Extremes in body mass index affect overall survival in women with cervical cancer

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HIGHLIGHTS

- Underweight and overweight/obese women with cervical cancer have worse RFS and OS.
- There is no difference in stage at diagnosis across BMI categories.
- Optimizing weight in cervical cancer patients may improve outcomes.

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ABSTRACT

Objective. To examine the effect of BMI on pathologic findings, cancer recurrence and survival in cervical cancer patients.

Methods. A retrospective cohort study of cervical cancer patients treated from July 2000 to March 2013 was performed. BMI was calculated, and patients were classified by BMI. The primary outcome was overall survival (OS). Secondary outcomes included stage, histopathology, disease-specific survival (DSS) and recurrence free survival (RFS). Kaplan–Meier survival curves were generated and compared using Cox proportional hazard ratios.

Results. Of 632 eligible patients, 24 (4%) were underweight, 191 (30%) were normal weight, 417 (66%) were overweight/obese. There was no difference in age ($p = 0.91$), stage at presentation ($p = 0.91$), grade ($p = 0.46$), or histology ($p = 0.76$) between weight categories. There were fewer White patients in the underweight (54%) and overweight/obese (58%) groups compared to the normal weight (71%) group ($p = 0.04$). After controlling for prognostic factors, underweight and overweight/obese patients had worse median RFS than normal weight patients (7.6 v 25.0 months, $p = 0.01$ and 20.3 v 25.0 months, $p = 0.03$). Underweight patients also had worse OS (10.4 v 28.4 months, $p = 0.031$) and DSS (13.8 v 28.4 months, $p = 0.04$) compared to normal weight patients. Overweight/obese patients had worse OS than normal weight patients (22.2 v 28.4 months, $p = 0.03$) and a trend toward worse DSS (21.9 v 28.4 months, $p = 0.09$).

Conclusion. Both extremes of weight (underweight and overweight/obesity) were associated with worse survival in patients with cervical cancer. Optimizing weight in cervical cancer patients may improve outcomes in these patients.

1. Introduction

Low body mass index (BMI) has been associated with poor prognosis in a variety of cancer types including cervical cancer [1–3]. The concept of cachexia and unintentional weight loss in cancer has been long accepted, but as adult obesity rates reach epidemic proportions in the United States the effect of body weight on cancer outcomes becomes less clear [4]. Recent estimates show that the majority (65%) of Americans are either overweight or obese and a third of adults meet the criteria for obesity (BMI > 30) [5]. Obesity is associated with an increased risk of developing and dying from multiple types of malignancies including endometrial, breast, colon, ovarian, and pancreatic cancers [6]. While increasing BMI has been associated with increased death rates from cancer, there is inconsistent data on the effects of BMI on cervical cancer survival [3,6–10].

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The primary objective of our study was to evaluate the effect of BMI on overall survival from cervical cancer. We also sought to evaluate any variation in histopathology, stage, and risk of recurrence based on BMI.

2. Methods

2.1. Study design, setting, and participants

Following Institutional Review Board approval (#12-1603) at the University of North Carolina at Chapel Hill (UNC), a single-institution retrospective cohort study was performed. All patients diagnosed with cervical cancer and treated at UNC from July 1, 2000 until March 30, 2013 were eligible for inclusion. UNC is a tertiary care academic hospital in a suburban setting with a large catchment area serving the women of North Carolina. The STROBE guidelines were followed in the implementation and reporting of this study [11].

Patients diagnosed with cervical cancer were identified via a database of the weekly Gynecologic Oncology Multidisciplinary Disposition Conference. All gynecologic cancer patients treated at UNC are presented at this conference; therefore, this database is the most accurate way to identify all cervical cancer patients at our institution. Patients were eligible if chart review showed a pathologic diagnosis of International Federation of Gynecology and Obstetrics (FIGO) stages IAI to IVB cervical cancer [12]. A gynecologic pathologist confirmed all pathologic diagnoses. BMI was then calculated using documented height and weight at the time of initial presentation to the gynecologic oncology clinic. Women without available BMI information were excluded from the study.

2.2. Variables and data sources

The primary outcome of interest was overall survival (OS). OS was defined as the time from the biopsy date documenting cancer to death from any cause. The primary exposure of interest was BMI. BMI was evaluated as a categorical variable. Patients were defined as underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), and overweight/obese (BMI ≥ 25) as previously described by Kizer et al [3].

Secondary outcomes included stage at diagnosis, histopathology, recurrence free survival (RFS), and disease-specific survival (DSS). RFS was defined as the time from the biopsy date documenting cancer to the date of disease recurrence (by imaging or exam) or death from any cause. DSS was defined as the time from biopsy date to death from cervical cancer. Patients with unknown or non-cancer related causes of deaths were excluded from this analysis.

Demographic, pathologic and clinical data were obtained via electronic medical record review. Pathologic variables of interest included stage, grade, and tumor histology. Clinical variables of interest included treatment modality, recurrence, and death. The date of last followup was designated to be any documented hospital or clinic visit and recurrence data was obtained from physician notes, laboratory data and imaging reports. Death data was captured from electronic medical records and from the Social Security Death Index (http://www.genealogybank.com/gbnk/ssdi/).

2.3. Study size and bias

This cohort was a convenience sample of patients with available electronic medical records for review and thus no de novo power analysis was performed for study size. The selected study timeframe for the cohort was intended to allow adequate followup time for death and recurrence data. In order to evaluate for potential selection bias and confounders, demographic and pathologic variables are obtained to evaluate for any significant differences between weight categories.

2.4. Statistical methods

Cox regression modeling was used to explore associations between BMI and time-to event outcomes including RFS, DSS and OS. The Kaplan–Meier method was used to estimate RFS, DSS, and OS curves. The log-rank test was used to test for differences between curve estimates. Parametric modeling was used to obtain BMI hazard ratios with 95% confidence intervals while controlling for age, race, smoking status, grade, stage, and histology. Chi-squared test, with Fisher's exact test as appropriate, was used to test two-group and/or nominal categorical variable comparisons. The nonparametric Jonckheere–Terpstra method was used to test for significant differences across ordered categories for contingency tables where at least one of the variables was ordinal including BMI categories. The Wilcoxon rank-sum test (using normal scores) was used for continuous variables undergoing two-group comparisons and Kruskal–Wallis test was used for continuous variables undergoing three or more comparisons. SAS (v 9.2, Cary, NC) statistical software was used.

3. Results

A total of 671 patients with cervical cancer were identified during the study timeframe. Thirty-nine (5.5%) patients did not have data available for BMI calculation at the time of initial presentation (diagnosis) and thus were excluded from the analysis. Of the remaining 632 patients, the median BMI was 28 (range 11.9–63.1). The distribution of weight is as follows: 4% were underweight (n = 24), 30% (n = 191) were of normal weight, and 66% (n = 417) were overweight or obese. There was no difference in age, stage, grade, histology, or smoking status between weight classes. Underweight and overweight/obese patients were less likely to be White than normal weight patients (54% v 58% v 71%, p = 0.04). Early stage disease (Stages IA and IB) was seen in 63% of underweight, 71% of normal weight, and 70% of overweight/obese (p = 0.91). There was no difference in the proportion of high-grade cancers (grade 3) seen in each weight group with 33% of underweight, 32% of normal weight, and 35% of overweight/obese (p = 0.46). There was no difference in tumor histology between weight groups with

Table 1
Clinical variables by weight category.

	Underweight (n = 24)	Normal (n = 191)	Overweight and obese (n = 417)	p-Value
Age	45.4 (±14.8)	46.7 (±14.8)	46.7 (±13.3)	0.91
Race				0.04
White	13 (54)	135 (71)	242 (58)	
Black	6 (25)	38 (20)	114 (27)	
Other	5 (21)	18 (9)	61 (15)	
Stage				0.91
IA	4 (17)	31 (16)	59 (14)	
IB	11 (46)	104 (54)	234 (56)	
II	3 (13)	26 (14)	57 (14)	
III	4 (17)	25 (13)	52 (12)	
IV	2 (8)	5 (3)	15 (4)	
Grade				0.46
1	1 (4)	25 (13)	50 (12)	
2	6 (25)	66 (35)	129 (31)	
3	8 (33)	61 (32)	147 (35)	
Unknown	9 (38)	39 (20)	89 (21)	
Histology				0.76
Squamous	16 (67)	129 (67)	286 (69)	
Adenocarcinoma	6 (25)	44 (23)	85 (20)	
Smoking status[a]				0.49
Never	10 (42)	83 (43)	176 (42)	
Former	2 (8)	11 (6)	23 (6)	
Current	4 (17)	47 (25)	77 (18)	
Unknown	8 (33)	50 (26)	141 (34)	

Continuous variables are reported as mean (± standard deviation); categorical variables are reported as n (%).

[a] Smoking status as documented in medical record at the time of cancer diagnosis.

Table 2
Treatment modality for stage IB patients by weight category.

	Underweight n (%)	Normal weight n (%)	Overweight/obese n (%)	p-Value
IB1				0.09
Surgery	7 (100)	79 (96)	147 (89)	
XRT	0 (0)	3 (4)	19 (11)	
IB2				**<0.001**
Surgery	1 (25)	17 (77)	18 (26)	
XRT	3 (75)	5 (23)	50 (74)	

XRT = primary radiation for treatment.
Bolded p values are those <0.05 (i.e. those that met statistical significance).

67% having squamous histology in the underweight group, 67% of normal weight, and 69% of overweight/obese (p = 0.76). Demographic and clinical data are summarized in Table 1.

When examining treatment modality, we found a trend toward less primary surgical management for stage IB1 tumors in overweight/obese patients (89%) compared to normal weight (96%) and underweight patients (100%) (p = 0.09). Both overweight/obese (74%) and underweight (75%) patients were more likely to receive radiation for primary treatment of stage IB2 tumors than normal weight women (23%) (p < 0.001). This data is summarized in Table 2.

In evaluating survival, we controlled for age, race, smoking status, stage, grade, and histology in all reported models below. We found worse median RFS in underweight patients compared to normal weight patients (7.6 v 25.0 months, p = 0.009) and overweight/obese patients (20.3 v 25.0 months, p = 0.026) compared to normal weight patients (Fig. 1). With regard to our primary outcome, overweight/obesity was associated with a significant decrease in overall survival in our cohort compared to normal weight patients (22.2 v 28.4 months, p = 0.031) and underweight patients did the worst at 13.8 months (p = 0.018) (Fig. 2). When limiting the analysis to disease-specific overall survival, there was a clinically significant difference in median DSS between overweight/obese and normal weight patients, but statistical significance was not reached (21.9 v 28.4 months, p = 0.089). Underweight patients had worse DSS than normal weight patients (13.8 v 28.4 months, p = 0.042) (Fig. 3). Hazard ratios for survival are shown in Table 3.

4. Discussion

In understanding the effect of BMI on cervical cancer outcomes it is important to recognize that both extremes of weight appear to negatively impact survival. Kizer et al. studied patients with Stage IB1 cervical cancer with positive nodes and ≥Stage IB2 cervical cancer undergoing curative intent chemoradiation. These authors found significantly decreased median 5 year survival in patients with a BMI <18.5 kg/m^2 (33%) compared to normal weight (BMI 18.5–24.9 kg/m^2) and overweight/obese patients (BMI > 25 kg/m^2) at 60% and 68%, respectively [3]. They concluded that increasing BMI is protective. However, more recently, a large single institution study from MD Anderson found morbidly obese (BMI > 35 kg/m^2) patients to have worst disease specific survival. Further after controlling for known prognostic indicators, they noted no difference in survival for underweight, normal weight, overweight, and obese patients [10]. These authors noted significant differences in baseline demographics between their weight groups, which were not seen in our cohort. Our data support the theory that low BMI is associated with poor prognosis, but also show that increasing weight is not protective. Rather, overweight and obese patients in our cohort did worse than their normal weight counterparts (Fig. 2).

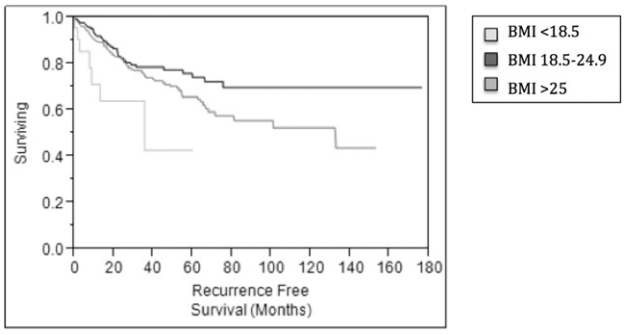

Fig. 1. Recurrence free survival by weight category.

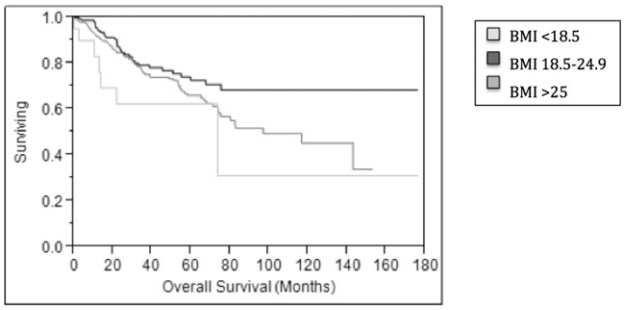

Fig. 2. All-cause overall survival by weight category.

A potential unifying hypothesis connecting both extremes of weight to poor cancer prognosis is chronic systemic inflammation. Both patients with cancer cachexia/sarcopenia and overweight/obese patients are in a heightened inflammatory state, which may lead to increased cell proliferation and inhibition of apoptosis [13,14]. However, this is likely not the only mechanism of poor outcomes. Co-morbid medical conditions might account for some of the differences in survival particularly in morbidly obese patients. However, the MD Anderson cohort [10] showed worse disease-specific survival and recurrence-free survival in obese patients suggesting that differences in mortality are in fact cancer related. Others have suggested delayed diagnosis in obese patients due to lack of screening in this population [15–20]; however, we did not detect a difference in stage in our cohort [20,21].

There may also be a difference in medical care received between overweight and obese patients and normal weight patients. Overweight and obese women appear less likely than normal weight patients to undergo radical hysterectomy for early stage cervical cancer, as seen in a prior study and confirmed in our cohort [22]. Performing radical surgery in obese patients with cervical cancer can present significant technical challenges. Surgeons may be reluctant to perform a radical hysterectomy in obese patients due to concerns surrounding increased intraoperative morbidity, patient medical comorbidities, and the surgical complexity of operating on obese patients. Studies would suggest that underweight patients actually have higher surgical complication rates than obese women, and radical hysterectomies should be performed in obese women for the usual indications [3,22]. Multiple studies have shown that open radical hysterectomy can be safely performed in obese patients [22–25]. Despite widespread use, data on outcomes in

Table 3
Recurrence free survival, overall survival and disease-specific survival by weight category.

	Hazard ratio	Lower 95%	Upper 95%
RFS			
Normal weight	Referent	Referent	Referent
Overweight & obese	0.76	0.61	0.95
Underweight	0.17	0.06	0.61
OS			
Normal weight	Referent	Referent	Referent
Overweight & obese	0.67	0.44	0.98
Underweight	0.32	0.15	0.81
DSS			
Normal weight	Referent	Referent	Referent
Overweight & obese	0.64	0.39	1.04
Underweight	0.26	0.09	0.09

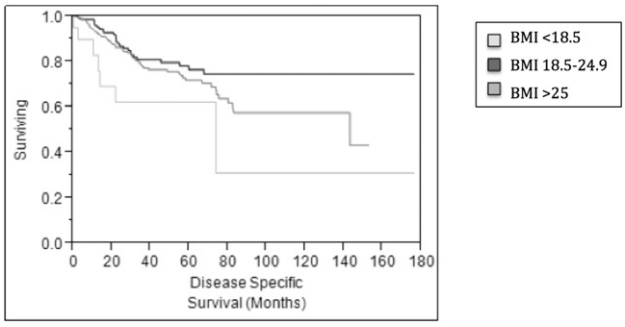

Fig. 3. Disease-specific survival by weight category.

minimally invasive radical hysterectomies is more limited but overall reassuring [26,27]. Obese women stand to gain the most benefit from the use of minimally invasive surgery with regard to complication rates and recovery.

Finally, variation in the efficacy and delivery of primary chemoradiation therapy could contribute to differences in outcomes. There is limited data on the efficacy of radiation therapy in obese cervical cancer patients, but the efficacy of primary radiation treatment in other disease sites, such as prostate cancer, have shown higher rates of radiation failure with increasing BMI [28]. Chemotherapy capping for radio-sensitizing cisplatin could impact the efficacy of primary chemoradiation treatments in the obese population. Further, studies in endometrial cancer have shown significant challenges with adjuvant radiation in obese patients largely due to challenges with treatment planning, setup errors, dosimetry, and minimizing toxicity to normal tissue [29].

We acknowledge multiple limitations in our study. First, the retrospective nature of this cohort study has inherent limitations and biases. The patients in this cohort are all from a single tertiary referral institution located in the southern United States and thus the results may not be broadly generalizable. We were unable to show a statistical difference in DSS in overweight and obese patients, but feel that sample size limitations and lack of information on cause of death contributed to the loss of statistical power. Despite these limitations, this study shows that the extremes of weight are detrimental to survival in women with cervical cancer and further investigation regarding the cause of poor prognosis is warranted. Providers should optimize weight in underweight and overweight/obese patients to attempt to improve outcomes in these women. Interventions that target nutritional counseling and physical activity should be explored in these populations.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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