The impact of BMI extremes on disease-free survival and overall survival following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Samer A. Naffouje[1], Kiara A. Tulla[1], Zaynab Khalaf[2], George I. Salti[3,4]

[1]Department of General Surgery, University of Illinois Hospital and Health Sciences System, Chicago, IL, USA; [2]College of Medicine, University of Illinois at Chicago, Chicago, IL, USA; [3]Division of Surgical Oncology, University of Illinois Hospital and Health Sciences System, Chicago, IL, USA; [4]Department of Surgical Oncology, Edward Hospital Cancer Center, Naperville, IL, USA

Contributions: (I) Conception and design: SA Naffouje, GI Salti; (II) Administrative support: GI Salti; (III) Provision of study materials or patients: SA Naffouje, GI Salti; (IV) Collection and assembly of data: SA Naffouje, KA Tulla, Z Khalaf; (V) Data analysis and interpretation: SA Naffouje, GI Salti; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Samer A. Naffouje, MD. University of Illinois at Chicago Health and Sciences System, 840 S Wood Street, Suite 376 CSN, Chicago, IL 60612, USA. Email: snaffouj@uic.edu.

Background: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are increasingly being offered to patients with peritoneal carcinomatosis (PC). On the other hand, the prevalence of obesity is also increasing and expected to reach unprecedented rates in the upcoming decades. Therefore, managing patients on either extreme of the body mass index (BMI) range is anticipated to become a routine challenge and it becomes imperative to understand the impact of BMI, as a spectrum, on the long-term outcomes of CRS and HIPEC. We aim to study the short and long-term outcomes of CRS and HIPEC in patients on both extremes of the BMI spectrum.

Methods: Patients with PC who underwent CRS and HIPEC over 10 years for ovarian, colorectal, and pseudomyxoma peritonei (PMP), and whose BMI was recorded were retrospectively included. Patients were divided based on their weight strata. The primary outcomes were disease-free survival (DFS) and overall survival (OS).

Results: A total of 126 patients were included. Fifty-seven point one percent were females and mean age was 59.31±1.57 years. No difference was noted between the groups in regards to demographics, perioperative characteristics, and immediate postoperative outcomes. Underweight group had a trend toward a higher peritoneal cancer index and lower rates of complete cytoreduction. Optimum BMI for OS and DFS was in the obesity range in colorectal PC, in the overweight range in ovarian PC, and in borderline obesity in PMP. Regression analysis identified underweight as an independent risk factor for shorter DFS, whereas underweight and morbid obesity were risk factors for shorter OS, after adjustment for other factors such as incomplete cytoreduction, tumor histology, and grade.

Conclusions: OS and DFS vary across the BMI strata. Ovarian PC demonstrates earlier recurrence and shorter survival, whereas colorectal PC demonstrates the "obesity paradox" as patients move into the realm of obesity. BMI extremes, low or high, generally carry a poor prognosis for OS.

Keywords: Body mass index (BMI); cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS and HIPEC); disease-free survival (DFS); overall survival (OS)

Introduction

The excess of body fat content, as measured by increased body mass index (BMI), has been associated with an increased risk of several cancer occurrences. The International Agency for Research on Cancer (IARC) confirmed the correlation between obesity and many malignancies such as esophageal, gastric cardia, hepatobiliary, colorectal, gynecologic, and postmenopausal breast cancers (1). This correlation has been reputable through several meta-analyses and reviews (2,3). Moreover, the biologic basis of causality was explained by systemic and microenvironmental immune responses, insulin-like growth factors, and steroid hormones pathways (4-6), further clarifying and contribution of obesity in the increasing incidence of cancer.

However, studying the impact of obesity on survival after the diagnosis of cancer in the recent years revealed rather surprising results. Obese patients with colorectal cancer, B-cell lymphomas and renal cell carcinomas demonstrated lower rates of mortality and improved survival compared to their peers of normal weight (7-10). This "obesity paradox" that refers to the improved survival in obese patients, in contrary to the common or expected belief, is an evident phenomenon in other disciplines of healthcare. Obese end-stage renal disease (ESRD) patients on renal replacement therapy outlive their normal-weight peers and outlive their hemodialysis accesses (11). Similarly, obese patients with coronary disease and type II diabetes tend to have a longer survival than those with normal BMI (12-14). On the other hand, the role of BMI, as a routinely reported physiologic parameter, in cancer recurrence has been an area of debate. Visceral adiposity, as measured by visceral fat area on computed tomography, has shown to correlate better with disease recurrence in rectal cancer compared to BMI which produces variable observations and less accurate recurrence prediction (15). In ovarian cancer, increased BMI was associated with a higher likelihood to have the disease limited to the ovaries, but clearly associated with a higher risk of disease recurrence and shorter overall survival (OS) when the disease is spread outside the adnexa (i.e., stages III–IV) (16).

In the current practice, peritoneal carcinomatosis (PC) is approached with a potentially curative intent by offering cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS and HIPEC) to a selected group of patients, in whom the most common origin of PC is gynecologic and colorectal. The relation between BMI and disease-free survival (DFS) and OS has not been explicitly studied in CRS and HIPEC despite the consensus on the importance of the nutritional status on long-term oncologic outcomes. Herein, we aim to study the immediate outcomes, as well as DFS/OS of patient from different BMI strata after CRS and HIPEC.

Methods

This is a retrospective analysis of patients who underwent CRS and HIPEC between 2007–2017 at a single institution for diagnoses of PC from colorectal (including appendiceal) adenocarcinoma, ovarian epithelial cancer, and pseudomyxoma peritonei (PMP). All patients had their demographic and perioperative characteristics collected and stored in a prospectively maintained database in accordance with an IRB-approved protocol at our institution (EEH 00003456). Comorbidities were reported per the Charlson comorbidity index (17). Peritoneal carcinomatosis index (PCI) was calculated intraoperatively as described by Dr. Sugarbaker (18). Grading of postoperative complications was done in accordance with the Clavien-Dindo classification system (19).

Patients were followed postoperatively with serial computed tomographies every 3 months for 2 years along with tumor markers, based on which disease recurrence was detected and determined. We divided the patients according to their BMI strata into underweight (BMI <18.50 kg/m^2), normal weight (BMI 18.50–24.99 kg/m^2), overweight (BMI 25.00–29.99 kg/m^2), obese (BMI 30.00–34.99 kg/m^2), and morbidly obese (BMI ≥35.00 kg/m^2) groups. Primary outcomes of the study were DFS and OS. Secondary goal was the comparison of immediate surgical outcomes between the different BMI groups.

We used the standard inferential tests to compare the characteristics between the groups including Chi-square, Kruskal-Wallis, and ANOVA. Kaplan-Meier method was utilized to draw the DFS and OS plots and compare medians. Cox-regression analysis was applied to determine the independent predictors of DFS and OS. Joinpoint regression was used to determine the optimal BMI for DFS and OS with tumor histology as the by-variable. Significance was set at <0.05 throughout the analysis.

Results

A total of 126 patients who underwent CRS and HIPEC were included. Mean age was 59.31±1.57 years, and 54

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Table 1 Demographics and characteristics of population (N=126)

Variables	Value
Age, mean ± SD (median) (years)	59.31±1.57 (61.00)
Sex, n (%)	
Males	54 (42.9)
Females	72 (57.1)
BMI, mean ± SD (median) (kg/m^2)	27.10±5.83 (28.00)
Charlson comorbidity index, n (%)	
0	54 (42.9)
1	40 (31.7)
≥2	32 (25.4)
Follow-up (median) (months)	19
Clavien Dindo, n (%)	
None (grade 0)	81 (64.3)
Minor (grade I/II)	29 (23.0)
Major (grade III/IV)	14 (11.1)
Mortality (grade V)	2 (1.6)
Primary, n (%)	
Appendiceal	22 (17.5)
Colon	38 (30.2)
Ovarian	19 (15.1)
Pseudomyxoma peritonei	47 (37.3)
Tumor grade, n (%)	
Well differentiated	58 (46.0)
Moderately differentiated	27 (21.4)
Poorly differentiated	41 (32.5)
Length of hospitalization, mean ± SD (median) (days)	10.12±5.41 (8.00)
PCI, mean ± SD (median)	14.06±9.33 (13.00)
Complete CRS, n (%)	114 (90.5)
EBL, mean ± SD (median) (mL)	378.7±300.0 (329.3)
Surgery duration, mean ± SD (median) (min)	393.70±116.44 (377.50)
Albumin, mean ± SD (median) (mg/dL)	3.60±0.46 (3.50)

PCI, peritoneal carcinomatosis index; CRS, cytoreductive surgery; EBL, estimated blood loss; SD, standard deviation.

(42.9%) were males. The breakdown of the primary histology was appendiceal (n=22; 17.5%), colorectal (n=38; 30.2%), ovarian (n=19; 15.1%), and PMP (n=47; 37.3%). Appendiceal and colorectal adenocarcinoma were bundled during the analysis of survival. The median follow-up was 19 months. Two patients had repeat CRS and HIPEC for disease recurrence and one patient had two reoperations during the study period. Each patient was included in the analysis as a single entry. The operative outcomes of the re-operations were not analyzed given the inherent bias in case complexity and survival expectancy. Patients were recorded to have a recurrence at time of reoperation and followed to measure the OS.

Mean PCI was 14.06±9.33, and 90.5% of patients underwent macroscopic cytoreduction. Eleven point one percent of patients had major morbidities (grade III–IV) and two postoperative mortalities were reported. Demographic and perioperative characteristics of our patient population are summarized in *Table 1*.

When patients were divided per their BMI strata as described, no significant difference was noted between the groups in regards to demographics, operative details, and postoperative complications despite a trend toward a higher PCI and lower rates of complete cytoreduction in the underweight group. Comparative results of the BMI groups are shown in *Table 2*.

Kaplan-Meier survival plots demonstrated that the underweight, normal weight, and morbidly obese groups had significantly shorter medians of DFS and OS compared to the overweight, obese, and morbidly-obese groups. No difference was noted in DFS between the overweight, obese, and morbidly-obese groups. Morbidly-obese patients had shorter OS compared to overweight and obese groups (48.00±23.20 *vs.* 66.00±12.66 and 68.00±27.74 months, respectively; P=0.011). Kaplan-Meier curves for DFS and OS are demonstrated in *Figure 1*. Univariate and multivariate Cox regression analyses were applied to determine the independent predictors of DFS and OS in our patient population. Our results suggest that tumor grade and incomplete cytoreduction were independent predictors of recurrence and long-term survival. In regards to BMI groups, being underweight carried a poor prognosis if diagnosed with PC for DFS and OS, whereas being morbidly-obese was a poor prognosticator for OS only. There was no difference in DFS or OS in the overweight and obese groups. Results of the Cox regression are shown in *Table 3*.

Finally, joinpoint regression was applied to study the

Table 2 Descriptive and inferential comparisons of the BMI category groups

Variables	Underweight (N=15)	Normal (N=31)	Overweight (N=43)	Obese (N=21)	Morbidly obese (N=16)	P value
Age, mean ± SD (years)	61.93±13.12	57.83±12.93	60.11±12.20	58.61±11.67	58.43±7.10	0.817
Sex, n (%)						0.087
Males	6 (40.0)	14 (45.2)	23 (53.5)	9 (42.9)	2 (12.5)	
Females	9 (60.0)	17 (54.8)	20 (46.5)	12 (57.1)	14 (87.5)	
Charlson index, n (%)						0.270
0	9 (60.0)	14 (45.2)	21 (48.8)	7 (33.3)	3 (18.8)	
1	3 (20.0)	11 (35.5)	14 (32.6)	6 (28.6)	6 (37.5)	
≥2	3 (20.0)	6 (19.4)	8 (18.6)	8 (38.1)	7 (43.8)	
Follow-up, mean ± SD (months)	18.53±13.31	21.58±15.11	27.72±22.63	24.90±19.97	24.62±22.28	0.521
Clavien-Dindo, n (%)						0.231
None (grade 0)	7 (46.7)	24 (77.4)	24 (55.8)	16 (76.2)	10 (62.5)	
Minor (grade I/II)	5 (33.3)	7 (22.6)	13 (30.2)	2 (9.5)	2 (12.5)	
Major (grade III/IV)	3 (20.0)	0 (0.0)	5 (11.6)	3 (14.3)	3 (18.8)	
Mortality (grade V)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (6.3)	
Primary, n (%)						0.430
Appendix	1 (6.7)	7 (22.6)	7 (16.3)	5 (23.8)	2 (12.5)	
Colon	6 (40.0)	9 (29.0)	14 (32.6)	6 (28.6)	3 (18.8)	
Ovary	5 (33.3)	6 (19.4)	4 (9.3)	2 (9.5)	2 (12.5)	
PMP	3 (20.0)	9 (29.0)	18 (41.9)	8 (38.1)	9 (56.3)	
Tumor grade, n (%)						0.453
Well diff.	6 (40.0)	10 (32.3)	24 (55.8)	9 (42.9)	9 (56.3)	
Moderately diff.	4 (26.7)	7 (22.6)	10 (23.3)	3 (14.3)	3 (18.8)	
Poorly diff.	5 (33.3)	14 (45.2)	9 (20.9)	9 (42.9)	4 (25.0)	
LOS (median) (months)	11	9	10	9	11	0.440
PCI, mean ± SD	16.80±7.87	12.4±9.39	14.76±8.67	13.61±10.97	13.43±10.21	0.623
Complete CRS, n (%)	10 (66.7)	25 (80.6)	36 (83.7)	19 (90.5)	14 (87.5)	0.095
EBL, mean ± SD (mL)	380±305	388±386	385±265	365±352	354±390	0.997
Surgery duration, mean ± SD (min)	406±125	401±128	396±89	366±131	394±136	0.829
Albumin (mg/dL)	3.4±0.5	3.7±0.5	3.6±0.4	3.6±0.3	3.4±0.5	0.443

BMI, body mass index; SD, standard deviation; PMP, pseudomyxoma peritonei; LOS, length of stay; PCI, peritoneal carcinomatosis index; CRS, cytoreductive surgery; EBL, estimated blood loss; diff., differentiated.
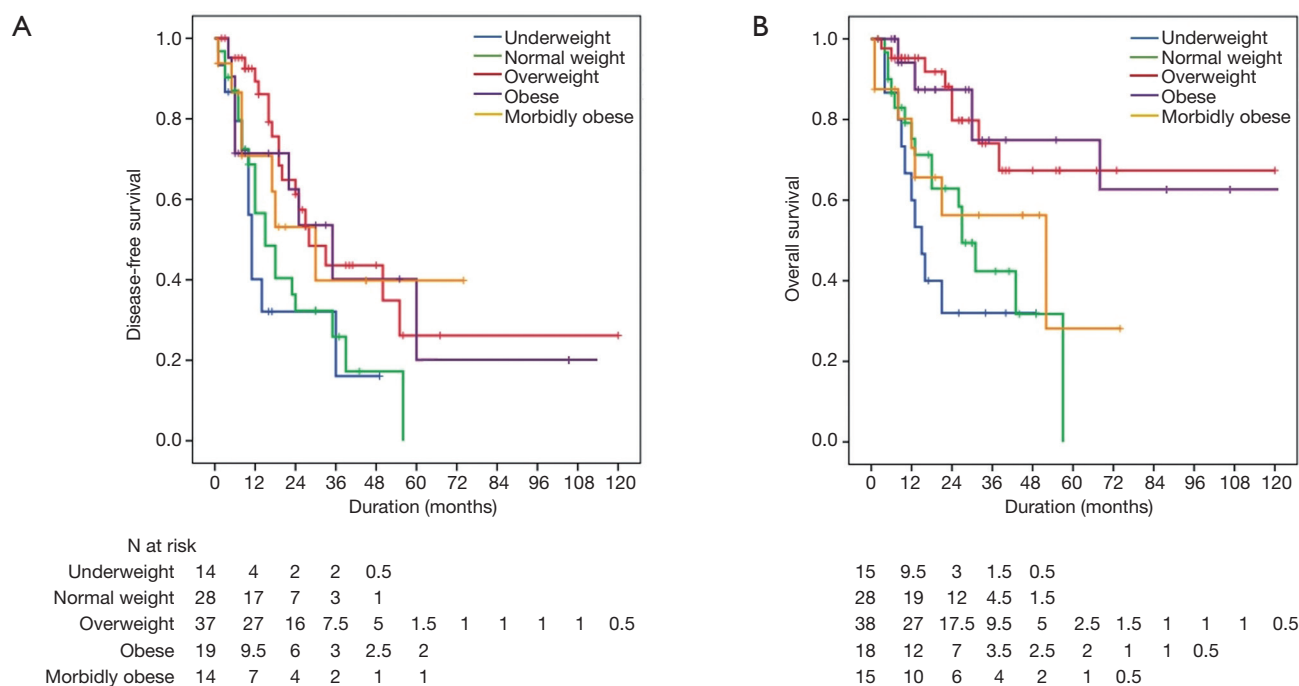
Figure 1 Kaplan-Meier survival curves of the five BMI category groups. (A) Disease-free survival: underweight, 11.00±0.85 months; normal weight, 15.00±3.62 months; overweight, 35.00±5.63 months; obese, 31.00±8.88 months; morbidly obese, 29.00±9.23 months (P=0.035); (B) overall survival: underweight, 15.00±2.57 months; normal weight, 27.00±3.16 months; overweight, 66.00±12.66 months; obese, 68.00±27.74 months; morbidly obese, 48.00±23.20 months (P=0.001).

trend of DFS and OS across the BMI spectrum. Patients were studied per their primary histology. Our results indicate that optimum BMI for DFS and OS in colorectal PC were 34 and 32 kg/m^2, respectively; 28 and 26 kg/m^2 in ovarian PC, respectively; and 28 and 30 kg/m^2 for PMP, respectively. Results of the Joinpoint regression analysis are demonstrated in *Figure 2*.

Discussion

It is currently projected that two-thirds of adults in the United States are considered overweight or obese (20), with a striking expansion of the morbid obesity group, faster than the overall increase in the obesity prevalence itself (21,22). This alarming fact indicates that facing obesity and morbid obesity will become a routine challenge in every surgical discipline in the years to come.

As the application of CRS and HIPEC for peritoneal surface malignancies (PSM) is increasing worldwide, it becomes imperative to understand the influence of obesity on the short- and long-term outcomes of CRS and HIPEC. Furthermore, we noted that the impact of high BMI on the

oncologic outcome has been investigated more thoroughly than that of low BMI. Therefore, we aimed in this work to study how BMI, as a spectrum, would influence the patients' survival as it trends towards either extreme.

Our results suggest a variability in recurrence and survival outcomes across the BMI range based on the histology of the primary tumor. Overweight patients with PC from ovarian origin tend to have an optimal DFS and OS which worsen as BMI moves toward either BMI extreme. Albeit HIPEC did not take part in the surgical management in their study, Tran *et al.* (23) demonstrated in their study on 104 patients that optimal cytoreduction in disseminated ovarian cancer is not affected by BMI. Rather, it is the long-term survival that is inversely proportional to the increasing BMI strata.

Upon further assessment of our patient subgroups, we redemonstrate the protective impact of obesity in PSM from appendiceal and colorectal origins, as the optimum of BMI for DFS and OS were 34 and 32, respectively. Votanopoulos *et al.* (24) reported similar conclusions of comparable short-term outcomes, yet improved survival in obese patients with PSM of lower gastrointestinal origin

Table 3 Univariate and multivariate Cox regression analysis for survival predictors in our patient population

| Variables	DFS multivariate regression		OS multivariate regression	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age	NS	NS	1.334 (1024–1.090)	0.044
Sex	NS	NS	NS	NS
Males				
Females				
Charlson index	NS	NS	NS	NS
0				
1				
≥2				
Major morbidity	NS	NS	NS	NS
Primary			NS	NS
Appendix	0.317 (0.044–2.271)	0.253		
Colon	1.212 (0.303–4.855)	0.786		
Ovary	0.137 (0.025–0.750)	0.022		
PMP	Referent	–		
Tumor grade				
Well diff.	Referent	–	Referent	–
Moderately diff.	8.077 (1.852–35.231)	0.005	2.517 (0.280–22.603)	0.410
Poorly diff.	14.744 (3.824–56.853)	<0.001	7.777 (1.069–56.589)	0.043
PCI	NS	NS	NS	NS
Albumin	NS	NS	NS	NS
Incomplete cytoreduction	5.659 (1.628–19.663)	0.006	9.849 (1.533–63.261)	0.016
BMI category				
Underweight	45.826 (8.492–247.293)	<0.001	21.583 (2.560–181.985)	0.005
Normal weight	2.851 (1.047–7.767)	0.040	3.898 (0.946–16.055)	0.060
Overweight	Referent	–	Referent	–
Obese	3.245 (0.738–11.231)	0.163	3.592 (0.513–25.180)	0.198
Morbidly obese	1.004 (0.168–6.014)	0.124	1.823 (1.111–18.744)	0.043

DFS, disease-free survival; OS, overall survival; PMP, pseudomyxoma peritonei; PCI, peritoneal carcinomatosis index; diff., differentiated; NS, not significant.

after CRS and HIPEC. Additionally, in our study we report that survival in PMP follows a similar pattern in regards to BMI stratification, with borderline-obesity being the optimum for long-term survival.

In regards to our secondary outcomes, our data are in agreement with several other institutional and national registry analyses that obesity does not impose a significant increase in immediate complications following CRS and HIPEC (24-26). What we highlight in our study is that extremely low BMI, a widely understudied risk factor, was associated with worse DFS and OS in all histology subgroups. It is worth mentioning that underweight
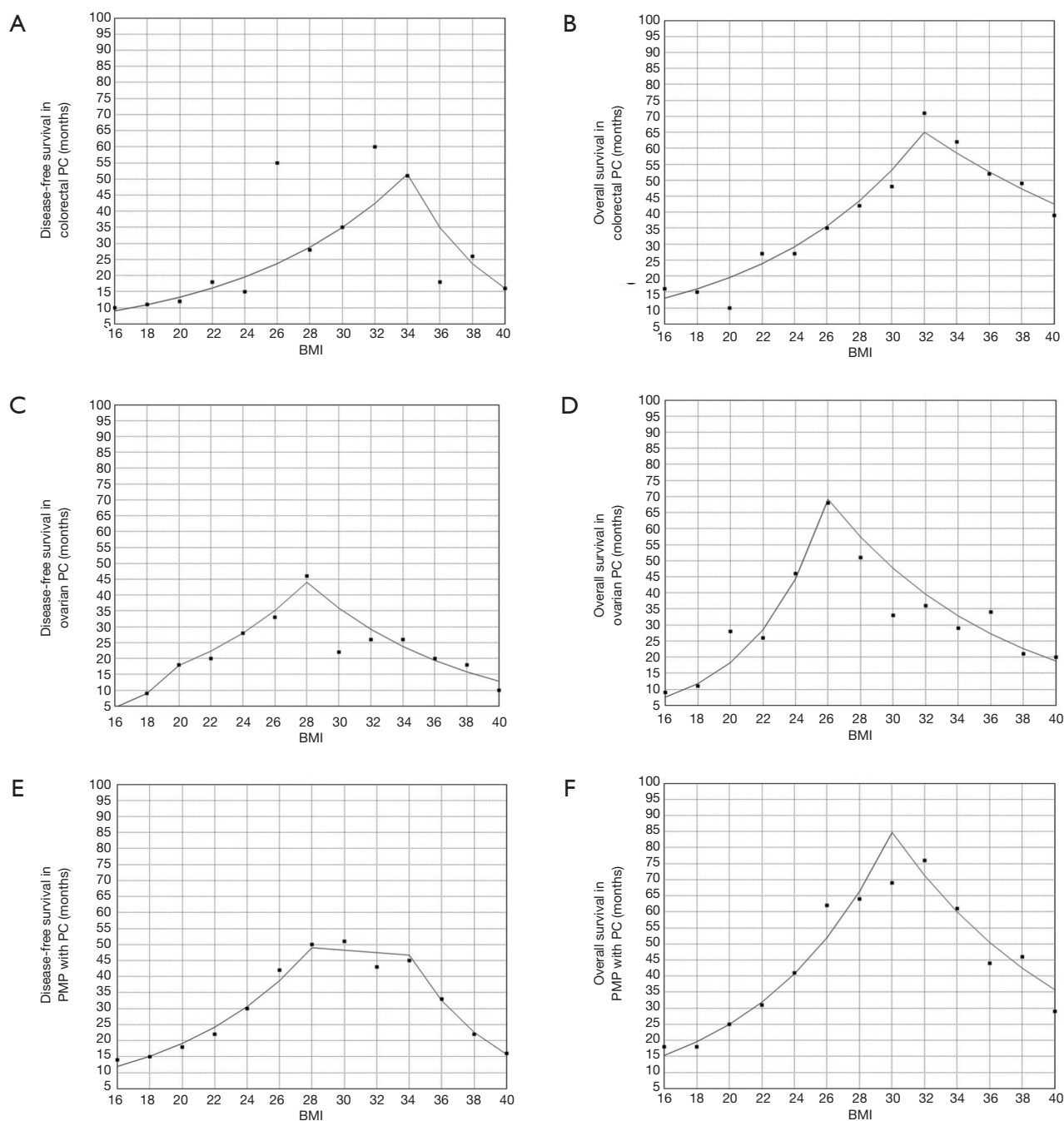
Figure 2 Joinpoint analysis demonstrating the correlation between increasing BMI and median survival. (A) Optimum BMI for disease-free survival in colorectal PC was 34 kg/m^2; (B) optimum BMI for overall survival in colorectal PC was 32 kg/m^2; (C) optimum BMI for disease-free survival in ovarian PC was 28 kg/m^2; (D) optimum BMI for overall survival in ovarian PC was 26 kg/m^2; (E) optimum BMI for disease-free survival in PMP with PC was 28 kg/m^2; (F) optimum BMI for overall survival in PMP with PC was 30 kg/m^2. PC, peritoneal carcinomatosis; BMI, body mass index; PMP, pseudomyxoma peritonei.

patients had a trend toward a higher PCI mean and lower rates of CC0/1, indicating a wider spread of their disease. Nonetheless, the BMI stratum of underweight was an independent predictor of poorer DFS and OS compared to the normal weight patients in our regression model. Of note, extremely low BMI was not necessarily associated with significantly lower levels of preoperative albumin. Increased tumor burden and cachexia would be expected etiologies of low BMI, higher PCI, thus lower rates of CC0/1 in the underweight group. However, that was not evident in our patient population.

On the other extreme, albeit a comparable DFS in morbidly obese patients their weight stratum reflected a significantly shorter OS. This finding might suggest that morbid obesity imposes a risk of non-cancer related death in the years that follow CRS and HIPEC.

The shortcomings of this study revolve around the retrospective nature of the analysis and the long-span of inclusion. They both contribute to data loss, inconsistency in data collection, and heterogeneity within the groups in the study. The approaches and techniques of CRS and HIPEC were standardized during the period of the study leading to improved outcomes, in addition to the relatively long learning curve this complex procedure requires till proficiency (27,28). However, we attempted to compensate for these inherent limitations by excluding patients with missed data points, as well as by following the proper statistical methods to adjust for potential confounders as described in the methods.

Conclusions

Our analysis of BMI, as a spectrum, concludes that weight strata affect OS and DFS per the primary histology. Ovarian PC demonstrates earlier recurrence and shorter survival, whereas colorectal PC demonstrates the "obesity paradox" as patients move into the realm of obesity. BMI extremes, low or high, generally carry a poor prognosis for OS and DFS in PSM patients undergoing CRS and HIPEC compared to their normal-weight peers.

Acknowledgements

Footnote

Conflicts of Interest: This work has been presented at the

SSO 13th International Symposium of Regional Cancer Therapies 2018 in Jacksonville, FL.

Ethical Statement: Our study is conducted under an approved IRB protocol (EEH 00003456) and patients' informed consent, and is enrolled in the National Clinical Trials registry NCT02082886.

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