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Preoperative erectile function and the pathologic features of prostate cancer

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ABSTRACT

Purpose: We evaluated whether preoperative erectile function is associated with pathologic features in the patients who underwent radical prostatectomy (RP).

Materials and Methods: We reviewed medical records of 1,743 men who underwent RP from November 2003 through May 2012. Of these, 50 patients who had prior hormone therapy and 272 patients who had lacking data of International Index of Erectile Function-5 (IIEF-5) were excluded. Men whose IIEF-5 was in the lower 25 percentile were assigned as Low Erectile Function group and the others were assigned as Control group. We compared pathologic features using univariable and multivariable logistic regression analysis between two groups.

Results: A total of 1,421 patients were included in the analysis. Patients' age was 65.8 ± 6.7 years and prostate-specific antigen (PSA) was 12.8±16.1 ng/mL. Median and low 25 percentile of IIEF-5 were 14 and 8, respectively. Low Erectile Function group (IIEF-5<8) had higher risk to have high Gleason score (≥7(4+3), odds ratio (OR) 1.642, p<0.001) and large tumor volume (≥5 mL, OR 1.292, p=0.042). Even after adjusting age, year of surgery, body mass index, Charlson comorbidity index, PSA, clinical stage and biopsy Gleason score, Low Erectile Function group still had higher risk of high Gleason score (OR 1.910, p<0.001) and large tumor volume (OR 1.390, p=0.04) by multivariable logistic regressions.

Conclusions: Lower erectile function before RP was associated with higher Gleason's score and larger tumor volume in final pathology. Thus, erectile function could be a surrogate barometer for prostate cancer aggressiveness.

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INTRODUCTION

Prostate cancer (PC) is the second common cancer diagnosed and represents the sixth leading cause of death in male cancer patients worldwide (1). PC incidence rates increase in nearly all countries except in a few high-income regions. At present, any kind of radical prostatectomy (RP) is the most commonly used treatment modality for localized PC. However, there is concern about adverse pathologic outcome after RP because of heterogeneous nature of PC. With proper estimation of final pathology, some patients can choose active surveillance or radiation therapy instead of RP (2). Some patients can expect adjuvant or salvage treatment after RP (3).

Erectile dysfunction (ED) is one of the most common side effects and major reason of decrea-

sed quality of life during and after various types of treatment for PC (4-6). Preoperative erectile function is a very important predictor after PC treatment (4). Preoperative ED is also associated with various medical conditions such as obesity, hyperlipidemia, diabetes mellitus (DM), and metabolic syndrome (7, 8). ED is a multifactorial phenomenon associated with these medical conditions. Thus degree of ED may correlate with affected number and degree of these medical conditions. Furthermore, there have been some reports that many of these medical conditions are related to adverse pathologic features of PC (9-11). Consequently, decreased erectile function before RP could serve as a barometer for adverse pathologic outcomes. However, this correlation is not fully understood. Thus, we evaluated whether preoperative erectile function is associated with pathologic features in patients who underwent RP.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (Seongnam, Republic of Korea). The IRB number is B-1301/186-105.

PATIENTS

We collected the data from a prospectively registered database of an RP cohort in our institution. A total of 1,743 consecutive patients who underwent RP from November 2003 through May 2012 were evaluated. Among them, 50 patients who had prior hormone therapy and 272 patients who lacked data for the International Index of Erectile Function-5 (IIEF-5) were excluded. Thus, a total of 1,421 cases were included in the analysis. Men whose IIEF-5 was in the lower 25th percentile were assigned to the Low Erectile Function (LEF) group, and the others were assigned to the Control group. The 25th percentile was the predetermined discrimination point before analysis to evade bias.

PATHOLOGIC EXAMINATION

One experienced genitourinary pathologist (G. C) processed and examined all surgical specimens. Specimen handling and reporting followed the internationally standardized protocols (12, 13). The pathologic stage was evaluated based on the sixth edition of the American Joint Cancer Committee Cancer staging criteria. The prostate was sectioned into 4-mm slices as the protocol. The positive surgical margin was recorded if cancer was involved at the inked surface. Tumor volume was routinely measured using the grid method.

Statistical analysis

Clinicopathologic variables, including pathologic stage, Gleason's score and tumor volume, were compared between LEF and Control group using either Student t-test or chi-square test. Clinical factors including erectile function group were evaluated to associate with adverse pathologic features by means of univariate and multivariate logistic regression analyses. Tested adverse pathologic outcomes were high Gleason's score (≥7 (4+3) and tumor volume (>5 mL). Evaluated clinical factors were age, body mass index (BMI), year of surgery, Charlson comorbidity index (CCI; 0 vs. 1 vs. ≥2), pre-biopsy prostate-specific antigen (PSA), clinical stage (T1 vs. T2 vs. T3), biopsy Gleason' score (≤ 6 vs. 7 vs. ≥8), as well as erectile function group (Control vs. LEF group). All statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY). For all statistical comparisons, a p value <0.05 (2-sided) was considered significant.

RESULTS

The basic characteristics of the 1,421 patients stratified by erectile function are presented in Table-1. The patients' age was 65.8±6.7 years, and the PSA was 12.8±16.1 ng/mL. The median and lower 25th percentile of the IIEF-5 were 14 and 8, respectively. A total of 346 (24.3%) patients were assigned to the LEF group (IIEF-5<8), and the remaining 1075 (75.5%) were assigned to the Control group (IIEF-5≥8). As expected, the LEF group showed an older age (p<0.001), higher prevalence of DM (p<0.001), and higher CCI (p<0.001) (Table-1). The clinicopathologic features of the LEF group more often included poorly differentiated pathology in both the pre-surgical (p<0.001) and

Table-1 - Patient demographics and clinical characteristics stratified by erectile function (<25 percentile, IIEF-5<8 vs. ≥25 percentile, IIEF-5≥8).

Variables	Low Erectile Function group (n=346)	Control group (n=1075)	p value
Age (years)	69.16±5.18	64.69±6.80	<0.001
Body mass index (kg/m^2)	24.09±2.74	24.42±2.57	0.820
Diabetes mellitus (%)	74 (21.4)	138 (12.8)	<0.001
Charson comorbidity index (%)			<0.001
0	240 (69.4)	893 (83.1)	
1	96 (27.7)	172 (16.0)	
≥2	10 (2.9)	10 (0.9)	
PSA (ng/mL)	12.31±12.65	12.94±17.07	0.780
Clinical stage (%)			0.703
≤T1c	227 (65.6)	688 (64.0)	
≥T2a	119 (34.6)	387 (36.0)	
Gleason's score, biopsy (%)			<0.001
≤6	166 (48.1)	535 (50.4)	
7	126 (36.5)	381 (35.9)	
≥8	53 (15.4)	146 (13.7)	
Prostate volume (mL)	38.07±16.66	38.02±15.79	0.900
Operation time (min)	151.88±43.05	157.59±45.95	0.550
EBL (mL)	331.72±356.19	362.25±417.59	0.223
Pathologic stage (%)			0.277
≤T2c	225 (65.1)	740 (68.9)	
≥T3a	121 (34.9)	335 (31.1)	
Gleason's score, pathologic (%)			0.007
≤6	42 (12.1)	199 (18.5)	
7	256 (74.0)	768 (71.4)	
≥8	48 (13.9)	108 (10.0)	
Tumor volume (mL)	12.52±112.85	6.57±17.94	0.048

final pathologies (p=0.007) compared to the Control group. Furthermore, the LEF group had a larger tumor volume than the Control group (p=0.048).

The LEF group had a higher risk of a high Gleason score (≥7 (4+3), odds ratio (OR) 1.642, 95% confidence interval (CI) 1.281-2.106, p<0.001) and large tumor volume (≥5 mL, OR 1.292, 95% CI 1.010–1.654, p=0.042). Even after adjusting for age, year of surgery, BMI, CCI, PSA, clinical stage, and biopsy Gleason score, the LEF group still had

a higher risk of a high Gleason score (OR 1.910, 95% CI 1.348–2.705, p<0.001) and large tumor volume (OR 1.390,95% CI 1.015 – 1.900, p=0.04) by multivariate logistic regression (Tables 2 and 3).

DISCUSSION

ED is a common disorder that affects men older than 40 years of age (8). Like a PC statistics, prevalence of ED increases exponentially by age after 50 years of age, even though worldwide basis shows a wide variation. ED increases to 20-40% in men aged between 60 to 69 years, 50-100% in men in their 70s and 80s (14). In case of the United States white men, the latent PC was found in 37%, 44%, 65% and 83% of the autopsy cases in the fifth, sixth, seventh, and eighth decades of age, respectively (15). Furthermore, the proportion of significant PC also exponentially increased with age after 60s and thereafter (16).

The etiology of ED could be classified as psychogenic, organic, or their combination. The organic causes are neurogenic, hormonal, arterial, cavernosal, and etc. ED is also associated with various medical conditions such as diabetes mellitus, hyperlipidemia, higher BMI or obesity, and consequently metabolic syndrome (8). Cardiovascular disease, in particular coronary artery disease is a strong risk factor for ED, too. ED was confirmed to be associated with significant increase in future cardiac events (17, 18). The evidence indicates that the etiology of ED is multifactorial, and ED is also associated with many systemic diseases.

However, some systemic conditions associated with ED have been revealed having correlation with negative oncologic outcome in PC. Higher BMI was associated with an increased tumor volume (9), higher Gleason grade, positive surgical margins, and early biochemical progression after RP (19). Our group also studied the association between obesity and pathological outcomes after RP in Korean men (11). We found that higher BMI was significantly associated with extraprostatic extension (p=0.014) and positive surgical margin

Table-2 - Univariate and multivariate logistic regression analysis to predict high Gleason's score (≥7 [4+3]).

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
IIEF-5<8	1.642 (1.281–2.106)	<0.001	1.910 (1.348–2.705)	<0.001
Age (years)	1.046 (1.028–1.064)	<0.001	1.016 (0.992-1.040)	0.195
Body mass index (kg/m^2)	1.026 (0.984– .070)	0.226	1.055 (0.997–1.115)	0.064
Year of surgery	1.155 (1.098–1.215)	<0.001	1.156 (1.082–1.236)	<0.001
Charlson comorbidity index		0.652		0.932
1 vs. 0	1.124 (0.852–1.484)	0.407	1.057 (0.727-1.536)	0.771
≥2 vs. 0	0.836 (0.319–2.192)	0.716	1.184 (0.329–4.260)	0.796
LogPSA (ng/mL)	17.208 (11.469–25.820)	<0.001	6.212 (3.811–10.127)	<0.001
Clinical Stage		<0.001		0.065
T2 vs. T1	2.133 (1.699–2.678)	<0.001	1.444 (1.062–1.966)	0.019
T3 vs. T1	>100	-	>100	-
Biopsy Gleason's score		<0.001		<0.001
7 vs≤6	8.387 (6.156–11.426)	<0.001	6.768 (4.865–9.414)	<0.001
≥8 vs.≤6	98.390 (56.907–170.112)	<0.001	71.329 (40.049–127.039)	<0.001

Table-3 - Univariate and multivariate logistic regression analysis to larger tumor volume (>5 mL).

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
IIEF-5<8	1.292 (1.010–1.654)	0.042	1.390 (1.015–1.900)	0.040
Age (years)	1.029 (1.013–1.046)	0.001	1.015 (0.993–1.036)	0.177
Body mass index (kg/m^2)	1.038 (0.996–1.082)	0.073	1.066 (1.014–1.122)	0.012
Year of surgery	0.942 (0.898–0.988)	0.014	0.858 (0.809–0.910)	<0.001
Charlson comorbidity index		0.233		0.844
1 vs. 0	0.922 (0.699–1.214)	0.562	0.930 (0.664–1.301)	0.930
≥2 vs. 0	0.400 (0.133–1.203)	0.103	0.765 (0.222–2.630)	0.765
LogPSA (ng/mL)	47.590 (29.778–76.057)	<0.001	31.068 (18.842–51.228)	<0.001
Clinical Stage		<0.001		0.040
T2 vs. T1	2.156 (1.723–2.697)	<0.001	1.420 (1.081–1.865)	0.012
T3 vs. T1	8.797 (0.979–79.059)	0.052	1.838 (0.074–45.930)	0.711
Biopsy Gleason's score		<0.001		<0.001
7 vs. ≤6	3.197 (2.488–4.108)	<0.001	2.040 (1.534–2.711)	<0.001
≥8 vs. ≤6	8.855 (6.210–12.626)	<0.001	4.437 (2.945–6.685)	<0.001

(p=0.019) only after multivariate-adjusting not in univariate analysis. In the present study, BMI was shown to have positive trend in higher Gleason's score and larger tumor volume without significance. When adjusting other variable, BMI was significantly associated with larger tumor volume (OR 1.066, 95% CI 1.014-1.122, p=0.012). Compared with observations from a Western cohort, this association might not be prominent. We suggest that this disparity may be due to Korean men being generally leaner than their Western counterparts. Mean BMI of our cohort was 24.3 kg/m^2 and obese men (BMI≥30 kg/m^2) only accounted for 2.2% (31/1,421).

Interestingly, several pieces of evidence have indicated that patients with DM are at decreased risk for the development of PC, which is contrary to other malignancies (20). A meta-analysis of 19 cohort or case-control study showed protective effect of DM for developing PC (relative risk (RR) 0.84, 95% CI 0.76–0.93, p<0.01) (21). A recent nationwide Swedish study incorporating more than 0.2 million men confirmed this reverse association (OR 0.80, 95% CI 0.76–0.85) (22). Meanwhile, our group demonstrated that DM was associated with higher odds of detection of overall PC (OR 1.46, 95% CI 1.06–2.01) more specifically high grade PC (OR 1.54, 95% CI 1.03–2.29) via contemporary multi-core (≥12) biopsy (23). Furthermore, our group reported that diabetics classified hemoglobin A1c less than 6.5% had significantly higher rate of extraprostatic extension of tumor and high pathologic Gleason's score (10). Our recent study indicated that diabetics had short PSA doubling time after RP than non-diabetics during follow-up (24). A pooled analysis for long--term overall mortality showed DM is associated with higher risk (HR 1.57, 95% CI 1.12–2.20) (25). Thus, we can plausibly predict that DM may have a protective effect against the development of PC, whereas pre-existing DM may lead to poor pathologic and oncologic outcomes. (26).

Thus, DM could be one explanation for patients with low erectile function having adverse pathologic features in our study.

Metabolic syndrome, a cluster of risk factors of cardiovascular disease and DM, is a common medical condition in the United States and is present in one quarter of the population, with an incidence that increases with age (26). Although the definition may vary, metabolic syndrome typically consists of DM or impaired glucose tolerance, hypertension, dyslipidemia, and obesity, which generally overlap with the medical conditions discussed above. A population-based study in Finnish men demonstrated that metabolic syndrome was related to a higher risk of having PC (RR 1.9, 95% CI 1.1–3.5) (27). Furthermore, a large matched case-control study reported from Vattikuti Urology Institute showed that metabolic syndrome men had higher Gleason grade ($p<0.001$), higher pathologic stage ($p<0.001$), and greater upgrading of Gleason grade ($p<0.001$) (28).

As discussed earlier, many systemic conditions associated with ED also associateswith an aggressive PC biology. Thus, we hypothesize that these medical conditions have a common pathway of PC development or aggressive transformation. At the least, erectile function itself could be a surrogate barometer for PC aggressiveness. In the present study, we confirmed that patients who had severe ED (IIEF-5<8) had larger tumors and higher Gleason's scores even after adjusting for other factors. As mentioned, the etiology of ED itself is multifactorial and complicated, and thus, we cannot fully understand the exact mechanism of this phenomenon. However, it could be related to an altered hormonal milieu, such as testosterone or sex hormone-binding globulin (SHBG). Low testosterone which could lower erectile function was suggested to have poor prognostic factors and higher tumor volume (29). Low testosterone was also associated with extroprostatic disease (30).

Hypogonadism may make PC more aggressive; however, the reverse is also plausible. Several studies demonstrated that serum levels of total and free testosterone were significantly elevated after radical prostatectomy (31, 32). Thus aggressive PC could be the possible cause of severe ED by inhibiting hypothalamic-pituitary axis. Our group previously reported the association between serum SHBG level with extraprostatic disease and higher Gleason score in clinically localized PC patients (33). Stimulation of cyclic adenosine monophosphate by the prostate was suggested as a possible mechanism. Significant role of SHBG in stem-like properties of PC has recently been demonstrated by cell lines study (34). SHBG was co-upregulated with related factors such as CD44, CD90, Oct3/4 and Nanog during progression. Furthermore, blocking SHBG gene rendered down regulation of theses stemness related factors. Higher SBHG expression in human PC specimens examined by immunohistochemistry is significantly associated with aggressive pathologic features (34). Thus, SHBG may involve with direct mechanism of cancer progression. Regarding obesity, adipose tissue itself has been regarded as an endocrine organ because it regulates multiple hormones via aromatase. Testosterone could be converted to estradiol by adipocytes and PC (35). This is strongly regarded as one mechanism of prostate carcinogenesis and tumor progression. Many adipokines such as leptin, interleukin-6, and adiponectin have been proved to have strong association with aggressive PC (36). The insulin/insulin-like growth factor-1 (IGF-1) axis is another commonly proposed mechanism. Poor glycemic control and hyperinsulinemia could lead to tumor aggressiveness. Chronically elevated glucose levels would lead to compensatory hyperinsulinemia. Insulin itself and IGF-1, which is regulated by insulin, promote proliferation and inhibit apoptosis in PC (37, 38). The DM-related micro-environment could be responsible for transformation to aggressive PC. Long-standing DM may cause vascular damage in both the prostate and corpus cavernosum, which is a contributing factor in the pathogenesis of benign prostatic hyperplasia and ED (39). Impaired circulation of the prostate also could induce tumor hypoxia, which may result in a more clinically aggressive tumor phenotype (40). Shared genetic susceptibility between obesity and diabetes mellitus with PC is also worth consideration. Genome wide studies showed at least 17 common

obesity loci and 18 type 2 diabetes loci (41). PC related gene could overlap with these loci. Regarding dyslipidemia related mechanism, low high-density lipoprotein and high triglyceride levels also might be associated with high-grade PC (42). In vitro, triglycerides induce the proliferation of androgen-independent PC-3 cells.

The major limitation of the present study might be its retrospective nature in a single-center cohort. Furthermore, it may be subject to inherent biases during patient selection since 16% (272/1743) of the patients were excluded due to missing IIEF-5 results. Other limitations are the lacks of information about sex-hormone level, the cause of ED, and long-term follow-up outcomes. Nevertheless, our results provide new insight into the association between erectile function and PC pathophysiology. We believe our hypothesis deserves to be evaluated in a larger, multicenter cohort or in a prospective manner. We suggest that the future study should collect more specific information such as sex-hormone level or penile Doppler.

CONCLUSIONS

Lower erectile function before RP was significantly associated with some adverse pathologic outcomes, such as a higher Gleason score and larger tumor volume, even after adjusting for other variables. Thus, decreased erectile function could be a surrogate barometer for aggressive features of PC.

ABBREVIATIONS

BMI = body mass index
CI = confidence interval
ED = erectile dysfunction
DM = diabetes mellitus
HR = hazard ratio
IIEF-5 = the international index of erectile function-5
LEF = the low erectile function
OR = odds ratio
PC = prostate cancer
RP = radical prostatectomy
SEARCH = Shared Equal Access Regional Cancer Hospital

CONFLICT OF INTEREST

None declared.

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