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INFLUENCE OF BODY MASS INDEX ON BIOCHEMICAL RECURRENCE IN PATIENTS WITH NEGATIVE MARGINS AFTER RADICAL PROSTATECTOMY

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ABSTRACT – *Background:* *Obesity is frequently linked with tumors of the kidney, breast, colon, endometrium, and prostate cancer (PCa). However, data regarding the mechanism by which obesity is related to the prognosis of PCa are still controversial.*

Aim*: The purpose of this study was to examine a possible correlation between obesity and biochemical recurrence (BCR) in patients treated with Radical Prostatectomy (RP) for localized prostate cancer.*

Patiens and Methods: *From 2005 to 2014, 259 patients underwent RP and had BMI data available were enclosed in this study retrospectively. Patients were categorized with BMI into three groups: obese (BMI ≥ 30 kg/m2), overweight (BMI 25 to 30 kg/m2), and normal weight (BMI ≤ 25 kg/m2). Patients with a surgical treatment of prostatic disease, neoadjuvant therapy, positive surgical margin status after RP or incomplete clinical data were excluded from study. We tested the effect of BMI on the rate of pathological Gleason Score (GS), extracapsular extension (ECE), seminal vesicle invasion (SVI) and lymph node invasion (LNI) in univariate and multivariate analysis.*

Results: *Obese men were older at the time of the surgery, had significantly higher grade disease (p <0.002) and had higher stage disease, as 27.1% of obese men had pT3 disease compared with 10.2% normal weight men and 17.4% overweight men. Overall, the mean follow-up time was 52 months (range 12-98), during which 26.6% of patients developed BCR of disease. On multivariate analysis for identifying significant predictors of BCR, which included pathological variables (GS, ECE, SVI and LNI) preoperative serum PSA level (p <0.001), GS (p = 0.032) and BMI (p < 0.002) were found to be independent predictors of BCR.*

Conclusions: *Obese patients with localized PCa had worse pathologic outcomes, and had a greater predicted risk of BCR after RP compared with normal weight patients.*

KEY WORDS: *Body mass index, Obesity, Prostate cancer, Prostate antigen specific, Biochemical recurrence, Prostatectomy.*

INTRODUCTION

Prostate cancer (PCa) and the prevalence of overweight are considered among the most common health problems currently affecting European men and the primary cause of mortality in the United States[1]. Obesity is associated with a number of chronic diseases, such as diabetes, coronary artery disease, and hypertension[2]. Furthermore, it is frequently linked with tumors of the kidney, breast, colon, endometrium, and prostate cancer[3,4]. However, data regarding the mechanism by which obesity is related to the incidence and prognosis of PCa are still controversial[5,6]. One of the possible mechanisms is its influence on the testosterone level[5] and technical difficulties in dissecting the prostate during radical prostatectomy[7]. In patients undergoing Radical Prostatectomy (RP) persistent

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high prostate specific antigen (PSA) serum levels are associated to biochemical recurrence (BCR) and cancer progression[8,9]. In this retrospective study we reviewed patients who underwent RP for localized PCa with negative margins postoperatively and analysed the possible correlation between obesity and BCR.

PATIENTS AND METHODS

Between May 2005 and December 2014, we retrospectively reviewed the medical records of 259 patients who underwent RP (118 with laparoscopic technique and 141 with open technique) for clinically localized PCa (stage cT1 to cT2N0M0) at our single tertiary care, referral centre. Patients with a surgical treatment of prostatic disease, neoadjuvant therapy, positive surgical margin status after RP or incomplete clinical data were excluded from our study. Preoperative data [age, height, weight, PSA, prostate volume (PV), clinical stage, digital rectal examination (DRE), and prostate biopsy Gleason grade] and pathological data [postoperative Gleason Score (GS), pathological stage, seminal vesicle invasion (SVI), lymph node invasion (LNI)] were collected retrospectively for analysis. Clinical and pathological stages were assigned based on the 2002 tumor node metastasis (TNM) system. The Gleason grading was based on the recommendations of the 2005 international society of urological pathology consensus conference. All surgical specimens were analysed internally by our Pathology Department specializes in genitourinary pathology. The RP and pelvic lymphadenectomy were performed by three experienced surgeons, using standard operative techniques. Patients were then categorized with Body Mass Index (BMI) into three groups according to the World Health Organisation (WHO) classification of obesity: obese (BMI $\geq$ 30 kg/m^2) with 85 patients, overweight (BMI 25 to 30 kg/m^2) with 86 patients, and normal weight (BMI $\leq$ 25 kg/m^2) with 88 patients.

BMI was calculated on all patients in whom height and weight information was known preoperatively. In the majority, patient-reported height and weight data were entered into the clinical records at the time of initial presentation. For some patients, those data were inserted retrospectively after review of anesthesia records. Patient height and weight were utilized to calculate BMI using the following formula: BMI = weight (kilograms)/height (meters)[6]. In general, patients were seen every 3 months the first year, every 6 months the second and third years, and yearly thereafter unless thereafter unless there was evidence of BCR, in which case more frequent follow-up was required. A serum PSA level was defined at each follow-up date. Recurrence of PCa after RP was defined as a serum PSA level of $\geq$ 0.2 ng/mL for two consecutive measurements.

Statistical analysis

The association between BMI as a categorized variable and baseline clinical and pathologic features were tested using the Student's t-test or the Mann Whitney U test, depending of their distribution. Normally distributed variables are presented as mean plus or minus standard deviation, and non-normally distributed variables are presented as median and interquartile range. Multivariate analysis was performed according to the Cox proportional hazards regression model to identify independent prognostic factors. In multivariate analysis, variables of age, PSA, PV, BMI, GS, ECE, SVI, and LNI were included as required. Statistical analyses were performed using Microsoft Excel 2010 platform version 10.1. A $p<0.05$ was considered to indicate statistical significance.

RESULTS

For the 259 patients in our study who underwent RP, the mean ± SD and median age was 63.2±6.3 and 62.4 years, respectively. Median total PSA was 4.8 ng/mL (range 2.7-17), median prostate volume was 42.8 mL (range 18-128) and 88 (34%) patients presented a positive DRE. The mean ± SD and median BMI was 28.2 ± 4.3 kg/m^2 and 27.5 kg/m^2, respectively. A total of 85 (32.8%) patients were classified as obese (BMI $\geq$30 kg/m^2). Table 1 shows the clinical and pathological characteristics of the patients categorized according to BMI. Compared with normal weight and overweight men, obese men were older at the time of the surgery ($p = 0.234$) and had significantly higher grade disease ($p <0.002$). Moreover, the obese men had a lower PSA concentration ($p <0.002$), a large prostate volume ($p <0.001$), and were less likely to have abnormal DRE findings ($p <0.001$). Obese patients were inclined to have higher stage disease, as 27.1% (23/85) of obese men had pT3 disease compared with 10.2% (9/88) normal weight men and 17.4% (15/86) overweight men. Histological evaluation of biopsy cores and RP specimens showed that high GS $\geq$ 7 was more common in obese men than in normal weight patients ($p <0.001$). Despite this, the LNI was more frequently positive in obese patient than in normal patients [38.9% (33/85) *vs.* 29.5% (26/88), $p <0.001$] and the SVI was more frequently invaded [16.5% (14/85) *vs.* 6.8% (6/88), $p <0.002$]. The relationship between the clinical stage (determined preoperatively by DRE and histological evaluation of

Table 1. Clinical and pathological characteristics according to BMI of patients undergoing radical prostatectomy for localized prostate cancer.

Characteristic of patients (n: 259)	*Normal weight (<25 kg/m²) (n: 88)*	*Overweight (≥25 to <30 kg/m²) (n: 86)*	*Obese (≥30 kg/m²) (n: 85)*	*p-value*
Age (years), mean ± SD	63.2±7.1	63.4±6.7	65.2±7.4	NS
Mean PSA level, ng/mL	6.3 (2.5-17)	6.8 (2.2-20)	4.6 (3.2-19)	<0.002
Mean prostate volume, mL	31.1 (17-64)	56.3 (31-98)	72.5 (60-145)	<0.001
Abnormal DRE, n. (%)	39 (44.3)	34 (39.5)	15 (17.7)	<0.001
Clinical stage, n. (%)				NS
• pT1	39 (44.3)	34 (39.6)	31 (36.5)	
• pT2	49 (55.7)	52 (60.4)	54 (63.5)	
RP Gleason score, n. (%)				<0.002
• ≤6	56 (63.6)	49 (57)	32 (37.7)	
• =7	25 (28.4)	28 (32.6)	37 (43.5)	
• ≥8	7 (8)	9 (10.4)	16 (18.8)	
Pathologic stage, n. (%)				<0.001
Organ-confined disease	53 (60.3)	49 (57)	29 (34.1)	
Extraprostatic extension	3 (3.4)	5 (5.8)	9 (10.6)	
Seminal vesicle invasion	6 (6.8)	3 (3.5)	14 (16.5)	
Lymph node invasion	26 (29.5)	29 (33.7)	33 (38.8)	
Follow-up (years), mean ± SD	4.3±3.8	4.2±3.9	4.3±3.7	NS

SD = standard deviation; PSA = prostate-specific antigen; DRE = digital rectal examination; PCa = prostate cancer; RP = radical prostaterctomy; NS = not significant.

biopsy cores) and pathologic stage shown that patients who were obese were more likely to be clinically understated than were normal patients [65.9% (56/85) *vs.* 39.8% (35/88), p <0.001]. Obese men had larger prostate size and ample perirectal fat. The clinical implication was that at the time of DRE and prostate biopsy it was more difficult to detect the tumor stage of prostate in obese patients (Table 2).

Overall, the mean follow-up time was 52 months (range 12-98 months), during which 68 (26.6%) patients developed BCR of disease. Among such subjects significant difference was observed in BCR when patients were divided into three groups by WHO definition of obesity (BMI ≥30 kg/m²). On multivariate analysis for identifying significant preoperative predictors of BCR, which included variables of age, PSA, PV, BMI, clinical stage, and biopsy Gleason grade were not shown to be a significant predictor of BCR, except BMI (p <0.001). When pathological variables (pathological GS, ECE, SVI and LNI) replaced variables of clinical stage and biopsy Gleason grade in the multivariate analysis, preoperative serum PSA level (p <0.001), GS (p =0.032) and BMI (p <0.002) were found to be independent predictors of BCR (Table 3).

DISCUSSION

Accurate prediction of pathological stage and BCR following treatment for localised PCa is significant for patients treatment planning[10]. Recently obesity has been investigated as a potential novel marker to predict relapse in clinically localised PCa after

Table 2. Clinical staging error stratified by BMI groups.

BMI, kg/m²	*Clinical Understaging*	*Accurate Clinical Staging*	*Clinical Overstaging*	*p-value*
<25, n. (%)	35 (39.8)	53 (60.2)	0	<0.001
25-30, n. (%)	37 (43)	49 (57)	0	
>30, n. (%)	56 (65.9)	29 (34.1)	0	

BMI = Body Mass Index.

Table 3. Multivariate analysis for identifying independent predictor for time to biochemical recurrence after radical prostatectomy.

Preoperative variables			
Variables	*Hazard Ratio*	*95% CI*	*p-value*
Age	0.981	0.956-1.033	NS
PSA	1.066	1.041-1.077	NS
Prostate volume	0.987	0.958-1.004	NS
BMI	1.333	0.745-2.532	<0.001
Clinical stage	1.052	0.662-2.634	NS
Biopsy Gleason score	1.734	1.065-3.213	NS
Pathologic variables			
Variables	*Hazard Ratio*	*95% CI*	*p-value*
Age	0.978	0.952-1.029	NS
PSA	1.052	1.034-1.069	<0.001
Prostate volume	0.989	0.961-1.009	NS
BMI	1.374	0.721-2.438	<0.002
Pathologic Gleason score	2.679	1.317-6.245	0.032
Extraprostatic extension	1.034	0.661-1978	NS
Seminal vesicle invasion	1.553	0.832-2.758	NS
Lymph node invasion	1.332	0.825-2.107	NS

NS = not significant; PSA = prostate-specific antigen; BMI = Body Mass Index.

RP[11,12]. Increasing BMI has been shown to increase the risk of BCR and mortality following RP[13]. This may be due, in part, to poor surgical technique and a greater risk of positive SM[14]. Therefore, postoperative serum PSA level can result from either advanced disease or poor surgical technique. To address this, in our study we previously excluded patients underwent RP with positive SM, where obesity remained alone as a useful predictor of BCR[4,13].

Freedland et al[14] showed that obesity affected the GS, positive SM, ECE, and LNI. Furthermore, they have been suggested that BMI is positively related to capsular incision, because RP is technically more difficult in obese patients, which results in a greater likelihood of less than technically ideal operation.

As other possible mechanisms some authors include steroid hormones such as serum testosterone level or obesity-related cytokines as leptin, insulin and IGF-1. Recently, late-onset hypogonadism has been reported to induce obesity[15]. Patients with low total testosterone also more frequently present with poor pathological features, including capsular invasion and BCR[16,17]. The mechanism is still unclear; however, adiposity-related cytokines such as adiponectin and leptin might influence tumor aggressiveness following RP[5]. In our study, we did not search retrospectively the relationship between the total testosterone level and BCR after RP for lack of data in clinical records.

We showed that higher BMI at surgery was significantly associated with BCR, ECE, SVI, and LNI in patients undergoing RP. These findings are consistent with the study by Siddiqui et al[18] in that the obese patients had more advanced biopsy and pathologic GS. However, pelvic lymph node dissection were conducted in a similar proportion of obese and normal patients (both 75%), and no difference was found in the rate of node-positive disease.

Benez et al[19] suggested that the PSA level was underestimated in obese men and that lower PSA levels were largely due to hemodilution by the large plasma volume in men with BMI $\geq$30 kg/m^2.

In our study, patients with a higher BMI were older, had a lower PSA concentration, a larger prostate volume, and were less likely to have abnormal DRE findings (p <0.001). These data, in line with prior studies[20,21], showed that obese patients had larger prostate size and ample perirectal fat. The clinical implication is that at the time of DRE and prostate biopsy it is more difficult to find a cancer. Remzi et al[22] shown that prostate volume was the greatest contributor to missing cancers in obese patients. Moreover, the reduced detectability of PCa among obese men is only relevant for asymptomatic clinically localized disease.

For these reasons, this study suggests a positive correlation between BMI and PCa detection, particularly high grade of PCa detection, at surgery. Lower PSA serum levels and large prostate size associated with high BMI, indicated a potential risk for delayed diagnosis and poor pathological outcomes in obese men[20].

Several limitations need to be acknowledged. A first limitation, we had no data available regarding the ethnic background of the patients. These details could be of special interest, because in multi-ethnic populations, some subgroups might have more unfavourable PCa characteristics than others[23,24]. However, although we did not expressly documented race, the majority of the patients of our study cohort were white and Italian population. Thus, the number of Asian and black patients was very small and surely did not exceed 1% of the entire cohort. Second, this is a single centre study with a limited number of patients and small number of obese subjects. Third, this retrospective study concerned also patients with PCa eligible only for RP; as a consequence older patients (≥ 74 years old) who are not candidates for surgery, were excluded. This may have influenced the results generalizability and preclude comparative investigation of a potentially risky PCa in obese *vs.* normal men.

Moreover, the weight and height data used were reported by the patients at the time of surgery or were documented from the anesthesia records, this has represented another limitation of our study. Theories relating potential risk of PCa and BMI are founded on the endocrine and biochemical properties of adipose tissue, which affect circulating androgen levels[25]. We classified obesity as a BMI (≥30 kg/m^2), as determine by the WHO. However, an individual with a high muscle mass would have a greater BMI than a less-muscular person of equal height but could also have a comparable or even lower body fat percentage. Future studies should be directed at using other clinically relevant end points including metastasis, PCa-specific mortality, and overall mortality.

CONCLUSIONS

According to our monocentric experience, obese patients were older at the time of the RP, had worse clinical and pathologic outcomes, and had a greater predicted risk of recurrence after RP compared with normal weight patients. Certainly randomised clinical trials and additional studies will be essential to establish the effects of obesity on tumor behavior and overall PCa outcome.

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Conflict of Interest
The Author declare that there are no conflicts of interest.

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