Mortality after Radical Cystectomy: Impact of Obesity Versus Adiposity after Adjusting for Skeletal Muscle Wasting

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Abstract

Purpose—We assess the impact of obesity, as measured conventionally by body mass index vs excess adiposity as measured by fat mass index, on mortality after radical cystectomy for bladder cancer, adjusting for the presence of skeletal muscle wasting.

Materials and Methods—This retrospective cohort study included 262 patients treated with radical cystectomy for bladder cancer between 2000 and 2008 at the Mayo Clinic. Lumbar skeletal muscle and adipose compartment areas were measured on preoperative imaging. Overall survival was compared according to gender specific consensus fat mass index and skeletal muscle index thresholds as well as conventional body mass index based criteria. Predictors of all cause mortality were assessed by multivariable modeling.

Results—Increasing body mass index correlated with improved overall survival (p=0.03) while fat mass index based obesity did not (p=0.08). After stratification by sarcopenia, no obesity related 5-year overall survival benefit was observed (68% vs 51.4%, p=0.2 obese vs normal and 40% vs 37.4%, p=0.7 sarcopenia vs sarcopenic/obese). On multivariable analysis class I obesity according to body mass index (HR 0.79, p=0.33) or fat mass index criteria (HR 0.85, p=0.45) was not independently associated with all cause mortality after adjusting for sarcopenia (HR 1.7, p=0.01) as well as age, performance status, pTN stage and smoking status. However, in patients with normal lean muscle mass each 1 kg/m^2 increase in weight or adipose mass was associated with a 7% to 14% decrease in all cause mortality.

Conclusions—After adjusting for lean muscle wasting, neither measurements of obesity nor adiposity were significantly associated with all cause mortality in patients treated with radical cystectomy, although subanalyses suggest a potential benefit among those with normal lean muscle mass.

Keywords

sarcopenia; obesity; mortality; cystectomy; body mass index

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Worldwide approximately 1.1 billion adults are estimated to be overweight and an additional 475 million are obese. Despite the substantial adverse health outcomes associated with obesity,[1] there is a growing body of literature suggesting that overweight and obese surgical patients have decreased all cause mortality compared to leaner patients.[2] This counterintuitive finding has been coined "the obesity paradox"[3,4] but has yet to be described among patients treated with radical cystectomy, in whom the impact of obesity remains unclear.[5–8]

It was estimated that in the United States approximately 75,000 patients would be diagnosed with urothelial carcinoma of the bladder in 2014,[9] of whom approximately 75% were overweight or obese,[6] and for whom the standard of care is neoadjuvant chemotherapy followed by radical cystectomy with bilateral pelvic lymph node dissection and urinary diversion. Unfortunately, even in contemporary series the combined surgical and disease morbidity results in 5-year overall survival rates of only 42% to 58%.[10,11]

In a recent study of a contemporary radical cystectomy cohort we observed a significant risk of increased mortality in patients with sarcopenia, or severe skeletal muscle wasting.[12] We also observed an inverse trend, consistent with the obesity paradox, toward decreased mortality with increasing BMI on unadjusted analysis. However, after adjusting for tumor specific factors, comorbidity and skeletal muscle wasting, BMI was no longer independently associated with all cause mortality.

We hypothesize that our previous findings were related to the nonspecificity of BMI as a measure of body composition, such that patients with a low BMI were likely those who also had skeletal muscle wasting, which strongly predicts poor outcomes in patients with cancer.[12] Thus, we explored the association between obesity as classified by BMI vs FMI, a measure of adiposity and overall survival after RC, adjusting for the presence of lean muscle wasting.

Methods

Patient Selection

After institutional review board approval we retrospectively identified 515 consecutive patients treated with RC and urinary diversion between 2000 and 2008. Patients were excluded from analysis if preoperative digital imaging was not available within 30 days of surgery (244) or if image analysis was precluded by poor image quality (9), leaving 262 patients (225 men and 37 women) available for analysis.[13,14]

Body Composition Analysis

A representative axial image at the level of L3 was identified by one of 2 radiologists (GDS, MRM). Then cross-sectional skeletal muscle and adipose areas were measured according to attenuation thresholds using SliceOmatic software (v.5.0, Tomovision, Quebec, Canada) by 1 investigator (SPP) who was blinded to patient outcome. Skeletal muscle area was identified using an attenuation threshold of −29 to +150 HU.[12,15] SMI was calculated by normalizing the total skeletal muscle area by height squared (cm^2/m^2). Patients were

classified as sarcopenic according to gender specific international consensus reference values, which represent muscularity below the fifth percentile for healthy young adults (male—SMI less than 55 cm^2/m^2, female—SMI less than 39 cm^2/m^2).[14]

Total adipose tissue area includes the total cross-sectional area of all visceral (−150 to −50 HU), intramuscular and subcutaneous adipose tissue (−190 to −30 HU, cm^2) on the L3 axial CT image. Whole body FM (kg) was then calculated using the equation,

$$\mathrm{FM(kg)} = 0.042 \times (\mathrm{total \ \ adipose \ \ area \ \ at \ \ L3 \ \ in \ cm^2}) + 11.2^{16}$$

FMI was calculated by normalizing FM (kg) by height squared (m^2). Patients were classified as obese if they met the NHANES 2009 criteria for class I obesity (male—FMI greater than 9 kg/m^2, female—FMI greater than 13 kg/m^2).[17] Table 1 shows a comparison of FMI and BMI based criteria for obesity. Agreement of obesity classification was assessed using the kappa statistic for obesity as categorized by BMI vs FMI.

Patients were then grouped according to combined SMI and FMI classifications of low SMI and high FMI (sarcopenic obese), normal SMI and high FMI (obese), normal SMI and FMI (normal), and low SMI and normal FMI (sarcopenic). Representative axial CT for patients in each group is shown in figure 1.

Statistical Analysis

We compared clinicopathological variables across the 4 groups. Continuous features were summarized with means (SD) or medians (IQR) as appropriate and compared using the t-test or Wilcoxon rank sum test. Categorical features were summarized with frequency counts (percentages), and compared using the chi-square and Cochran-Armitage trend tests.

The primary outcome of interest was overall survival, defined as the total length of time between the dates of RC and patient death, for which time and cause were verified via death certificate. OS was compared between BMI and FMI strata, as well as among the 4 patient groups defined by FMI/SMI using the log rank test.

Associations with death from any cause were evaluated using univariable and multivariable Cox proportional hazards regression models. Two multivariable models were created, incorporating obesity as classified by BMI or FMI. A subanalysis was performed assessing the impact of obesity on nonsarcopenic patients. C-statistics were calculated for each model. Statistical analyses were performed using the SAS® software package. All tests were 2-sided and p <0.05 was considered statistically significant.

Results

To test for possible bias introduced by the exclusion of patients with missing digital imaging, clinicopathological features and the survival of patients with missing data were compared to patients included in the analytic cohort, demonstrating no significant differences (data not shown). The distribution of obesity classification as defined by BMI or

FMI based criteria is presented in figure 2, A, demonstrating poor agreement between these measures of obesity (kappa statistic 0.41, 95% CI 0.33–0.49, p <0.0001).

Figure 2, B shows the distribution of patients according to sarcopenia and class I FMI based obesity compared to categorization by traditional BMI criteria. For example, a patient with normal muscularity by SMI criteria and normal adiposity by FMI criteria (27) may have a BMI that ranges anywhere from 18.5 to 39.9 kg/m^2. Conversely, only 12% (8 of 66) of the patients with a normal BMI had a normal SMI and FMI, whereas 83% (55 of 66) met the criteria for sarcopenia and 4.5% (3 of 66) were sarcopenic obese.

Clinicopathological features of the 262 patients are presented in supplementary table 1 (http://jurology.com/), stratified by body composition. Patients with sarcopenia were significantly older than nonsarcopenic patients regardless of obesity status (p=0.01). The highest rates of current/prior smoking were noted in sarcopenic obese patients (90.3% vs normal 61.5%, sarcopenic 81.2% and obese 78.9%, p=0.01). Otherwise there were no significant differences among the patient groups.

Median anthropomorphic measurements are presented in supplementary table 2 (http://jurology.com/). Overall 67.6% (177) of patients were sarcopenic. Median BMI was 27.7 kg/m^2. Median FMI ranged from 7.7 to 8.0 kg/m^2 in normal and sarcopenic patients to 10.6 to 11.6 kg/m^2 in obese and sarcopenic obese patients.

At last followup 174 (66.4%) patients had died, of whom 116 (44.2%) died of bladder cancer. Median followup was 6.3 years (IQR 5.7-9.5). Overall survival demonstrated an inverse, stepwise association with BMI strata (fig. 3, A), such that 5-year OS was 30%, 41.4%, 46% and 54.1% for patients with BMI less than 18.5, 18.5 to 24.9, 25 to 29.9 and 30 or greater kg/m^2, respectively (p=0.03). A similar trend was noted when comparing strata of adiposity with 5-year OS of 35%, 45% and 51% for normal/fat deficit, excess fat and obese, respectively (p=0.08; fig. 3, B), although this did not achieve statistical significance.

OS was also compared between FMI obese and nonobese patients, stratified by sarcopenia (fig. 3, C). Among nonsarcopenic patients those who were obese and those who were nonobese had a similar 5-year OS (68% vs 51%, p=0.2). Similarly, among sarcopenic patients the 5-year OS was similar for those with obesity and those without (40% vs 37.4%, p=0.72). However, overall sarcopenic patients had a shorter OS than those without sarcopenia, regardless of obesity (p=0.008 overall).

Table 2 depicts univariable associations between clinicopathological features and all cause mortality. There was no significant association between BMI based obesity classification and ACM (HR 0.68, p=0.14), while FMI obesity was associated with a trend toward increased ACM (HR 0.75, p=0.06). As a continuous variable FMI was associated with a 7% decrease in the risk of ACM per unit increase in kg/m^2 (HR 0.93, p=0.008) and BMI was associated with a 4% decrease in the risk of ACM per unit increase in kg/m^2 (HR 0.96, p=0.005).

In multivariable models adjusted for age, smoking status, ASA® and ECOG score, and pTN stage, neither obesity as categorized by BMI (HR 0.79, p=0.33) nor FMI (HR 0.85, p=0.45)

criteria was independently associated with ACM, while sarcopenia was independently associated with a 67% to 71% increased risk of ACM (HR 1.67–1.71, p=0.01, c-index 0.73, table 3).

However, a subanalysis of nonsarcopenic patients demonstrated a trend toward a decreased risk of ACM associated with obesity by FMI criteria (HR 0.53, 95% CI 0.28–1.0, p=0.05) and by BMI criteria (HR 0.58, 95% CI 0.32–1.07, p=0.08) after adjustment for age, ASA score and tumor stage (supplementary table 3, http://jurology.com/). When these features were assessed as continuous variables, we observed a 7% decrease in the risk of ACM per unit increase of 1 kg/m^2 in BMI and a 14% decrease in the risk of ACM per 1 kg/m^2 increase in FMI.

Discussion

In this study we observed that the determination of obesity by BMI resulted in misclassification of body composition compared to assessments of skeletal muscle and adipose compartments by SMI and FMI derived from standard preoperative cross-sectional imaging. As highlighted by our data, weight normalized by height inadequately portrays excess lean muscularity or adiposity. Simply put, BMI measures excess weight but not excess fat.

Consistent with the reported obesity paradox,[18,19] on unadjusted analysis we observed an inverse stepwise association between strata of BMI or FMI and mortality. However, on adjusted analysis, variation in lean muscularity attenuated this relationship. Essentially, in the setting of skeletal muscle wasting (sarcopenia), there does not appear to be any benefit or additive harm specifically associated with excess adipose tissue, although interestingly, in the subanalysis of nonsarcopenic patients, multivariable analyses demonstrated an association between decreasing ACM with increasing BMI and FMI. To our knowledge, this study is the first to specifically assess how obesity impacts survival after radical cystectomy relative to lean muscularity and adiposity and to describe the obesity paradox in this population.

Among patients with urothelial carcinoma, prior reports have conflicted regarding the impact of obesity on post-RC survival. Chromecki et al observed that obesity (BMI greater than 30 kg/m^2) is associated with increased recurrence, cancer specific mortality and ACM,[6] while others reported no association between obesity and ACM[20] or improved survival in obese patients.[8] Additionally, obese patients have been reported to have lower rates of perioperative complications and surgical costs than normal weight patients, an observation in accord with the obesity paradox.[21] Of note, in further analysis in the current cohort we observed that neither obesity by BMI nor FMI criteria was independently associated with cancer specific mortality on multivariate analysis accounting for sarcopenia (data not shown).

The observation that excess fat mass is not protective after controlling for skeletal muscle wasting has been observed in patients undergoing chemotherapy.[22] Similarly, Prado et al reported that sarcopenia independently predicted survival in obese patients with solid organ

tumors involving the respiratory and gastrointestinal tracts.[23] These results and the findings from the current study suggest that the presence of sarcopenia undermines any apparent benefit noted with obesity, such that any protection afforded by fat mass occurs only in the setting of normal lean muscle mass, as demonstrated in the subanalysis of nonsarcopenic patients. The mechanism by which excess fat or excess weight is associated with improved survival in the setting of normal lean muscle mass remains to be established, but may be related to additional gains in lean muscularity or nutritional reserve.

It is important to recognize the possibility of occult skeletal muscle wasting in the setting of obesity. Axial CT images routinely obtained as part of preoperative staging offer the opportunity to define skeletal muscle and adipose tissue compartments, permitting detailed characterization of a patient's body composition.[12,13,24] Regional analysis of lean and adipose tissue on axial CT at the level of L3, as performed here, has been validated in patients with cancer against dual energy x-ray absorptiometry scans, outperforming bioelectrical impedance analysis in terms of sensitivity and specificity.[16]

Limitations of this study include selection bias inherent to the retrospective study design, which also precluded our ability to correlate measurements of skeletal muscle wasting or obesity with metrics of nutritional status such as albumin,[25,26] or functional measures of frailty such as handgrip strength or walking speed. Additionally, digital CT was unavailable for 244 patients treated with RC at our institution during the study period, as our institution is a referral center, thus preoperative imaging was frequently obtained at the patient's local or referring institution and not uniformly digitized. The effect of possible bias introduced by these missing data was addressed by comparing the characteristics of patients without imaging to those included in the study. Our analytic cohort was similar to patients with missing digital scans with respect to all clinicopathological features including BMI, urothelial cancer stage and grade, comorbidity, performance status and overall survival. Finally, given the trend toward a significant association between BMI and FMI as continuous variables on multivariate analysis, it is possible that a larger study may demonstrate that obesity is an independent predictor of overall survival in addition to sarcopenia.

Despite these limitations, to our knowledge the current study is the first to describe the impact of misclassification of body composition using BMI based definitions in a surgical cohort. The results of this study suggest that the obesity paradox, as described on the basis of BMI, may relate to weight differences due to skeletal muscle wasting rather than differences in adipose burden. The implications of this finding are that encouragement of weight gain alone through increased caloric intake in cachectic patients with cancer is unlikely to be successful in improving outcomes. Rather, interventions might focus on restoring skeletal muscle mass as well as physical robustness. In addition, these data highlight the importance of assessing obese patients for the occult presence of skeletal muscle wasting. Given that sarcopenia is increasingly acknowledged as a risk factor in the patient undergoing radical cystectomy[12,27,28] and with the increasing use of neoadjuvant chemotherapy before surgery, which in and of itself may contribute to muscle wasting,[29] the identification of patients with lean muscle wasting at diagnosis may provide a window of opportunity to offer these patients interventions to optimize them for surgery and preempt

further muscle wasting.[30] Although SMI and FMI are not yet readily measurable in daily clinical practice, the development of automatic algorithms to calculate these measurements from standard CT imaging is under way. This will allow urologists to incorporate these novel body composition measurements into clinical risk stratification and to potentially select patients who would benefit from preoperative intervention.

Conclusions

Precise anthropomorphic measurement of body composition quantifying adiposity and lean muscle mass demonstrates the lack of specificity of BMI in conveying body composition, and that obesity by conventional BMI or by FMI based criteria is not independently associated with overall survival after radical cystectomy. However, among patients with normal muscularity there is a trend toward improved survival in those with increasing weight and adiposity, consistent with the obesity paradox. Further study of the interaction between lean muscle mass and adipose burden is necessary to validate these findings, which may represent a novel and quantitative tool for preoperative risk stratification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations and Acronyms

ACM	all cause mortality
BMI	body mass index
CT	computerized tomography
ECOG	Eastern Cooperative Oncology Group
FM	fat mass
FMI	fat mass index
NHANES	National Health and Nutrition Examination Survey
OS	overall survival
RC	radical cystectomy
SMI	skeletal muscle index

Sarcopenic Obese
FMI 10.6 kg/m^2
BMI 30.3 kg/m^2
SMI 6.3 cm^2/m^2

Sarcopenic
FMI 4.9 kg/m^2
BMI 16.2 kg/m^2
SMI 32.1 cm^2/m^2

Normal
FMI 6.4 kg/m^2
BMI 26.2 kg/m^2
SMI 57.1 cm^2/m^2

Obese
FMI 12.7 kg/m^2
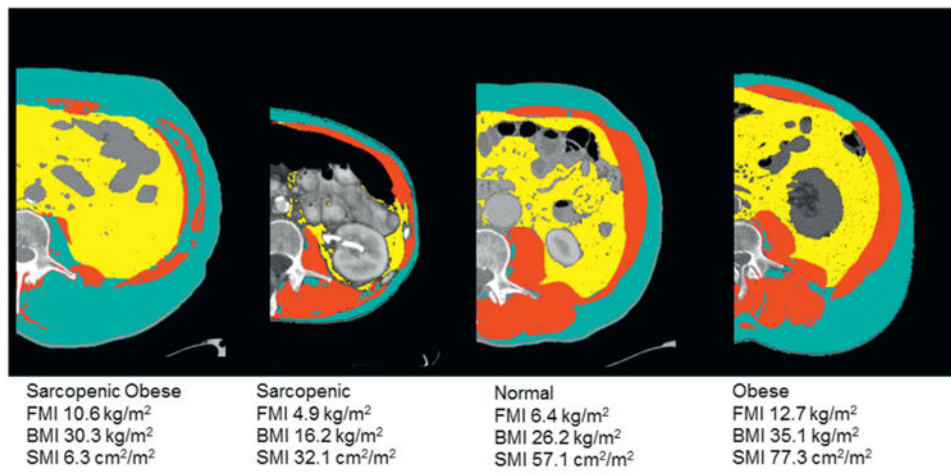BMI 35.1 kg/m^2
SMI 77.3 cm^2/m^2

Figure 1.
Representative images for each cohort of body composition demonstrating differences in skeletal muscle area (red), and visceral (yellow) and subcutaneous/intramuscular adipose areas (teal) among sarcopenic, normal, obese and sarcopenic obese individuals.
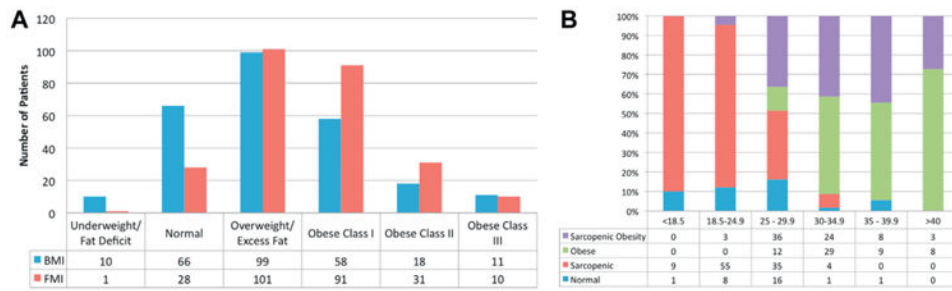
Figure 2.
A, comparison of study cohort distribution according to WHO classification of obesity by BMI to classification ranges for FMI generated from NHANES cohort (kappa 0.412, 95% CI 0.33–0.49, p <0.0001). *B*, percentage of patients (262) according to body composition type of sarcopenic, sarcopenic obese, normal and obese per BMI strata (kg/m^2).
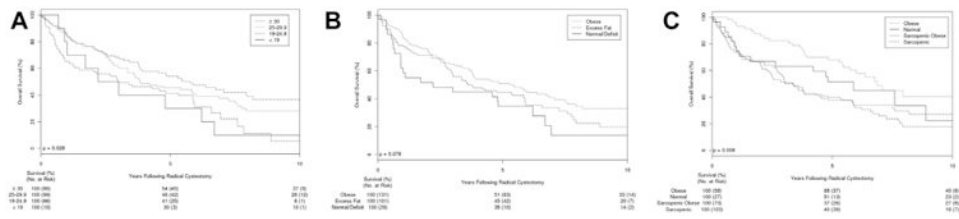
Figure 3.
A, OS according to WHO defined BMI categories. *B*, OS according to FMI categories. Patients with fat deficit were combined into normal adipose tissue category due to low number (3). *C*, OS according to body composition according to obesity status by FMI based criteria and presence or absence of sarcopenia. OS was similar between nonsarcopenic patients with and without obesity (p = 0.17), and between sarcopenic obese and sarcopenic patients (p = 0.72).

Table 1

Obesity classification criteria according to WHO classification of obesity by BMI and FMI generated from the NHANES cohort

Category	BMI (kg/m^2)	Category	Male FMI (kg/m^2)	Female FMI (kg/m^2)
Underweight	Less than 18.5	Severe fat deficit, moderate fat deficit, mild fat deficit, normal	Less than 2, 2–less than 2.3, 2.3–less than 3, 3–6	Less than 3.5, 3.5–less than 4, 4–less than 5, 5–9
Normal	18.5–24.9			
Overweight (pre-obese)	25–29.9	Excess fat	Greater than 6–9	Greater than 9–13
Obese:	30.0 or Greater	Obese:	Greater than 9	Greater than 13
Class I (mild obesity)	30.0–34.9	Class I	Greater than 9–12	Greater than 13–17
Class II (moderate obesity)	35–39.9	Class II	Greater than 12–15	Greater than 17–21
Class III (morbid obesity)	40.0 or Greater	Class III	Greater than 15	Greater than 21

Table 2

Univariable associations with ACM

	HR	95% CI	p Value
Pt features:			
Age at surgery*	1.03	1.01–1.05	0.0002
Smoking status (Ref = no/never)	1.51	1.00–2.3	0.05
Gender (Ref = female)	1.17	0.76–1.79	0.49
ASA score (Ref = ASA 1-2)	1.90	1.38–2.6	<0.0001
ECOG*	1.33	1.10–1.60	0.002
Pathological features:			
Tumor stage at surgery (Ref = pT2 or less)	2.36	1.75–3.19	<0.0001
Nodal stage at surgery (Ref = N0/X)	1.90	1.38–2.60	<0.0001
Continuous body composition features:*			
FMI (kg/m^2)	0.93	0.87–0.98	0.008
BMI (kg/m^2)	0.96	0.94–0.99	0.005
SMI (cm^2/m^2)	0.98	0.96–0.99	0.003
Skeletal muscle attenuation	0.99	0.98–1.00	0.12
Categorical body composition features:			
Obese class I/II/III (Ref = normal/excess fat)	0.75	0.56–1.01	0.06
Obese (Ref = BMI less than 30 kg/m^2)	0.68	0.53–1.09	0.14
Sarcopenia (Ref = no)	1.75	1.24–2.50	0.001
4-Level body composition:			
Normal	Ref	Ref	Ref
Sarcopenic	1.40	0.82–2.41	0.22
Obese	0.69	0.38–1.28	0.24
Sarcopenic obesity	1.29	0.74–2.27	0.40

*
Continuous variable: represents the hazard ratio for an increase of 1 unit of the variable being tested.

Table 3

Multivariable associations with ACM comparing models using obesity as classified by BMI or FMI

	HR (95% CI)	p Value
Model 1 BMI:		
Age at surgery[*]	1.03 (1.01–1.05)	0.006
Smoking status (Ref = no/never)	1.25 (0.81–1.94)	0.31
ASA score (Ref = ASA 1-2)	1.82 (1.27–2.62)	0.001
ECOG[*]	1.14 (0.93–1.41)	0.21
Tumor stage at surgery (Ref = pT2 or less)	2.33 (1.69–3.20)	<0.0001
Nodal stage at surgery (Ref = N0/X)	1.58 (1.12–2.23)	0.009
Sarcopenia (Ref = no)	1.71 (1.14–2.57)	0.01
Class I obesity or greater (BMI criteria, Ref = no)	0.79 (0.50–1.26)	0.33
c-index 0.73		
Model 2 FMI:		
Age at surgery[*]	1.03 (1.01–1.05)	0.002
Smoking status (Ref = no/never)	1.24 (0.81–1.92)	0.33
ASA score (Ref = ASA 1-2)	1.80 (1.26–2.58)	0.001
ECOG[*]	1.15 (0.931–141)	0.19
Tumor stage at surgery (Ref = pT2 or less)	2.33 (1.70–3.21)	<0.0001
Nodal stage at surgery (Ref = N0/X)	1.59 (1.13–2.24)	0.008
Sarcopenia (Ref = no)	1.67 (1.11–2.50)	0.01
Class I obesity or greater (FMI criteria, Ref = no)	0.85 (0.56–1.29)	0.45
c-index 0.73		

Similar models incorporating BMI and FMI as continuous variables demonstrated no independent relationship between increases in BMI (HR 0.98, p=0.1, c-index 0.7) or FMI (HR 0.94, p=0.08, c-index 0.7).

[*] Continuous variable: represents the change in hazard ratio for an increase of 1 unit of the variable being tested.