis. Chi-square analysis was used to compare the ratios in the two study groups. Survival analyzes were performed using the Kaplan Meier analysis method. Cox regression analysis was used for the determinant factors. Enter model was used with parameters having a $p<0.05$.

Results

Of the 53 metastatic GC patients enrolled in this study, 18 (33.9%) were in the BMI <18kg/m^2 group and 35 (66.1%) were in the BMI ≥18 kg/m^{2}group. Four (7.5%) patients had diabetes mellitus and 14 (36.4%) had hypertension. According to tumor histology, 33 (62.3%) patients had adenocarcinoma, 2 (3.8%) had signet ring cell carcinoma, and 18 (34.0%) had mucinous adenocarcinoma. Poor grade tumor was observed in 6 (11.3%) patients. The sites of metastasis of the patients at the time of diagnosis were: the peritoneum (73.6%), liver (35.8%), distant lymph node (26.4%), lung (13.2%), and bone (3.8%). At the median 12-month follow-up, all 53 of the GC patients had died (Table 1).

There was no statistically significant difference according to the BMI groups in terms of age, comorbidities, or tumor histology and grade. There were more females in the BMI ≥ 18.5 kg/m2 group than the BMI <18.5 kg/m2 group ($p=0.019$). The number of patients with liver metastasis was higher in the BMI <18.5 kg/m2 group than the BMI ≥ 18.5 kg/m2 group ($p=0.006$). Differences in the ECOG PS status were found based on the BMI groups ($p=0.001$) (Table 1).

There were statistically significant differences between the two BMI groups with a median OS (mOS) of 1 month in the BMI <18kg/m^2 patients and 3 months in the BMI ≥18 kg/m^2 patients ($p<0.001$) (Figure 1).

In the univariate analyses, age (hazard ratio [HR], 0.976), hypertension (HR, 2.151), chronic ischemic heart disease (HR, 3.351), chronic obstructive pulmonary (HR, 4.580), BMI <18kg/m^2 (HR, 2.921), liver metastasis (HR, 3.743), and peritoneum metastasis (HR, 2.366) were associated with OS (Table 2).

In the multivariate analyses, age (HR, 0.975), chronic obstructive pulmonary (HR, 6.535), BMI <18kg/m^2 (HR, 2.921), liver metastasis (HR, 3.539), and peritoneum metastasis (HR, 2.318) were associated with OS (Table 2).

Discussion

In the present study, we aimed to evaluate the effect of cachexia on survival in metastatic GC patients treated with BSC using real-life data. We observed that OS was shorter in the metastatic GC patients treated with BSC in which cachexia was present at the time of diagnosis in comparison to the non-cachectic patients.

Cachexia is known as a cancer-related multifactorial malnutrition syndrome. It is defined by the loss of skeletal muscle mass and fat mass. Moreover, it cannot be fully treated by conventional nutritional support, so it eventually leads to progressive functional loss. Cachexia affects about 50–70% of all cancer patients, based on the tumor stage and tumor type. It may be the primary cause of cancer deaths; it is found in nearly 20% of all cancer-related deaths (12-14).

Table 1. Patients' characteristics

		Patients (n=53)		18.5< BMI (n=18)		BMI ≥18.5 (n=35)		p
		n	%	n	%	n	%	
Gender	Women	17	32.1	2	11.1	15	42.9	0.019
	Men	36	67.9	16	88.9	20	57.1	
Age(year)	Median (min-max)	66 (22-92)		65.5 (22-92)		68(29-86)		0.686
Diabetes mellitus		4	7.5	0	0	4	11.4	0.287
Hypertension		14	26.4	5	27.8	9	25.7	0.872
Chronic ischemic heart disease		5	9.4	0	0	5	14.3	0.153
Congestive heart failure		4	7.5	0	0	4	11.4	0.287
Chronic obstructive pulmonary disease		2	3.8	1	5.6	1	2.9	0.634
Smoking		31	58.5	11	61.1	20	57.1	0.781
Height	Cm	161.5+13.0		166.2+13.3		159.1+12.3		0.070
Weight	Kg	56.0+10.5		47.8+7.2		60.0+9.5		<0.001
BMI	Kg/m2	21.4+4.0		16.8+1.5		23.7+2.7		<0.001
Histology	Adenocarcinoma	33	62.3	12	66.7	21	60	0.572
	Signet ring cell carcinoma	2	3.8	0	0	2	5.7	
	Mucinous adenocarcinoma	18	34	6	33.3	12	34.3	
Grade	Good	6	11.3	1	5.6	5	14.3	0.512
	moderate	22	41.5	7	38.9	15	42.9	
	Poor	25	47.2	10	55.6	15	42.9	
Liver metastasis		19	35.8	11	61.1	8	22.9	0.006
Peritoneum metastasis		39	73.6	16	88.9	23	65.7	0.070
Distant lymph node metastasis		14	26.4	4	22.2	10	28.6	0.620
Lung metastasis		7	13.2	2	11.1	5	14.3	0.746
Bone metastasis		2	3.8	1	5.6	1	2.9	0.625
ECOG PS	2	6	11.3	0	0	6	17.1	0.001
	3	30	56.6	7	38.9	23	65.7	
	4	17	32.1	11	61.1	6	17.1	
Last status	exitus	53	100	18	100	35	100	

Abbreviations: BMI, Body mass index; **ECOG PS,** Eastern cooperative oncology group performance scale

Cachexia was found to be about 7.49% in GC patients in a study including several types of solid tumors (15). Many previous studies have investigated the prognostic effect of cachexia on outcomes in GC patients (3, 9, 11). Preoperative cachexia was found to predict worse prognosis in younger GC patients in comparison to older patients in a prospective study conducted by Chen et al. (16). A study conducted by Kim et al. demonstrated that preoperative low BMI adversely affected survival in stage I/II GC patients and increased postoperative complications in stage III/IV (17). One study demonstrated that low BMI had a poor prognostic impact on GC patients with peritoneal dissemination who were treated with chemotherapy (18).

Most previous studies evaluated the effect of cachexia on complications and survival in GC patients who underwent surgery (16, 17, 19-21). Our study is the first study to focus on cachexia in GC patients who were treated with BSC; we found that a BMI <18.5 kg/m^2 at the time of diagnosis in metastatic GC patients treated with BSC was associated with poor survival. A BMI <18.5 kg/m^2 at the time of diagnosis increased the risk of mortality by 2.3 times. In our study, the occurrence of liver metastasis was significantly higher in patients with a BMI <18.5 kg/m^2 than in

Table 2. Univariate Analysis For OS

Characteristics		HR	95% CI for HR	p
Gender	Woman vs man	1.546	0.846-2.822	0.156
Age	year	0.976	0.958-0.994	0.010
Diabetes mellitus	Yes vs. No	2.444	0.754-7.913	0.136
Hypertension	Yes vs. No	2.151	1.070-4.322	0.032
Chronic ischemic heart disease	Yes vs. No	3.351	1.172-9.576	0.024
Congestive heart failure	Yes vs. No	2.629	0.802-8.615	0.110
Chronic obstructive pulmonary disease	Yes vs. No	4.580	1.046-20.044	0.043
Height	Cm	1.017	0.995-1.039	0.127
Weight	Kg	0.983	0.955-1.013	0.262
BMI	≥18.5 vs. 18.5<	2.921	1.539-5.543	0.001
	Adenocarcinoma (ref)			0.697
histology	Signet ring cell carcinoma	0.533	0.124-2.283	0.396
	Mucinous adenocarcinoma	0.986	0.540-1.799	0.964
	Good			0.164
grade	moderate	1.376	0.519-3.648	0.521
	Poor	2.199	0.822-5.880	0.116
Liver metastasis	Yes vs. No	3.743	1.988-7.046	0.001
Peritoneum metastasis	Yes vs. No	2.366	1.169-4.788	0.017
Distant lymph node metastasis	Yes vs. No	0.723	0.385-1.356	0.312
Lung metastasis	Yes vs. No	0.931	0.417-2.077	0.861
Bone metastasis	Yes vs. No	1.346	0.323-5.953	0.683
ECOG PS	4 vs. 2-3	2.593	1.393-4.824	0.003

Abbreviations: BMI, Body mass index; **ECOG PS,** Eastern cooperative oncology group performance scale

Table 3. Multivariate Analysis For OS

Characteristics		HR	95 % CI for HR	P
Age	Year	0.975	0.954-0.995	0.016
Hypertension	Yes vs. No	1.390	0.625-3.087	0.419
Chronic ischemic heart disease	Yes vs. No	2.438	0.748-7.948	0.139
Chronic obstructive pulmonary	Yes vs. No	6.535	1.374-31.091	0.018
BMI(kg/m2)	18.5<vs. ≥18.5	2.164	1.070-4.378	0.032
Liver metastasis	Yes vs. No	3.539	1.761-7.113	<0.001
Peritoneum metastasis	Yes vs. No	2.318	1.083-4.959	0.030
ECOG PS	4 vs. 2-3	1.344	0.698-2.585	0.376

Abbreviations: BMI, Body mass index; **ECOG PS,** Eastern cooperative oncology group performance scale

patients with a BMI ≥18.5 kg/m². A lower BMI probably increased cachexia and the mortality rate in those patients.

Fortunately, cachexia can be potentially recovered by multimodal modality, including nutritional support, drugs, and exercise (22). We recommend that more attention should be paid to improving the BMI of GC patients with a poor performance status. A higher BMI will enable chemotherapy treatment to be utilized in this group of patients.

Our study has some limitations. This was a single-center retrospective study. Also, the number of cases was relatively low.

In conclusion, we found that the presence of cachexia at the time of diagnosis in metastatic GC patients treated with BSC was an independent poor prognostic factor for OS. In these patients, we recommend that more effort be paid to treating cachexia to improve the survival rate.

Institutional review board statement: This study and all relevant procedures were performed

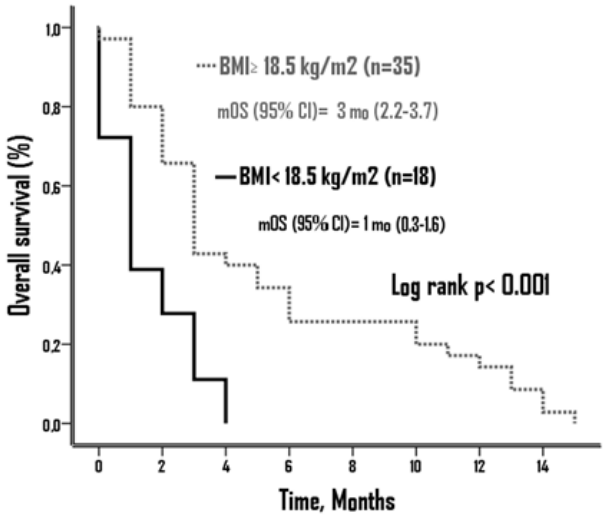

Fig. 1. Overall Survival According to BMI Groups

in accordance with the Helsinki Declaration after obtaining the ethical board approval from the Van Yüzüncü Yıl University Ethics Committee.

Informed consent statement: The patients were not required to give informed consent for this study because the study utilized the anonymous retrospective data obtained after each patient accepted the treatment by a written consent.

Conflict-of-interest statement: All authors declare no conflicts-of-interest.

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