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Obesity is Associated with Upgrading in Prostate Cancers

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Background: Prostate cancer (PCa) is the second most common cancer and sixth most common cause of cancer associated death among men in the world. Multiple studies demonstrated the relationship between obesity and PCa in the recent years.

Aim: The present study aimed to investigate the impact of obesity on postoperative oncological results after radical prostatectomy.

Materials and methods: A total of 110 patients who were treated radical prostatectomy between January 2011 and April 2016 were analyzed retrospectively. The patients who had information about age, height, weight, biopsy results, PSA level and pathological results were recorded. The patients were classified to three groups according to the BMI; normal ($BMI < 25 \text{ kg/m}^2$), overweight ($BMI \geq 25$ and $< 30 \text{ kg/m}^2$) and obese ($BMI \geq 30 \text{ kg/m}^2$).

Results: The present study included 101 patients. Of these patients; 26, 57 and 18 patients were in groups respectively. The age at the presentation and PSA level was lower and higher than the other patients. The proportion of locally advanced disease and high grade PCa were the highest in obese patients at prostatectomy specimen examination. The upgrading is significantly associated with obesity.

Conclusion: This study demonstrated that obese men are younger and had higher PSA concentration at the diagnosis of PCa. High grade PCa, locally advanced disease and upgrading was seen much more in patients with $BMI \geq 30 \text{ kg/m}^2$ at final pathology. The difference reached significance for upgrading between groups.

BACKGROUND

Prostate cancer (PCa) is one of the most common cancer among men in world.¹ Multiple epidemiological studies showed that obesity is associated with increased risk and death of some cancer types including PCa. Obesity and overweight affect more than 30% of the population in United States according to the World Health Organization criteria.² Two-thirds of them are overweight (body mass index, $BMI \geq 25 \text{ kg/m}^2$) and one-third are obese ($BMI \geq 30 \text{ kg/m}^2$).¹ The relationship between obesity and prostate cancer is unclear.³ Some studies have demonstrated that obesity is an independent risk factor for biochemical recurrence, positive surgical margin and worse functional outcomes after radical retropubic prostatectomy.⁴⁻⁷ Furthermore, the authors reported that obesity was significantly correlated with aggressive PCa and cancer-associated mortality in analysis of 17 cohort studies.⁸ In addition, the authors found that, increasing BMI was associated with higher prostate weight, and high Gleason score

(GS) and pT stage.³ The association between BMI and worse outcomes was demonstrated in patients with prostate cancer eligible for active surveillance.⁹ On the contrary, the authors reported that there was no association between obesity and PCa.¹⁰

AIM

We evaluated the pathological results of the patients and compared the preoperative and postoperative data according to the BMI categories.

MATERIALS AND METHODS

We reviewed the patients who received radical prostatectomy between January 2011 and April 2016 retrospectively. There were 110 patients in our database. The patients who had information about age, height, weight, biopsy results, PSA concentration, PSA density and surgical specimen data including T stage, GS, surgical margin status and prostate weight were recorded. PSA density was calculated by dividing the PSA level to the prostate weight

after the pathological examination. Upgrading was defined as any increase in GS between biopsy and radical prostatectomy specimens. The patients who were treated by laparoscopic and perineal surgery was excluded because of homogeneity. Perineal and laparoscopic surgery was performed in 6 patients. The remaining three patients were excluded because of missing data. The patients were divided into three groups according to their BMI. The body mass index was calculated by dividing the weight (kg) by the square of the height (m²) using the World Health Organization definitions. Patients were divided as: normal (BMI<25 kg/m²), overweight (BMI≥25 and <30 kg/m²) and obese (BMI≥30 kg/m²).

The prostate biopsy was performed with the patient in lateral decubitus position under local anesthesia. The number of biopsy cores were between 8 and 12. All preoperative biopsies and the radical prostatectomy specimens were evaluated by experienced urogenital pathologist in our hospital. In pathological examination: the prostate tissue was

weighted after the removal of the seminal vesicles, base and apex were amputated and sectioned at 3 mm increments in the vertical parasagittal plane. Surgical margin was reported as positive if any cancer cells were in contact. The tumors were graded for Gleason system according to the 2005 Consensus Conference of the International Society of Urological Pathology. All cases were staged according to the TNM system. High grade prostate cancer (HGPCa) was defined as presence of GS 7 or bigger at biopsy and prostatectomy.

The data were verified for normal distribution using Kolmogorov-Smirnov test. Analysis of variance (ANOVA) test (Kruskal-Wallis) was used for the comparison of the groups using median values. Chi-square test was used for percentages variables. The data were expressed as median and percentages in tables. The value of p<0.05 was considered statistically significant (MedCalc Statistical Software demo version 16.2.0, Ostend, Belgium; <https://www.medcalc.org>; 2016).

Table 1. Preoperative parameters of the patients

	Group 1	Group 2	Group 3	p
No of patients (n)	26	57	18	
Age (median) yrs	66	67	62	0.159
PSA (median) ng/ml	6.3	7.8	8.7	0.433
PSA density (median)	0.14	0.12	0.19	0.371
Prostate weight (median)	50	50	45	0.543
Gleason score (median)	6	6	6	0.997
HGPCa n (%)	7 (26.9)	15 (26.3)	5 (27.8)	0.992
Biopsy core (median)	8	10	9	0.584
Positive biopsy core (median)	2	2	4	0.195

HGPCa: high grade prostate cancer

Table 2. Pathological results of the patients

	Group 1	Group 2	Group 3	p
Gleason score (median)	6	6	7	0.296
HGPCa n (%)	4 (15.38)	15 (26.31)	7 (38.89)	0.212
Localized PCa n (%)	21 (80.77)	47 (82.45)	12 (66.67)	0.346
Locally advanced PCa n (%)	5 (19.23)	10 (17.55)	6 (33.33)	0.346
Upgrading n (%)	2 (7.70)	12 (21.05)	7 (38.89)	0.043*
Positive surgical margin n (%)	2 (7.70)	6 (10.52)	1 (5.55)	0.786

HGPCa: high grade prostate cancer

*statistically significant

RESULTS

There were 101 patients (mean age, 64.60 ± 5.51 yrs) in the present study. The BMI of the patients was less than 25 kg/m^2 in group 1, equal to $25\text{-}30 \text{ kg/m}^2$ in group 2, and more or equal to 30 kg/m^2 in group 3. **Table 1** shows the preoperative data of the patients. The median age and PSA level of the patients in the groups was 66, 67, 62 years and 6.3, 7.8, 8.7 ng/ml, respectively. The obese patients were younger and had higher PSA concentration than the other patients without significant difference.

The pathological results of prostatectomy specimens are shown in **Table 2**. Locally advanced disease was reported in 21 patients. Of these patients 5 (19.23%) were in group 1, 10 (17.54%) were in group 2, and 6 (33.33%) were in group 3 ($p=0.346$). High grade prostate cancer was detected in 26 patients. Of these 26 patients 4, 15, and 7 were in groups 1, 2 and 3, respectively ($p=0.212$). There was a statistically significant difference for upgrading in obese patients than in the others ($p=0.04$). The positive surgical margin incidence was 8.91% ($n=9$). The proportion of the positive surgical margin was 7.7, 10.5 and 5.5% in groups.

DISCUSSION

Obesity is associated with increased risk of cancer-related death and biochemical recurrence after radical prostatectomy.¹¹ Non-biological explanations are poor surgical technique in surgery and less aggressive treatment in obese men. There are three mechanisms to explain the correlation between obesity and aggressive PCa: the insulin/insulin-like growth factor (IGF)-1 axis, sex hormones and adipokine signalling.¹ Diet-induced hyperinsulinemia has shown that the tumor growth in different PCa xenograft models and primary human PCa expresses the insulin receptor, suggesting insulin may be important stimulator of the PCa growth. Hyperinsulinemia and obesity cause the increase of IGF-1 level that promote the cancer growth. The low testosterone and increased estradiol levels in obese men may explain the link between obesity and aggressive PCa. Although adiponectin has antitumor activity, serum level of the adiponectin in obese men was low. Leptin has a protumor effect in PCa pathogenesis and the leptin concentration increases in obesity.

Another important cytokine is interleukin-6 (IL-6) that is elevated in obesity. The PCa cells produce IL-6 and express IL-6 receptor that allow them to respond to this pleiotropic and proinflammatory adipokine via autocrine way.

The authors reported that there was an association between BMI and upgraded, upstaged disease, seminal vesicle invasion.⁹ In another study, the investigators found that BMI was positively correlated with pT stage and pathologic GS.³ Freedland et al.¹¹ found that higher BMI was associated with larger tumor volume, higher rates of positive surgical margin with statistically significant difference and higher rates of extracapsular extension without significant difference. Amling et al.¹² found that obese patients with PCa were younger, had high grade and advanced disease at terminal pathology. Authors from Turkey reported that obesity did not correlate with worse oncological and functional outcomes in patients who underwent radical perineal prostatectomy.² The present study has shown that obesity is associated with upgrading ($p=0.043$) and the rate of locally advanced disease HGPCA was higher in obese patients than in the others.

The age and PSA level of the patients with high BMI are different in the studies. While Altay et al.² and Amling et al.¹² reported that increased BMI was positively correlated with PSA levels, Freedland et al.¹¹ found that BMI was associated lower PSA levels. The studies of Freedland et al.¹¹ and Amling et al.¹² showed that patients with high BMI were younger, Altay et al.² reported that the age at presentation of the obese patients was higher than that of the others. In the present study, the patients with high BMI were younger with high PSA levels than the other patients.

Positive surgical margin after radical prostatectomy is one of the prognostic factor to achieve cure of the PCa.¹³ There are some factors that make surgery rather difficult such as higher BMI, and large prostate; previous abdominal and prostate surgery have negligible impact for positive surgical margin. The positive surgical margin rate was reported between 6.1 and 53% in the studies.^{2,11} There was significant difference for positive surgical margin between BMI categories¹¹, the other study revealed that the rate of positive surgical margin is lower (6.1%) in patients with BMI $>30 \text{ kg/m}^2$ than BMI $<25 \text{ kg/m}^2$ (6.9%) with no significant difference. The present study revealed that the positive surgical margin is lower in obese men than in the others with an incidence of 5.55%. This study includes small number of patients and this is one of the reason of low incidence.

The present study has certain limitations. First, the study is retrospective in design including small number of patients. Postoperative follow-up data for

biochemical recurrence, cancer specific survival and death are missing which might be more important than pathological results. The patients who were treated with nonsurgical techniques were not evaluated. The proportion of the patients with BMI $\geq$ 30 is 16.83%, which is relatively low.

The study suggested that obese patients had smaller prostate weight and higher level of PSA than the other patients. High grade and locally advanced PCa was seen much more in patients with BMI $\geq$ 30. Obese men are at high risk for upgrading at final pathology. Further studies are needed to define the association between obesity and adverse oncological outcomes.

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Ожирения связано с риском прогрессии рака предстательной железы

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Введение: Рак предстательной железы (РПЖ) является вторым наиболее распространённым видом рака и шестой по распространённости причиной смерти от рака среди мужчин в мире. Многочисленные исследования продемонстрировали взаимосвязь между ожирением и РПЖ в последние годы.

Цель: Настоящая работа была направлена на исследование влияния ожирения на послеоперационные онкологические результаты после радикальной простатэктомии.

Материалы и методы: В общей сложности 110 пациентов, которым проводилась радикальная простатэктомия в период с января 2011 года по апрель 2016 года, были проанализированы ретроспективно. Были зарегистрированы пациенты с наличной информацией о возрасте, высоте, весе, результатах биопсии, уровне ПСА (простат-специфического антигена) и патологических результатах. Пациенты были классифицированы по трём группам в соответствии с ИМТ; нормальный (ИМТ <25 кг / м²), избыточный вес (ИМТ > 25 и <30 кг / м²) и ожирение (ИМТ > 30 кг / м²).

Результаты: В настоящее исследование включён 101 пациент. Из них 26, 57 и 18 пациентов составили отдельные группы. Возраст при представлении и уровни простат-специфического антигена (ПСА) были ниже и выше, чем у других пациентов. Пропорция местно-распространённого заболевания и высокопатогенного РПЖ была самой высокой у пациентов с ожирением при обследовании образцов простатэктомии. Риск развития РПЖ в значительной степени связан с ожирением.

Заключение: Это исследование установило, что мужчины с ожирением были более молодого возраста и имели более высокую концентрацию ПСА при диагностике РПЖ. Высокопатогенный РПЖ, местно-распространённое заболевание и риск прогрессии РПЖ были установлены в большей степени у пациентов с ИМТ > 30 кг / м² при конечной патологии. Разница достигла значимости для установления риска прогрессии РПЖ между группами.