ORIGINAL ARTICLE

Influence of Obesity on Cancer-Related Outcomes After Pancreatectomy to Treat Pancreatic Adenocarcinoma

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Objective: To examine the influence of obesity, as measured by body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), on clinicopathologic factors and survival after pancreatectomy to treat adenocarcinoma.

Design: Retrospective review and statistical analysis using prospectively collected data.

Setting: Referral center with a dedicated multidisciplinary pancreas cancer program.

Patients: Two hundred eighty-five consecutive patients with data available for BMI calculation who underwent potentially curative pancreas resection to treat adenocarcinoma from January 1, 1999, to October 31, 2006.

Main Outcome Measure: Influence of BMI and other known prognostic variables on the incidence of lymph node metastasis and disease-free and overall survival.

Results: We identified a subset of obese patients (BMI >35) who were at 12-fold risk of lymph node metastasis compared with nonobese patients (BMI ≤35). The estimated disease-free and overall survival rates were decreased in the obese patients, and the risk of cancer recurrence and death after pancreatectomy was nearly twice that in nonobese patients.

Conclusions: Obese patients with a BMI of more than 35 are more likely to have node-positive pancreatic cancer and decreased survival after surgical resection. Data suggest that the negative influence of BMI of more than 35 on cancer-related end points is unrelated to the potential complexity of performing major oncologic surgery in obese patients.

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During the last 20 years, obesity rates have dramatically increased in the United States.[1] This epidemic and the consequent disease states associated with obesity represent a national health crisis.[2] In many obesity-related diseases and malignant neoplasms, an increased prevalence of pancreatic cancer has been reported in numerous epidemiologic and cohort studies focusing on obese patients.[2-11] Further, obesity has been associated with decreased survival in patients with pancreatic adenocarcinoma, although the mechanism remains unknown.[3-10,12]

Early work by Gilsdorf and Spanos[13] described the relationship between pancreatic resection, obesity, and postoperative morbidity and mortality. Since that article, little research has been performed on cancer-related survival and obesity in patients who have undergone surgery to treat adenocarcinoma of the pancreas. However, parameters are readily available to measure obesity with the availability of body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), a simple index of weight and height used to define classes of weight in adults. The World Health Organization uses BMI to classify individuals as underweight (<18.5); having normal weight (18.5-24.99); preobese (25.0-29.99); or having class I obesity (30.0-34.99), class II obesity (35.0-39.99), or class III obesity (≥40).[14]

The objective of this study was to determine the association of BMI with other perioperative prognostic factors and its effect on outcome in patients who underwent pancreatic resection to treat adenocarcinoma. We hypothesized that obese patients would have more advanced tumors and decreased survival after resection. In this study, we identified an association between higher BMI and pancreatic cancer metastasis to regional lymph nodes, an increased risk of cancer recurrence, and decreased overall survival.

METHODS

After institutional review board consent, we used the institutional pancreatic cancer database managed by the Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, to identify all patients who underwent potentially curative pancreatic resection for pancreatic adenocarcinoma from January 1, 1999, to October 31, 2006. Clinicopathologic data were obtained directly from the institutional database, and BMI was obtained from the electronic medical record at the time of pretreatment referral to our center. Final pathologic stage was determined according to the American Joint Commission on Cancer.[15]

We sought to measure the influence of the complete range of BMI on the end points in question. Therefore, before we performed any statistical analysis, patients were divided into 5 BMI groups, first separating them into quartiles (<23, 23-25, 26-29, and ≥30) and then splitting the top group roughly in half (30-35 and >35) to separate patients with class I obesity from those with class II or III obesity as defined by World Health Organization criteria.[14] Measured variables included: BMI, age, length of hospital stay (LOS) in days (the day of surgery was considered day 1, and the day of discharge was not counted), time of surgery (minutes from incision to application of the wound dressing as obtained from the anesthesia record), estimated cubic centimeters of blood loss during surgery (EBL) as obtained from the anesthesia record, the occurrence of major postoperative complications as previously defined,[16] tumor size in centimeters (as measured at pathologic evaluation of the resected specimen), pathologic margin status (for pancreaticoduodenectomy specimens, margins were assessed as previously described[17]), presence or absence of lymph node metastasis, and administration of preoperative or postoperative therapy or both. Continuous variables (age, LOS, time of surgery, EBL, tumor size, number of lymph nodes examined, and number of positive lymph nodes per patient) were expressed as median values, and categorical variables (number of patients with any positive margin or any positive lymph nodes, and administration of adjuvant or neoadjuvant therapy) were expressed as a number value and percentage of the group. The 5 BMI groups were compared using the Kruskal-Wallis test for continuous variables and the Fisher exact test for categorical variables.

The group with a BMI of more than 35 was identified as unique from the others; therefore, we compared this group with all other patients to assess the influence of a BMI of more than 35 on lymph node metastasis and survival. Lymph node positivity was assessed using generalized estimating equations (GEEs)[18] and logistic regression models. The survival outcomes were assessed using Cox proportional hazards models. A backward selection method was then used to sequentially remove variables with a value of $P > .10$, and the remaining variables were considered in multivariate Cox proportional hazards models and multivariate GEEs and multivariate logistic regression models. The Kaplan-Meier product limit method was used to summarize overall and disease-free survival from the date of tissue diagnosis. $P \leq .05$ was considered statistically significant.

RESULTS

PATIENT DATA

From January 1, 1999, to October 31, 2006, 296 patients underwent surgery to treat adenocarcinoma of the pancreas, including pancreaticoduodenectomy in 262 patients (89%), subtotal distal pancreatectomy in 31 (10%), and total pancreatectomy in 3 (1%). Data for calculating BMI were complete for 289 of 296 patients (98%). The 7 patients with unknown BMI were excluded from further analysis. We also excluded 4 additional patients who underwent resection of the primary pancreatic tumor in the setting of M1 disease; the diagnosis of stage IV adenocarcinoma of pancreatic origin was not known at the time of surgery and only became apparent after review of all permanent-section pathology reports. This resulted in a study population of 285 patients for all subsequent descriptive statistics and calculations. Clinicopathologic data for these 285 patients are given in **Table 1**. Final pathologic stage according to the American Joint Commission for Cancer criteria was distributed as follows: IA, 24 (8%); IB, 14 (5%); IIA, 88 (31%); and IIB, 159 (56%).

The median time to last follow-up or death for the entire group of 285 patients was 16.0 months, with surviving patients followed up for a median of 19.8 months. At last follow-up, 133 patients were alive; 90 (32%) had no evidence of disease and 43 (15%) were alive with disease. One hundred fifty-two patients (53%) died during follow-up, 137 (90%) as a result of the disease and 15 (10) from causes that could not be attributed to disease recurrence. The median (range) disease-free and overall survival was 15 (7 months; not reached [ie, the follow-up time is insufficient to determine the upper end of the range]) and 25 (12-58 months), respectively.

CLINICOPATHOLOGIC VARIABLES OF BMI GROUPS

The results of a statistical comparison of basic demographic and treatment variables between the 5 BMI groups are given in Table 1. No differences were identified in the sex distribution ($P = .44$) or median age ($P = .54$) of the BMI groups. An increase in EBL was identified in patients in the groups with a BMI of 26 to 29, 30 to 35, and more than 35 when each was compared with the group with a BMI of less than 23 as a reference; however, the median EBL in each group did not increase in accord with increasing BMI. In addition, no difference in major postoperative morbidity was identified in any BMI group ($P = .71$). We also compared the use of adjuvant or neoadjuvant therapy in addition to surgery and found that patients in the group with BMI of more than 35 were less likely to receive preoperative therapy ($P = .07$), although most patients in each group received neoadjuvant or adjuvant therapy (Table 1).

A comparison of pathologic findings of the surgical specimens for each of the 5 BMI groups is given in Table 1. There was a significant increase in the size of tumors in the group with a BMI of more than 35 ($P = .04$) compared with the group with a BMI of less than 23. There was also a significant difference in the number of patients with positive lymph nodes in the group with a BMI of more than 35 ($P < .001$) compared with the group with a BMI of less than 23 as reference. In concordance with this observation, the group with a BMI of more than 35 had a greater number of positive lymph nodes in each specimen ($P = .001$) compared with the group with a BMI of less than 23. Although not given in Table 1, these differences in pathologic findings are reflected in the stage

Table 1. A Comparison of Demographic, Therapeutic, and Pathologic Factors in Patients Grouped According to BMI

Variable	All Patients	No. of Patients by Quartile					*P* Value
		1st	2nd	3rd	4th	5th	
BMI category (median; range)		<23 (21.5; 15.6-22.9)	23-25 (24.5; 23.0-25.9)	26-29 (27.8; 26.0-29.9)	30-35 (32.4; 30.4-32.8)	>35 (39.9; 35.3-61.7)	
No. of patients	**285**	62	84	78	41	20	
Sex							
Male	**161**	29	48	49	24	11	
Female	**124**	33	36	29	17	9	
Male/female ratio	1.3	0.8	1.3	1.6	1.4	1.2	.44
Age, median, y	63	61	65	64	62	61	.54
LOS, median, d	10	10	9	10	10	9	.87
Operative time, median, min	420	415	398	447	424	450	.28
Estimated blood loss, median, mL	700	525	538	800[a]	700[a]	800[a]	.007
Major postoperative complications, No. (%)	**33** (12)	7 (11)	13 (15)	10 (13)	2 (5)	1 (5)	.71
Therapy, No. (%) of patients							
Preoperative	**209** (73)	49 (79)	60 (71)	56 (72)	34 (83)	10 (50)	.07
Postoperative	**43** (15)	11 (18)	10 (12)	12 (15)	4 (10)	6 (30)	.27
Preoperative or postoperative	**240** (84)	56 (90)	67 (80)	64 (82)	37 (90)	16 (80)	.31
Any positive margin, No. (%)	**31** (11)	7 (11)	9 (11)	10 (13)	3 (7)	2 (10)	.94
No. of lymph nodes examined per patient, median	19	19	20	20	19	19	.87
Tumor size, cm	2.7	2.5	2.5	2.8	2.5	3.0[a]	.04
Any positive lymph node, No. (%)	**160** (56)	26 (42)	43 (51)	50 (64)	22 (54)	19 (95)[a]	<.001
No. of positive lymph nodes identified per patient, median	1.0	0	1.0	1.0	1.0	2.5[a]	.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); LOS, length of hospital stay.
[a] Significantly different when group with BMI less than 23 was used as a reference for comparison.

Table 2. Multivariate Logistic Regression Model for Presence of Positive Lymph Nodes in Biopsy Specimens After Pancreatectomy to Treat Adenocarcinoma

Variable	Parameter Estimate (SE)	*P* Value	OR (95% CI)
BMI >35 vs ≤35	2.45 (1.04)	.02	12.16 (1.58-93.55)
Tumor size, 1-U increase	0.31 (0.10)	.003	1.36 (1.11-1.67)
Preoperative therapy	−0.79 (0.32)	.01	0.45 (0.25-0.84)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; OR, odds ratio.

distribution in the BMI groups. Specifically, the group with BMI of more than 35 had the highest percentage of patients with stage IIB disease (19 of 20; 95%) and the lowest percentage of patients with stage IIA disease (1 of 20 [5%]). No patients in the group with a BMI of more than 35 had stage IA or IB disease.

RELATIONSHIP BETWEEN BMI AND LYMPH NODE METASTASIS

Although a BMI of more than 35 was associated with a high incidence of lymph node metastasis, this could be because of the observed decreased use of preoperative therapy in this group.[19] Therefore, we used more stringent statistical analyses to control for the use of preoperative therapy and to determine the presence or absence of a relationship between BMI and lymph node metastasis. We used a univariate GEE method to estimate the effect of categorized BMI on lymph node metastasis and found that lymph nodes from patients with a BMI of more than 35 were at 2.28-fold greater risk of positivity than lymph nodes from patients with a BMI of 35 or less ($P=.001$). The multivariate GEE model suggested that the use of preoperative therapy had a significant effect on lymph node positivity and, after adjusting for treatment, tumor size was no longer significantly associated with lymph node positivity. The increase in tumor size in the group with a BMI of more than 35 may have been attributable to the less frequent use of preoperative therapy in that group and not simply a function of BMI. Nevertheless, a BMI of more than 35 remained significantly associated with lymph node status after adjustment for the use of preoperative treatment: resected lymph nodes from patients with a BMI of more than 35 were at approximately 2-fold risk of being positive compared with lymph nodes from patients with a BMI of 35 or less ($P=.002$).

We used logistic regression to examine the relationship between a BMI of more than 35 and the presence of lymph node metastases. In a univariate logistic regression model, patients with a BMI of more than 35 were at 16.5-fold risk of having at least 1 positive lymph node compared with patients with a BMI of 35 or less ($P=.007$). Multivariate analysis (**Table 2**) confirmed the influence of preoperative therapy ($P=.02$) and tumor size ($P=.003$) on lymph node status. However, after adjusting for the use of preoperative therapy, patients with a BMI of more than 35 still were at approximately 12-fold risk of having positive lymph nodes compared with patients with a BMI of 35 or less ($P=.02$). Thus, both the GEE and logistic regression statistical models support a significant relationship between BMI and lymph node metastasis.

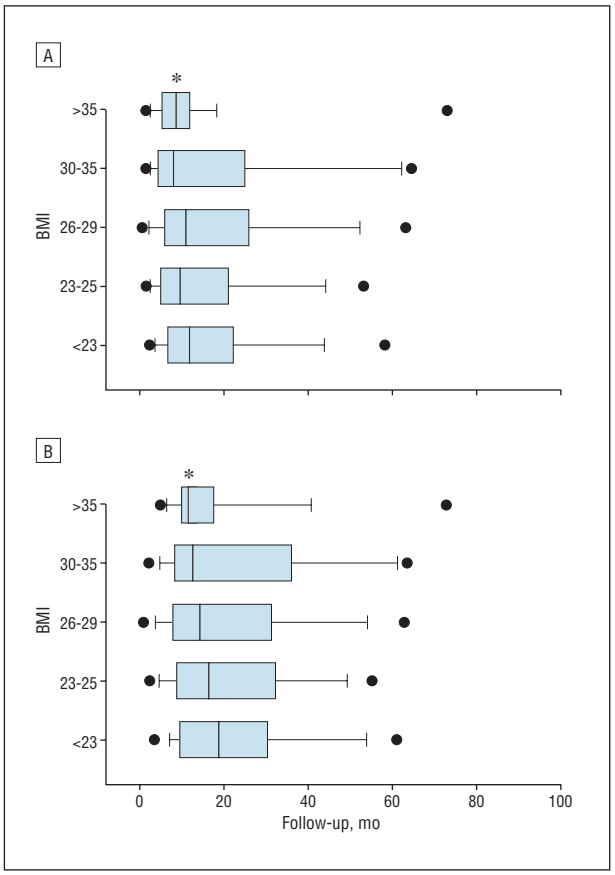

Figure 1. Distribution of cancer recurrence (A) and death (B) during follow-up according to body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared). The 25th and 75th percentiles are defined by the box with the line inside of the box representing the median value. The whiskers mark the 5th and 95th percentiles; the individual marks are values outside of these. *The statistically significant increase in the risk of relapse (P=.006) and death (P=.02) in the group with a BMI of more than 35.

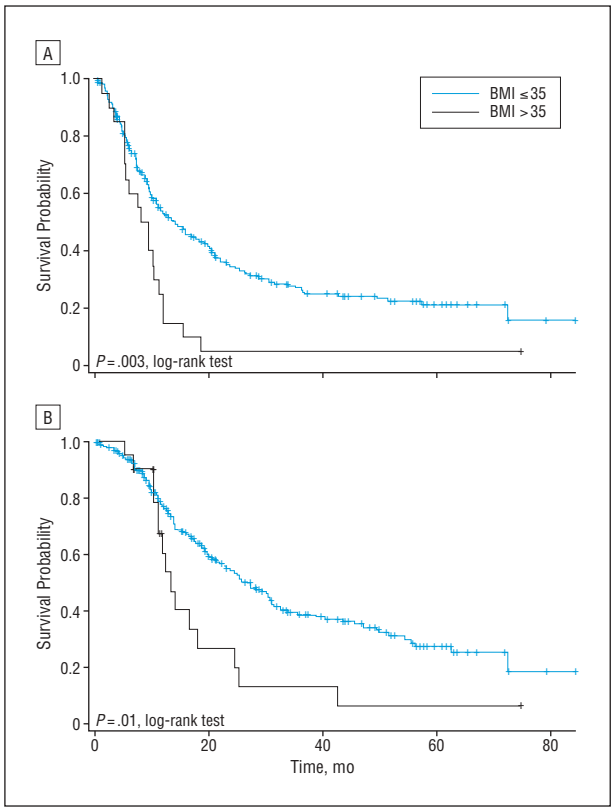

Figure 2. Kaplan-Meier estimates of disease-free survival (A) and overall survival (B) according to body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared).

BMI AND CANCER RECURRENCE AFTER PANCREATECTOMY

We examined the relationship between BMI and disease recurrence after pancreatectomy. The distribution of cancer recurrence in the various BMI groups during follow-up is shown in **Figure 1**A. These box plots show the time to recurrence in months by percentile distribution of patients in each BMI group. The median time to recurrence in the group with a BMI of more than 35 was 8.5 (95% confidence interval, 5.2-11.3) months and, when all groups were compared with the group with a BMI of less than 23, only the group with a BMI of more than 35 demonstrated a statistically significant increase in the risk of relapse (P=.006). On the basis of these results, we compared disease-free survival in patients with a BMI of more than 35 with all other patients. Cancer recurrence was observed in 95% (19 of 20) of patients in the group with a BMI of more than 35 vs 61% (161 of 264) of all other patients (P=.005). Kaplan-Meier estimates also demonstrated decreased disease-free survival in patients with a BMI of more than 35 (P=.003, log-rank test) (**Figure 2**A).

All variables given in Table 1 were examined using a univariate Cox proportional hazards model; patients with a BMI of more than 35 were at approximately 2-fold risk of recurrence compared with patients with a BMI of 35 or less (P=.005). Variables with a value of $P>.10$ at univariate analysis were then removed, leaving a BMI of more than 35, LOS, time of surgery, EBL, tumor size, and lymph node status as variables for the multivariate Cox proportional hazards model. Of these, a BMI of more than 35 (P=.045), LOS (P=.01), and positive lymph node status (P=.002) (**Table 3**) were associated with cancer recurrence. After adjusting for other variables, this model estimated that patients with a BMI of more than 35 were at approximately 1.7-fold risk of recurrence after surgery compared with patients with a BMI of 35 or less (P=.003).

BMI AND DEATH AFTER PANCREATECTOMY

As shown in Figure 1B, of all BMI groups, patients with a BMI of more than 35 had the shortest median (range) survival (13.2 [10.9-18.1] months), and this was significantly (P=.02) less than for patients with a BMI of less than 23 (27.4 [20.0-45.5] months). On the basis of this result, we again compared the group with a BMI of more than 35 with all patients with a BMI of 35 or less to quantify the risk of death after pancreatectomy and found that patients with a BMI of more than 35 were at nearly 2-fold risk of death compared with those with a BMI of 35 or less (P=.02). At the last follow-up, 15 of 20 patients (75%) in the group with a BMI of more than35 had died vs 137

Table 3. Multivariate Analysis for Disease Recurrence or Death After Pancreatectomy to Treat Adenocarcinoma

Variable	Parameter Estimate (SE)	*P* Value	95% Hazard Confidence	Ratio Limits
Disease recurrence				
BMI >35 vs ≤35	0.50 (0.25)	.045	1.65	2.69
LOS, 1-d increase	0.02 (0.009)	.01	1.02	1.04
Positive lymph nodes, yes vs no	0.57 (0.16)	.002	1.78	2.41
Death				
BMI >35 vs ≤35	0.49 (0.28)	.08	1.64	2.84
LOS, 1-d increase	0.04 (0.01)	<.001	1.04	1.06
Positive lymph nodes, yes vs no	0.45 (0.18)	.01	1.57	2.21

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); LOS, length of hospital stay.

of 265 patients (52%) with a BMI of 35 or less. Kaplan-Meier estimates of overall survival also demonstrated that patients with a BMI of more than 35 had significantly decreased overall survival ($P=.01$, log-rank test) (Figure 2B). Using a univariate Cox proportional hazards model to estimate the effect of categorized BMI on survival, we found that patients with a BMI of more than 35 were at 1.95-fold risk of death compared with patients with a BMI of 35 or less ($P=.02$). Variables with a value of $P>1.0$ at univariate analysis were removed, and multivariate analysis was performed. Variables for multivariate analysis included a BMI of more than 35, LOS, time of surgery, EBL, tumor size, and lymph node status. Using this model (Table 3), we found that LOS ($P<.001$) and lymph node status ($P=.01$) were significantly associated with survival; however, a BMI of more than 35 was not associated ($P=.08$) with decreased survival. Altogether, the data support a strong relationship between a BMI of more than 35 and disease recurrence after pancreatectomy and a weaker association with subsequent death.

COMMENT

Using a homogeneous consecutive cohort of patients undergoing surgical resection with curative intent, we measured the incremental effect of increasing BMI on common variables related to pancreatectomy performed to treat adenocarcinoma by dividing the patients into cohorts according to BMI. The significant findings in this study include identification of an association between a BMI of more than 35 and pancreatic cancer metastasis to regional lymph nodes, increased risk of cancer recurrence, and decreased overall survival.

In contrast to findings of a previous article,[13] we found that surrogate measures of surgical complexity such as EBL and operative time were not higher in patients with increasing BMI. In addition, we found no association between increasing BMI and a complicated or prolonged postoperative hospital course. An important factor that defines the oncologic completeness of pancreatectomy is the number of lymph nodes examined and a negative resection margin. In both cases, we could identify no differences between the BMI groups. These data suggest that increasing BMI did not impair our ability to perform safe and oncologically sound pancreas resection in patients with adenocarcinoma.

In the present study, we observed that patients in the group with a BMI of more than 35 were less likely to receive preoperative therapy than were patients in the other BMI groups. In general, at our institution, all patients with a confirmed tissue diagnosis of pancreatic cancer are considered candidates for preoperative (neoadjuvant) therapy if they weigh less than the treatment table limit of approximately 181 kg (400 lb). This is greater than the recorded weight of all patients in the group with a BMI of more than 35; thus, we are uncertain of the reason for this observed difference. It is possible that concern about weight-related comorbidities influenced referral patterns for radiotherapy. The decreased use of preoperative therapy in the group with a BMI of more than 35 could have resulted in the observed increase in the number of positive lymph nodes in the surgical specimens[19] from patients in this group. Therefore, we controlled for the use of preoperative therapy and found that the influence of BMI on lymph node metastasis remained strong. In addition, in the small subset of patients who did not receive preoperative therapy, the group with a BMI of more than 35 had the most patients with positive lymph nodes. To our knowledge, the relationship between obesity and lymph node metastases observed in this study is the strongest reported in the literature to date, and it is supported by clinical and laboratory studies showing a relationship between obesity and cancer progression.[20-24]

The independent influence of postoperative LOS on tumor recurrence and death was unrelated to BMI and warrants discussion. In a review of the literature, we could not identify a previously reported relationship between LOS and survival after pancreatectomy. In the present study, we found no association between the occurrence of major postoperative complications and increased LOS. From this observation, we hypothesize that the increased LOS reflected the overall performance status of the patient and was influenced by perioperative events not considered major complications (eg, delayed gastric emptying). We have previously identified poor performance status (defined by a score of <80% on the Karnofsky performance scale) as an independent prognostic factor of decreased disease-free survival after chemoradiotherapy for locally advanced pancreatic cancer[25]; however, drawing any conclusions about the relationship between preoperative performance status, LOS, and survival after pancreatectomy requires a focused prospective analysis.

The retrospective nature of this study limits conclusions that can be drawn about a relationship between elevated BMI and the biologic activity of pancreatic adenocarcinoma. There are likely many unmeasured factors unique to patients with a BMI of more than 35 that could negatively influence patient outcome. First, we do not have complete data on lifestyle risk factors such as alcohol consumption or smoking that could confound our interpretation of the results. Second, we do not have complete data on the medical comorbidities that are well-documented to be present in individuals with class II or III obesity and that may contribute to morbidity and death. Nevertheless, we observed few deaths (n=15 [5%]) unrelated to recurrent pancreatic cancer, which supports cancer recurrence as the primary risk for death in these patients.

Previous epidemiologic studies found that a BMI of more than 35 is associated with a 2.61 relative risk of death from pancreatic cancer.[4] Our findings extend these observations to those patients who undergo surgery to treat pancreatic cancer and suggest that obesity is a host factor affecting tumor biology independent of the difficulties (patient- and treatment-related) involved in delivering oncologic care in obese patients. Future investigations should include a search for systemic or tumor biomarkers in this group of patients that could provide additional insight.

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