Severe obesity prior to diagnosis limits survival in colorectal cancer patients evaluated at a large cancer centre

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Background: In contrast to the consistent evidence for obesity and colorectal cancer (CRC) risk, the impact of obesity in CRC patients is less clear. In a well-characterised cohort of CRC patients, we prospectively evaluated class I and class II obesity with survival outcomes.

Methods: The CRC patients (N = 634) were followed from the date of diagnosis until disease progression/first recurrence (progression-free survival (PFS)) or death (overall survival (OS)). Body mass index (BMI) was calculated from reported usual weight prior to diagnosis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in models adjusted for clinicopathologic, treatment, and lifestyle factors.

Results: Over a median follow-up of 4 years, 208 (33%) patients died and 235 (37%) recurred or progressed. Class II obesity, as compared with either overweight or normal weight, was associated with an increased risk of death (HR and 95% CI: 1.55 (0.97–2.48) and 1.65 (1.02–2.68), respectively), but no clear association was observed with PFS. In analyses restricted to patients who presented as stages I–III, who reported stable weight, or who were aged <50 years, obesity was associated with a significant two- to five-fold increased risk of death.

Conclusions: In CRC patients evaluated at a large cancer centre, severely obese patients experienced worse survival outcomes independent of many other factors.

Colorectal cancer (CRC) remains the second leading cause of cancer mortality among US men and women combined, with an estimated 132 700 new cases and 49 700 deaths expected in 2015 (American Cancer Society, 2015). Refinements in screening and treatment strategies have improved survival of this disease; and currently, over 1 million CRC survivors are living in the United States (American Cancer Society, 2015).

Obesity is an established risk factor involved in the development of CRC via inflammation, metabolism, hormone and cytokine signalling that may continue to play a significant role in disease recurrence and survival outcomes among CRC patients after treatment (Demark-Wahnefried et al, 2012; Bardou et al, 2013; Gibson et al, 2014). Despite concentrated public health efforts, no significant changes or improvements in overall US obesity rates have been observed over the past 10 years, whereas the rates of morbid obesity continue to increase (Flegal et al, 2012; Sturm and Hattori, 2013). Currently, more than one-third of all adults, as well as CRC survivors, living in the United States are obese (body mass index (BMI) ≥ 30 kg m⁻²) (Flegal et al, 2012; Sturm and Hattori, 2013). Approximately 15% of middle-aged adults (age 40–59 years;
Ogden et al (2014) meet the criteria for class II obesity (BMI $\geq 35 \text{kg m}^{-2}$) including the age group (50+ years) most commonly diagnosed and treated for colorectal and other cancers (American Cancer Society, 2015). This not only presents a significant problem for cancer prevention, but as we improve our treatment capabilities, it may also present challenges for long-term survival in obese cancer patients.

The American Cancer Society recommendations for cancer patients and survivors are similar to those for cancer prevention and state that in addition to not smoking, eating a healthy diet, and being physically active, individuals maintain a normal weight (Doyle et al, 2006). However, a U-shaped relationship with improved survival among overweight, as compared with normal and underweight, CRC patients has also been observed (Hines et al, 2009; Sinicrope et al, 2010; Baade et al, 2011; Min et al, 2012; Schlesinger et al, 2014; Wu et al, 2014), and suggests that moderate adiposity or overweight status may be protective for initially enduring the arduous cancer process (Parkin et al, 2014; Renehan, 2014; Schlesinger et al, 2014). With tumour stage, treatment, and cancer-associated weight loss linked to inconsistencies in prior analyses of BMI and CRC cancer patient survival (Sinkens et al, 2011; Parekh et al, 2012; Bordou et al, 2013; Boyle et al, 2013; Sinicrope et al, 2013; Azvolinsky, 2014; Parkin et al, 2014), clarifying whether obesity is an independent prognostic factor and what is not a healthy weight for cancer patients remains both a clinically relevant and timely concern. In a cohort of well-characterised CRC patients, we prospectively evaluated the association of class I (BMI 30–34.9 kg m$^{-2}$) and class II (BMI $\geq 35 \text{kg m}^{-2}$) obesity with survival outcomes.

Materials and Methods

Study cohort. As reported previously (Ye et al, 2012), 1103 histologically confirmed colorectal adenocarcinoma patients were recruited between January 1990 and June 2008 at the University of Texas MD Anderson Cancer Center (MDACC). Of these, 745 patients were newly diagnosed (within 1 year of referral to the cancer centre); and over 90% were diagnosed within 3 months of recruitment into the study. We collected epidemiological data through a self-administered questionnaire and abstracted treatment and clinicopathologic data from patients’ electronic medical records. Of these, 634 patients had complete data, including BMI, for the current analysis. The study was approved by the Institutional Review Board of MD Anderson Cancer Center and informed consent was obtained from each study participant.

Study variables. We examined the following survival end points: progression/recurrence-free survival (PFS) defined as the time from pathologic diagnosis until disease progression or first recurrence; and overall survival (OS) defined as the time from pathologic diagnosis until the date death from any cause, as captured by the MDACC tumour registry (Eng and Skibber, 2013). In patients without a reported death date, follow-up was defined as the date of last contact. BMI (kg m$^{-2}$) was calculated from the patient’s height and self-reported usual weight prior to diagnosis and categorised as normal (BMI < 25 kg m$^{-2}$), overweight (BMI 25 to < 30 kg m$^{-2}$), class I obesity (BMI 30 to < 35 kg m$^{-2}$), and class II obesity (BMI $\geq 35 \text{kg m}^{-2}$) according to WHO guidelines (Word Health Organization, 2000). Periagnostic weight change (prior to the initiation of treatment) was further informed by electronic medical record data and defined as weight loss, weight stable, weight gain, or unknown. We derived an 8-level categorical treatment variable based on common combinations used in clinical practice: (1) surgery only; (2) Fluorouracil (5-FU) chemotherapy with molecular target therapy (MTT) and/or 5-FU with radiation; (3) Capecitabine (CAPE) or other chemotherapy with MTT and/or CAPE or other chemotherapy with radiation; (4) surgery and 5-FU with MTT; (5) surgery and CAPE or other chemotherapy with MTT; (6) surgery and CAPE with radiation; (7) surgery and other chemotherapy with radiation; and (8) unknown treatment (<2%). Inclusion vs exclusion of the missing categories for clinicopathologic variables of interest (all $\leq 2\%$) did not meaningfully change the estimates observed.

Statistical analysis. To assess the association of demographic and clinical variables with survival, we used the $\chi$ and nonparametric log-rank test, as appropriate. We evaluated the association of prediagnostic BMI in relation to prospective survival outcomes using Cox proportional hazards regression models adjusted for age, sex, alcohol drinking status, clinical stage, grade, treatment modality, and weight change (defined in Table 1). Additional adjustment for history of diabetes, smoking status, and other covariates did not meaningfully alter estimates presented. Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values for trend (using the median value within each category) are reported across BMI categories. The proportional hazards assumption was satisfied by evaluating the cross-product of BMI and time ($P = 0.73$). Survival curves were generated using the Kaplan–Meier method and statistical significance was measured using the log-rank test. We also assessed whether associations with BMI varied by CRC risk and prognostic factors mentioned in previous reports (American Cancer Society, 2014; Parkin et al, 2014; Renehan, 2014; Wu et al, 2014), including age, sex, smoking status, history of diabetes, weight change, and tumour stage. Statistical tests for interaction evaluated the significance of categorial cross-product terms in the multivariable adjusted models. All statistical analyses were performed using STATA version 10.0 (Stata Co., College Station, TX, USA). P-values are two sided and considered statistically significant at $P < 0.05$.

Results

Characteristics of the 634 colon and rectal cancer patients are presented in Table 1. Over a median follow-up of 4 years post diagnosis, 208 (33%) patients died and 235 (37%) recurrent or progressed. Majority of the CRC patients were over 50 years of age, white, male, and overweight or obese; approximately half reported never smoking or consuming alcohol. Among those with known disease stage (98%), two-thirds had localised or locally advanced disease. Obese patients (BMI $\geq 30 \text{kg m}^{-2}$), as compared with nonobese patients (BMI < 30 kg m$^{-2}$), were more likely to be male and to report a positive history of type II diabetes mellitus (data in Supplementary Table S1). Weight loss prior to diagnosis was reported in 37% of lean patients (BMI < 25 kg m$^{-2}$) as compared with 27%, 26%, and 10% of overweight (BMI 25 to < 30 kg m$^{-2}$), class I obesity (BMI 30 to < 35 kg m$^{-2}$), and class II obesity (BMI $\geq 35 \text{kg m}^{-2}$) respectively (Supplementary Table S1). No other significant differences across BMI categories were observed for age at diagnosis, tumour characteristics, or treatment modality. Patients who reported recent weight loss, as compared with patients who reported stable weight, were more likely to be current smokers (pair-wise $P = 0.08$) and to have advanced tumours ($P < 0.001$; data not shown).

The associations of demographic, clinical, and treatment characteristics with 10-year OS among CRC patients are shown in Table 2. Survival significantly differed by tumour characteristics (stage and grade), treatment modality, and weight change. Similar associations were observed for stage and treatment modality with PFS; however, no differences were observed by BMI or weight change (data in Supplementary Table S2).

The univariate analysis revealed a U-shaped relationship between BMI and survival, with the highest risk of death observed
among the lowest (BMI < 25 kg m⁻²) and highest (BMI ≥ 35 kg m⁻²) categories (Table 3 and Figure 1). The lowest risk of death was observed among the overweight patients (BMI 25–29.9 kg m⁻²), which was set as the referent category. However, following adjustment for age, sex, alcohol status, weight change, tumour, and treatment characteristics, this relationship was attenuated for the BMI < 25 kg m⁻² category. In the multivariable model with overweight as the referent category, we observed a nearly significant direct association between class II obesity and 10-year OS (BMI ≥ 35 vs BMI 25–29.9 kg m⁻²) (ref), HR: 1.55; 95% CI: 0.97–2.48). Consistent associations were observed across BMI categories in multivariable models with lean patients (BMI < 25 kg m⁻²) as the referent category (HR and 95% CI: 1.00 (ref); 0.99 (0.67–1.46); 1.11 (0.74–1.67); 1.65 (1.02–2.68), respectively; P-trend = 0.08; data in text only).

In analyses restricted to patients with localised or locally advanced disease, both class I and class II obesity, as compared with overweight, were associated with significantly worse OS (Table 3), but null associations were observed in metastatic patients.
(Figure 2). Similarly, the finding for severe obesity was more pronounced among patients who reported stable weight (Table 3), whereas no association was observed among the group that reported weight loss ($P_{\text{trend}} = 0.91$) or that did not specify ($P_{\text{trend}} = 0.87$; data not shown). Class II obesity also remained significantly associated with OS in analyses restricted to patients who were never smokers (HR: 2.09, 95% CI: 1.07–4.08, $P = 0.03$; Figure 2), patients without a history of type II diabetes (HR: 1.98, 95% CI: 1.17–3.37, $P = 0.01$; data in text only), and patients diagnosed prior to age 50 years (HR: 4.94, 95% CI: 1.66–14.70, $P = 0.004$; Figure 2).

No statistically significant associations were observed across BMI categories and PFS in overall multivariable models (HR and 95% CI: 0.89 (0.63–1.26), 1.00 (ref), 0.97 (0.67–1.40), 1.28 (0.82–1.99), $P = 0.32$; data presented in Supplementary Table S3). However, in analyses restricted to never smokers, class II obesity was associated with an increased risk of progression/metastatic patients, older patients, or among patients who experienced prior weight loss. When adjusted for other important demographic and clinicopathologic factors, including treatment, severe obesity was associated with a two-fold to five-fold increased risk of death as compared with overweight patients. Similarly, among CRC patients who did not experience weight loss prior to diagnosis and treatment, severe obesity was associated with a more than two-fold risk of death, but no clear association was observed among metastatic patients, older patients, or among patients who experienced prior weight loss. When adjusted for other important demographic and clinicopathologic factors, including treatment, we observed no excess risk among lean or overweight patients.

Severe or class II obesity has been previously linked to significantly worse survival outcomes as compared with all other BMI categories and independent of other prognostic factors in patients with colon (Murphy et al, 2000; Dignam et al, 2006; Sinicrope et al, 2010), pancreatic (Fleming et al, 2009; Yuan et al, 2013), and breast cancer (Pajares et al, 2013). Excess adipose tissue, as the body’s largest active endocrine organ, may limit survival in cancer patients via energy balance and

### Table 3. Association between prediagnostic BMI (kg m$^{-2}$) and 10-year mortality in colorectal cancer patients

| Variables | Univariate | Multivariate$^*$ |
|-----------|------------|------------------|
|           | HR 95% CI  | $P_{\text{trend}}$ | HR 95% CI  | $P_{\text{trend}}$ |
| All patients (N = 634) |
| <25       | 1.60 1.13–2.26 | 1.04 0.71–1.52 | 1.22 0.84–1.77 | 1.13 0.76–1.68 | 1.45 0.93–2.25 | 1.55 0.97–2.48 | 0.14 |
| 25–29.9   | 1.00 Ref | 1.00 Ref | 1.00 Ref | 1.00 Ref | 2.06 1.08–3.92 | 2.21 1.11–4.40 | 0.009 |
| 30–34.9   | 1.00 Ref | 1.00 Ref | 1.00 Ref | 1.00 Ref | 3.38 1.72–6.64 | 3.49 1.68–7.22 | 0.007 |
| >35       | 1.22 0.84–1.77 | 1.13 0.76–1.68 | 1.45 0.93–2.25 | 1.55 0.97–2.48 | 0.14 |
| Stage I–III patients (N = 409) |
| <25       | 1.70 0.85–3.41 | 1.59 0.74–3.43 | 2.06 1.08–3.92 | 2.21 1.11–4.40 | 0.009 |
| 25–29.9   | 1.00 Ref | 1.00 Ref | 1.00 Ref | 1.00 Ref | 3.38 1.72–6.64 | 3.49 1.68–7.22 | 0.007 |
| 30–34.9   | 2.06 1.08–3.92 | 2.21 1.11–4.40 | 3.38 1.72–6.64 | 3.49 1.68–7.22 | 0.007 |
| >35       | 3.38 1.72–6.64 | 3.49 1.68–7.22 | 0.007 |
| Stable-weight patients (N = 379) |
| <25       | 1.25 0.76–2.07 | 1.17 0.66–2.09 | 1.36 0.75–2.46 | 2.60 1.42–4.76 | 0.01 |
| 25–29.9   | 1.00 Ref | 1.00 Ref | 1.00 Ref | 1.00 Ref | 2.60 1.42–4.76 | 0.01 |
| 30–34.9   | 1.05 0.61–1.79 | 1.36 0.75–2.46 | 2.60 1.42–4.76 | 0.01 |
| >35       | 2.35 1.38–3.98 | 2.60 1.42–4.76 | 0.01 |

Abbreviations: CI = confidence interval; BMI = body mass index; HR = hazard ratio; Ref = reference.

$^*$Model adjusted for age, sex, alcohol drinking status, weight change, clinical stage, grade, and treatment modality.

DISCUSSION

Although several other groups have explored the link between BMI and CRC patient outcomes, we aimed to address some of the unresolved analytic inconsistencies leading to the ‘insufficient evidence for a strong link between adiposity and survival,’ as noted in the review by Parkin et al (2014). With careful consideration of important risk and prognostic factors, the association between prediagnostic BMI and OS in all CRC patients was modest. Our most robust and consistent findings were for more extreme levels of obesity and among patient subgroups, as observed previously (Parkin et al, 2014; Renihan, 2014; Wu et al, 2014). Among patients with local or locally advanced disease and among patients diagnosed aged <50 years, both class I and class II obesity were associated with a two-fold to five-fold increased risk of death as compared with overweight patients. Similarly, among CRC patients who did not experience weight loss prior to diagnosis and treatment, severe obesity was associated with a more than two-fold risk of death, but no clear association was observed among metastatic patients, older patients, or among patients who experienced prior weight loss. When adjusted for other important demographic and clinicopathologic factors, including treatment, we observed no excess risk among lean or overweight patients.

Severe or class II obesity has been previously linked to significantly worse survival outcomes as compared with all other BMI categories and independent of other prognostic factors in patients with colon (Murphy et al, 2000; Dignam et al, 2006; Sinicrope et al, 2010), pancreatic (Fleming et al, 2009; Yuan et al, 2013), and breast cancer (Pajares et al, 2013). Excess adipose tissue, as the body’s largest active endocrine organ, may limit survival in cancer patients via energy balance and
inflammatory pathways in the tumour microenvironment and in the systemic circulation that stimulate tumour growth, progression, and metastasis (Bardou et al, 2013; Shah et al, 2015). However, only two (Dignam et al, 2006; Sinicrope et al, 2010) of nine previous studies reported significant direct associations between peridagnostic BMI and CRC survival (Meyerhardt et al, 2003, 2004, 2008; Hines et al, 2009; Baade et al, 2011; Campbell et al, 2012; Kuiper et al, 2012; Yamamoto et al, 2012; Schlesinger et al, 2014). In contrast, nearly all prospective cohort studies with data on peridagnostic BMI reported higher mortality rates among obese, as compared with normal-weight, CRC patients (Doria-Rose et al, 2006; Haydon et al, 2006; Prizment et al, 2010; Campbell et al, 2012; Kuiper et al, 2012; Fedirko et al, 2014; Campbell et al, 2015). The most recent report from the Colon-Cancer Family Registry also found that prediagnostic obese BMI increased mortality in CRC patients irrespective of tumour molecular subtype (Campbell et al, 2015). Much of the variability in the results between pre- and post-diagnostic BMI is attributed to potential reverse causality because of unintentional, cancer-associated weight loss in the period prior to and around diagnosis that is more common among patients with advanced disease.

Differences in CRC patient survival by tumour characteristics, treatment modality, and peridagnostic weight change, which have not been comprehensively captured in previous prospective cohorts assessing peridagnostic BMI with survival outcomes, appeared to affect our findings. Moderate and severe obesity was most strongly associated with a higher risk of death among stage I–III patients. However, we have previously shown a potential joint prognostic effect of inflammation and obesity in metastatic CRC patients (Shah et al, 2015). Inclusion of older patients and patients reporting weight loss appeared to attenuate or mask associations observed between obesity and OS in all CRC patients; however, none of these factors appeared to strongly impact PFS. One potential explanation is that advanced-stage patients, and similarly older patients or patients experiencing weight loss, represent a group more susceptible to the physiologic stress of cancer as well as aggressive treatment modalities, whereas, obese patients who survive the cancer experience are simply more likely to develop and die from other obesity-related causes (Renehan, 2014). In a recent pooled prospective analysis of BMI and subsequent cancer risk in CRC survivors, individuals who were overweight or obese were at moderate increased risk of developing subsequent obesity-associated cancers. However, the risk observed for second cancers was similar to that of the first primary malignancy and suggested that the elevated risk in CRC survivors may be related to the higher prevalence of overweight and obesity in this group, rather than increased susceptibility (Gibson et al, 2014). Without more specific information on cause of death and few compelling findings for PFS in our analysis, we are not able to further postulate from what or why severely obese cancer patients were more likely to die. However, our findings for the detrimental effects of more extreme levels of obesity among CRC patients are consistent with the results of two large pooled analyses. In over 25 000 patients enrolled in adjuvant chemotherapy trials, only severe obesity, as compared with normal weight, was associated with worse disease-free survival (Sinicrope et al, 2013). Similarly, across 20 prospective population-based cohorts, class III obesity (BMI ≥ 40 kg m⁻²) among cancer-free individuals at baseline was associated with a significantly increased risk of death from malignant neoplasms (Kitahara et al, 2014).

The combination of electronic medical record and patient questionnaire data collected within a single large cancer centre allowed us to begin to address previous limitations from both clinical and population-based cohorts lacking sufficient data on one or more key risk or prognostic factors, such as peridagnostic BMI, drinking and smoking habits, weight change, tumour characteristics, or treatment. Although we had a limited number of underweight patients to evaluate risk or prognostic factors, such as prediagnostic BMI, drinking and smoking habits, weight change, tumour characteristics, or treatment. Although we had a limited number of underweight patients to evaluate relationships in this group, we had a sufficient number of patients with BMI > 35 kg m⁻² at diagnosis, allowing us to explore additional and more extreme levels of obesity that are increasingly emerging among cancer patient populations. However, some of our findings among smaller subgroups of patients should be viewed with caution, as it is possible that because of the number of analytic comparisons, some of the more modestly significant results may be attributable to chance. It is also worth noting that although we had patient reports on peridagnostic weight loss and clinicopathologic data, we did not have information on measured vs self-reported BMI prior to cancer diagnosis or on the specific cause of death. Although the possibility of misclassification of BMI category and residual confounding by unmeasured or shifting factors remains, our strata-specific findings suggest that this would been most likely to have further attenuated the associations we observed for class II obesity.
Class I and class II obesity was associated with significantly worse survival among patients with localised and locally advanced disease, as well as among younger patients. In conjunction with previous literature, these findings continue to suggest that the link between adiposity and CRC patient survival is complex and that clinicopathologic factors may explain some but not all of this relationship. Given the ever increasing proportion of obese and severely obese adults, and of cancer survivors, concentrated research, surveillance, and intervention efforts are needed to understand and improve long-term outcomes in obese patients presenting with CRC.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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