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Obesity Is an Independent Prognostic Variable in Colon Cancer Survivors

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Abstract

Purpose—Obesity is associated with an increased risk of colon cancer. However, the influence of body mass index (BMI) on the prognosis of colon cancer survivors and its relationship to gender remains unknown.

Experimental Design—BMI (kg/m²) was categorized in patients with tumor-node-metastasis stage II and III colon carcinomas ($n = 4,381$) enrolled in seven randomized trials of 5-fluorouracil-based adjuvant chemotherapy. Cox proportional hazards models were used to determine the association of BMI with disease-free survival (DFS) and overall survival (OS).

Results—Among colon cancer patients, 868 (20%) were obese (BMI, ≥ 30 kg/m²), of which 606 were class 1 (BMI, 30–34 kg/m²) and 262 were class 2,3 (BMI, ≥ 35 kg/m²). Obese versus normal-weight patients were more likely to be younger, have distal tumors, show intact DNA mismatch repair, and have more lymph node metastases ($P < 0.017$). In a multivariate analysis, BMI was significantly associated with both DFS ($P = 0.030$) and OS ($P = 0.0017$). Men with class 2,3 obesity showed reduced OS compared with normal-weight men [hazard ratio, 1.35; 95% confidence interval, 1.02–1.79; $P = 0.039$]. Women with class I obesity had reduced OS [hazard ratio, 1.24; 95% confidence interval, 1.01–1.53; $P = 0.045$] compared with normal-weight women. Overweight status was associated with improved OS in men ($P = 0.006$), and underweight women had significantly worse OS ($P = 0.019$). BMI was not predictive of therapeutic benefit.

Conclusions—Obesity is an independent prognostic variable in colon cancer survivors and shows gender-related differences. These data suggest that obesity-related biological factors can influence clinical outcome.

The prevalence of obesity, as determined by body mass index (BMI), continues to steadily increase in the United States (1). Large prospective cohort studies have shown that obesity and a sedentary lifestyle confer an increased risk of developing colorectal cancer (CRC) relative to normal-weight individuals (2–8). The Cancer Prevention Study II prospectively followed >900,000 U.S. adults and found a 1.5- to 1.8-fold increased risk of incident colon cancers for obese individuals (9). Studies indicate that the observed associations between obesity and CRC risk are generally stronger in men than in women (8–11). To date, fewer studies have examined the association between BMI and risk of cancer recurrence and

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mortality in patients with established colon cancer (12–14). In a study of 1,053 patients with surgically resected stage III colon cancer treated in an adjuvant chemotherapy trial conducted by the Cancer and Leukemia Group B (CALGB), obesity was not significantly associated with a higher risk of colon cancer recurrence or death compared with normal-weight patients (14). Among participants in two colon cancer adjuvant trials conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), very obese patients (class 2,3: BMI, ≥ 35 kg/m²) were shown to have an increased risk of recurrence and death compared with normal-weight patients (13). Whereas the association of BMI and risk of CRC seems stronger in men, conflicting data exist about obesity and gender in relation to prognosis in colon cancer survivors (12,13). Although obesity was reported to be associated with a significant increase in mortality among women with stage II and III colon carcinomas (12), no evidence for a differential association of BMI and outcome by gender was reported in the NSABP studies (13).

The mechanism by which obesity influences colon cancer prognosis remains poorly understood. Evidence suggests that hyperinsulinemia and perturbations in the insulin-like growth factor (IGF) axis may be important mechanisms by which obesity can confer an increased risk of colon cancer, and such factors may also influence recurrence and death (15–18). We determined the association of obesity, as measured by BMI, with colon cancer recurrence and death in patients with curatively resected stage II and III colon cancers who participated in National Cancer Institute–sponsored randomized clinical trials of 5-fluorouracil–based adjuvant chemotherapy. We also determined whether an association of BMI and prognosis was related to patient gender. Because sporadic colon cancers with defective DNA mismatch repair (MMR) are more frequent in older women (19), we studied the relationship between obesity, MMR status, and patient gender. Lastly, we explored whether BMI was related to the therapeutic response to adjuvant chemotherapy.

Materials and Methods

Study population

The study population ($n = 4,381$) consisted of participants in seven colon cancer adjuvant therapy trials sponsored by the U.S. National Cancer Institute and conducted by Mayo Clinic/North Central Cancer Treatment Group (NCCTG) and the Southwest Oncology Group. The details and findings of the individual studies have been previously reported (20–23). All patients had tumor-node-metastasis (TNM) stage II or III colon carcinomas (24) that had been surgically resected with curative intent. Of these 4,381 patients, 3,226 received effective 5-fluorouracil–based adjuvant chemotherapy and the remaining 1,155 patients received either ineffective treatment ($n = 516$) or no treatment ($n = 639$). Demographic variables were obtained at study entry, and patients were required to have a baseline Eastern Cooperative Oncology Group performance score of 0 to 2 (25). Institutional Review Boards at the study sites had approved these trials, and all participants provided written informed consent. Furthermore, this study was conducted under an active Institutional Review Board–approved protocol to examine and correlate prognostic marker data from adjuvant colon cancer trials.

Determination of height, weight, and BMI

At study enrollment, patient height and weight were measured and recorded by trained staff. These measurements were also used to calculate chemotherapy dosages. In none of the trials was the computed body surface area “capped” for chemotherapy dosing. We calculated BMI (kg/m²) by dividing the weight (kilograms) by the patient’s squared height (meters). BMI categories were created on the basis of WHO classifications and prior reports (12,26). For this analysis, BMI was categorized as underweight (BMI, <20 kg/m²), normal weight (BMI,

20–24.9 kg/m²), overweight (BMI, 25–29.9 kg/m²), class 1 obesity (BMI, 30–34.9 kg/m²), and class 2,3 obesity (BMI, ≥35 kg/m²).

Analysis of DNA MMR

MMR status was determined in primary colon carcinomas from NCCTG adjuvant studies, where tumor blocks and sufficient tissue were available. Tumors were analyzed for MMR protein expression using immunohistochemistry ($n = 893$), as previously described (27). Alternatively, tumors had been analyzed for microsatellite instability (MSI; $n = 217$) or for both MSI and MMR proteins ($n = 198$), as previously reported (28,29). MSI was classified as MSI-high, MSI-low, or microsatellite stable, with the latter two groups being combined for the analysis (29,30). Tumors were regarded as showing defective MMR if there was absence of nuclear staining for any MMR protein or if they were MSI-high.

Statistical analyses

χ^2 and Wilcoxon rank-sum tests were used to test for an association between the categorical BMI and other clinicopathologic variables. The Co-chran-Armitage test was used to test for a trend across the BMI ordered categories for the two-level clinicopathologic variables. Overall survival (OS; censored at 8 y) was calculated as the number of years from random assignment to the date of death or last contact. Disease-free survival (DFS; censored at 5 y) was calculated as the number of years from random assignment to the first of either disease recurrence or death. The distributions of OS and DFS were estimated using Kaplan-Meier methodology. Univariate and multivariate Cox proportional hazards models (31) were used to explore the association of BMI with other clinicopathologic variables and with DFS and OS. The score and likelihood ratio test P values were used to test the significance of each covariate in the univariate and multivariate models, respectively, after stratifying by the patient's original treatment study. Interaction effects between BMI and other variables of interest were tested in multivariate Cox models with the use of the likelihood ratio test. Statistical tests were two-sided, with $P \leq 0.05$ considered significant. P values were not adjusted for multiple comparisons. Statistical analyses were done using SAS software (SAS Institute).

Results

BMI baseline characteristics

The study population included 4,381 participants from seven randomized trials of 5-fluorouracil-based adjuvant chemotherapy for tumor-node-metastasis stage II and III colon cancer. Using our predetermined BMI categories (see Materials and Methods), 868 (20%) were obese, 1,605 (37%) patients were overweight, 281 (6%) were underweight, and 1,627 (37%) were of normal weight (Table 1). Obese patients were further classified into class 1 (BMI 30–34.9 kg/m²) and class 2,3 (BMI ≥ 35 kg/m²) obesity, where 606 (70%) of the 868 obese patients were class 1 and the remaining 262 (30%) were class 2,3. Median BMI in the entire cohort was 25.7 (range, 14.0–70.3). Obese and normal-weight patients both received a median of six cycles of adjuvant chemotherapy from our NCCTG cohort ($P = 0.9436$).

Association of BMI with clinicopathologic variables

We examined the association of the categorical BMI with demographic and clinicopathologic variables (Table 1). Across BMI categories, we found significant associations between BMI and tumor stage and site, where obese patients had the highest rate of stage III tumors and were more likely to have distal colon cancers (Table 1). Distal tumors were defined relative to the splenic flexure with those at the flexure included in the distal category. Obesity was associated with a higher number of metastatic lymph nodes in

that obese patients were more likely to have greater than three metastatic lymph nodes (N2 disease; ref. 24) compared with normal-weight patients (28% versus 22%; $P = 0.017$; Table 1). Age was also associated with BMI ($P = 0.0005$) in that obese and underweight patients were younger than were normal and overweight patients (Table 1). Similarly, gender was associated with BMI ($P < 0.0001$), where underweight patients were more likely female, overweight patients were more likely male, and normal-weight and obese patients were evenly split by gender. No relationship between BMI and patient performance status was found.

The prevalence of defective MMR colon cancers was 14.5% (Table 1), and the frequency was higher in women than in men (18% versus 11%; $P = 0.001$). Defective MMR was associated with older age in women ($P = 0.0005$) but not in men ($P = 0.5818$; $P_{\text{interaction}} = 0.0009$). Obese patients had a lower rate of defective MMR compared with normal-weight patients (9.5% versus 15.5%; $P = 0.0347$; Table 1), and this association was stronger in patients younger ($P = 0.0037$) compared with those older than 60 years of age ($P_{\text{interaction}} = 0.0310$; adjusted for covariates).

Impact of BMI on cancer recurrences or death

After a median follow-up of 8 years, 1,585 (36%) of the 4,381 eligible patients experienced cancer recurrence, and 1,833 (42%) had died. In a univariate analysis, the categorical BMI was significantly associated with both DFS and OS (Table 2). Specifically, patients who were obese (BMI, ≥ 30 kg/m²) had worse DFS and OS rates compared with normal-weight patients that were of borderline statistical significance. When obesity was further categorized, those with class 2,3 obesity (BMI, ≥ 35 kg/m²) had worse DFS [hazard ratio (HR), 1.23; 95% confidence interval (95% CI), 1.01–1.49; $P = 0.0370$] and OS (HR, 1.18; 95% CI, 0.98–1.44; $P = 0.0879$) rates compared with normal-weight patients (Table 2). The prognosis of underweight or overweight patients did not differ univariately compared with normal-weight patients (Table 2). The prognostic effect of other clinicopathologic variables is shown in Table 2. We found that patients with higher tumor stage (stage III versus II), poor differentiation, intact MMR status, increased number of metastatic lymph nodes, and none or ineffective treatment had worse rates of DFS and OS by univariate analysis. In addition, male gender and increased age were also associated with worse OS. The relationship between BMI and survival was not significantly modified by age or stage.

In a multivariate analysis, the categorical BMI remained significantly associated with both DFS (overall $P = 0.0297$) and OS (overall $P = 0.0017$; Table 3) after adjusting for age, stage, adjuvant treatment status, and gender. Class 2,3 obese patients showed a trend toward worse DFS ($P = 0.0725$) and OS ($P = 0.0805$; Table 3). Underweight patients had a significantly worse OS ($P = 0.0258$), whereas overweight patients had better OS ($P = 0.0500$) after adjusting for these same covariates (Table 3). The HRs and 95% CIs for both DFS and OS by the individual BMI categories are shown in Fig. 2A. As shown by the HRs, an adverse prognostic effect of BMI is seen for both underweight and class 2,3 obese patients. When the data were analyzed by patient gender (Table 3), we found that BMI was significantly associated with OS in men (overall $P = 0.0021$) and was of borderline significance in women (OS; overall $P = 0.0674$; adjusted $P_{\text{interaction}} = 0.081$ for categorical BMI and gender for OS). Specifically, men with class 2,3 obesity had a significantly worse OS (HR, 1.35; 95% CI, 1.02–1.79; $P = 0.0391$) compared with normal-weight men (Table 3; Fig. 1A). In women, class 1 obesity was associated with worse OS compared with normal-weight women (HR, 1.24; 95% CI, 1.01–1.53; $P = 0.0447$; Fig. 1B), whereas this same effect was not observed in men (Table 3; Fig. 1A). Overweight men had a significantly improved OS ($P = 0.0063$) compared with normal-weight men after adjustment for covariates (Table 3). The poor prognosis of underweight patients was more evident in women (OS; $P = 0.019$; Table 3). A comparison of the OS HRs (95% CI) by BMI category

and gender is shown graphically in Fig. 2B to illustrate the gender-related differences. Age, tumor stage, and treatment were at least of borderline significance for OS among all patients and in both genders (Table 3).

Because normal-weight and overweight patients had the best prognoses, we combined these groups and conducted a secondary analysis. Using these combined groups as the reference (BMI, 20–30), we found that obesity (class 1–3; BMI, >30) was associated with a significantly worse DFS ($P = 0.0254$) and OS ($P = 0.0093$) after adjusting for age, stage, treatment, and gender. Given the findings for individual BMI categories and patient outcome, we determined whether a curvilinear or quadratic relationship could also describe the results observed. We found that continuous BMI displayed a significant curvilinear relationship with OS ($P = 0.0071$) after adjustment for age, stage, treatment, and gender.

Predictive analysis

We determined whether BMI was predictive for 5-fluorouracil-based chemotherapy outcome among all patients and within stage III patients. In the multivariate models, there was no significant relationship between BMI and treatment efficacy (adjusted $P > 0.15$) for any of the BMI categories tested.

Discussion

Although obesity and a sedentary lifestyle are known to increase the risk of developing colon cancer (2–7), only recently have studies examined whether obesity can influence the outcome of survivors of this disease. To determine whether obesity is associated with differences in colon cancer recurrence and/or survival, we studied stage II and III colon cancer patients from completed adjuvant chemotherapy trials. Using study baseline BMI measurements, we observed that obesity (BMI, ≥ 30 kg/m²) was significantly associated with an increased number of metastatic regional lymph nodes compared with normal-weight patients. The number of lymph node metastases is an accepted adverse prognostic variable in colon cancer patients (24). Obese patients were more likely to have distal versus proximal colon cancers, and distal tumors have been shown to have higher rates of chromosomal instability, *p53* mutation, and DNA aneuploidy that may confer a worse prognosis (32,33).

We found that obese patients showed higher rates of cancer recurrence and mortality compared with normal-weight patients that was most evident overall for class 2,3 (BMI, ≥ 35 kg/m²) obesity. In a multivariate analysis, class 2,3 obesity was associated with a 19% increase in the risk of death (i.e., OS) compared with normal-weight patients. It is important to note that unlike the NSABP colon cancer adjuvant trials (13), our studies did not limit chemotherapy dosing based on body surface area, and therefore, the less favorable outcomes among obese patients are not related to differences in the amount of chemotherapy received. In support of the prognostic effect of obesity, we found that chemotherapy dosing and the number of cycles of adjuvant chemotherapy received were similar in obese versus normal-weight subjects. Although we did not have data on the total number of lymph nodes removed at surgical resection, we further addressed the adequacy of surgical resection by examining local recurrence rates in patients where such data were available ($n = 243$). Across all BMI categories studied, local recurrence rates were similar ($P = 0.67$) and did not differ significantly among obese versus normal-weight patients ($n = 130$; $P = 0.20$). Therefore, our data suggest that obesity did not adversely affect the adequacy of surgical resection when local recurrence is used as a surrogate. Regrettably, we did not have colon cancer-specific survival data; however, DFS is a useful surrogate for such information and results for DFS and OS were similar.

We determined whether the prognostic effect of obesity was related to patient gender. Data about BMI, gender, and prognosis have been conflicting in patients with established colon cancer. In an adjuvant chemotherapy trial, obese women (BMI, ≥ 30.0 kg/m²) but not men experienced significantly worse overall mortality (12). In an analysis of pooled adjuvant colon cancer studies conducted by a single cooperative group (NSABP), no differences between obesity and colon cancer outcome by gender were found (13). However, we found a stronger relationship between BMI and clinical outcome in men compared with women. Men who were very obese (BMI, ≥ 35 kg/m²) had a 35% increased risk of death that was statistically significant, whereas very obese women had only an 11% increased risk of death that was not significant compared with normal-weight patients after adjustment for covariates. Women with class 1 (BMI, 30–34 kg/m²) obesity, however, had worse OS ($P = 0.045$) compared with normal-weight women, whereas this same effect was not observed in men. These data are consistent with the finding that the association of BMI and colon cancer incidence and mortality is stronger and more linear in men than in women (9,10,34–39). Stronger associations for BMI and prognosis in men compared with women may be explained, in part, by the observation that BMI is more closely related to the amount of abdominal or central adiposity in men than in women (40,41). In this regard, a 20% increase in the risk of colon cancer recurrence or death was observed for every 10-cm increase in waist circumference (42). Another potential explanation for gender differences in colon cancer prognosis is an effect modification by menopausal status and/or hormone replacement therapy in that a protective effect of hormone replacement therapy has been associated with a significant reduction in colon cancer mortality (3,43,44).

Patient gender was related to the molecular pathway of colon tumorigenesis in that colon cancers with defective MMR were more prevalent in older women but not in men (19,45). In this regard, we found that defective MMR was associated with older age in women but not in men ($P_{\text{interaction}} = 0.0009$). An excess of colon cancers with defective MMR found in older women as shown here may be related to a withdrawal of estrogens (45,46). Interestingly, we found that obese patients had significantly fewer colon cancers with defective MMR compared with normal-weight patients. Similarly, obesity and lack of physical activity were associated with a lower prevalence of colon cancers with defective MMR in women but not in men in a population-based, case-controlled study (45). Obesity is associated with increased levels of circulating estrogen (47), and estrogen may protect against the development of colon cancers with defective MMR in women (45).

We found that colon cancer mortality was increased among underweight (BMI, < 20.0 kg/m²) patients in a multivariate analysis. A worse outcome for underweight patients has been a consistent finding among studies, and underweight may reflect underlying comorbidities that increase mortality risk (48). Mortality in underweight CRC patients was more often due to noncan-cer-related causes than was mortality in normal-weight patients (13). We also observed that overweight patients had significantly better OS rates in a multivariate analysis. This effect was limited to men, whereby overweight men showed significantly improved OS ($P = 0.006$) after adjusting for age, stage, and treatment. Some longitudinal studies have shown that overweight subjects without a cancer history have the lowest mortality among BMI categories when examining BMI and risk of death (49,50). This finding may reflect a limitation of BMI in that it makes no distinction between body weight from muscle versus fat, and therefore, muscular individuals can be categorized as overweight or obese when they are not. Together, our data show the complex relationship of BMI and clinical outcome whereby the prognostic effect of BMI varies by category. Based on WHO guidelines and prior studies (13,26), we analyzed BMI as a categorical variable. The results of this analysis suggested that BMI has a curvilinear or quadratic relationship with OS. We also modeled BMI as a continuous curvilinear variable and found that it was associated with OS ($P =$

0.0071). Therefore, our data show consistent results when modeling BMI as a categorical variable or as a continuous curvilinear variable.

The mechanism underlying the effect of obesity on the clinical behavior of colon cancers remains poorly understood but may involve interactions among insulin, IGFs, and IGF-binding proteins (16,17,51–54) that have all been implicated in colon cancer development. Increased circulating levels of insulin and free IGF-I have been associated with obesity and physical inactivity (18,55,56). Furthermore, both insulin and IGF-I promote cell proliferation and inhibit apoptosis in colon cancer cells (57,58), suggesting that they may promote the growth of micrometastases. In a prospective case-control study nested within the Physicians' Health Study, men in the highest quintile for IGF-I had 2.5 times the risk of CRC as did men in the lowest quintile (51). An analysis of the Nurses' Health Study cohort found a comparable risk increase among women, with a relative risk of 2.17 for those in the highest quartile of IGF-I compared with those in the lowest (15). Studies have also shown (16,52) an increase in CRC risk with increasing levels of C-peptide, a marker of insulin production, and in men with the high levels of the hormone leptin (59,60). Another mechanism that may contribute to differences in colon cancer survival based on BMI is suggested by data for fatty acid synthase (FASN) expression (61). Among normal-weight and minimally overweight patients (BMI, <27.5 kg/m²), FASN positivity was associated with a reduction in mortality, whereas among moderately overweight and obese patients (BMI, ≥27.5 kg/m²), FASN overexpression conferred a significant increase in mortality (61). FASN plays an important role in *de novo* lipogenesis and is physiologically regulated by energy balance in that exercise and energy restriction downregulate FASN (62).

Important strengths of our study include its large size, accuracy of BMI measurements done at study entry by trained staff rather than self-reporting of height and weight, and rigorous collection of recurrence and survival data during an extended follow-up period. Limitations include the retrospective design and measurement of obesity by BMI versus measures of central obesity such as waist-to-hip ratio or waist circumference that may be more predictive of the risk of developing colon cancer than BMI (3,42,63). We were also unable to analyze factors such as diet, physical activity, or menopausal status and hormone replacement therapy use that may have independent associations with colon cancer outcomes as well as risk of death from other causes. Importantly, Meyerhardt et. al. (14) reported that changes in weight (either gain or loss) during the period of adjuvant chemotherapy in colon cancer patients were not associated with clinical outcome.

Our findings extend the effect of obesity beyond its known association with colon cancer risk by showing that obesity is an independent prognostic variable in colon cancer survivors that shows differences by gender. Obesity was a poor prognostic factor despite adjuvant chemotherapy. Such information has the potential to influence patient management decisions and surveillance strategies. Further study is needed to determine the mechanism of the adverse effect of obesity on survivors of colon cancer. Lastly, our findings suggest the potential for evaluating interventions among obese survivors of colon cancer with the goal of improving patient outcomes.

Translational Relevance

Multiple studies have shown that obesity is associated with an increased risk of developing colon cancer; however, the influence of obesity on the prognosis of colon cancer survivors is poorly understood. Furthermore, the link between obesity and colon cancer risk seems stronger in men, yet conflicting data exist about colon cancer outcomes based on gender. We determined the association of body mass index with clinical outcome in colon carcinoma patients who participated in seven randomized trials of 5-

fluorouracil-based adjuvant chemotherapy. Twenty percent of patients were obese (body mass index, ≥ 30 kg/m²) and were more likely to have distal tumors, show intact DNA mismatch repair, and have increased lymph node metastases compared with normal-weight patients. Moreover, obesity was an independent and adverse prognostic variable in colon cancer survivors with distinct gender-related differences. These data suggest that interventions to reduce rates of obesity may improve colon cancer outcomes.

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Fig. 1.
Relationship between obesity and clinical outcome for stage II and III colon cancer patients participating in adjuvant chemotherapy trials. A, OS in men only. B, OS in women only.

Fig. 2.

A, HRs and 95% CIs for DFS and OS in relation to BMI category in all patients. B, HRs and 95% CIs for OS by BMI category in men versus women. HRs were adjusted for age, stage, treatment, and gender.

Table 1

Clinical characteristics by BMI categories

	Underweight (n = 281)	Normal (n = 1,627)	Overweight (n = 1,605)	Obese (n = 868)	Total (n = 4381)	Overall P*	Obese vs normal P†
Histologic grade‡						0.1370	0.6825
1/2	124 (68.9%)	763 (73.5%)	786 (76.1%)	388 (74.5%)	2,061 (74.4%)		
3/4	56 (31.1%)	275 (26.5%)	247 (23.9%)	133 (25.5%)	711 (25.6%)		
Stage						0.0129	0.0516
III	200 (71.7%)	1,235 (76%)	1,219 (76.1%)	684 (79.4%)	3,338 (76.5%)		
II	79 (28.3%)	390 (24%)	382 (23.9%)	177 (20.6%)	1,028 (23.5%)		
Tumor site						0.0144	0.0575
Distal	78 (43.3%)	497 (47.9%)	512 (49.7%)	275 (53%)	1,362 (49.2%)		
Proximal	102 (56.7%)	541 (52.1%)	518 (50.3%)	244 (47%)	1,405 (50.8%)		
MMR						0.0082	0.0347
Intact	40 (75.5%)	339 (84.5%)	370 (85.1%)	201 (90.5%)	950 (85.5%)		
Defective	13 (24.5%)	62 (15.5%)	65 (14.9%)	21 (9.5%)	161 (14.5%)		
Gender						<0.0001	0.6163
Women	205 (73%)	840 (51.6%)	623 (38.8%)	439 (50.6%)	2,107 (48.1%)		
Men	76 (27%)	787 (48.4%)	982 (61.2%)	429 (49.4%)	2,274 (51.9%)		
Age						0.0005	0.0382
Mean (SD)	57.8 (14.25)	61.0 (12.11)	61.7 (10.50)	60.6 (10.24)	61.0 (11.38)		
Median	60.5	63.0	63.0	61.3	62.1		
Range	18.0–84.2	18.3–89.0	22.0–89.7	23.7–83.3	18.0–89.7		
Treatment status						0.0349	0.0293
Ineffective	81 (28.8%)	438 (26.9%)	437 (27.2%)	199 (22.9%)	1,155 (26.4%)		
Effective	200 (71.2%)	1,189 (73.1%)	1,168 (72.8%)	669 (77.1%)	3,226 (73.6%)		
Lymph nodes						0.0714	0.0171
0	66 (28.2%)	333 (25.9%)	342 (27.4%)	148 (23.8%)	889 (26.2%)		
1–3	113 (48.3%)	670 (52.1%)	632 (50.6%)	299 (48.1%)	1,714 (50.5%)		
>3	55 (23.5%)	284 (22.1%)	275 (22%)	174 (28%)	788 (23.2%)		
T stage						0.3508	0.8280
T1,2	19 (8.4%)	141 (10.9%)	145 (11.5%)	71 (11.3%)	376 (11%)		

	Underweight (<i>n</i> = 281)	Normal (<i>n</i> = 1,627)	Overweight (<i>n</i> = 1,605)	Obese (<i>n</i> = 868)	Total (<i>n</i> = 4381)	Overall <i>P</i> [*]	Obese vs normal <i>P</i> [†]
T _{3,4}	206 (91.6%)	1,148 (89.1%)	1,115 (88.5%)	559 (88.7%)	3,028 (89%)		

* Kruskal-Wallis test for continuous data; χ^2 test for variables with 3+ categories; Cochran-Armitage test for trend *P* value for variables with only 2 categories.

[†] χ^2 test for categorical data and Wilcoxon rank-sum test for continuous data.

[‡] Grade 1/2: well/moderate differentiation; grade 3/4: poor/undifferentiated.

Table 2Univariate analysis in all patients ($n = 4,381$)

Variable	DFS, HR (95% CI)	P^*	OS, HR (95% CI)	P^*
Categorical BMI (overall)		0.0477		0.0218
Underweight vs normal	1.08 (0.89–1.31)	0.4336 [†]	1.13 (0.93–1.36)	0.2209 [†]
Overweight vs normal	0.94 (0.84–1.05)	0.2880 [†]	0.93 (0.83–1.03)	0.1623 [†]
Obese vs normal	1.13 (0.99–1.28)	0.0670 [†]	1.13 (0.99–1.28)	0.0622 [†]
Class 1 obese	1.08 (0.94–1.25)	0.2768 [†]	1.10 (0.96–1.27)	0.1785 [†]
Class 2,3 obese	1.23 (1.01–1.49)	0.0370 [†]	1.18 (0.98–1.44)	0.0879 [†]
Stage				
II vs III	0.45 (0.39–0.52)	<0.0001	0.47 (0.41–0.53)	<0.0001
Gender				
Men vs women	1.05 (0.95–1.15)	0.3348	1.10 (1.00–1.20)	0.0490
Histologic grade [‡]				
Grade 3/4 vs grade 1/2	1.41 (1.24–1.61)	<0.0001	1.43 (1.26–1.63)	<0.0001
Tumor site				
Proximal vs distal	0.90 (0.80–1.01)	0.0836	1.02 (0.91–1.15)	0.6984
MMR status				
Defective vs intact	0.68 (0.49–0.94)	0.0174	0.71 (0.53–0.96)	0.0252
Age (1-unit increase)	1.00 (0.996–1.004)	0.9007	1.01 (1.005–1.014)	<0.0001
Number of lymph nodes		<0.0001		<0.0001
1–3 vs 0	1.75 (1.50–2.04)		(1.51–2.04)	
>3 vs 0	3.57 (3.04–4.20)		3.58 (3.05–4.19)	
Treatment status				
Effective vs ineffective/none	0.61 (0.52–0.72)	<0.0001	0.69 (0.59–0.81)	<0.0001

* Score test P value from a Cox regression model after stratifying by study.[†] Wald X^2 P value for the individual categories shown.[‡] Grade 1/2: well/moderate differentiation; grade 3/4: poor/undifferentiated.

Table 3

Multivariate analysis of BMI and OS

All patients (n = 4,366)		
Variable	HR (95% CI)	P*
Categorical BMI (overall)		0.0017
Underweight vs normal	1.24 (1.03–1.50)	0.0258 [†]
Overweight vs normal	0.90 (0.80–1.00)	0.0500 [†]
Class 1 obese vs normal	1.07 (0.93–1.23)	0.3717 [†]
Class 2,3 obese vs normal	1.19 (0.98–1.45)	0.0805 [†]
Age	1.01 (1.01–1.02)	<0.0001
Stage (II vs III)	0.47 (0.41–0.53)	<0.0001
Treatment (effective vs control/ineffective)	0.72 (0.62–0.85)	<0.0001
Gender (men vs women)	1.15 (1.04–1.26)	0.0045
Men (n = 2,268)		
Variable	HR (95% CI)	P*
Categorical BMI (overall)		0.0021
Underweight vs normal	1.14 (0.81–1.61)	0.4474 [†]
Overweight vs normal	0.82 (0.71–0.95)	0.0063 [†]
Class 1 obese vs normal	0.94 (0.78–1.15)	0.5599 [†]
Class 2,3 obese vs normal	1.35 (1.02–1.79)	0.0391 [†]
Age	1.01 (1.01–1.02)	<0.0001
Stage (II vs III)	0.51 (0.43–0.61)	<0.0001
Treatment (effective vs control/ineffective)	0.64 (0.51–0.80)	<0.0001
Women (n = 2,098)		
Variable	HR (95% CI)	P*
Categorical BMI (overall)		0.0674
Underweight vs normal	1.32 (1.05–1.67)	0.0194 [†]
Overweight vs normal	1.01 (0.85–1.19)	0.9366 [†]
Class 1 obese vs normal	1.24 (1.01–1.53)	0.0447 [†]
Class 2,3 obese vs normal	1.11 (0.84–1.45)	0.4651 [†]
Age (1-y increase)	1.01 (1.00–1.02)	0.0052
Stage (II vs III)	0.41 (0.34–0.51)	<0.0001
Treatment (effective vs control/ineffective)	0.83 (0.66–1.04)	0.0948

* Likelihood ratio *P* value after stratifying by study.

[†] Wald χ^2 *P* value.