Published in final edited form as:
Ann Surg Oncol. 2013 November ; 20(12): 3899–3904. doi:10.1245/s10434-013-3087-2.

Obesity and Peritoneal Surface Disease: Outcomes after Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy for Appendiceal and Colon Primary Tumors

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Abstract

Background—It is estimated that 37 % of the U.S. population is obese. It is unknown how obesity influences the operative and survival outcomes of cytoreductive surgery (CRS)/ hyperthermic intraperitoneal chemotherapy (HIPEC) procedures.

Methods—A retrospective analysis of a prospective database of 1,000 procedures was performed. Type of malignancy, performance status, resection status, hospital and intensive care unit stay, comorbidities, morbidity, mortality, and survival were reviewed.

Results—A total of 246 patients with body mass index (BMI) of >30 kg/m^2 underwent 272 CRS/HIPEC procedures. Ninety-five (38.6 %) were severely obese (BMI > 35 kg/m^2). A total of 135 (49.6 %) procedures were performed for appendiceal and 60 (22.1 %) for colon cancer. Median follow-up was 52 months. Both major and minor morbidity were similar for obese and non-obese patients. The 30-day mortality rates for obese and nonobese patients were 1.5 and 2.5 %, respectively. Median intensive care unit and hospital stay were 1 and 9 days, regardless of BMI. The 30-day readmission rate was similar between obese and non-obese patients (24.8 vs. 19.4 %, $p = 0.11$). Median survival for low-grade appendiceal cancer (LGA) was 76 months for obese patients and 107 months for non-obese patients ($p = 0.32$). Survival was worse for severely obese patients (median survival 54 months) versus non-obese patients with LGA ($p = 0.04$). Survival was similar for obese and non-obese patients with peritoneal surface disease (PSD) from colon cancer or high-grade appendiceal cancer.

Conclusions—Obesity does not influence postoperative morbidity or mortality of patients with PSD, regardless of primary tumor. Severe obesity is associated with decreased long-term survival only in patients with LGA primary disease; however, application of CRS/HIPEC still offers meaningful prolongation of life. Obesity should not be considered a contraindication for CRS/ HIPEC procedures.

Obesity has been shown to be a risk factor for a variety of cancers, including esophageal, pancreatic, colorectal, melanoma, leukemia, and non-Hodgkin lymphoma.[1–3] In addition, it

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Presented at the 2013 Gastrointestinal Cancer Symposium, San Francisco, CA, January 2013, and at the 66th Annual Meeting of the Society of Surgical Oncology, National Harbor, MD, March 2013; winner of the Society of Surgical Oncology 2013 Clinical Research Poster Contest.

DISCLOSURE The authors have nothing to disclose.

has been associated with diabetes, nonalcoholic steatohepatitis, and cardiovascular disease.[4] The prevalence of obesity in the United States has been steadily increasing over the last 25 years, reaching 37.5 % of U.S. adult population in 2010.[5] Therefore, the incidence of obese patients presenting with peritoneal surface disease (PSD) is expected to follow a similar trend.

Cytoreductive surgery (CRS) followed by intraperitoneal hyperthermic chemotherapy (HIPEC) has shown improved survival outcomes for selected cohorts of patients with PSD.[6–10] The impact of obesity on outcomes of patients undergoing CRS/HIPEC has not been well described.

We sought to evaluate the differences in procedure specific morbidity and mortality after CRS/HIPEC between obese and non-obese patients, regardless of primary disease. The secondary goal was to describe the impact of obesity on overall survival of patients who underwent CRS/ HIPEC for PSD from appendiceal and colon primaries.

METHODS

This is a retrospective analysis of a prospectively maintained database of 1,000 CRS/HIPEC procedures performed from 1991 to 2012. Institutional review board approval was obtained for this study. Patients were characterized as obese if their body mass index (BMI) was ≥30 kg/m^2. Following the World Health Organization classification, patients were further classified as moderately obese (BMI 30–34.9 kg/m^2) and severely obese (BMI ≥ 35 kg/m^2).[11] Data relevant to our analysis included demographics, age, race, gender, Eastern Cooperative Oncology Group performance status, R status of resection, type of malignancy, comorbidities, morbidity, mortality, and survival. Eligibility criteria for CRS/HIPEC were histologic or cytologic diagnosis of peritoneal carcinomatosis and complete recovery from prior systemic chemotherapy or radiation treatments, resectable or resected primary lesion, debulkable peritoneal disease, and no extra-abdominal disease. The presence of peripheral liver metastases, if easily resectable, was not a contraindication.

All patients had a complete history and physical examination, tumor markers, and CT of the chest, abdomen, and pelvis before the CRS/HIPEC procedures were performed. The CRS/ HIPEC procedure was conducted as previously described by our group.[12] HIPEC was administered similarly throughout the study period using the closed abdominal technique, and chemotherapeutic agents were selected on the basis of the primary tumor and the patient's previous response to systemic chemotherapy. Dosages were calculated on the basis of body surface area for patients treated with cisplatin (250 mg/m^2), oxaliplatin (200 mg/m^2), or carboplatin (1,000 mg/m^2). Surgical morbidity and mortality were recorded according to the Clavien and Dindo classification system.[13] R0 and R1 resections were grouped together as complete cytoreductions. Cytoreductions with residual macroscopic disease were characterized as R2 and subdivided on the basis of the size of residual disease (R2a ≤ 5 mm, R2b ≤ 2 cm, R2c > 2 cm).

Descriptive statistics, including means and standard deviations for continuous data and frequencies and percentages for categorical data, were calculated. Fisher's exact tests were used to test for statistically significant differences in categorical variables, and Wilcoxon rank sum tests were used to test for group differences in continuous variables. Overall survival (OS) was calculated from the date of CRS/HIPEC (or first CRS/HIPEC in cases where a patient underwent more than one procedure) to the last known date of follow-up or the date of death. Estimates of survival were calculated by the Kaplan–Meier (product limit) method. Group comparisons of OS were performed by the approximate Chi square statistic

for the log-rank test. Statistical significance was defined as a p value of <0.05. All analyses were performed by SAS 9.3 software (SAS, Cary, NC).

RESULTS

The study cohort included 246 patients with BMI ranging from 30 to 63.3 kg/m^2 who underwent 272 CRS/HIPEC procedures from 1991 to 2012. Of those procedures, 105 (38.6 %) were performed in severely obese (BMI ≥ 35 kg/m^2) patients. Primary disease included 135 (49.6 %) appendix and 60 (22.1 %) colon cancer. Additional patient characteristics are listed in Table 1. Median follow-up for obese patients was 52 months.

Obesity and Surgical Outcomes

Surgical outcomes were evaluated for all procedures regardless of primary tumor to determine whether CRS/HIPEC for obese patients was associated with greater risk than non-obese patients. When all procedures among obese patients (n = 272) were compared to those among nonobese patients (n = 653) (BMI ≥ 30 kg/m^2 vs. <30 kg/m^2), there was no difference in length of operation, minor morbidity, major morbidity, or mortality between the two groups. These observations held true when obese patients were further subdivided on the basis of degree of obesity (Table 2). No differences in the number of days spent in the intensive care unit or the hospital were noted regardless of degree of obesity. The 30-day readmission rate was similar between obese and non-obese patients; however, obese patients were more likely to have a late (31–90 day) readmission compared to the non-obese cohort (Table 2).

When 30-day morbidity was examined by type of complication, there was no difference in the types of complications experienced by obese and non-obese patients (Table 3). Obese patients were more likely to experience late (31–90 day) urinary tract infection (UTI) (p = 0.05) and anemia requiring transfusion (p = 0.03). When evaluated further by degree of obesity, moderately obese patients were more likely to have a late gastrointestinal bleeding (p = 0.04), and severely obese patients had a higher rate of late exploratory laparotomy (p = 0.04), intra-abdominal abscess (p = 0.03), interventional radiology guided drain placement (p = 0.01), UTI (p = 0.04), anemia (p = 0.04), and arrhythmia (p = 0.05) than the non-obese subjects.

Obesity and Survival

As a result of differences in biological behavior between different primary disease, survival was calculated independently for PSD from colon and appendiceal cancer. In addition appendiceal cancer was divided in low- and high-grade lesions.

Median OS for all obese patients with LGA primary disease (n = 61) was worse than for non-obese patients (n = 162), but this difference did not reach statistical significance. Patients with PSD from high-grade appendiceal or colonic primary disease experienced similar OS (Table 4). When obese patients with LGA were subdivided into moderately and severely obese, the severely obese patients experienced significantly lower OS compared with moderately obese and non-obese patients (p = 0.04). Subanalysis based on degree of obesity revealed no difference in survival for severely obese patients with high-grade appendiceal or colonic primary disease when compared with moderately obese and non-obese counterparts (Fig. 1).

Cause of Death

To better understand the inferior survival that was observed in LGA severely obese patients, cause of death was classified as due to either progression of disease (n = 36), comorbidities

(*n* = 7), surgical complications (*n* = 19), or unknown (*n* = 31). When excluding causes of death other than progression of disease in patients with LGA primary disease, OS for severely obese patients compared to moderately obese and non-obese patients was no longer significantly different ($p = 0.23$), indicating that other causes of death were responsible for the decreased survival observed in severely obese patients. For patients with a documented cause of death not related to the surgery (*n* = 43), severely obese patients were more likely to die from comorbid disease than were less obese patients. Specifically, 14.3 % (4 of 28) of the non-obese patients, 14.3 % (1 of 7) of the moderately obese patients, and 25.0 % (2 of 8) of the severely obese patients died from comorbidities; however, this trend did not reach statistical significance ($p = 0.83$).

DISCUSSION

Our data showed that there is no difference in the overall major and minor, 30- and 31- to 90-day morbidity between obese and non-obese patients undergoing CRS/HIPEC for PSD. Even though the overall morbidity is the same, BMI-based variations in the incidence of specific complications do exist. Moderately obese patients in general experienced complications that did not require surgical intervention, while severely obese patients had a morbidity pattern that often required hospitalization in a tertiary facility, surgical exploration, and use of interventional radiology services. These variations in morbidity patterns may have implications both on treatment cost and need for available resources. Further subanalysis of the severely obese group to determine a BMI limit where the cumulative risk was prohibitive for undertaking CRS/HIPEC was not feasible as a result of power attenuation. Interestingly, the variations in the complication pattern between obese and non-obese groups was not translated into increased length of stay, 30-day readmission, or mortality. These findings are in agreement with two large studies of heterogeneous groups of patients undergoing nonbariatric general surgery procedures, in which obese patients did not have increased mortality or morbidity.[14,15] At the heart of the finding that obesity is not associated with worsened outcomes in many cases in which one would expect is the so-called obesity paradox, where obese patients actually have better outcomes than non-obese patients, likely as a result of the deleterious impact of malnutrition on recovery from surgery.

When we examined the impact of obesity on survival, we found no relationship between moderate or severe obesity and long-term survival for patients with PSD from colon and high-grade appendiceal primary disease undergoing CRS/HIPEC. Similarly, a recent study has shown that although obese-level BMI correlated with worse survival in patients with localized colon cancer, there was no difference in survival between obese and non-obese patients with metastatic disease.[16]

On the contrary, the presented severely obese patients with LGA primary disease had significantly worse survival than the non-obese and moderately obese patients, yet despite the worse survival, nearly half of all severely obese patients with LGA primary disease experienced long-term survival beyond 5 years. Given similar operative mortality between obese and non-obese patients and similar survival in patients with LGA primary disease who died from disease progression, the observed survival difference must be due to factors other than their PSD or surgical treatment. We attribute the difference to the extended survival experienced by patients with LGA primary disease treated with CRS/HIPEC, which allows the impact of obesity-related comorbidities to take effect. Although our results support this conclusion, our lack of statistical significance is likely explained by power attenuation. A recent meta-analysis examining all-cause mortality from obesity similarly demonstrated that moderate obesity was not associated with increased mortality, while severe obesity was

significantly associated with worse all-cause mortality (hazard ratio 1.29, 95 % confidence interval 1.18–1.41).[17]

In conclusion, obesity does not influence postoperative morbidity and mortality of patients with PSD, regardless of primary tumor. Severely obese patients with PSD treated with CRS/HIPEC experience a complication pattern likely to require resources available in a tertiary facility. Obesity does not influence long-term survival for high-grade appendiceal and colon cancer patients with PSD. Severe obesity (BMI ≥ 35 kg/m^2) is associated with decreased long-term survival only in patients with LGA primary disease, yet application of CRS/HIPEC offers meaningful prolongation of life in this cohort. Obesity should not be considered a contraindication for CRS/HIPEC procedures.

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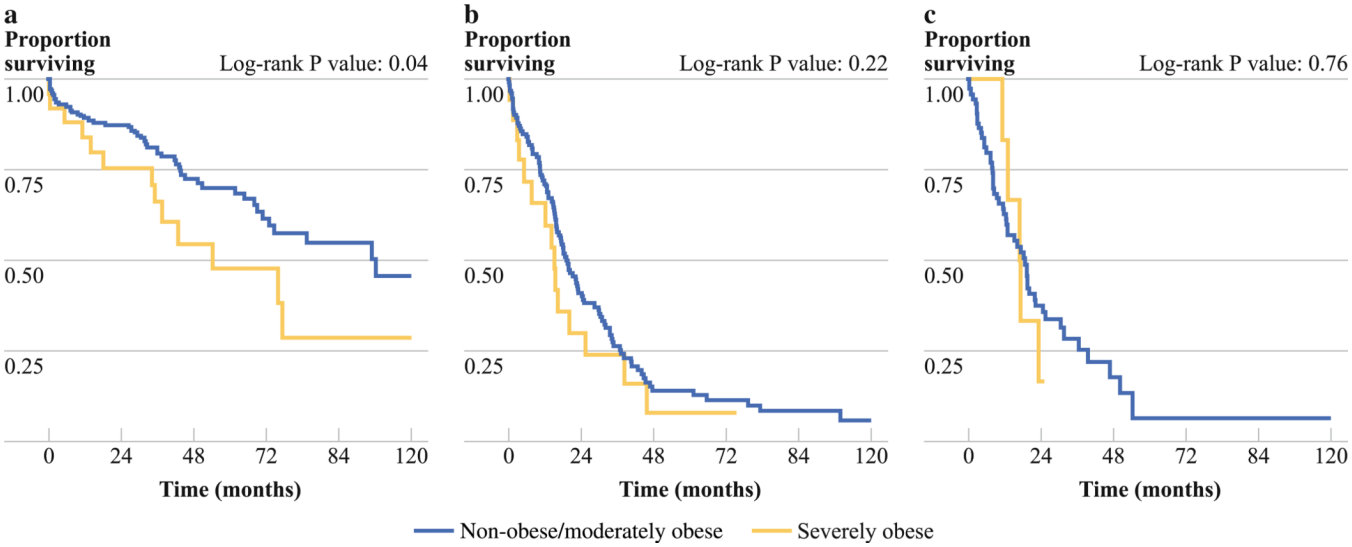

FIG. 1.

Survival comparison for patients with peritoneal surface disease based on obesity. Survival was significantly different based on BMI for patients with peritoneal surface disease undergoing CRS/HIPEC for **a** low-grade appendiceal primary disease but not for **b** colonic primary disease or **c** high-grade appendiceal primary disease

TABLE 1

Patient characteristics

Characteristic	Non-obese (*n* = 653)	Obese (*n* = 272)
Female, *n* (%) (*n* = 923)	346 (53.1)	149 (55.0)
Age, y, median (range)	54 (18–82)	52 (11–78)
Diabetes, *n* (%) (*n* = 905)	35 (5.4)	51 (18.8)
Heart disease, *n* (%) (*n* = 904)	52 (8.0)	25 (9.2)
Lung disease, *n* (%) (*n* = 905)	20 (3.1)	12 (4.4)
ECOG, *n* (%) (*n* = 909)		
0	299 (45.8)	118 (43.4)
1	244 (37.4)	106 (39.0)
2	79 (12.1)	33 (12.1)
≥3	21 (3.2)	9 (3.3)
Type of primary tumor, *n* (%)		
Low-grade appendiceal	189 (69.2)	84 (30.8)
High-grade appendiceal	74 (77.9)	21 (22.1)
Colorectal	145 (22.2)	60 (22.1)
Other	181 (27.7)	77 (28.3)
Resection type, *n* (%) (*n* = 912)		
R0/1	294 (45.4)	137 (50.6)
R2a	197 (30.2)	64 (23.5)
R2b	96 (14.7)	39 (14.3)
R2c	57 (8.7)	28 (10.3)
Chemotherapeutic agent		
Mitomycin C	520 (79.6)	205 (75.4)
Carboplatin	30 (4.6)	8 (2.9)
Cisplatin	37 (5.7)	15 (5.5)
Oxaliplatin	72 (11.0)	44 (16.2)
No. of organs resected, median (range)	3 (0–9)	3 (0–8)

ECOG Eastern Cooperative Oncology Group performance status

TABLE 2

Postoperative morbidity of CRS/HIPEC procedures in obese patients

Characteristic	Variable (days)	Non-obese (n = 653)	Obese (n = 272)	p^a	BMI 30–34.9 kg/m^2 (n = 167)	p^a	BMI > 35 kg/m^2 (n = 105)	p^a
Minor morbidity, *n* (%)	30	103 (15.8)	57 (21.0)	0.07	34 (20.4)	0.16	23 (21.9)	0.12
	31–90	32 (4.9)	20 (7.4)	0.16	14 (8.4)	0.09	6 (5.7)	0.64
Major morbidity, *n* (%)	30	129 (19.8)	55 (20.2)	0.86	35 (21.0)	0.75	20 (19.0)	1.00
	31–90	39 (6.0)	22 (8.1)	0.25	11 (6.6)	0.72	11 (10.5)	0.09
Mortality, *n* (%)	30	16 (2.5)	4 (1.5)	0.46	1 (0.6 %)	0.22	3 (2.9)	0.74
	31–90	12 (1.8)	5 (1.8)	1.00	4 (2.4 %)	0.75	1 (1.0)	1.00
Readmission, *n* (%)	30[b]	100 (19.4)	54 (24.8)	0.11	36 (25.2)	0.16	18 (24.0)	0.36
	31–90[c]	128 (26.7)	72 (34.6)	0.04	48 (35.8)	0.05	24 (32.4)	0.33
Mean operation time, (h)		8.4	8.5	0.70	8.4	0.88	8.6	0.36
Median hospitalization, (days)		9	9	0.17	9	0.14	9	0.60
Median ICU stay, (days)		1	1	0.29	1	0.09	1	0.76

BMI body mass index, *ICU* intensive care unit

[a] Compared to non-obese cohort

[b] n = 733

[c] n = 658

TABLE 3

Thirty-day complication pattern in obese

Complication	Non-obese (*n* = 653), *n* (%)	Obese (*n* = 272), *n* (%)	*p*
Repeat exploration (all cause)	51 (7.8)	21 (7.7)	1.00
Wound dehiscence	18 (2.8)	9 (3.3)	0.67
IR-guided drain placement	37 (5.7)	22 (8.1)	0.18
Respiratory failure	38 (5.8)	13 (4.8)	0.64
Pneumonia	35 (5.4)	18 (6.6)	0.44
Pulmonary effusion requiring thoracentesis	9 (1.4)	4 (1.5)	1.00
Pulmonary effusion requiring thoracostomy	24 (3.8)	9 (3.3)	0.85
Pneumothorax	10 (1.5)	2 (0.7)	0.53
Deep vein thrombosis	13 (2.0)	4 (1.5)	0.79
Pulmonary embolus	4 (0.6)	5 (1.8)	0.13
Myocardial infarction	4 (0.6)	0	0.33
Arrhythmia	18 (2.8)	8 (11.1)	0.83
Gastrointestinal bleed	4 (0.6)	2 (0.7)	1.00
Enteric leak, managed nonoperatively	4 (0.6)	3 (1.1)	0.43
Ileus	31 (4.7)	15 (5.5)	0.62
Enterocutaneous fistula	8 (1.2)	4 (1.5)	0.76
Nausea/vomiting	13 (2.0)	9 (3.3)	0.24
High-output ostomy	14 (2.1)	8 (2.9)	0.48
Wound infection	21 (3.2)	13 (4.8)	0.25
Abscess, treated with antibiotics	15 (2.3)	6 (2.2)	1.00
Infectious diarrhea	7 (1.1)	5 (1.8)	0.35
Noninfectious diarrhea	11 (1.7)	4 (1.5)	1.00
Bacteremia	32 (4.9)	10 (3.7)	0.49
Urinary tract infection	28 (4.3)	12 (4.4)	1.00
Acute renal failure requiring dialysis	12 (1.8)	5 (1.8)	1.00
Urinary retention	11 (1.7)	5 (1.8)	1.00

IR interventional radiology

TABLE 4

Impact of obesity on survival of patients with peritoneal surface disease treated with CRS/HIPEC

Obesity level	Low-grade appendiceal				High-grade appendiceal				Colon			
	n	Median OS (months)	5/10-y survival (%)	*p*[a]	*n*	Median OS (months)	3-y survival (%)	*p*[a]	*n*	Median OS (months)	3/5-y survival (%)	*p*[a]
Non-obese	162	107	70/47	Ref	67	19	28	Ref	101	18	27/15	Ref
All obese	61	76	59/37	0.32	15	17	20	0.40	55	18	22/9	0.42
Moderately obese (BMI 30–34.9 kg/m^2)	35	108	68/45	0.88	9	13	22	0.38	37	19	20/9	0.71
Severely obese (BMI ≥ 35 kg/m^2)	26	54	48/29	0.05	6	17	–	–	18	15	24/8	0.25

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *OS* overall survival, *BMI* body mass index

[a]Compared to non-obese cohort