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Original article

Radical prostatectomy neutralizes obesity-driven risk of prostate cancer progression

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Abstract

Introduction: Obesity negatively affects several prostate cancer (PCa) outcomes, including mortality to PCa. However, the validity of several such associations is still under debate, including its effect on pathological stage at radical prostatectomy (RP) and subsequent biochemical recurrence (BCR), which represents the focus of this study.

Methods: We relied on patients with PCa treated with RP at the Martini-Klinik Prostate Cancer Center between 2004 and 2015. First, multivariable logistic regression analyses tested for association between obesity and non–organ-confined disease ($\geq$pT3 or pN1). Second, multivariable Cox regression analyses examined obesity effect on BCR. Last, in a propensity score–matched cohort, Kaplan-Meier analyses assessed BCR-free survival according to body mass index (kg/m^2) (BMI) strata ($\geq$30 vs. $<$25).

Results: Of 16,014 individuals, 2,403 (15%) men were obese (BMI $\geq$ 30). Median follow-up was 36.4 months (interquartile range: 13.3–60.8). Obese patients were more likely to harbor non–organ-confined disease at final pathology (odds ratio = 1.27; 95% CI: 1.13–1.43; $P < 0.001$) but did not have higher BCR rates (hazard ratio = 0.98; 95% CI: 0.86–1.11; $P = 0.7$). Similarly, BCR-free survival was not different between obese and nonobese men, after propensity score matching (log rank $P = 0.9$).

Conclusion: Obesity (BMI $\geq$ 30) might predispose to higher rates of non–organ-confined disease at RP. However, obesity was not an independent predictor of BCR after surgery. Consequently, the unfavorable effect of obesity on PCa might be limited to local spread of the disease and might be neutralized after RP.

Keywords: Biochemical recurrence; BCR; BMI; Body mass index; Metastases; Obesity; Outcomes; Prostate cancer; Radical prostatectomy; Survival

1. Introduction

As the prevalence of obesity increased dramatically over the past decades, the interest in its potential detrimental effects on cancer or cancer control measures has also increased [1]. Besides the major contribution to cardiovascular disease and diabetes [2], obesity also contributes to the risk and mortality of several cancer primaries, including prostate cancer (PCa) [3]. Changes in the microenvironment [4] of obese patients might increase the incidence of PCa, might lead to higher rates of aggressive disease at diagnosis, as well as might negatively affect cancer control outcomes quantified as biochemical recurrence (BCR), metastatic

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progression, and cancer-specific mortality after primary local treatment [5–8].

Despite relatively robust data supporting the association between obesity and various PCa metrics, the urologic community continues to critically debate the existing evidence. In particular, a current meta-analysis was not able to validate the suggested increased incidence of PCa in obese men [9]. Moreover, obesity was inversely associated with the risk of harboring PCa in more than one population-based study [10–12].

Although several studies recorded more aggressive disease in obese men at diagnosis [6,9,13], single-center experience stated otherwise [14]. Additionally, prospective data suggest that the increased risk of aggressive disease in obese men might rather depend on the race, with higher risk in African Americans [15].

Similarly, multiple studies recorded unfavorable longitudinal cancer control outcomes in obese men [3,5,7,16]. However, specific long-term longitudinal oncologic outcomes after radical prostatectomy (RP), including cancer-specific survival, suggest little if any effect of body mass index (BMI) [13].

Based on the aforementioned controversy, we decided to investigate the Martini-Klinik Prostate Cancer Center database and focused on the effect of obesity on 2 specific end points, namely the rates of harboring non–organ-confined disease at surgery and the rate of BCR after RP.

2. Material and methods

2.1. Study population

We relied on the Martini-Klinik Prostate Cancer Center database. We included patients with PCa treated with RP between January 2004 and March 2015. Patients with neoadjuvant androgen deprivation therapy as well as those with palliative or salvage RP were excluded. This resulted in 16,014 assessable patients.

2.2. Covariates

BMI (kg/m^2), age, year of surgery, prostate-specific antigen (PSA), biopsy Gleason score, clinical tumor stage (cT), pathological tumor stage (pT), pathological Gleason score, nodal stage (Nx vs. pN0 vs. pN1), non–organ-confined disease ($\geq$pT3 or pN1), margin status (R0 vs. R1), number of removed lymph nodes, surgical approach (open RP] vs. robot-assisted RP), nerve-sparing status, operating room time, and blood loss were tabulated. BCR was assessed during follow-up.

2.3. Statistical analyses

Our statistical analyses consisted of 4 steps. First, we investigated differences in clinical, pathological, and treatment characteristics according to different BMI strata ($\geq$30 vs. 25–30 vs. $<$25). Second, in multivariable logistic regression analyses, we tested the effect of obesity on the rates of non–organ-confined disease ($\geq$pT3 or pN1) at final pathology. In the third step of our analyses, we focused on patients with 12 or more months of follow-up ($n = 13{,}218$) and used multivariable Cox regression analyses to test the effect of obesity on BCR rates (events = 2,417) after RP.

Finally, we applied propensity score matching to obese (BMI $\geq$ 30) and nonobese (BMI $<$ 25) patients. The propensity score–matched cohort was balanced according to clinical and pathological characteristics such as age, PSA, year of surgery, pT, pN, surgical margin status, and pathological Gleason score, respectively. Kaplan-Meier analyses then tested for the effect of obesity (BMI $\geq$ 30 vs. BMI $<$ 25) on BCR rates.

Means, medians, and interquartile ranges were reported for continuous variables. Frequencies and proportions were reported for categorical variables. The *t*-test, the Mann-Whitney test, and the chi-square test were used to compare the statistical significance of differences in means, medians, and proportions, respectively. All statistical tests were performed using R. All tests were 2-sided with a significance level set at $P < 0.05$.

3. Results

3.1. Baseline descriptives

Overall, 16,014 patients with PCa treated with RP were identified. Of those, 2,403 (15.0%) were obese (BMI $\geq$ 30), 8,233 (51.4%) men were overweight (BMI: 25–30), and 5,378 (33.6%) had a BMI $<$ 25. The proportion of obese patients increased over time from 8.9% in 2004 to 15.9% in 2015 ($P < 0.001$).

We recorded statistically significant differences in clinical, pathological, and treatment characteristics according to BMI strata ($\geq$30 vs. 25–30 vs. $<$25). Specifically, obese patients (BMI $\geq$ 30) were younger than their nonobese counterparts (median age: 64 vs. 65 vs. 65 y, $P < 0.001$). Conversely, obese man had higher median PSA (7.1 vs. 6.9 vs. 6.9 ng/ml, $P = 0.009$) and more frequently harbored Gleason $\geq 4+4$ at prostate biopsy (16.1 vs. 12.7 vs. 12.1%, $P < 0.001$).

Similarly, obese men more frequently harbored Gleason $\geq 4+4$ at final pathology (8.2 vs. 5.6 vs. 5.1%, $P < 0.001$). Obese men were also more likely to harbor unfavorable pT stage $\geq$ pT3b (14.0 vs. 11.2 vs. 10.6%, $P < 0.001$) and lymph node metastases (8.8 vs. 7.4 vs. 7.1%, $P = 0.04$) at final pathology, respectively. Additionally, obese men more frequently harbored non–organ-confined disease ($\geq$pT3 or pN1) at final pathology (36.0 vs. 31.9 vs. 30.2%, $P < 0.001$), and they more frequently exhibited a positive surgical margin (22.4 vs. 16.9 vs. 14.9%, $P < 0.001$).