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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).