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Impact of Obesity on Outcomes After Definitive Dose Escalated Intensity Modulated Radiation Therapy For Localized Prostate Cancer

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Abstract

INTRODUCTION—Previous publications have shown conflicting results regarding body mass index (BMI) and prostate cancer (CaP) outcomes after definitive radiotherapy prior to the dose escalation era. Our goal is to determine whether increasing BMI is associated with CaP outcomes in men with localized CaP treated with dose escalated radiotherapy.

METHODS—We identified patients with localized (T1b-T4N0M0) CaP treated with definitive intensity modulated radiation therapy (IMRT) and image guidance (IGRT) from 2001–2010. BMI was analyzed as a continuous variable. Adjusting for confounders, multivariable competing risk and Cox proportional hazards regression models were used to assess the association between BMI category and the risk of biochemical failure (BF), distant metastasis (DM), cause-specific mortality (CSM) and overall mortality (OM).

RESULTS—Of the 1,442 patients identified, there were 20% with BMI < 25 kg/m², 48% with BMI 25–29.9 kg/m², 23% with BMI 30–34.9 kg/m², 6% with BMI 35–39.9 kg/m², and 4% with BMI 40 kg/m². Median follow-up was 47.6 months (range 1–145) with median age of 68 years (range 36–89). Median dose was 78Gy (range 76–80) and 30% of patients received androgen deprivation therapy. Increasing BMI was inversely associated with age ($p < 0.001$) and pre-treatment PSA ($p = 0.018$). On multivariable analysis, increasing BMI was associated with increased risk of BF (HR=1.03[95% CI 1.00–1.07], $p = 0.042$), DM (HR=1.07[1.02–1.11], $p = 0.004$), CSM (HR=1.15[1.07–1.23], $p < 0.001$), and OM (HR=1.05[1.02–1.08], $p = 0.004$).

CONCLUSION—For CaP patients receiving dose-escalated IMRT with IGRT, increasing BMI appears to be associated with an increased risk of biochemical failure, distant metastases development, cause-specific and overall survival.

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Keywords

obesity; body mass index; prostate cancer; radiation therapy; IMRT

INTRODUCTION

Obesity is an epidemic affecting more than one-third of adults in the United States and the incidence has more than doubled in the last 40 years.¹ Increasing body mass index (BMI) is associated with increasing prevalence for multiple conditions including hypertension, dyslipidemia, type 2 diabetes, and coronary heart disease, among others.² Obesity has also been shown to be associated with an increased risk of cancers such as endometrial, breast, renal, and esophageal cancer.^{2, 3} However, the association with prostate cancer is unclear. Evidence linking obesity to prostate cancer incidence has been inconsistent.^{3–5} A recent meta-analysis showed decreased localized prostate cancer incidence and increased advanced prostate cancer incidence in obese men.⁶ Increasing BMI has also been associated with pathologic progression in men with low-risk prostate cancer undergoing active surveillance.⁷ Data supporting the association of BMI and prostate cancer mortality is compelling.^{4, 5} The Physicians' Health Study shows that obese men had a significantly higher risk of prostate cancer mortality compared with men with a healthy BMI.⁸ A prospective study of more than 250,000 men showed that despite a lower incidence of prostate cancer, men with higher BMI have a significant elevation of prostate cancer mortality compared with those with normal BMI.⁴

Literature available for obese patients treated with external beam radiation therapy (EBRT) has yielded conflicting results; multiple studies have shown an increasing risk of biochemical failure (BF) in obese men^{9, 10} whereas others have not.¹¹ The majority of patients in these studies were treated to 70Gy or less with the traditional four-field technique or 3D-conformal radiation therapy. Multiple studies have shown the cancer control benefit of dose escalation^{12, 13} and studies using brachytherapy for primary treatment of localized prostate cancer have not shown BMI to be associated with PSA failure.^{14, 15} In addition, Geinitz et al suggests that increase in daily shifts and difficulty of daily set-up in obese patients may attribute to inferior prostate cancer specific outcomes.¹¹ It is important to provide further data on men with localized prostate cancer treated in the dose-escalation era with intensity modulated radiation therapy (IMRT) and daily image guidance (IGRT). Therefore, we sought to evaluate the effect of obesity on prostate cancer specific outcomes in a large cohort of patients treated with dose-escalated IMRT with daily IGRT.

METHODS

From 2001–2010, 1,442 patients with clinically localized (T1b–T4N0M0) prostate cancer were treated with definitive IMRT at our institution and had complete baseline analysis data available in our prospectively collected prostate cancer database. Informed consent was obtained for inclusion in the IRB approved database. Weight and height were documented prior to the initiation of EBRT. Patients were stratified using the National Comprehensive Cancer Network risk grouping criteria.¹⁶ Computed tomography (CT)-based planning was

performed for all patients. Magnetic resonance imaging (MRI) simulation was routinely performed for all patients unless patients had a contraindication for MRI (e.g. pacemaker) and image fusion was performed. Both CT and MRI were used for delineation of the target volume.

All patients were treated with IMRT. The techniques for IMRT treatment have been previously described.¹⁷ Daily imaging was utilized for all patients. Methods include implantation of gold fiducial markers with electronic portal imaging device, cone beam CT scans, or continuous real-time tracking of implanted radiofrequency beacons. B-type acquisition ultrasound was also used prior to March 2010.

The target volumes for IMRT were previously described.¹⁸ Dose per fraction was 2Gy unless otherwise specified. Briefly, low-risk prostate cancer patients were treated to 76-78Gy to the prostate and proximal seminal vesicles (PTV1). Intermediate- risk patients were treated to 76-80Gy to PTV1 and 56Gy to the distal seminal vesicles (PTV2) in 38–40 fractions. High-risk patients were treated to 76-80Gy to PTV1 and 56Gy to PTV2 and regional lymph nodes in 38–40 fractions. More than 95% of the PTVs received the prescription dose.

BMI is defined as weight in kilograms divided by the square of height in meters and was evaluated as a continuous variable. Biochemical failure (BF) was defined according to the RTOG-ASTRO Phoenix consensus¹⁹ and rerun with the previous ASTRO consensus using three consecutive rises.²⁰ The time to BF, distant metastasis (DM), cause specific mortality (CSM), and overall mortality (OM) was calculated from date of start of radiation. Patients without an event were censored at the time of their last PSA measurement. Patient deaths were coded as prostate cancer-related only if it was stated in the death certificate, medical record, or physician's note.

Statistics

Baseline differences by BMI categories were assessed using Chi-square tests. Continuous BMI was used to assess an increasing linear relationship with each outcome. Cox proportional hazards regression²¹ was used for all endpoints to assess the association with BMI when considered alone and with other covariates. Results are presented as hazard ratios for Cox models. The proportional hazards assumption for each covariate was evaluated and the assumption held for all covariates except for T-stage and Gleason score for the BF outcome. For BF, we estimated hazard ratios for BMI and other covariates using a stratified Cox proportional hazards model²². Although adjustments were performed for all covariates, hazard ratios cannot be generated for T-stage and Gleason score because the proportional hazards assumption does not hold. In multivariable analysis (MVA), covariates included androgen deprivation therapy (ADT) use, pre-treatment prostate-specific antigen as a log-transformed variable (iPSA), and age. Gleason score and T-stage were included as covariates for DM, CSM, and OM, and as stratification variables for BF. For BF and OM, history of diabetes, heart disease, and hypertension were included as covariates. Comorbidities were not included in MVA models for DM or CSM because of the low number of events.

To illustrate the association of BMI and the outcomes, survival curves were generated from the Cox model results for increasing BMI values while holding other covariates at their mean values.²³ For the stratified Cox model used for BF, as there is a separate baseline survival function for each strata, we estimated freedom from BF at an intermediate risk strata (T-stage=T2, Gleason score=7) while holding other covariates at their mean values. All statistical tests are two-sided and analyses were performed using SAS statistical software (version 9.3) and Stata (version 12).

RESULTS

Of the 1,442 patient identified, there were 284 men (20%) with BMI<25 kg/m², 688 (48%) with BMI 25–29.9 kg/m², 326 (23%) with BMI 30–34.9 kg/m², 92 (6%) with 35–39.9 kg/m², and 52 (4%) with BMI 40 kg/m². Median follow-up was 47.6 months (range 1–149) with median age of 68 years (range 36–89). Median dose was 78Gy (range 76–80) and 30% of patients received ADT. Increasing BMI was inversely associated with age ($p<0.001$), iPSA ($p=0.018$), and history of diabetes ($p<0.001$) and hypertension ($p<0.001$). All other characteristics were balanced. (Table 1) There were 146 BF, 56 DM, 17 CSM, and 133 deaths overall. BF predated DM and CSM in all men.

PSA failure

On univariate analysis (UVA) BMI as a continuous variable was not associated with increased risk of BF ($p=0.063$). However, after accounting for covariates, increasing BMI and iPSA were significant for increased risk of BF (all $p<0.05$, Table 2). Cumulative incidence of BF at 5 years was 11.4% overall (95% CI:9.4–13.7%). The relationship of increasing BMI on estimated freedom from BF over time, adjusted for other covariates, is shown in Figure 1A.

Distant metastasis

On UVA, increasing BMI was associated with increased risk of DM (HR=1.05[1.00–1.10], $p=0.032$). On MVA, this associated remained statistically significant (HR=1.07[1.02–1.11], $p=0.004$, Table 3). Other significant variables on MVA were Gleason score, T-stage, and iPSA (all $p<0.05$). Figure 1B shows the impact of increasing BMI on freedom from distant metastasis estimated from the Cox model while holding other covariates at the mean values. DM rate at 5 years is 4.7%(95% CI:3.5–6.1%) for the entire cohort.

Cause specific mortality

CSM at 5 years was 0.8%(0.4–1.6%) overall. On UVA, BMI was significantly associated with CSM when analyzed as a continuous variable (HR=1.11[1.04–1.18], $p=0.001$). On MVA, increasing BMI was significantly associated with increased CSM ($p<0.001$, Table 4). T-stage was also statistically significant for CSM ($p=0.002$). The relationship of increasing BMI on cause specific survival is shown in Figure 1C after adjusting for other covariates using the Cox model.

Overall mortality

OM at 5 years for the entire cohort is 8.5% (6.8–10.3%). BMI was significantly associated with OM on UVA as a continuous variable (HR 1.03 [1.00–1.07], $p=0.025$). After adjusting for covariates, increasing BMI was significant when analyzed as a continuous variable ($p=0.004$, Table 5). Other significant factors include age, iPSA, and history of diabetes and hypertension (all $p<0.05$). Figure 1D shows the impact of increasing BMI on overall survival over time after adjusting for covariates.

DISCUSSION

To our knowledge, no previous study has investigated the association between BMI and prostate cancer specific outcomes among patients treated with definitive EBRT in the era of dose-escalated IMRT with daily IGRT. This study supports the association of obesity with increased risk of prostate-cancer specific outcomes and overall mortality in patients treated with definitive dose-escalated IMRT with daily IGRT.

Multiple technical and biologic mechanisms have been proposed for the association between increasing BMI and increase in prostate-cancer specific outcomes. Previous studies have postulated that worse outcomes could partly be attributed to technical issues such as difficulty of daily setup due to abdominal adipose tissue obscuring skin tattoos and the lack of image guidance in the cohorts of patients examined.^{9, 10} This is often based on reports of the strong correlation of increased shifts in obese men compared to their normal weight counterparts and patient adjustments on up to 80% of treatment days when they are treated with daily IGRT.^{24, 25} All patients in our study underwent daily localization with either radiofrequency transponders which track the prostate in real-time or with imaging prior to their treatment to verify prostate position. This would prevent any geographical miss in our patient population and the potential for under-dosing the CTV which may have occurred in previous studies. Therefore the association of increased BMI and worse prostate-cancer specific outcomes seen in this cohort of patients is unlikely to be explained by technical misses.

Another hypothesized technical mechanism for worse prostate-specific outcomes with increasing BMI is the use of lower radiation doses in the treatment of prostate cancer in previous studies with the median radiation dose often at 70Gy or below^{10, 11}. Multiple prospective, randomized trials have demonstrated superior cancer control utilizing dose escalation,^{12, 13} with studies showing that the most significant therapeutic factor affecting BF after definitive RT is radiation dose.²⁶ Despite the fact that all patients in our study were treated with dose escalation (76Gy), an association with worse BF, DM development, CSM, and OM was seen with increasing BMI. Studies examining the effect of BMI on BF after brachytherapy (which delivers an ablative dose to the prostate) for localized prostate cancer failed to show a relationship.^{14, 15} It is possible that the significant dose escalation achieved with prostate brachytherapy can mitigate the detrimental effects of increasing BMI.

Another theory for increased risk of DM, CSM, and OM with high BMI is hemodilution of PSA from increased blood volume because the total volume of PSA does not differ by BMI.²⁷ Patients with higher BMI have been shown to have lower serum PSA compared to

men with normal weight²⁸ which is also supported by our analysis. Hemodilution may cause PSA levels to meet threshold for biopsy later than their normal weight counterparts and may promote the diagnosis of higher risk disease at presentation²⁹, as well as a decreased incidence of prostate cancer diagnosis.⁴ In our cohort, however, there was no statistical difference in clinical T-stage or Gleason score between the men in various BMI groups, suggesting that hemodilution may not significantly impact results for this cohort.

One biological mechanism for worse survival outcomes in obese men is due to more rapid progression to DM after BF. In a study describing patients who underwent radical prostatectomy and received ADT prior to the onset of metastases in the SEARCH database, patients with higher BMI were more likely to develop metastases and had a trend for greater risk of progression to castration-resistant prostate cancer.³⁰ In addition, case reports have shown prostate cancers to have a more aggressive biology at the time of relapse with decreased PSA production³¹.

Studies have linked increased BMI with more aggressive prostate cancer biology.^{32, 33} However, no significant difference in Gleason scores within the BMI groups in our study was seen. Other obesity-related biological mechanisms include higher levels of insulin³² and IGF-1³⁴ leading to elevated circulating growth factors, decreased levels of testosterone, and higher levels of estrogen³⁵, as well as high inflammatory factors such as leptin³⁶ and IL-6³⁷. Changes in these factors all lead to increased tumor proliferation, reduced tumor apoptosis, and transformation into androgen independence²⁷. This can in turn transition to prostate cancer progression leading to death.

Limitations of the current study include the single institution retrospective design and small numbers of prostate cancer deaths with broad hazard ratio confidence intervals indicative of wide variability. In a NIH-AARP study linking questionnaire respondents to state cancer registries,⁴ there were 10 times as many prostate cancer deaths as seen in our cohort. However, there were nearly 7 times as many prostate cancer cases and the impact of obesity in men treated with RT could not be estimated because no treatment information was provided. Additionally, inclusions for prostate cancer deaths can be nuanced and be difficult to determine with absolute certainty outside of a prospective trial. Therefore despite stringent definitions of CSM in our cohort, care should be taken when applying to the general prostate population. Other limitations include height and weight data was generally taken at the time of initial consult which can be months before initiation of definitive EBRT and therefore may not represent the BMI of the patient at the time of radiation initiation. BMI changes over time were also not accounted for and weight gain has been shown to increase risk of prostate cancer mortality⁴. Other measures of obesity such as abdominal visceral adipose tissue and waist circumference, which may be a more accurate measurement of obesity³⁸, were not assessed. Lastly, adjustments for multiple comparisons across outcomes were not performed because the outcomes are related.

CONCLUSION

To the authors' knowledge, this is the first study to report the association between obesity and prostate-cancer outcomes after dose-escalated IMRT with daily localization for

localized prostate cancer. Increasing BMI appears to be associated with an increased risk of biochemical failure, distant metastases development, and prostate-cancer specific and overall mortality. Further studies should be conducted to better elucidate this relationship.

Acknowledgments

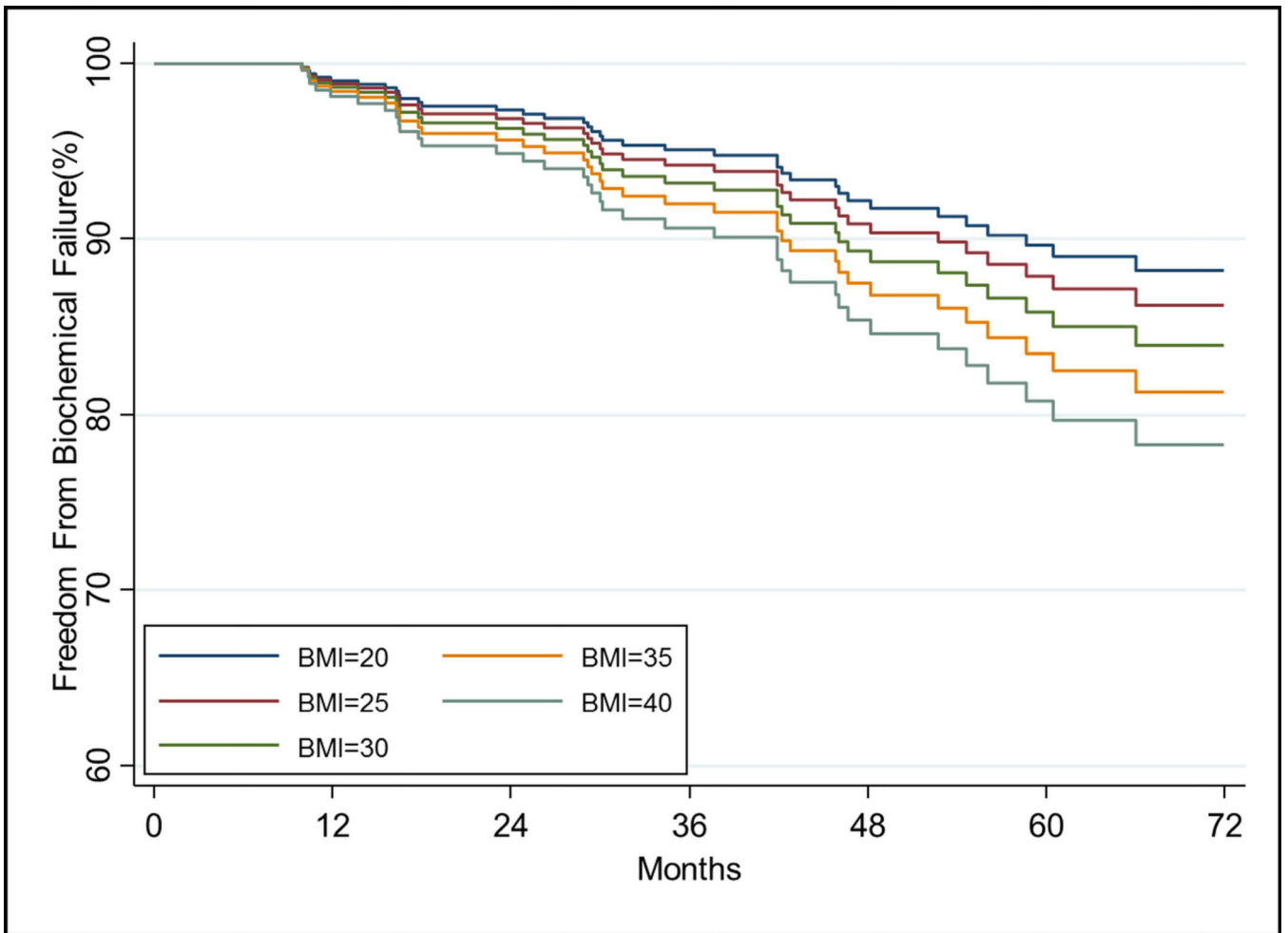
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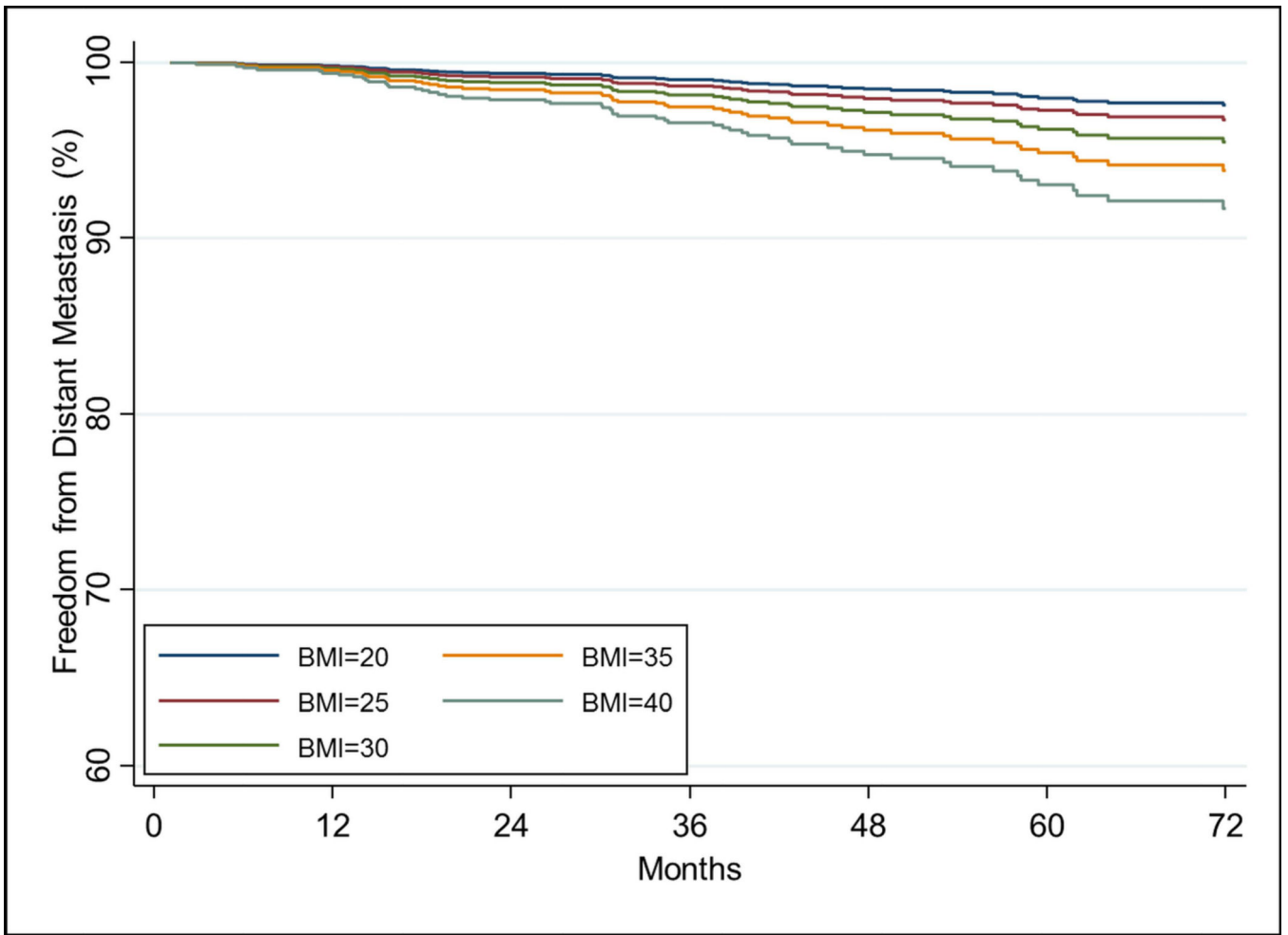
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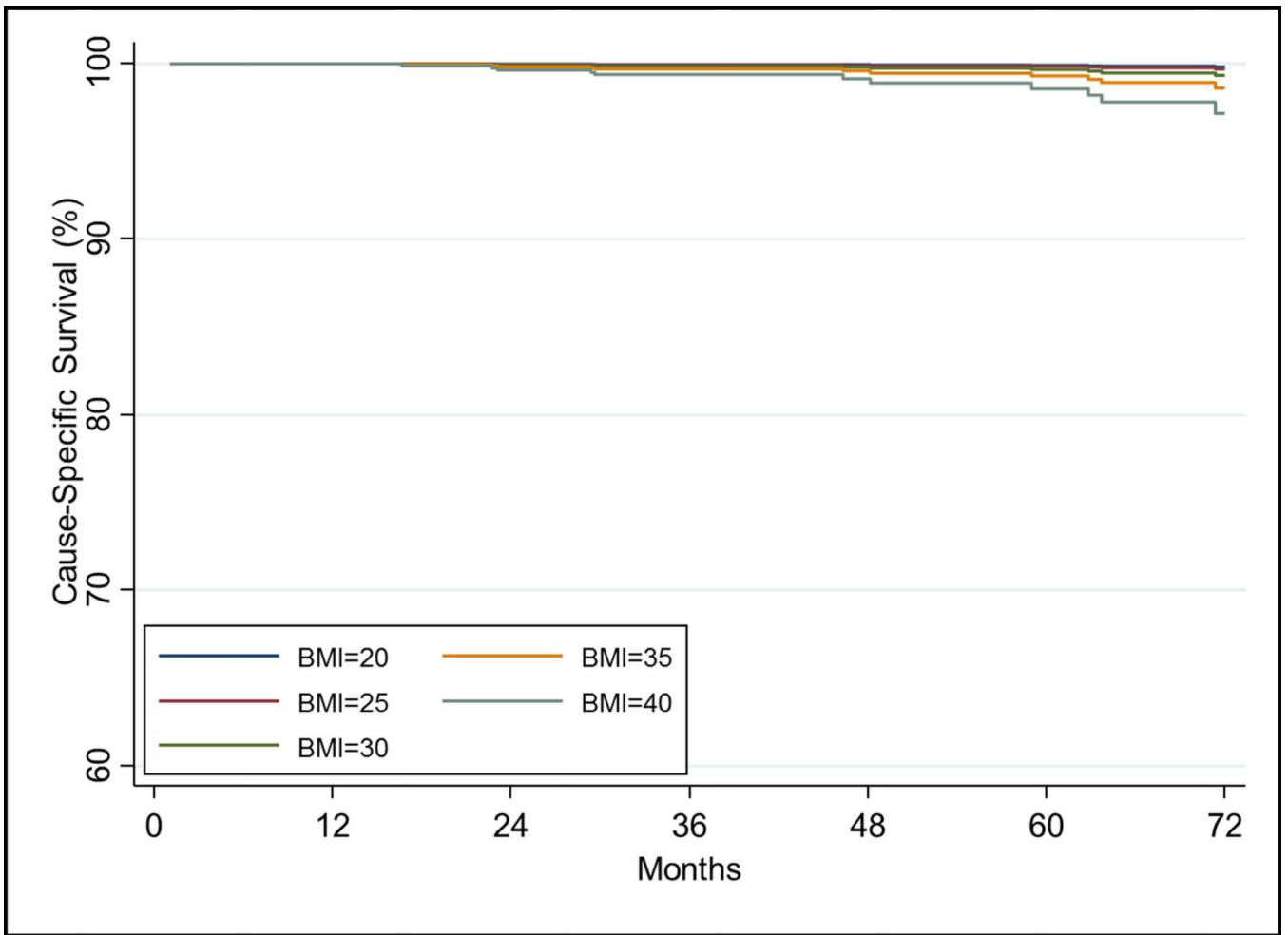
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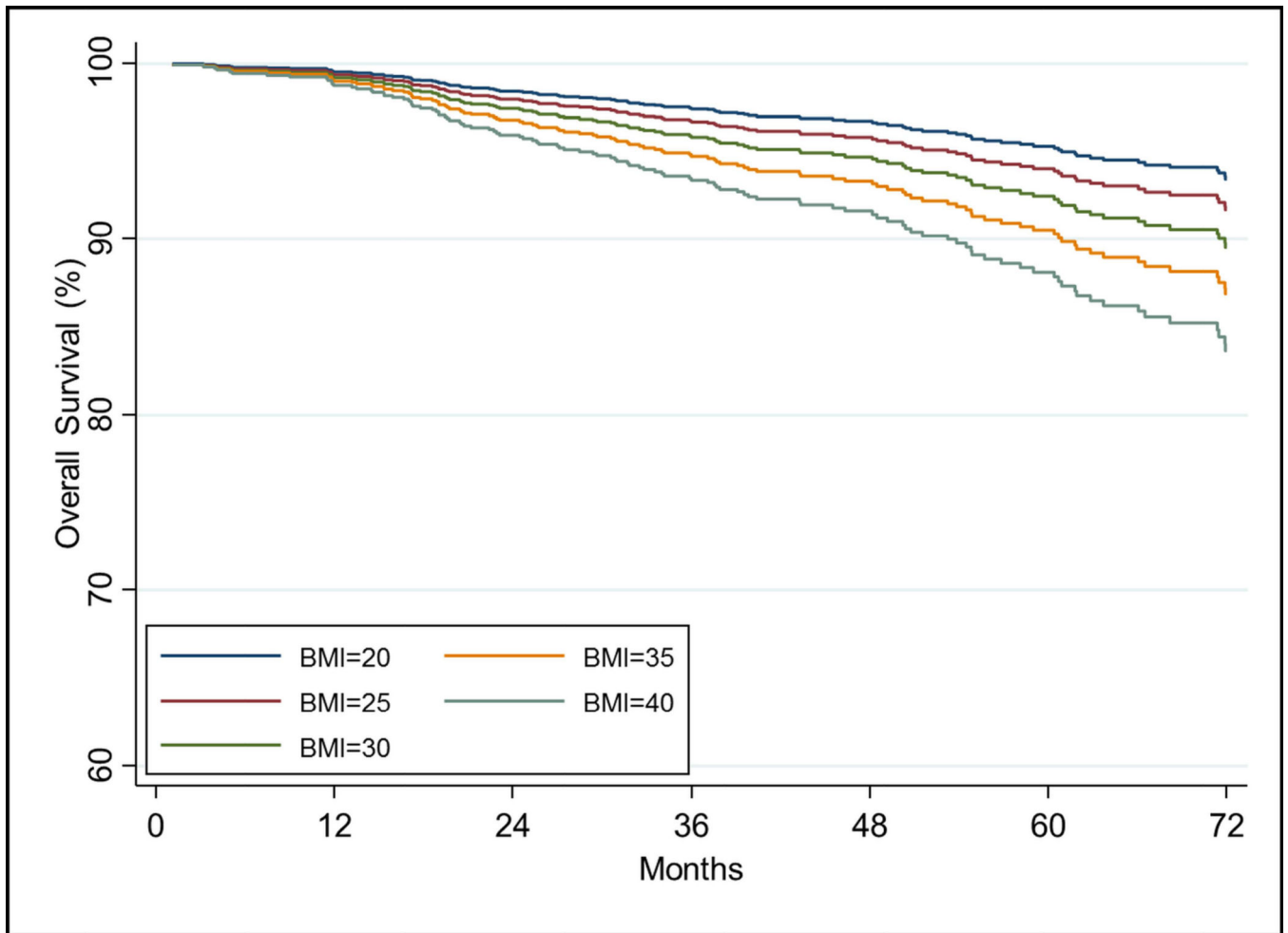


Figure 1.

The relationship of increasing BMI on a) freedom from biochemical failure using the stratified Cox model using T-stage=2 and Gleason score=7 and other covariates at their mean value. The relationship of increasing BMI on b) freedom from distant metastasis, c) cause-specific survival, and d) overall survival estimated from the Cox model while holding other covariates at the mean value.

Table 1

Patient Baseline and Treatment Characteristics

Characteristic	ALL	BMI					p-value
		<25 kg/m ²	25–29.9 kg/m ²	30–34.9 kg/m ²	35–39.9 kg/m ²	40 kg/m ²	
		N (%)	N (%)	N (%)	N (%)	N (%)	
Total		284 (20%)	688 (48%)	326 (23%)	92 (6%)	52 (4%)	
Age at Start of RT							<0.001
36–59 yrs	241 (17%)	30 (11%)	112 (16%)	64 (20%)	19 (21%)	16 (31%)	
60–69 yrs	590 (41%)	102 (36%)	266 (39%)	159 (49%)	42 (46%)	21 (40%)	
70–79 yrs	539 (37%)	128 (45%)	278(40%)	90 (28%)	28 (30%)	15 (29%)	
80 yrs	72 (5%)	24 (8%)	32 (5%)	13 (4%)	3 (3%)	0 (0%)	
Gleason Score							0.339
6	640 (44%)	129 (45%)	311 (45%)	146 (45%)	36 (39%)	18 (35%)	
7	571 (40%)	107 (38%)	269 (39%)	128 (39%)	46 (50%)	21 (40%)	
8–10	231 (16%)	48 (17%)	108 (16%)	52 (16%)	10 (11%)	13 (25%)	
T-stage							0.083
T1	946 (66%)	178 (63%)	434 (63%)	228 (70%)	68 (74%)	38 (73%)	
T2	412 (29%)	92 (32%)	210 (31%)	82 (25%)	19 (21%)	9 (17%)	
T3/4	84 (6%)	14 (5%)	44 (6%)	16 (5%)	5 (5%)	5 (10%)	
iPSA, ng/mL							0.018
0–<10	1055 (73%)	198 (70%)	502 (73%)	240 (74%)	77 (84%)	38 (73%)	
10–<20	273 (19%)	53 (19%)	143 (21%)	61 (19%)	6 (6%)	10 (19%)	
20+	114 (8%)	33 (12%)	43 (6%)	25 (8%)	9 (10%)	4 (8%)	
Risk Group							0.697
Low	458 (32%)	93 (33%)	218 (32%)	101 (31%)	32 (35%)	14 (27%)	
Intermediate	646 (45%)	117 (41%)	317 (46%)	151 (46%)	40 (43%)	21 (40%)	
High	338 (23%)	74 (26%)	153 (22%)	74 (23%)	20 (22%)	17 (33%)	
ADT Use							0.142
No	1003 (70%)	202 (71%)	483 (70%)	218 (67%)	70 (76%)	30 (58%)	
Yes	439 (30%)	82 (29%)	205 (30%)	108 (33%)	22 (24%)	22 (42%)	
Dose, cGy							0.199
7600	688 (48%)	122 (43%)	345 (50%)	158 (49%)	38 (41%)	25 (48%)	
7800	323 (22%)	71 (25%)	142 (21%)	67 (21%)	30 (33%)	13 (25%)	
8000	431 (30%)	91 (32%)	201 (29%)	101 (31%)	24 (26%)	14 (27%)	
Comorbidities							
Diabetes	275 (19%)	39 (14%)	101 (15%)	80 (25%)	28 (30%)	27 (52%)	<0.001
Hypertension	834 (58%)	139 (49%)	370 (54%)	215 (66%)	69 (75%)	41 (79%)	<0.001
Heart Disease	260 (18%)	51 (18%)	126 (18%)	60 (18%)	16 (17%)	7 (13%)	0.934

BMI, body mass index; ADT, androgen deprivation therapy; iPSA, pre-treatment prostate specific antigen

Table 2

Association between BF and BMI and covariates

Variable	HR*	95% CI	p-value
BMI, continuous(kg/m ²)	1.03	1.00–1.07	0.042
Log iPSA(ng/mL)	2.02	1.60–2.52	<0.001
Age(years)	1.00	0.98–1.02	0.992
ADT Use(yes vs no)	0.74	0.47–1.17	0.192
Comorbidities(yes vs no)			
Diabetes	1.09	0.71–1.69	0.691
Hypertension	1.17	0.83–1.66	0.373
Heart Disease	0.80	0.51–1.25	0.322

BF, biochemical failure; BMI, body mass index; HR, hazard ratio; ADT, androgen deprivation therapy; iPSA, pre-treatment prostate specific antigen.

* Hazard ratios are from a single stratified Cox proportional hazards model, adjusted for T-stage and Gleason score as stratification variables.

Table 3

Association between DM and BMI and covariates

Variable	HR	95% CI	p-value
BMI, continuous(kg/m ²)	1.07	1.02–1.11	0.004
Gleason Score			
7 vs 6	2.48	1.14–5.36	0.220
8–10 vs 6	3.78	1.43–9.96	0.007
T-stage			
T2 vs T1c	2.55	1.40–4.65	0.002
T3/4 vs T1c	3.52	1.47–8.42	0.005
Log iPSA(ng/mL)	1.94	1.40–2.67	<0.001
Age(years)	1.02	0.98–1.05	0.322
ADT Use(yes vs no)	0.71	0.34–1.45	0.347

DM, distant metastasis; CSM, cause-specific mortality; OM, overall mortality; BMI, body mass index; HR, hazard ratio; ADT, androgen deprivation therapy; iPSA, pre-treatment prostate specific antigen.

Table 4

Association between CSM and BMI and covariates

Variable	HR	95% CI	p-value
BMI, continuous(kg/m ²)	1.15	1.07–1.23	< 0.001
Gleason Score			
7 vs 6	3.15	0.48–14.65	0.143
8–10 vs 6	2.59	0.42–15.98	0.304
T-stage			
T2 vs T1c	6.29	1.90–20.80	0.003
T3/4 vs T1c	6.47	1.16–36.08	0.033
Log iPSA(ng/mL)	2.41	1.29–4.50	0.006
Age(years)	1.06	0.99–1.14	0.089
ADT Use(yes vs no)	1.25	0.37–4.27	0.722

DM, distant metastasis; CSM, cause-specific mortality; OM, overall mortality; BMI, body mass index; HR, hazard ratio; ADT, androgen deprivation therapy; iPSA, pre-treatment prostate specific antigen.

Table 5

Association between OM and BMI and covariates

Variable	HR	95% CI	p-value
BMI, continuous(kg/m ²)	1.05	1.02–1.08	0.004
Gleason Score			
7 vs 6	1.19	0.78–1.80	0.417
8–10 vs 6	1.18	0.65–2.14	0.595
T-stage			
T2 vs T1c	1.21	0.82–1.78	0.327
T3/4 vs T1c	1.44	0.75–2.76	0.269
Log iPSA(ng/mL)	1.35	1.06–1.73	0.016
Age(years)	1.08	1.05–1.11	<0.001
ADT Use(yes vs no)	1.04	0.66–1.65	0.858
Comorbidities(yes vs no)			
Diabetes	1.54	1.03–2.28	0.034
Hypertension	1.48	1.01–2.17	0.045
Heart Disease	1.19	0.81–1.76	0.373

DM, distant metastasis; CSM, cause-specific mortality; OM, overall mortality; BMI, body mass index; HR, hazard ratio; ADT, androgen deprivation therapy; iPSA, pre-treatment prostate specific antigen.