Impact of Obesity on Adverse Pathological Characteristics After Radical Prostatectomy

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Research Article

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Abstract

Background: The effect of obesity on pathological features was different from country to country in other studies. To investigate whether obesity affected pathological characteristics of PCa after laparoscopic radical prostatectmy (LRP) in Chinese man.

Methods: Medical record of 670 Chinese patients who underwent LRP between 2018 and 2020 were retrospectively reviewed. Patient height and weight were meaured before surgery to calculate the body mass index (BMI). They were categorized into three groups according to Chinese classification of obesity: normol weight (BMI<24.0kg/m^2),overweight (24.0 ≤ BMI <28.0kg/m^2) and obese(BMI≥28.0kg/m^2). The associations between BMI and operating age, preoperative prostate-specific antigen (PSA) level, were assessed with the Kruskal-Wallis test. The associations between BMI and pathological features were assessed with chi −square test.

Results: Of the 670 patients, 31.5% patients were normal weight, 51.3% were overweight, 17.2% were obese. Operating age (P=0.029) tend to decrease as BMI increased. Seminal vesicle invasion differ significantly among BMI categoties (P=0.003), and other adverse pathologic characteristics , such as positive surgical margin (PSM) (P=0.851), International Society of Urological Pathology (ISUP) grade(P=0.194), extracapsular extension(P=0.460) were not associated with BMI categoties. In the Logistic regression model, higher BMI was an independent risk factors for seminal vesicle invasion after adjusting for multiple clinical preoperative characteristics.

Conclusions: Overweight and obese Chinese PCa patients treated by LRP had lower operating age compared to normal weight patients. Seminal vesicle invasion was associated with higher BMI and other adverse pathologic characteristics are not significantly affected by BMI.

Background

PCa is estimated that there will be almost 1.3 million new cases and 359000 associated deaths worldwide in 2018, ranking as the second most frequent cancer and the fifth leading cause of cancer death in men.It is the most frequently diagnosed cancer among men in over one-half of the countries of the world,espically in developed countries[1]. Attributed to the westerniaztion of lifestyle and daily diet, the prevalence of PCa was increasing rapidly in China[2].

At present, RP is the most common treatment for clinical localized PCa[3]. The object of RP is complete removal of the cancer, while whenever possible, preserving pelvic organ function[4]. As such, a PSM is often regarded as resulting from a less than ideal operation. Morever, mang studies showed that a PSM after RP is associated with an increased risk of PCa recurrence[5–7].

PSMs might from extension of tumor and/or poor technique. Tumor progression is often associated with delayed diagnosis and treatment. It has been suggested that obesity makes the early detection of PCa more diffcult due to less PSA screening, lower accuracy of digital rectal examination in obese men.

Moreover, obese men have lower PSA values due to increased blood volume and PSA hemodilution. Among men with PCa, PSA value are 7% lower in overweight patients, 14% lower in obese patients and 18% lower in severely obese patients, compared to men with normal weight patients[8]. Thus, obese men have lower rates of prostate biopsy, which leads to missed diagnosis of some early tumors; Technical challenges can result from many causes, for examples, poor paient anatomy compounded by challenges of operating within the narrow restricting confines of the prostatic fossa, the presence of inflammaion resulting in diffcult dissection, the bleeding resulting in a limited surgical field of vision and patient body habitus[9]. One of the commonly used measures of habitus is the BMI. Some studies have attempted to establish association between obesity and pathology after RP. The results of these studies have also varied from country to country, and the link between obesity and aggressive PCa is still under discussion[10–13]. The aim of our study is to determine whether adverse pathological features after RP are associated with obesity in China.

Methods

Patients

We rerospectively reviewed the records from 2018 to 2020 of 670 patients with PCa who underwent LRP at the Second Hospital of Tian Jin Medical University. Exclusion criteria were a history of prostate surgery, neoadjuvant hormonal therapy or chemotherapy and radiation therapy. The effect of BMI on the pathology result was analyzed. BMI□kg/m^2□was calculated by dividing weight of the patient in kilograms by the squared height in meters. Patients were stratified into 3 groups according to their BMI, which was difined according to the “Chinese Adult Overweight and Obesity”: normal weight as BMI□24 kg/m^2, overweight as BMI≥24 kg/m^2 and□28 kg/m^2, and obese as BMI≥28 kg/m^2. Other collected clinical and pathological information includes operating age, preoperative PSA level, tumor grade (Gleason score), margin status, extracapsular extension, seminal vesicle invasion. Pathological evaluation of surgical specimens was performed according to the Gleason grading system , the ISUP 2014 grade and 2002 TNM classification. RP was achieved using laparoscopic approach.

Statistical analyses

The associations among the BMI and clinicopathologic characteristics were analyzed using the Kruskal-Wallis test for continuous variables and the chi- square test for categorical variables. The odds ratio (OR) for pathological outcomes were also estimated for each BMI category using muitiple logistic regression analysis after adjusting for patient age, biopsy ISUP grade, preoperative PSA level . All statistical analyses were performed using the SPSS 26.0 software (IBM, Armonk, NY, USA). All reported P-values were two-sided with statistical significance considered at P□0.05.

Results

Baseline patient characteristics

Patient characteristics by BMI subgroups are summarized in Table 1. In total, 670 PCa patients were entered in this study. As shown in Table.1, the mean BMI was 25.4kg/m^2(range, 17.4-36.3 kg/m^2) and 31.5%(211/670) patients were of normal weight, 51.3%(344/670) were overweight, 17.2%（115/670）were obese. The mean of age at surgery was 67 years old (range, 42-82) and median PSA level at surgery was 16.6ng/ml (range, 2.81-98.9 ng/ml). The mean age was significantly higher in the normal group than in the obese group(P=0.029). No significant association was found between the BMI and preoperative PSA level (P=0.49).

BMI and clinicopathological characteristics

As shown in Table.1, various pathological outcomes include pathological Gleason score, surgical margin, extracapsular extension , seminal vesicle invasion, TNM stage and biopsy Gleason score, which were assessed across BMI categories. There was no significant increased risk of PSMs in the higher BMI groups compared with the normal group(P=0.851). The pTNM stage tended to increase as BMI increased(P=0.019). BMI was related significantly to seminal vesicle invasion(P=0.003), but it had nothing to do with extracapsular extension(P=0.460). As shown in Table.2, in the Logistic regression model, higher BMI was an independent risk factors for seminal vesicle invasion after adjusting for age, preoperative PSA level and biopay ISUP（P＜0.001）.

Discussion

At present, RP is the treatment of chioce for most clinical localized PCa patients[3]. The prognosis of patients is affected by pathological conditions such as postoperative ISUP, surgical margin, extracapsular extension and Seminal vesicle invasion. So far, the exact mechanism between obesity and PCa aggressiveness is unclear. Previous studies have reported different associations between obesity and PCa, with the Amercian study sugessting that postoperative pathology in obese PCa patients was more aggressive than that of normal weight patients[12]. The studies in European countries have also reported obesity and adverse pathology characteristics after RP, such as higher Gleason score, positive surgical margins[14, 15]. However, most of these figures come from western rather than Asian countries, especially China. Asians are thinner and have a lower BMI than Westerners, suggesting that the effects of BMI may differ between Asian and Western race. Obesity rate is rising in China as lifestyles become more westernized, and may have a secondary impact on PCa. In order to minimize the differences with Western race, the BMI grouping of this study is based on the “Chinese Adult Overweight and Obesity”.

The effect of BMI on pathological features in our study was different from that reported in other studies. Our results showed among Chinese PCa patients undergoing LRP, higher BMI was statistically significant with seminal vesicle invasion, but other adverse pathological features such as PSMs, higher ISUP group, and extracapsular extension were not statiscally significant in different BMI subgroups. Similarly, Vidal et al[12].analyzed data of 5929 American men treated by RP, and found that both white and black men with higher BMI were more likely to have PSMs and seminal vesicle invasion in PCa patients. Multivariate analysis found that obesity was associated with increased risk of PSMs. In contrast, Isbarn et

al[11].analyzed 1538 European PCa and Narita et al[10].analyzed 1257 Japanese PCa who received RP and demonstrated multivariate analysis that BMI was not associated with adverse pathological outcomes. A study of 880 PCa patients in south Korea, also from East Asia, reached the opposite conclusion. The result showed that normal weight Korean PCa patients have a higher Gleason score compared to overweight and obese patients[13]. Differences of pathological characteristics in the above studies ,on the one hand may be due to the fact that some studies relied on historical data and used various main treatment methods, cases mixes and environmental risk factors, on the other hand may be caused by differences in ethic background. After all, the average BMI of Asians is much lower than that of Westerners. Even with the same BMI, Asian men have a higher body fat rate than Western men[16]. However, the reason for the difference in results between the studied Chinese patients and the Japanese and South Korean patients may be due to the biopsy driven by PSA screening. Compared with Japan and South Korea, China currently has a lower PSA screening rate[17].

The serum PSA level of obese men is lower than that of normal weight men of the same age[18]. The relationship between the two has been emphasized, but the underlying mechanism is still unclear. The most commonly accepted explanations are the effect of blood dilution and low serum testosterone[19, 20]. On the one hand, obese men have greater blood volume, which dilutes the tumor markers in the serum, such as PSA. On the other hand, the prostate is an androgen-dependent organ. Patients with higher BMI produce less testosterone[20], and the Chinese diet contains higher levels of estrogen. Elevated levels of estrogen cause PCa to be more dependent on androgens and more aggressive, simultaneously, lower testosterone levels may cause decreased prostate PSA secretion[21]. A recent study showed that the two effects may lead to a 81% and 19% reduction in serum PSA concentration in obese men[19]. At present, serum PSA testing is still the most important way to screen for PCa. As the PSA screening test is not popular in China, obese men have a reduced chance on undergoing biopsy compared to normal weight men. Therefore, PCa in Chinese patients usually has a higher pathological stage at the time of diagnosis[22]. This is also consistent with our study. In the higher BMI subgroup, the median PSA level decreased, while the final pathological stage increased. This may also indicate that the increased risk of postoperative seminal vesicle invasion in PCa patients with higher BMI is due to the disease itself rather than surgical skills, because the difference in positive margins in all BMI subgroups is not statistically significant.

It is worth noting that some studies have found that the fat around the prostate is biologically active, and can secrete factors that promote the growth of PCa, and may be related to more aggressive diseases[23, 24]. However, in this study, we did not find a link between obesity and extracapsular extension, which is inconsistent with the paracrine fat around the prostate that promotes the growth of PCa, and further research may be needed.

If the prognosis of obese PCa patients is poor, this indicates that weight control may be able to effectively reduce morbidity and mortality. However, several large cohort studies did not find the association between physical activity and locally advanced, high-risk PCa or treatment failure[25, 26]. Overweight or obesity is associated with an increased risk of some chronic diseases, such as diabetes and cardiovascular

disease. In this regard, physical activity may improve the prognosis of PCa patients. After all, the ultimate cause of death in some PCa patients is not the tumor itself[27].

The current research has several limitations. First, retrospective analysis of RP patients may have led to selection bias. Only those patients who are suitable for surgical treatment were included in the study cohort, so these results may not be applicable to patients undergoing other treatments. In addition, these patients are from the same hospital and may not be representative of the entire Chinese population. We did not investigate tumor volume, lymph node metastasis, or preoperative hormone levels. These results, especially changes in multiple hormones, may also affect the aggressiveness of the disease. Since the patient has not been followed up for a long time, the impact of BMI on the long-term prognosis cannot be clarified. In the future, multi-center, prospective, and well-controlled studies may be needed to further illustrate the relationship between obesity and PCa.

Conclusions

In this retrospective single-center study, including 670 Chinese PCa patients who underwent RP, operating age decreased with the increase of BMI. Patients with high BMI are at increased risk of seminal vesicle infiltration, while other adverse pathological results are not related to BMI.

Abbreviations

PCa: prostate cancer

RP: radical prostatectomy

BMI: body mass index

PSM: positive surgical margin

ISUP: International Society of Urological Pathology

PSA: prostate-specific antigen;

CI: Confidence interval

OR: odd ratio

SD: Standard deviations

Declarations

Ethics approval and consent to participate

The study involving human participants were approved by Ethics Committee of the Second Hospital of Tianjin Medical University. The data recording is part of the daily work of medical workers, thus , the informed consent was waived by an Institutional Review Board of Ethics Committee of the Second Hospital of Tianjin Medical University. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflict of interest associated with this manuscript.

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Author Contributions

SX, RL L carried out the studies, participated in collecting data, and drafted the manuscript. JT Z and TL performed the statistical analysis. JT Z and RL L participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Characteristics according to the level of BMI in Chinese PCa patients treated with LRP.

Variables	Samples	BMI subgroups			P-value
		Normal weight	Overweight	obese	
Patients, n (%)	670	211 (31.5)	344 (51.3)	115 (17.2)	
BMI, mean ± SD	25.2 ± 29.3	22.1 ± 1.62	25.7 ± 1.14	29.6 ± 1.42	
Age (years), mean ± SD	67.9 ± 6.71	68.8 ± 6.75	67.9 ± 6.03	66.3 ± 8.13	0.029*
Preoperative PSA Level (ng/ml), median	16.95	23.3	16.26	17.05	0.49*
Biobsy ISUP					
Grade n (%)					0.838
1	211 (31.5)	7 (34.5)	108 (31.3)	30 (26.1)	
2	127 (19.0)	40 (19.0)	66 (19.2)	21 (18.2)	
3	152 (22.7)	45 (21.3)	80 (23.3)	27 (23.5)	
4	125 (18.7)	38 (18.1)	60 (17.5)	27 (23.5)	
5	55 (8.2)	15 (7.1)	30 (8.7)	10 (8.7)	
Pathologic ISUP					
Grade n (%)					0.194
1	68 (10)	28 (13.3)	31 (9.0)	9 (7.8)	
2	165 (24.6)	50 (23.7)	91 (26.5)	24 (20.9)	
3	143 (21.4)	51 (24.2)	71 (20.6)	21 (18.3)	
4	189 (28.3)	56 (26.5)	98 (28.5)	35 (30.4)	
5	105 (15.7)	26 (12.3)	53 (15.4)	26 (22.6)	
Ptstage, n (%)					0.019
≤pT2	352 (52.5)	113 (53.6)	191 (55.5)	48 (41.7)	
pT3a	199 (29.7)	61 (28.9)	103 (30.0)	35 (30.5)	
pT3b	119 (17.8)	37 (17.5)	50 (14.5)	32 (27.8)	
Extracapsular, n (%)					0.460
Extension	199 (29.7)	61 (28.9)	103 (30.0)	35 (30.5)	
Seminal vesicle,n (%)					0.003
Invasion	119 (17.8)	37 (17.5)	50 (14.5)	32 (27.8)	
Surgical margin, n(%)					0.851
Positive	322 (48.1)	98 (46.4)	168 (48.8)	56 (48.7)	
Negitive	348 (51.9)	113 (53.6)	176 (51.2)	59 (51.3)	

*P values were calculated using Kruskal-Wallis test and others were determined using chi-square test

Table 2. Odds ratios and 95% confidence intervals of adverse pathologic features at the time of RP by BMI related to normal weight

Variable	OR	95%CI	P-value
ISUP grade≥3			
Overweight	1.019	0.602-1.725	0.943
Obese	1.378	0.675-2.815	0.379
BMI as continuous variable	1.038	0.957-1.126	0.372
Positive surgical margins			
Overweight	1.065	0.740-1.533	0.734
Obese	0.958	0.589-1.558	0.863
BMI as continuous variable	1.023	0.968-1.081	0.419
Extracapsular extension			
Overweight	0.973	0.652-1.451	0.892
Obese	1.240	0.717-2.146	0.442
BMI as continuous variable	1.038	0.975-1.105	0.244
Seminal vesicle invasion			
Overweight	1.371	0.734-2.560	0.322
Obese	3.733	1.830-7.614	<0.001
BMI as continuous variable	1.179	1.081-1.285	<0.001