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Phosphodiesterase-5 Inhibitor Use in Robot Assisted Radical Prostatectomy Patients Is Associated with Reduced Risk of Death: A Propensity Score Matched Analysis of 1,058 Patients

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Purpose: We investigated whether the use of a phosphodiesterase-5 inhibitor (PDE5i) after robot assited radical prostatectomy has a survival benefit over non-use patients because there are controversial results on the association between PDE5i use and survival outcomes for prostate cancer patients in literature.

Materials and Methods: We designed a retrospective, matched, large-sample cohort study of 5,545 patients who underwent robot assisted radical prostatectomy (RARP) during 2013–2021 in a single institute. The exclusion criteria was patients who were aged >70 years at surgery, American Society of Anesthesiologists (ASA) physical status classification grade 4 or 5, history of other malignancies, patients who started PDE5i 6 months after survery and patients with follow up period less than 24 months after surgery. Among the 1,843 included patients, 1,298 were PDE5i users, and 545 were PDE5i non-users. We performed propensity score matching (PSM) of PDE5i users (n=529) with non-users (n=529) by adjusting for the variables of age, Gleason grade group, pathological T stage, preoperative ASA physical status grade, and International Index of Erectile Function score.

Results: There were no significant difference in patient characteristics according to PSM. Kaplan–Meier curve revealed the difference of overall survival for PDE5i users and non-users (clustered log-rank test $p<0.05$). In a stratified Cox regression analysis, PDE5i use after RARP was associated with improved overall survival and reduced risk of death (hazard ratio 0.43; confidence interval 0.24–0.79; $p=0.007$). The limitation of this study was that the indication for the prescription of PDE5i was not given.

Conclusions: PDE5i administration after RARP were associated with overall survival of patients with prostate cancer. A further randomized control trial may reveal whether routine use of PDE5i after prostatectomy can improve survival of prostate cancer patient.

Keywords: Erectile dysfunction; Phosphodiesterase 5 inhibitors; Prostatectomy; Prostatic neoplasms; Survival

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INTRODUCTION

Phosphodiesterase-5 inhibitor (PDE5i), a drug prescribed for vasculogenic erectile dysfunction (ED), was originally developed to treat angina. The presence of ED, a vascular disease, suggests the possibility of underlying cardiovascular dysfunction [1]. Recently, PDE5i use has been reported to be a prognostic indicator for later cardiovascular mortalities in patients with ED and a history of diabetes or cardiovascular diseases [2,3]. PDE5i use may aid in the recovery of erectile function after prostatectomy. Yet, PDE5i use after prostatectomy has not been generalized and depends more on surgeon/patient preferences. In particular, there was a suspicion that PDE5i use may negatively impact biochemical recurrence after radical prostatectomy (RP) [4]. However, some studies showed no association between PDE5i use and biochemical recurrence [5-8]. Furthermore, Danley et al [9] reviewed 3,100 patients undergoing RP, of whom 1,372 were administered PDE5i, and reported that PDE5i use was associated with lower risks of biochemical recurrence and death.

However, in these studies, PDE5i users and non-users had a significant difference in terms of age, race, pathological T (pT) stage, and Gleason score, all of which may have strongly affected the survival parameters. Propensity score matching (PSM) can help reduce selection bias and overcome the heterogeneity at baseline in the comparison groups of a retrospective cohort study. There is a need to investigate the association between PDE5i use and oncological outcomes owing to the controversial evidence available in the literature. Therefore, we conducted a study on a cohort of patients with homogeneous racial background from a single institute to confirm whether PDE5i use has a survival benefit over non-use after prostatectomy of prostate cancer patients.

MATERIALS AND METHODS

1. Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Yonsei University College of Medicine (#4-2021-0780). The requirement for obtaining patient consent was waived due to the study's retrospective nature. The study was conducted in accordance with the Declaration of Helsinki.

2. Patient cohorts, study endpoints, and assessments

We designed a retrospective cohort analysis (Fig. 1). Using the Severance Clinical Research Analysis Portal, we retrieved cases of robot assisted radical prostatectomy (RARP) performed between September 2013 and March 2021. We collected clinical information of patients' age, pT stage, Gleason grade group (GGG), preoperative American Society of Anesthesiologists (ASA) physical status classification grade and International Index of Erectile Function (IIEF) score. Inclusion criteria were (1) age <70 years at the time of surgery, (2) clinically localized or locally advanced stage and (3) a medical record available for the above-mentioned clinical information. Exclusion criteria were (1) foreign nationality such that the survival status could not be tracked by the national healthcare registry, (2) preoperative ASA physical status grade ≥4 (severe systemic disease that is a constant threat to life), and (3) history of another malignancy. PDE5i use was determined by the prescription status of the PDE5i drug after surgery. PDE5i user was defined as those who have been ever prescribed of any PDE5i drug during follow-up period. Prescription data of PDE5i from other than our institution was not collected. To minimize potential selection bias, we applied additional exclusion criteria: (1) PDE5i initiation 6 months after RARP, (2) a follow-up period shorter than 24 months, including patients who died within 24 months after surgery. The primary endpoint was overall survival.

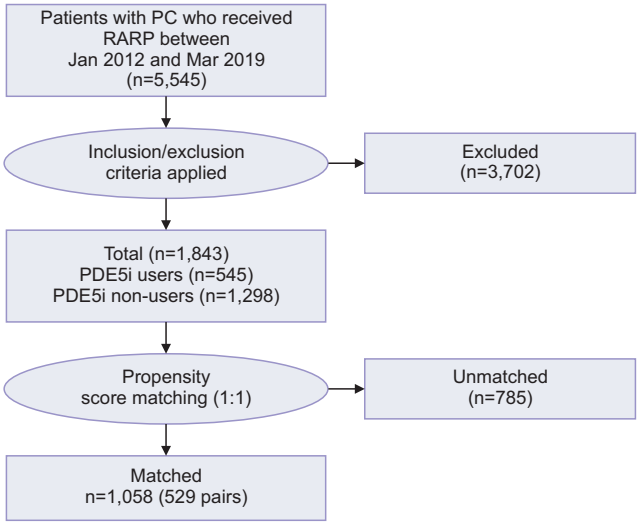

Fig. 1. Study design. PC: prostate cancer, RARP: robot assisted radical prostatectomy, PDE5i: phosphodiesterase-5 inhibitor.

3. Propensity score matching

We applied PSM to substitute preselected matching variables – age, GGG, pT stage, preoperative ASA physical status classification, and IIEF score – as covariates of logistic regression to obtain a PS for the PDE5i user group and the non-user group. We then matched patients who had similar PSs in the two groups. Caliper, or the maximum distance between PS allowed when performing matching, was defined by a standard deviation of PS×0.2. The matching was considered successful if the absolute value of the standardized mean difference (SMD) after matching was smaller than 0.1, which was visually confirmed through a love plot.

4. Statistical and survival analysis

Before the PSM, a Mann–Whitney U-test for continuous variables and a chi-square test for categorical variables were performed to compare the PDE5i user group and the non-user group. After the PSM, a Wilcoxon signed-rank test for continuous variables and a McNemar test or Bowkers' symmetry test for categorical variables were performed. A clustered log-rank test was performed to assess the presence of any significant difference between the two Kaplan–Meier (K–M) survival curves. Furthermore, the hazard ratio for overall survival according to PDE5i use was calculated through stratified Cox regression analysis. For statistical analysis, SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R package version 3.4.3 (http://www.R-project.org) were used.

RESULTS

A total of 1,843 patients met the inclusion/exclusion criteria, comprising 1,298 PDE5i users and 545 PDE5i non-users (Fig. 1). The median follow-up period was 47 months (interquartile range [IQR] 34–63 mo). After PSM, there was no significant difference in the baseline characteristics between PDE5i non-users and PDE5i users (Table 1). Additionally, the SMD (abso-

Table 1. Baseline characteristics of propensity score-matched PDE5i users and non-users

Variable	Before matching			After matching		
	PDE5i non-users (n=545)	PDE5i users (n=1,298)	p-value	PDE5i non-users (n=529)	PDE5i users (n=529)	p-value
Age at surgery (y)	65 (61–68)	62 (58–66)	<0.001[a]	65 (61–68)	65 (61–67)	0.90[b]
GGG			<0.001			0.531[c]
1	67 (12.3)	285 (22.0)		67 (12.7)	71 (13.4)	
2	175 (32.1)	485 (37.4)		175 (33.1)	181 (34.2)	
3	92 (16.9)	221 (17.0)		90 (17.0)	100 (18.9)	
4	63 (11.6)	126 (9.7)		62 (11.7)	56 (10.6)	
5	148 (27.2)	181 (13.9)		135 (25.5)	121 (22.9)	
pT stage			<0.001[d]			0.23[d]
pT2	314 (57.6)	876 (67.5)		308 (58.2)	312 (59.0)	
pT3	231 (42.4)	422 (32.5)		221 (41.8)	217 (41.0)	
ASA physical status grade			<0.001			0.82[c]
1	41 (7.5)	182 (14.0)		41 (7.8)	36 (6.8)	
2	330 (60.6)	809 (62.3)		321 (60.7)	321 (60.7)	
3	174 (31.9)	307 (23.7)		167 (31.6)	172 (32.5)	
IIEF score			<0.001			0.32
0	48 (8.8)	203 (15.6)		48 (9.1)	39 (7.4)	
1	89 (16.3)	364 (28.0)		89 (16.8)	88 (16.6)	
2	118 (21.7)	307 (23.7)		118 (22.3)	128 (24.2)	
3	66 (12.1)	147 (11.3)		65 (12.3)	83 (15.7)	
4	224 (41.1)	277 (21.3)		209 (39.5)	191 (36.1)	

Values are presented as median (interquartile range) or number (%).
PDE5i: phosphodiesterase-5 inhibitor, GGG: Gleason grade group, pT: pathological T, ASA: American Society of Anesthesiologists, IIEF: International Index of Erectile Function.
[a]Mann–Whitney U-test. [b]Wilcoxon matched-pair signed-rank test. [c]Chi-square test. [d]Fisher's exact test.
There was no significant difference in the baseline characteristics between PDE5i non-users and PDE5i users after propensity score matching.

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Table 2. Balance diagnostics before and after propensity score matching

Variable	Standardized mean difference		Percent balance improvement
	Before PSM	After PSM	
Distance	0.6897	0.0279	95.9
Age	0.5411	0.0016	99.7
GGG	0.3728	0.064	82.8
pT stage	0.1996	0.0153	92.3
ASA physical status grade	0.255	0.0326	87.2
IIEF score	0.474	0.0014	99.7

PSM: propensity score matching, GGG: Gleason grade group, pT: pathological T, ASA: American Society of Anesthesiologists, IIEF: International Index of Erectile Function.
Standardized mean difference (absolute value) for each covariate balance was less than 0.1, which confirmed successful matching.

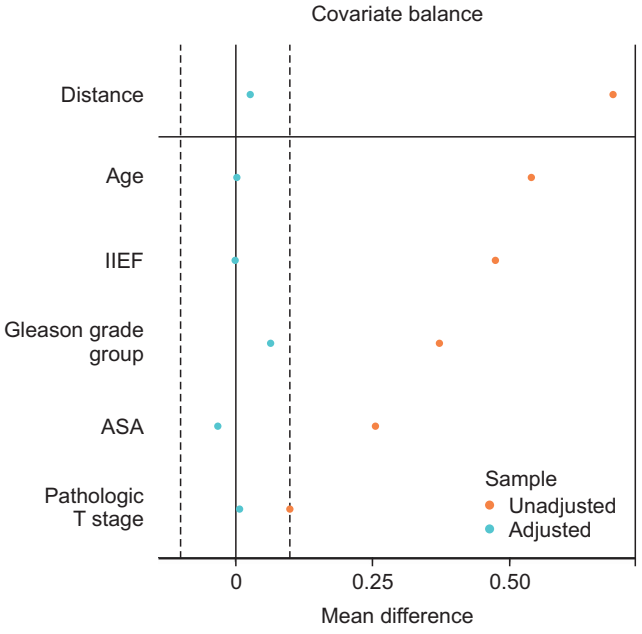
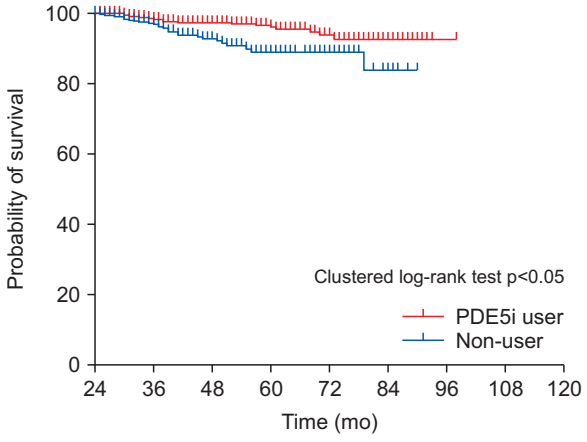


Fig. 2. Love plot for propensity score matching. IIEF: International Index of Erectile Function, ASA: American Society of Anesthesiologists.



Time (mo)	0	24	36	48	60	72	84	96	108
PDE5i user	529	529	404	300	191	91	26	2	0
Non-user	529	529	295	161	74	34	10	0	0

Fig. 3. Kaplan–Meier plot of overall survival after propensity score matching. PDE5i: phosphodiesterase-5 inhibitor.

lute value) for each covariate balance was less than 0.1, which confirmed successful matching (Table 2). A love plot shows all adjusted SMDs are within the -0.1 to 0.1 range (Fig 2). The median 'days of prescription' in PDE5i user group was 275 days (IQR 112–640 d). Details of PDE5i use among enrolled patients by types, dosage regimens and survival status are listed in Supplement Tables 1 and 2.

As we excluded cases with a follow-up period shorter than 24 months, including patients that died during this period, the K–M survival curves were constructed starting at 24 months post-operation. The K–M curves of survival for PDE5i users and non-users were significantly different (clustered log-rank test p<0.05) (Fig. 3). Stratified Cox regression analysis revealed that PDE5i use was associated with a reduced risk of death (hazard ratio 0.43; 95% confidence interval 0.24–0.79; p=0.007).

Lastly, we examined the characteristics of the deceased patients that occurred among PDE5i non-users (n=28) and PDE5i users (n=18). There was no significant difference in their age, GGG, pT stage, preoperative ASA physical status grade, and IIEF score (Table 3).

DISCUSSION

In this study, we observed that PDE5i use after RARP is associated with improved survival in prostate cancer patients matched for age, pT stage, GGG, preoperative ASA physical status classification, and IIEF score. A favorable outcome to PDE5i use was concerning because some patients who survived for a long period without tumor recurrence could have exhibited

Table 3. Characteristics of deceased cases

Variable	PDE5i non-users (n=28)	PDE5i users (n=18)	p-value
Age, y	64 (59–68)	64 (58–67)	0.72[a]
GGG			0.80[b]
1	1 (3.6)	0 (0)	
2	2 (7.1)	3 (16.7)	
3	2 (7.1)	1 (5.6)	
4	6 (21.4)	4 (22.2)	
5	17 (60.7)	10 (55.6)	
pT stage			0.75[b]
pT2	9 (32.1)	5 (27.8)	
pT3	19 (67.9)	13 (72.2)	
ASA physical status grade			0.17[b]
1	5 (17.9)	0 (0)	
2	14 (50.0)	11 (61.1)	
3	9 (32.1)	7 (38.9)	
IIEF score			0.18[b]
0	4 (14.3)	0 (0)	
1	6 (21.4)	4 (22.2)	
2	4 (14.3)	5 (27.8)	
3	1 (3.6)	3 (16.7)	
4	13 (46.4)	6 (33.3)	

Values are presented as median (range) or number (%).
PDE5i: phosphodiesterase-5 inhibitor, GGG: Gleason grade group, pT: pathological T, ASA PS: American Society of Anesthesiologists physical status, IIEF: International Index of Erectile Function.
[a]Mann–Whitney U-test. [b]Pearson's chi-squared test.

PDE5i initiation later during the follow-up period. To avoid such bias, we excluded patients who had been administered PDE5i 6 months after RARP, as well as those who died within 24 months since surgery for whom PDE5i might have not been offered. Yet, PDE5i use remained a significant factor for overall survival in the selected population.

Another concern was that administration of PDE5i may be a marker of a healthier patient rather than a cause of better survival. In particular, men who feel better and have increased sexual activity may be the patient population who is seeking PDE5i. Also, the prevalence and etiology of ED varies across age groups. Both sexual activity and erectile function gradually decrease with age in males and at 70 years of age, two thirds of men are reported to have ED [10,11]. While ED can be a result of psychological factors in young males, in the older population the most common cause of ED is cardiovascular disease which can critically affect their survival [12,13]. Thereby, we excluded men >70 years or with heavy-burden comorbidities in this analysis. However, we still observed differences in preoperative IIEF score, ASA class distribution, and age in PDE5i users and non-users. Lastly, patients with an advanced pathology may have been precluded of PDE5i use in the postoperative period. To minimize the impact of these confounding variables, we performed PSM of age, ASA physical status, IIEF score as well as GGG and pT stage. We still observed a very strong impact of PDE5i use (hazard ratio of 0.43 on overall survival).

The primary rationale behind this study is that PDE5i administration may alleviate the risk of cardiovascular-related death [2,3]. Reduced all-cause mortality have been reported in PDE5i users who had a history of coronary artery disease, compared to non-users [3] or alprostadil users [2]. We initially hypothesized that a similar effect of PDE5i administration is observed in prostate cancer patients –a protective effect seen in patients with coronary artery disease or diabetes. However, our analysis revealed that PDE5i administration was associated with reduced risk of death in all categories of the ASA physical status, including class I who is normally healthy, non-smoking, exhibiting no or minimal alcohol use, no acute or chronic disease, and normal age-adjusted body-mass index [14]. As preoperative IIEF was also adjusted in our regression model, the chance of selecting a healthier population in this group is considered very low. In this regard, the lack of data on the cause of death in some patients is a limitation of our study.

Andersson et al [2] used quintile division to describe the association of PDE5i prescription period and coronary artery disease outcomes. When quintiles (q) of filled PDE5i prescriptions were compared using q1 as reference, patients in q3, q4, and q5 had lower all-cause mortality. In that study, the mean number of daily doses PDE5i were: 4±1(q1), 10±2(q2), 21±5(q3), 58±20(q4), 340±425(q5). In our study, the median 'days of prescription' in PDE5i user group was 275 days (IQR 112–640 d). Considering that the median period of prescription is about 9 months, we assume that most of the patients in this study have been taking PDE5i for some time.

If the protective effect of PDE5 inhibition in our data cannot be explained by the impact on the comorbidities, then it may be related to prostate cancer itself. For biochemical recurrence after RP, earlier studies showed a positive association [4], most recent studies reported that PDE5i use had no impact on biochemical

recurrence [5-7], or that it lowers the risk of biochemical recurrence [9]. Similarly, PDE5i use was not associated with biochemical recurrence risk after radiation [8,15].

There are only a few clinical studies regarding PDE5i use or ED on prostate cancer development. Chavez et al [16] reported using a single institute data that PDE5i users had a significantly low chance of being diagnosed with prostate cancer than non-users. However, a re-analysis after age, serum prostate-specific antigen levels, and ethnicity matching revealed no associations [17]. Similarly, Jamnagerwalla et al [18] analyzed the REDUCE trial data and revealed no association between PDE5i and diagnosis of prostate cancer. The limitations of these studies are that the number of PDE5i users included was fairly small. Indeed, Jamnagerwalla et al [18] found an inverse trend between PDE5i use and prostate cancer diagnosis in North American territory where PDE5i use was highest. When the ED itself was considered, an increased risk of prostate cancer has been noted in ED patients of Asian populations [19,20].

The PDE5is have shown clinical benefits in benign prostatic hyperplasia patients, regardless of the presence of ED. Here, the supposed mechanism of action of PDE5i is to reduce chronic tissue inflammation by oxidative stress and inflammatory cytokine production [21]. Furthermore, experimental studies indicate that PDE5 blockade can decrease inflammatory marker production and oxidative stress indicators in non-genitourinary tissues [22,23]. Because chronic tissue inflammation is associated with prostate cancer development, metastasis, and resistance to therapy, long-term PDE5i use may help block inflammation in the pro-tumorigenic tissue. Also, *in vitro* studies suggest that PDE5is can directly inhibit prostate cancer cell proliferation and migration [24,25].

Our study has some strengths and limitations. Strengths include the use of an ethnically homogenous cohort with matched age, comorbidity, and pathology. We report the following limitations: First, we cannot note a uniform rationale for PDE5i prescription across the patient data we analyzed. The decision of PDE5i prescriptions may have been affected by different surgeon's preference or postoperative patient's demand that was not compensated by pre-operative IIEF score matching. Second, no information could have ben obtained on the history of taking PDE5i at other hospital before or after visit to our institution For further analysis, a comprehensive profiling of PDE5i prescription history by using nation-wide big data such as those from the National Health Care Insurance will be useful. Lastly, we could not deduce the exact cause of death in patients who died outside our institute.

CONCLUSIONS

In conclusion, we demonstrate that PDE5i administration after RARP is associated with improved overall survival in patients with prostate cancer. Given that our results are in line with those of other recent retrospective studies, which also have been powered by PSM. A prospective study is necessary to fully unravel the benefit of PDE5i administration.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: JL, HH, KSL, WSJ. Data curation: All authors. Formal analysis: JL, HH, KSL, SKK. Funding acquisition: JL, HH. Investigation: JL, HH. Methodology: HRK, JL. Resources: YDC. Software: HRK. Supervision: YDC. Validation: HRK. Visualization: HRK, JL. Writing – original draft: JL, HH, JEH, SKK. Writing – review & editing: HRK, JL, HH.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.220063.

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