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Original article

Body mass index was associated with upstaging and upgrading in patients with low-risk prostate cancer who met the inclusion criteria for active surveillance

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Abstract

Background: Obesity is associated with an increased risk of high-grade prostate cancer (PCa). The effect of body mass index (BMI) as a predictor of progression in men with low-risk PCa has been only poorly assessed.

In this study, we evaluated the association of BMI with progression in patients with low-risk PCa who met the inclusion criteria for the active surveillance (AS) protocol.

Methods: We assessed 311 patients who underwent radical prostatectomy and were eligible for AS according to the following criteria: clinical stage T2a or less, prostate-specific antigen level <10 ng/ml, 2 or fewer cores involved with cancer, Gleason score ≤ 6 grade, and prostate-specific antigen density <0.2 ng/ml/cc. Reclassification was defined as upstaged (pathological stage $>$pT2) and upgraded (Gleason score ≥ 7; primary Gleason pattern 4) disease. Seminal vesicle invasion, positive lymph nodes, and tumor volume ≥ 0.5 ml were also recorded.

Results: We found that high BMI was significantly associated with upgrading, upstaging, and seminal vesicle invasion, whereas it was not associated with positive lymph nodes or large tumor volume. At multivariate analysis, 1 unit increase of BMI significantly increased the risk of upgrading, upstaging, seminal vesicle invasion, and any outcome by 21%, 23%, 27%, and 20%, respectively. The differences between areas under the receiver operating characteristics curves comparing models with and without BMI were statistically significant for upgrading ($P = 0.0002$), upstaging ($P = 0.0007$), and any outcome ($P = 0.0001$).

Conclusions: BMI should be a selection criterion for inclusion of patients with low-risk PCa in AS programs. Our results support the idea that obesity is associated with worse prognosis and suggest that a close AS program is an appropriate treatment option for obese subjects.

Keywords: Body mass index; Prostate cancer; Active surveillance

1. Introduction

Widespread use of prostate-specific antigen (PSA) screening increased the number of tumors diagnosed at early stages, but it also led to overdiagnosis and overtreatment of

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a considerable number of patients with clinically insignificant prostate cancer (PCa) [1]. Active surveillance (AS) recently became an accepted alternative for patients with low-risk PCa–related mortality, allowing for delayed curative intervention if there is reclassification of cancer risk or evidence of disease progression [2]. However, risk factors for reclassification and progression are not adequately characterized. Obesity and overweight pose a major risk for serious diet-related chronic diseases, including type 2 diabetes, cardiovascular disease, hypertension and stroke, and certain forms of cancer, especially the hormonally related. In the last decade, multiple epidemiologic studies suggested that obesity is associated with increased risk and death from numerous cancer types including PCa [3,4]. Several biological derangements such as hyperinsulinemia, serum adipokine levels, elevated vascular endothelial growth factor levels, and alterations in sex hormone levels have negative implications for cancer progression [5]. In this study, we evaluated the effect of body mass index (BMI) on the prediction of upgrading, upstaging, positive lymph nodes, seminal vesicle invasion, and tumor volume $\geq$0.5 ml in a cohort of patients with very low-risk PCa who met the inclusion criteria for the PRIAS protocol but elected to undergo radical prostatectomy (RP).

2. Patients and methods

We retrospectively reviewed the medical records of 2,200 patients who underwent robotic RP for PCa between November 2008 and May 2014. None of the patients included in the current study received neoadjuvant androgen deprivation therapy or drugs that could alter the PSA values, such as dutasteride and finasteride. Patients with no biopsy slide or incomplete data were excluded. In total, 311 patients fulfilled the inclusion criteria for "Prostate Cancer Research International: Active Surveillance" [6] defined as follows: clinical stage T2a or less, PSA level $<$10 ng/ml, 2 or fewer cores involved with cancer after a biopsy scheme of at least 12 cores, Gleason score (GS) $\leq$6 grade, and PSA density (PSA-D) $<$0.2 ng/ml/cc. We compared the pathological findings between specimens after RP and prostate biopsies. RP specimens were processed and evaluated according to the Stanford protocol [7] by a single, experienced, genitourinary pathologist (G.R.) blinded to index tests results. PCa was identified and graded according to the definitions of the 2005 consensus conference of the International Society of Urological Pathology [8].

2.1. Statistical analysis

BMI was classified according to the 3 standard categories: 18-24 (normal weight), 25-29 (overweight), and $\geq$30 (obese). Classification of outcomes were upstaging (pathological stage $>$pT2) upgrading (GS $\geq$ 7), seminal vesicle invasion (yes/no), positive lymph nodes (yes/no), and large tumor volume ($\geq$0.5 ml).

Informative parameters for the distribution of continuous variables (age, BMI, PSA level, and PSA-D) were calculated, and their distributions were tested for normality by the Kolmogorov-Smirnov test. As age and BMI were not normally distributed, nonparametric tests were applied for analyses on these variables. Univariate analyses were performed to evaluate the association of patient and tumor characteristics with upgrading, upstaging, positive lymph nodes, seminal vesicle invasion, and large tumor volume. The association for continuous variables was assessed by *t* test (PSA level and PSA-D) or nonparametric 2-sample Wilcoxon test (age and BMI); the association for categorical variables was assessed using the chi-square test or the Fisher exact test, as appropriate. Variation of BMI according to each category of GS was also evaluated, considering the GS = 4 + 3 and the GS = 3 + 4 categories separately, with the nonparametric Wilcoxon test. Linear regression was performed to test for a linear trend between log-transformed BMI values and GS categories.

Multivariate unconditional logistic regression models were performed to assess the independent contribution of patient and tumor characteristics in the prediction of upgrading, upstaging, positive lymph nodes, seminal vesicle invasion, large tumor volume, and any of the previous outcomes; odds ratio and 95% CIs were

Table 1
Patient and tumor characteristics of the study population

	n (%)
Age[a]	62.71 (±5.61)
PSA level[a]	5.88 (±1.85)
PSA density[a]	0.12 (±0.04)
Clinical stage	
cT1c	282 (91%)
cT2a	28 (9%)
Pathological stage	
pT2a	37 (12%)
pT2b	10 (3%)
pT2c	199 (64%)
pT3a	53 (17%)
pT3b	11 (4%)
Gleason score	
6	172 (55%)
7	130 (42%)
3 + 4	79 (61%)
4 + 3	51 (39%)
≥8	8 (3%)
Positive cores	
1	163 (53%)
2	147 (47%)
BMI	
18–24	161 (52%)
25–29	80 (26%)
30+	69 (22%)

[a]Mean (± standard deviation).

Table 2
Univariate analysis for the association between patient and tumor characteristics with (a) upgrading, (b) upstaging, (c) positive lymph nodes, (d) seminal vesicle invasion, (e) tumor volume, and (f) any of the previous outcomes

	"Yes", *n* (%)	"No", *n* (%)	*P* value[a]
(a) *Upgrading*			
Age[b]	63.07 (±5.56)	62.41 (±5.65)	0.25
PSA level[b]	5.94 (±1.78)	5.83 (±1.90)	0.60
PSA density[b]	0.13 (±0.04)	0.12 (±0.04)	0.30
Positive cores			0.30
1	68 (42%)	95 (58%)	
2	70 (48%)	77 (52%)	
Clinical stage			0.17
cT1c	129 (46%)	153 (54%)	
cT2a	9 (32%)	19 (68%)	
BMI			**<0.0001**
18–24	46 (29%)	115 (71%)	
25–29	47 (59%)	33 (41%)	
30+	45 (65%)	24 (35%)	
(b) *Upstaging*			
Age[b]	62.81 (±5.19)	62.68 (±5.73)	0.93
PSA level[b]	5.99 (±1.86)	5.85 (±1.84)	0.59
PSA density[b]	0.12 (±0.04)	0.12 (±0.04)	0.94
Positive cores			0.11
1	28 (17%)	135 (83%)	
2	36 (24%)	111 (76%)	
Clinical stage			0.91
cT1c	58 (21%)	224 (79%)	
cT2a	6 (21%)	22 (79%)	
BMI			**<0.0001**
18–24	16 (10%)	145 (90%)	
25–29	20 (25%)	60 (75%)	
30+	28 (41%)	41 (59%)	
(c) *Positive lymph nodes*			
Age[b]	61.70 (±8.41)	62.74 (±5.51)	0.93
PSA level[b]	5.86 (±2.05)	5.88 (±1.84)	0.97
PSA density[b]	0.13 (±0.06)	0.12 (±0.04)	0.88
Positive cores			0.75
1	6 (4%)	157 (96%)	
2	4 (3%)	143 (97%)	
Clinical stage			0.23
cT1c	8 (3%)	274 (97%)	
cT2a	2 (7%)	26 (93%)	
BMI			1.00
18–24	6 (4%)	155 (96%)	
25–29	2 (3%)	78 (97%)	
30+	2 (3%)	67 (97%)	
(d) *Seminal vesicle invasion*			
Age[b]	65.00 (±3.41)	62.62 (±5.66)	0.18
PSA level[b]	5.89 (±1.58)	5.88 (±1.86)	0.99
PSA density[b]	0.11 (±0.04)	0.12 (±0.04)	0.27
Positive cores			0.23
1	8 (5%)	155 (95%)	
2	3 (2%)	144 (98%)	
Clinical stage			**0.01**
cT1c	7 (2%)	275 (98%)	
cT2a	4 (14%)	24 (86%)	
BMI			**0.01**
18–24	2 (1%)	159 (99%)	
25–29	2 (3%)	78 (98%)	
30+	7 (10%)	62 (90%)	
(e) *Tumor volume*	<0.5 ml, *n* (%)	≥0.5 ml, *n* (%)	
Age[b]	64.33 (±4.85)	62.61 (±5.65)	0.19
PSA level[b]	6.4 (±2.02)	5.85 (±1.83)	0.22
PSA density[b]	0.14 (±0.04)	0.12 (±0.04)	0.14
Positive cores			0.22
1	12 (7%)	151 (93%)	
2	6 (4%)	141 (96%)	
Clinical stage			1.00
cT1c	17 (6%)	265 (94%)	
cT2a	1 (4%)	27 (96%)	
BMI			0.40
18–24	12 (7%)	149 (93%)	
25–29	4 (5%)	76 (95%)	
30+	2 (3%)	67 (97%)	
(f) *Any outcome*			
Age[b]	63.03 (±5.56)	62.32 (±5.67)	0.20
PSA level[b]	5.94 (±1.86)	5.81 (±1.83)	0.55
PSA density[b]	0.12 (±0.04)	0.12 (±0.04)	0.51
Positive cores			0.32
1	84 (52%)	79 (48%)	
2	84 (57%)	63 (43%)	
Clinical stage			0.21
cT1c	156 (55%)	123 (45%)	
cT2a	12 (43%)	16 (57%)	
BMI			**<0.0001**
18–24	64 (40%)	97 (60%)	
25–29	55 (69%)	25 (31%)	
30+	49 (71%)	20 (29%)	

Note: significant *P* values are in bold.
[a] *t* Test or nonparametric 2-sample Wilcoxon test for continuous variables, as appropriate; chi-square test or Fisher exact test for categorical variables, as appropriate.
[b] Mean (± standard deviation).

calculated. Receiver operating characteristics curves were drawn for models with and without inclusion of BMI, and the corresponding areas under the curve of the 2 models were compared with the DeLong test. Finally, a nomogram was created to improve the clinical interpretation of our model, predicting the risk of unfavorable disease, defined as occurrence of upgrading or upstaging or both. Multivariable logistic regression was used to build the nomogram, considering both categorical (positive core and clinical stage) and continuous variables (PSA level and BMI).

Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using SAS software, Version 9.2, and R software with Hmisc and Design libraries (Hmisc and Design libraries http://cran.r-project.org/).

3. Results

The mean age (±standard deviation) of the study subjects was 63 (±6) years (Table 1). Most of the patients (91%) had clinical stage cT1c tumors and 64% had pathological stage pT2c tumors, followed by stage pT3a

tumors (17%). A total of 130 patients had a GS = 7; among them 61% had GS = 3 + 4 and 39% had GS = 4 + 3 (Table 1).

At univariate analysis, we found that high BMI was significantly associated with upgrading, upstaging, seminal vesicle invasion and any outcome, which was defined based on the presence of at least 1 unit increase of BMI one between upgrading, upstaging, positive lymph nodes, seminal vesicle invasion and large tumor volume (Table 2 and Fig. 1). BMI was not associated with positive lymph nodes or large tumor volume (Table 2 and Fig. 1). There was also a significant association with seminal vesicle invasion of clinical stage cT2a compared with stage cT1c ($P = 0.01$). Looking at the association between BMI and upgrading in more detail, we found higher BMI values with increasing GS (Table 3). A significantly higher BMI was also observed for patients with GS = 4 + 3 compared with patients with GS = 3 + 4 ($P = 0.02$, results not shown).

Table 3
Univariate analysis for the association between BMI and each category of GS

Gleason score	*n*	BMI mean (±SD)	*P* value[a]
6	172	24.53 (±3.37)	Ref.
3 + 4	79	26.51 (±3.97)	**0.0002**
4 + 3	51	28.24 (±4.46)	**<0.0001**
≥8	8	31.88 (±5.08)	**0.0005**

Note: significant *P* values are in bold. *P* value for linear trend <0.0001.
[a]Nonparametric 2-sample Wilcoxon test comparing each GS category with GS = 6 (reference).

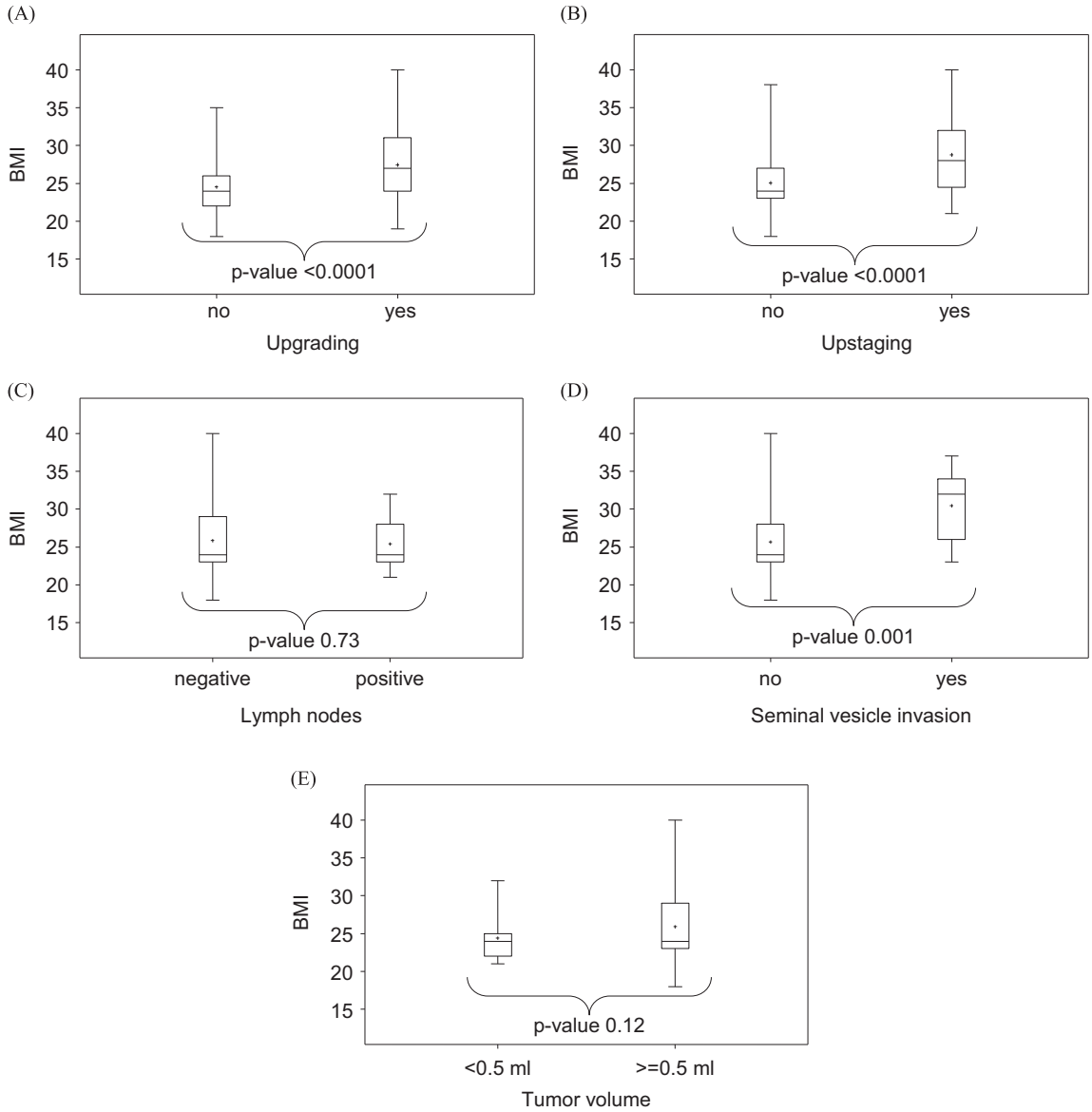


Fig. 1. Box plots representing the BMI of patients (A) with or without upgrading, (B) with or without upstaging, (C) with positive or negative lymph nodes, (D) with or without seminal vesicle invasion, and (E) with tumor volume < or ≥0.5 ml. Minimum and maximum BMIs are depicted by black whiskers. The box signifies the upper and lower quartiles. The median and the mean are represented by a black line and a small cross within the box, respectively.

At multivariate analysis, the association of BMI with upgrading, upstaging, seminal vesicle invasion, and any outcome was confirmed, as well as the association between clinical stage cT2a with seminal vesicle invasion (Table 4). According to the model with continuous BMI values, 1 unit increase of BMI significantly increased the risk of upgrading, upstaging, seminal vesicle invasion, and any outcome by 21%, 23%, 27%, and 20%, respectively. The differences between areas under the receiver operating characteristics curves comparing models with and without BMI were statistically significant for upgrading (Fig. 2), upstaging (Fig. 3), and any outcome (not shown) with *P* values for the differences of 0.0002, 0.0007, and 0.0001, respectively, whereas it was not significant for seminal vesicle invasion (not shown).

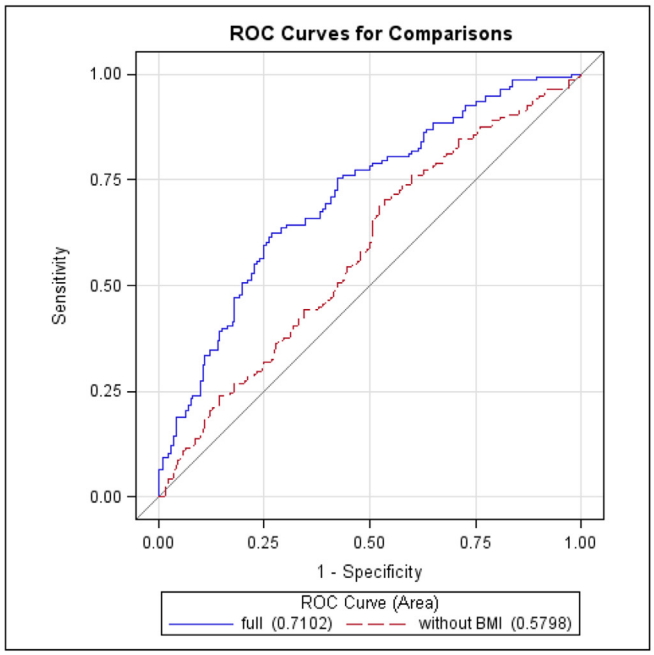
Fig. 4 shows a nomogram with PSA levels, positive cores, clinical stage, and BMI, predicting the risk of unfavorable disease. BMI seemed the predictor that contributed most on increasing the risk of unfavorable disease in this cohort of patients, with overweight patients having a risk of unfavorable disease, in the absence of other risk factors, of approximately 25%–85% for BMI of 25–40.

Table 4
Multivariate odds ratio (95% CI) and *P* value for predictors of (a) upgrading, (b) upstaging, (c) positive lymph nodes, (d) seminal vesicle invasion, (e) tumor volume, and (f) any of the above

		Model without BMI	*P* value	Model with continuous BMI	*P* value	Model with 3 classes of BMI	*P* value
(a)	PSA level	1.04 (0.92–1.17)	0.58	0.98 (0.86–1.12)	0.77	0.98 (0.86–1.12)	0.79
	Positive cores	1.28 (0.81–2.00)	0.29	1.20 (0.74–1.94)	0.46	1.16 (0.72–1.87)	0.55
	Clinical stage	0.55 (0.24–1.27)	0.16	0.51 (0.21–1.25)	0.14	0.54 (0.22–1.31)	0.17
	BMI			**1.21 (1.14–1.30)**	**<0.0001**		
	18–24	–	–			1.00 (reference)	
	25–29	–	–			**3.42 (1.93–6.05)**	**<0.0001**
	30+	–	–			**4.87 (2.63–8.99)**	**<0.0001**
(b)	PSA	1.04 (0.90–1.21)	0.60	0.98 (0.83–1.16)	0.83	0.98 (0.84–1.16)	0.85
	Positive cores	1.56 (0.90–2.72)	0.12	1.51 (0.83–2.74)	0.18	1.49 (0.83–2.67)	0.18
	Clinical stage	1.04 (0.40–2.68)	0.94	1.01 (0.36–2.85)	0.98	1.01 (0.37–2.78)	0.99
	BMI			**1.23 (1.15-1.33)**	**<0.0001**		
	18–24	–	–			1.00 (reference)	
	25–29	–	–			**2.90 (1.39–6.05)**	**0.004**
	30+	–	–			**6.20 (3.03–12.67)**	**<0.0001**
(c)	PSA	0.99 (0.70–1.40)	0.93	0.99 (0.70–1.41)	0.96	1.00 (0.70–1.41)	0.98
	Positive cores	0.72 (0.20–2.62)	0.62	0.73 (0.20–2.65)	0.63	0.74 (0.20–2.69)	0.64
	Clinical stage	2.67 (0.54–13.31)	0.23	2.67 (0.54–13.30)	0.23	2.64 (0.52–13.46)	0.24
	BMI			0.98 (0.84-1.14)	0.77		
	18–24	–	–			1.00 (reference)	
	25–29	–	–			0.75 (0.14–3.92)	0.73
	30+	–	–			0.74 (0.14–3.84)	0.72
(d)	PSA	0.98 (0.69–1.39)	0.89	0.94 (0.64–1.38)	0.75	0.92 (0.63–1.34)	0.67
	Positive cores	0.38 (0.10–1.48)	0.16	0.35 (0.08–1.44)	0.14	0.38 (0.09–1.54)	0.17
	Clinical stage	**6.95 (1.86–26.03)**	**0.004**	**7.14 (1.70–29.92)**	**0.01**	**6.21 (1.52–25.38)**	**0.01**
	BMI			**1.27 (1.11–1.46)**	**0.001**		
	18–24	–	–			1.00 (reference)	
	25–29	–	–			2.95 (0.39–22.34)	0.30
	30+	–	–			**9.18 (1.78–47.26)**	**0.01**
(e)	PSA	1.18 (0.91–1.53)	0.20	1.22 (0.94–1.58)	0.13	1.21 (0.93–1.56)	0.15
	Positive cores	0.53 (0.19–1.45)	0.22	0.57 (0.21–1.55)	0.28	0.56 (0.20–1.55)	0.26
	Clinical stage	0.56 (0.07–4.45)	0.59	0.53 (0.07–4.21)	0.54	0.58 (0.07–4.62)	0.61
	BMI			0.89 (0.77–1.03)	0.11		
	18–24	–	–			1.00 (reference)	
	25–29	–	–			0.64 (0.20–2.10)	0.46
	30+	–	–			0.35 (0.08–1.62)	0.18
(f)	PSA	1.04 (0.92–1.18)	0.53	0.99 (0.87–1.13)	0.89	0.99 (0.88–1.13)	0.94
	Positive cores	1.26 (0.80–1.98)	0.32	1.18 (0.73–1.90)	0.50	1.15 (0.71–1.84)	0.57
	Clinical stage	0.60 (0.27–1.31)	0.20	0.57 (0.24–1.33)	0.19	0.61 (0.26–1.39)	0.24
	BMI			**1.20 (1.12–1.28)**	**<0.0001**		
	18–24	–	–			1.00 (reference)	
	25–29	–	–			**3.20 (1.80–5.69)**	**<0.0001**
	30+	–	–			**3.80 (2.05–7.04)**	**<0.0001**

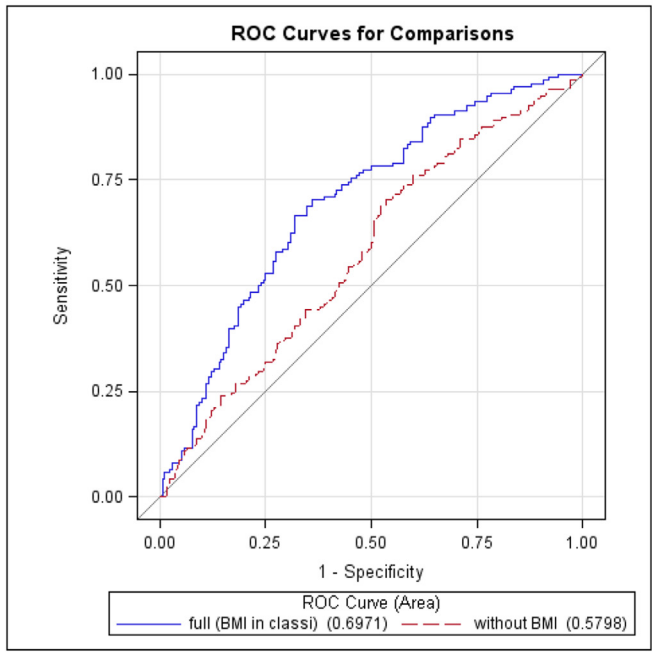
Note: significant odds ratios and *P* values are in bold.

(A)



P-value for the difference: 0.0003

(B)



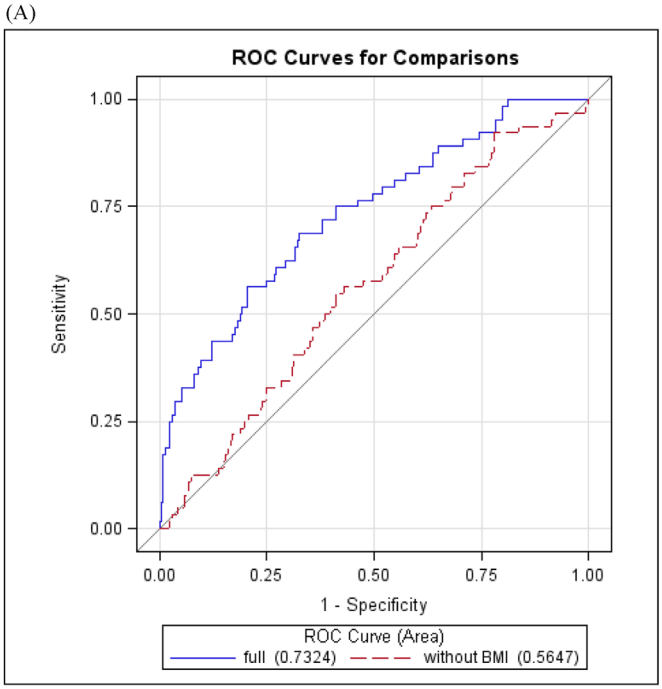
P-value for the difference: 0.0002

Fig. 2. ROC curves for upgrading comparing models with and without inclusion of BMI with (A) continuous BMI and (B) 3 classes of BMI. ROC, receiver operating characteristics. (Color version of figure is available online.)

4. Discussion

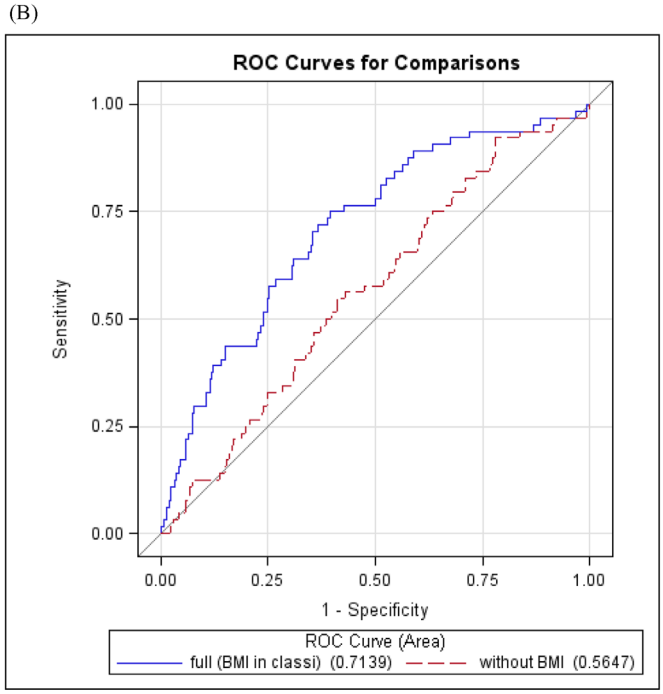
Although, in recent years, there has been progress toward identifying the best candidates for AS, risk factors for reclassification and progression are not adequately characterized. This is particularly worrisome in men with a life expectancy of more than 10 to 15 years. Recently, number of biopsy cores emerged as an independent

(A)



P-value for the difference: 0.0007

(B)



P-value for the difference: 0.0022

Fig. 3. ROC curves for upstaging comparing models with and without inclusion of BMI with (A) continuous BMI and (B) 3 classes of BMI. ROC, receiver operating characteristics. (Color version of figure is available online.)

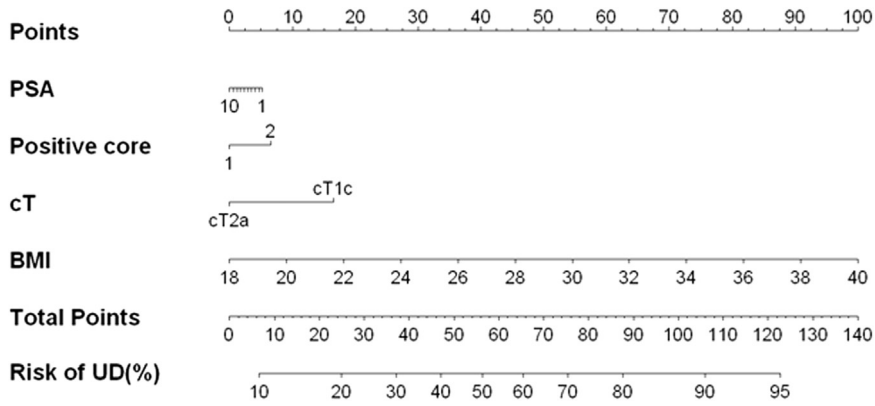


Fig. 4. Nomogram with PSA level, positive cores, clinical stage (cT), and BMI predicting the risk of unfavorable disease (UD), defined as occurrence of upstaging or upgrading or both.

predictor of pathologically insignificant PCa and unfavorable disease at RP [9], suggesting that the extent of initial biopsy sampling could improve patient selection and surveillance strategy planning [10]. The PRIAS study showed that in addition to age and PSA level at diagnosis, both PSA-D and the number of positive cores at diagnosis (2 compared with 1) are the strongest predictors for reclassification biopsy or switching to deferred treatment. It was found that the disease-specific survival rate was 100%, and it was concluded based on the short-term data that AS is a feasible strategy to reduce overtreatment [11]. Furthermore, emerging data indicated that demographic factors such as race or BMI may help differentiate better candidates for surveillance [12]. Obesity is a modifiable risk factor that warrants special attention. The lower testosterone level and hemodilution resulting from the increased plasma volume in obese men may be responsible for decreased serum PSA levels, leading to delayed diagnosis [13]. Increasing BMI is associated with shorter time to PSA treatment failure after RP [14] and androgen suppression therapy or radiation therapy for clinically localized PCa [15].

Circulating hormones (i.e., insulin, free insulinlike growth factor-1, and testosterone), cytokines (i.e., IL-6), and other factors such as leptin and adiponectin are altered in obese subjects and might promote PCa progression [5]. Besides, we and others previously demonstrated that insulinlike growth factor-binding protein, IL-6 soluble receptor, and adipokines are biomarkers of poor prognosis in patients with PCa [16–18]. Although the association between obesity and PCa incidence is controversial, literature data consistently indicated that obesity is associated with a reduced risk of low-risk, PSA-detected cancers and an increased risk of high-grade, lethal cancers [5,19]. Moreover, most large observational series have shown that obesity is a risk factor for adverse pathological features, higher advanced stage, risk for biochemical recurrence after RP, and risk of death from PCa [14,20,21].

On this basis, a key question is whether obesity is a risk factor for PCa progression in men with PCa who are on AS. To the best of our knowledge, few studies evaluated the ability of BMI for patient selection in AS of those with PCa [22,23]. In a recent study, a cohort of 565 men with low-risk PCa on initial biopsy selected for AS has been evaluated, showing that obesity is independently associated with a higher risk of pathological and therapeutic progression [24].

Our findings suggested that BMI is associated with an increased risk of upgraded and upstaged disease and it was significantly higher in patients with seminal vesicle invasion, but not in patients with positive lymph nodes and large tumor volume.

Moreover, models including BMI showed a significant increased ability to predict the risk of upgrading and upstaging, although their prediction accuracy is generally fair (areas under the curve ≥ 0.70).

These data further support the idea that obesity is associated with PCa aggressiveness. AS protocols in these patients should include close surveillance scheme in order to early identify tumors progression.

The present study had some limitations. First, our study was performed retrospectively, and the data were analyzed in selected patients who underwent RP rather than all patients with biopsy-confirmed PCa. Therefore, there might have been the inherent bias of a retrospective design and a selection bias. However, RP is necessary to confirm the pathological characteristics of insignificant PCa. Second, we focused primarily on the pathological findings but did not assess biochemical recurrence or PCa-specific mortality, which might be a more important issue than the adverse pathological characteristics.

5. Conclusion

In conclusion, compared with normal or overweight men eligible for AS, obese men are at a higher risk of upgraded and upstaged disease. These results encourage urologists to inform obese men eligible for AS about this risk of reclassification and may help improve treatment decision making.

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