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RESEARCH ARTICLE

Health-related quality of life of exposed versus non-exposed androgen deprivation therapy patients with prostate cancer: a cross-sectional study

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Abstract

Background The survival rate of prostate cancer is relatively higher than other cancers, therefore, the health-related quality of life (HRQoL) becomes a critical issue for the patients. There are limited quality of life data evaluating the difference between androgen deprivation therapy and non-androgen deprivation therapy. *Objective* To evaluate the HRQoL among prostate cancer patients with androgen deprivation therapy and non-androgen deprivation therapy in an Asian population. *Setting* The study was conducted at the urology outpatient department in a medical center and a regional hospital in southern Taiwan. *Methods* We collected the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Quality of Life Questionnaire-Prostate (QLQ-PR25) among prostate cancer patients with and without androgen deprivation therapy from December 2017 to June 2018. The androgen deprivation therapy subjects in this study were using goserelin, leuprolide, degarelix, bicalutamide, enzalutamide, cyproterone, and abiraterone. The non-androgen deprivation therapy subjects were only receiving radiation therapy or radical prostatectomy. To investigate the determinants of HRQoL between androgen deprivation therapy and non-androgen deprivation therapy, multiple linear regression was used. *Main outcomes measures* The scores of EORTC QLQ-C30 and QLQ-PR25. *Results* In total, 182 subjects participated in the study of which 116 (63.74%) were in androgen deprivation therapy user group with a mean age (± SD, standard deviation) of 75.94 years (± 8.31), and 66 (36.26%) subjects were in non-androgen deprivation therapy user group with a mean age of 70.6 years (± 7.1). androgen deprivation therapy users' quality of life was significantly lower than non-androgen deprivation therapy users (72.1 ± 19.3 vs. 77.8 ± 16.6, $p = 0.0493$). *Conclusions* The quality of life of patients with all-stages prostate cancer differs significantly between androgen deprivation therapy users and non-androgen deprivation therapy users. The HRQoL for androgen deprivation therapy users is worse than for the non-androgen deprivation therapy users. Additionally, the symptoms are the key determinants of the quality of life.

Keywords Androgen deprivation therapy · Prostate cancer · Quality of life · Radiation therapy · Taiwan

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Impact of practice

- Whether androgen deprivation therapy enhances the health-related quality of life of patients with prostate cancer is still unclear in Asian population.
- The health-related quality of life for androgen deprivation therapy users seems worse than that of the non-users.
- With the information of the patient-reported outcomes, health care providers and patients might know what effects of the therapy regimens would occur and how the therapy regimens affect the daily life.

Introduction

Prostate cancer (PC) was ranked seventh in the "Taiwan Cancer Causes of Death," with a mortality rate of 11.5 per 100,000 population [1]. Furthermore, PC was ranked fifth for new cancer cases and showed an increased incidence from 2004 to 2015 [2]. While PC is a common cancer among elderly males in Taiwan and the USA [3], advances in treatment have led to long-term survival [4]. However, longer treatment duration is associated with more serious adverse effects that negatively affect patient health-related quality of life (HRQoL) [5, 6].

HRQoL refers to an individual's expected physical, emotional, and social well-being and how it is affected by a medical condition or its treatment [7]. Patients with PC experience different adverse effects of treatment that affect HRQoL. Moreover, different treatments, such as radical prostatectomy (RP), radiation therapy (RT), and androgen deprivation therapy (ADT), are associated with different adverse effects and effects on HRQoL. Urinary, bowel, and sexual dysfunctions were the most common adverse effects of PC treatments. RP has a higher rate of sexual dysfunction and lower rate of bowel symptoms than RT [4]. Besides, ADT has less adverse effects except for sexual dysfunction. However, only a few studies evaluated HRQoL for patients using ADT.

Apart from the improvements in survival, the improvement in HRQoL has become an increasingly important issue, particularly in serious illnesses such as PC [8]. The US Food and Drug Administration suggested including patient-reported outcomes such as HRQoL in drug labeling [9]. The importance of HRQoL in PC has also been highlighted in Europe [10]. As a result, many clinical trials have also included the evaluation of HRQoL in PC treatment [11]. The concept of preference has been developed and measured for HRQoL in PC and has become a key variable used in cost–utility studies [12, 13].

A Spanish observational study reported that asthenia and pain are highly correlated with factors influencing poor HRQoL, among factors such as advanced stage, locally advanced, or metastatic phase PC. While urinary symptoms were most common, these were not related to HRQoL in the regression model. Furthermore, the study indicated that physicians often overestimate the health status of patients compared with the status evaluated by patients themselves. This shows that physicians seem to neglect the adverse effects of treatments that affect HRQoL and focus on disease improvement such as decreased prostate-specific antigen levels [14]. While some studies have evaluated HRQoL among PC patients with a variety of treatments, few have evaluated HRQoL in PC patients undergoing ADT [15, 16].

Aim of the study

The aim of the present study was to evaluate HRQoL among patients with PC undergoing ADT therapy compared with non-ADT therapy (RT or RP) in Asian population.

Ethics approval

This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20180089). All procedures were in accordance with the ethics committee and with the principles of the Declaration of Helsinki.

Method

Study population

Participants were selected from a medical center and a regional hospital in southern Taiwan. Inclusion criteria were being an outpatient with prostate cancer, plus one of the following: undergoing ADT for at least 28 days, or 1 month after completion of RP or RT. Exclusion criteria were patients < 20 years old, those involved in other clinical trials, or those diagnosed with other cancers.

Participants were divided into ADT and non-ADT groups according to treatments used. The ADT group included participants that underwent ADT after RP, RT combined with ADT, or ADT alone. Patients in this group received goserelin, leuprolide, degarelix, bicalutamide, enzalutamide, cyproterone, or abiraterone. The non-ADT group included participants that underwent either RP or RT alone.

Data collection

The present study used the Taiwan Chinese version of the European Organization for Research and Treatment of

Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Quality of Life Questionnaire-Prostate (QLQ-PR25) questionnaires to evaluate HRQoL among patients with PC. Both translated questionnaires were validated [17]. The QLQ-C30 is divided into three categories: global quality of life (QoL), function scales, and symptom scales. The QLQ-PR25 is divided into function and symptom scales. Items 52–55 regarding sexual function were only completed by sexually active participants.

Data collection was carried out from December 2017 to June 2018, and the index date was defined as the date that the participant completed the questionnaire. Participants' baseline characteristics were collected from 1 year before the index date until the index date. Baseline characteristics included personal information (age, education, occupation, marital status, and habitation), disease information (comorbidities and PC characteristics), and medication.

Statistical analyses

Primary outcomes were defined as QLQ-C30 and QLQ-PR25 scores difference between the ADT and non-ADT groups. Secondary outcomes were defined as determinants of QoL in patients with PC, and subgroups analyses were defined as QoL with different types of treatments in the ADT group, including ADT after RP, RT combined with ADT, and ADT alone, among participants at all-stages and stages I–III (excluding metastatic prostate cancer).

Baseline characteristics and scores were compared in different ways for ADT versus non-ADT groups. Student's *t* test or Mann–Whitney U test was used for continuous variables between two groups. Analysis of variance or Kruskal–Wallis test was used for continuous variables between the four treatment groups. Chi-square test was used for categorical variables. Multiple linear regression was used to investigate the determinants of QoL, and a stepwise selection was used to select the factors for the model (significance level of 0.15 for entering and 0.05 for stay).

QLQ-C30 and QLQ-PR25 scorings were conducted based on the EORTC scoring manual [18]. The raw score of all items was standardized to a scale of 0–100 with a linear transformation, where higher scores corresponded to higher response levels and showed better functioning on the global QoL scale and the functional subscales, and more symptoms on the symptom scales.

All data analysis was performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA) and IBM SPSS Statistics software version 20 (Armonk, NY: IBM Corp.), and statistical significance was set at two-sided p value < 0.05.

Results

A total of 197 PC patients were included in the study from December 2017 to June 2018. Of these, fifteen were excluded from the study: Three declined to complete the questionnaire and twelve were diagnosed with other cancers. Of the final 182 study participants, 116 participants were in the ADT group and 66 were in the non-ADT group (Fig. 1).

Table 1 shows the baseline characteristics. The mean age was 75.94 (± 8.31) in ADT group, which was significantly older than mean age 70.65 (± 7.12) in non-ADT group. Furthermore, for stages, most ADT users were diagnosed as stage III (47 subjects, 40.52%) or stage IV (48 subjects, 41.38%) PC, while non-ADT users were diagnosed as stage II (30 subjects, 45.45%). The distributions of stages were significantly different ($p < 0.0001$). In general, the ADT group had a more advanced diseases condition compared with the non-ADT group, including Gleason score ($p < 0.0001$), prostate-specific antigen level ($p < 0.0001$), relapse rate ($p < 0.0001$), and active treatment ($p < 0.0001$).

Table 2 shows the primary outcomes. QoL of ADT users was 72.15 (± 19.39) which was significantly lower in the ADT group than the non-ADT users whose QoL was 77.82 (± 16.62), $p = 0.0493$. There were significantly lower physical function score (85.91 ± 18.68 vs. 92.51 ± 10.04, $p = 0.0024$) and role function (90.20 ± 20.42 vs. 95.38 ± 13.01, $p = 0.0399$) and higher frequency of fatigue (16.47 ± 21.33 vs. 8.03 ± 14.63, $p = 0.0021$), nausea and vomiting (2.49 ± 10.22 vs. 0.26 ± 2.07, $p = 0.0262$), pain (11.40 ± 18.33 vs. 5.13 ± 11.38, $p = 0.0053$), and dyspnea (9.65 ± 18.14 vs. 3.08 ± 9.72, $p = 0.0019$) in ADT therapy than non-ADT. Furthermore, ADT users (5.53 ± 10.23) had significantly less frequency of sexual activity than the non-ADT users (9.23 ± 13.19), $p = 0.0147$.

Subgroup analysis of all-stages of the ADT group is shown in Table 3. HRQoL was analyzed among the three groups, ADT after RP (N = 29), RT combined with ADT (N = 44), and ADT alone (N = 43). QoL of ADT after RP users was 75.30 (± 18.77), RT combined with ADT users was 73.49 (± 15.59), and ADT alone users was 68.65 (± 22.97). Despite the ADT after RP group had better QoL compared with the other two groups, there were no significant differences among the three groups ($p = 0.3170$). In fact, ADT alone group had lower scores in physical functioning ($p = 0.036$), role functioning ($p = 0.0188$), and emotional functioning ($p = 0.0025$). In Table 3, ADT alone group compared to ADT after RP or ADT combined with ADT in the all-stages population had higher symptoms such as nausea and vomiting ($p = 0.0412$), appetite loss (0.0071), and financial difficulties ($p = 0.0062$). The

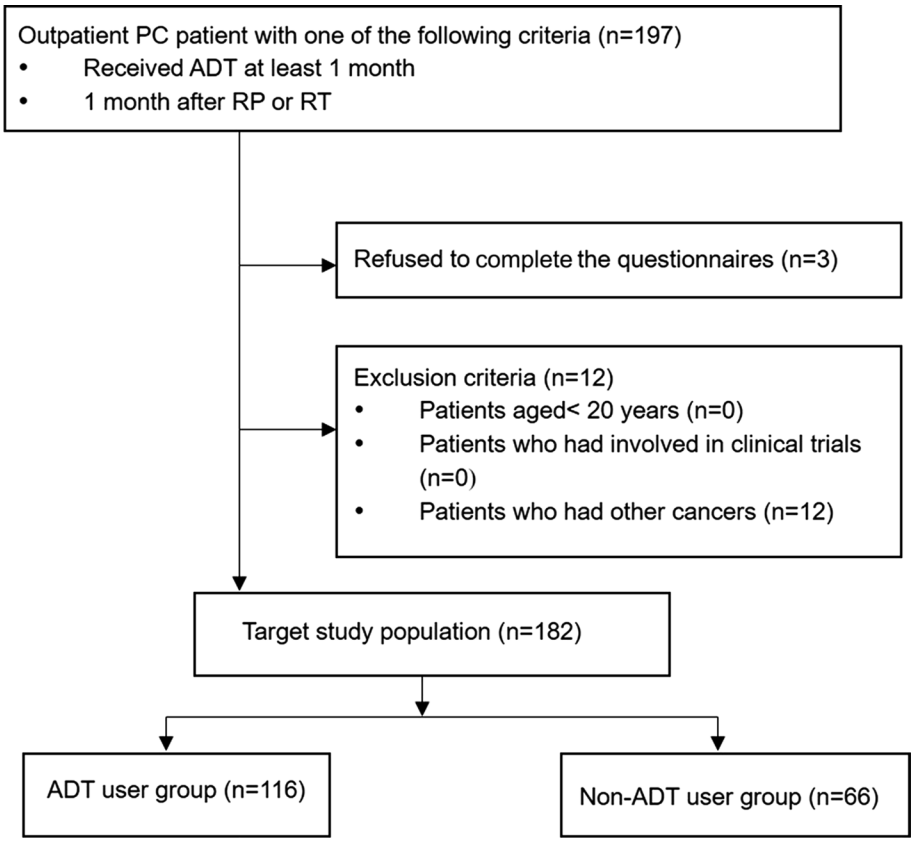

Fig. 1 Study flowchart

QLQ-PR25 results revealed that participants in the ADT alone group experienced problems than other two groups in incontinence (RP + ADT: 25.00 ± 29.55, RT + ADT: 9.52 ± 25.20, ADT alone: 52.38 ± 37.8; $p = 0.0493$), and RT with ADT group had lower problems in hormonal treatment-related symptoms (RP + ADT: 11.91 ± 9.41, RT + ADT: 6.57 ± 7.97, ADT alone: 11.51 ± 12.71; $p = 0.034$).

Furthermore, HRQoL of stages I–III of the ADT group is shown in Table 3; there were ADT after RP (N = 21), RT combined with ADT (N = 34), and ADT alone (N = 13). QoL of ADT after RP users was 76.67 (± 18.85), RT combined with ADT users was 73.28 (± 14.62), and ADT alone users was 68.59 (± 17.73); there were no significant differences among the three groups ($p = 0.3970$). However, only emotional functioning had lower scores in ADT alone than other groups, $p = 0.0114$. In Table 4, ADT alone therapy in stages I–III had higher symptoms such as nausea and vomiting ($p = 0.0285$), appetite loss (0.0053), constipation ($p = 0.0316$), and financial difficulties ($p = 0.0074$). The QLQ-PR25 results showed that ADT alone group had higher problem in sexual functioning (RP + ADT: 33.33 ± 0.0, RT + ADT: 22.22 ± 4.81, ADT alone: 50.00 ± 20.36; $p = 0.0191$), incontinence (RP + ADT: 41.67 ± 31.91, RT + ADT: 0.0 ± 0.0, ADT alone: 66.67 ± 38.49; $p = 0.0102$), and bowel symptoms (RP + ADT: 0.42 ± 1.86, RT + ADT: 2.94 ± 4.98, ADT alone: 8.97 ± 13.38; $p = 0.0065$).

eTable 1 shows univariate analysis of associations for QoL in stage I to IV population. In Table 5, multivariate analyses showed determinants of QoL. Marital status and role functioning had positive association with QoL, and nausea and vomiting, and insomnia had negative association.

Discussion

In the present study, around 60% of the study population received ADT therapy, either alone or in combination with other therapies, highlighting the importance of evaluating ADT.

Potosky et al. [19] reported that the risk of all-cause mortality was similar between ADT and non-ADT patients in clinically localized PC. The survival rates of PC in stages I–III did not differ widely using the Taiwan Cancer Registry, the National Health Insurance Research Database, and the Death Registry as the data sources [20]. The similar survival outcomes of different therapies for PC patients highlight the importance of using patient-reported outcomes when selecting treatments.

There were significant differences between the ADT and non-ADT groups in our study. First, the ADT group was

Table 1 Baseline characteristics of ADT and non-ADT user groups

	ADT ($n=116$)	Non-ADT ($n=66$)	p value
Age, mean (SD)	75.94 (8.31)	70.65 (7.12)	<0.0001
Education, *n* (%)			0.0171
Primary	32 (27.83%)	12 (18.18%)	
Junior high	17 (14.78%)	7 (10.61%)	
Senior high	32 (27.83%)	17 (25.76%)	
College	27 (23.48%)	22 (33.33%)	
Graduate	1 (0.87%)	7 (10.61%)	
Missing data	7 (6.03%)	1 (1.52%)	
Marital status, *n* (%)			0.1931
Single	2 (1.72%)	2 (3.03%)	
Married	104 (89.66%)	63 (95.45%)	
Widowed	9 (7.76%)	1 (1.52%)	
Missing data	1 (0.86%)	0 (0.00%)	
Occupation, *n* (%)			0.0732
Full-time	13 (11.21%)	15 (22.73%)	
Retired	101 (87.07%)	51 (77.27%)	
Missing data	2 (1.72%)	0 (0.00%)	
Habitation, *n* (%)			1.0000
With family	114 (98.28%)	65 (98.48%)	
Alone	1 (0.86%)	1 (1.52%)	
Missing data	1 (0.86%)	0 (0.00%)	
Comorbidity, *n* (%)			
Hypertension	73 (62.93%)	38 (57.58%)	0.4764
Dyslipidemia	27 (23.48%)	17 (25.76%)	0.7308
Diabetes mellitus	34 (29.31%)	12 (18.18%)	0.0967
Stroke	5 (4.31%)	3 (4.55%)	0.9407
CAD	16 (13.79%)	9 (13.64%)	0.9764
Heart failure	3 (2.59%)	3 (4.55%)	0.6693
CKD	8 (6.90%)	3 (4.55%)	0.7485
Liver cirrhosis	2 (1.72%)	0 (0.00%)	0.5352
COPD	8 (6.90%)	3 (4.55%)	0.7485
Asthma	4 (3.45%)	0 (0.00%)	0.2982
With urology medications	80 (68.97%)	40 (60.61%)	0.2526
Stage, *n* (%)			<0.0001
I	4 (3.45%)	9 (13.64%)	
II	14 (12.07%)	30 (45.45%)	
III	47 (40.52%)	25 (37.88%)	
IV	48 (41.38%)	0 (0.00%)	
Relapse, *n* (%)			<0.0001
Yes	55 (47.41%)	2 (3.03%)	
No	61 (52.59%)	64 (96.97%)	
Duration (year), mean (SD)	3.21 (8.11)	2.12 (7.68)	0.3818
Active treatment, *n* (%)			<0.0001
Yes	85 (73.28%)	2 (3.03%)	
No	31 (26.72%)	64 (96.97%)	
GS, *n* (%)			0.0008
Grade 1 (GS = 6)	24 (20.69%)	22 (33.85%)	
Grade 2 (GS = 3+4)	9 (7.76%)	16 (24.62%)	
Grade 3 (GS = 4+3)	15 (12.93%)	10 (15.38%)	
Grade 4 (GS = 8)	28 (24.14%)	8 (12.31%)	
Grade 5 (GS ≥ 9)	30 (25.86%)	7 (10.77%)	

Table 1 (continued)

	ADT ($n=116$)	Non-ADT ($n=66$)	p value
Missing data	10 (8.62%)	3 (4.55%)	
PSA at diagnosis (ng/mL), n (%)			< .0001
< 10	16 (13.79)	33 (50.00)	
10-19	28 (24.14)	15 (22.73)	
≥ 20	64 (55.17)	11 (16.67)	
Missing data	8 (6.90)	7 (10.61)	

ADT androgen deprivation therapy, *CAD* coronary artery disease, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *n* number, *SD* standard deviation, *GS* Gleason score, *PSA*, prostate-specific antigen

Table 2 HRQoL of ADT and non-ADT user groups

	ADT ($n=116$)	Non-ADT ($n=66$)	p value
QLQ-C30, mean (SD)			
QoL	72.15 (19.39)	77.82 (16.62)	0.0493
Physical functioning	85.91 (18.68)	92.51 (10.04)	0.0024
Role functioning	90.20 (20.42)	95.38 (13.01)	0.0399
Emotional functioning	91.96 (14.02)	92.69 (13.30)	0.7322
Cognitive functioning	92.54 (13.68)	94.10 (12.30)	0.4485
Social functioning	92.98 (13.28)	90.77 (16.15)	0.3236
Fatigue	16.47 (21.33)	8.03 (14.63)	0.0021
Nausea and vomiting	2.49 (10.22)	0.26 (2.07)	0.0262
Pain	11.40 (18.33)	5.13 (11.38)	0.0053
Dyspnea	9.65 (18.14)	3.08 (9.72)	0.0019
Insomnia	20.76 (29.21)	22.05 (30.78)	0.7806
Appetite loss	7.02 (19.06)	3.59 (14.58)	0.1793
Constipation	11.99 (22.67)	9.74 (19.30)	0.5028
Diarrhea	3.51 (10.27)	3.08 (11.37)	0.7951
Financial difficulties	4.97 (13.47)	3.59 (11.97)	0.4935
QLQ-PR25, mean (SD)			
Sexual activity	4.53 (10.23)	9.23 (13.19)	0.0147
Sexual functioning ($n=20$)	35.00 (17.48)	50.00 (19.64)	0.0880
Urinary symptoms	18.38 (13.20)	19.04 (16.20)	0.7696
Bowel symptoms	3.29 (6.89)	2.95 (6.15)	0.7415
Hormonal treatment-related symptoms	9.70 (10.50)	7.10 (8.01)	0.0643
Incontinence aid ($n=42$)	28.79 (34.57)	30.00 (35.71)	0.9116

ADT androgen deprivation therapy, *HRQoL* health-related quality of life, *n* number, *QLQ-C30* Quality of Life Questionnaire Core 30, *QLQ-PR25* Quality of Life Questionnaire-Prostate, *QoL* global quality of life, *SD* standard deviation

older than the non-ADT group. This may be due to clinical guidelines [21, 22] used to determine whether or not to use RP for patients based on life expectancy after considering other clinical indexes. The non-ADT group mostly received RP, and patients fulfilling other criteria and life expectancy > 10 years were suggested to undergo RP according to the guidelines. Based on our findings, a greater proportion of the ADT group was diagnosed with PC relapse compared with the non-ADT group. In line with the clinical guidelines, ADT was the first-line therapy for PC relapse patients in our study. The distribution of the Gleason score (GS) could support this, as the ADT group in our study was mostly diagnosed with grades 4 and 5, whereas the non-ADT group was mostly grade 1. Furthermore, there may be a higher probability of relapse with higher GS. These results are in line with a previous report that stated that GS is a predictor of biochemical recurrence [23].

Poorer HRQoL in the ADT group compared with the non-ADT group may be due to the ADT indication for patients with PC relapse or advanced stages PC. The non-ADT group

Table 3 HRQoL among subgroups of ADT user group

	RP + ADT ($n=29$)	RT + ADT ($n=44$)	ADT alone ($n=43$)	p value
QLQ-C30, mean (SD)				
QoL	75.30 (18.77)	73.49 (15.59)	68.65 (22.97)	0.3170
Physical functioning	93.10 (8.79)	85.61 (19.66)	81.43 (21.21)	0.0360
Role functioning	97.62 (7.47)	90.15 (23.38)	85.32 (21.84)	0.0188
Emotional functioning	96.73 (6.93)	95.27 (9.06)	85.32 (18.75)	0.0025
Cognitive functioning	92.86 (15.33)	93.18 (12.09)	91.67 (14.37)	0.8701
Social functioning	94.64 (12.05)	93.56 (12.56)	91.27 (14.83)	0.5478
Fatigue	17.86 (20.81)	15.40 (22.63)	16.67 (20.71)	0.8923
Nausea and vomiting	3.57 (13.11)	0.00 (0.00)	4.37 (12.78)	0.0412
Pain	7.74 (13.97)	8.71 (13.68)	16.67 (23.57)	0.0616
Dyspnea	9.52 (17.82)	6.06 (13.01)	13.49 (22.16)	0.1650
Insomnia	19.05 (26.34)	18.18 (30.03)	24.60 (30.41)	0.5624
Appetite loss	9.52 (25.43)	0.76 (5.03)	11.90 (21.87)	0.0071
Constipation	8.33 (23.35)	11.36 (21.50)	15.08 (23.52)	0.4664
Diarrhea	5.95 (13.00)	2.27 (8.50)	3.17 (9.90)	0.3251
Financial difficulties	1.19 (6.30)	2.27 (8.50)	10.32 (18.75)	0.0062
QLQ-PR25, mean (SD)				
Sexual activity	5.36 (12.05)	3.41 (9.22)	5.16 (10.07)	0.6511
Sexual functioning ($n=16$)	33.33 (0.00)	22.22 (4.81)	43.33 (21.57)	0.2779
Urinary symptoms	18.15 (12.74)	17.33 (12.61)	19.64 (14.27)	0.7179
Bowel symptoms	1.49 (3.96)	2.84 (5.07)	4.96 (9.40)	0.1011
Hormonal treatment-related symptoms	11.91 (9.41)	6.57 (7.97)	11.51 (12.71)	0.0340
Incontinence aid ($n=34$)	25.00 (29.55)	9.52 (25.20)	52.38 (37.80)	0.0493

ADT androgen deprivation therapy, *HRQoL* health-related quality of life, *n* number, *QLQ-C30* Quality of Life Questionnaire Core 30, *QLQ-PR25* Quality of Life Questionnaire-Prostate, *QoL* global quality of life, *RP* radical prostatectomy, *RT* radiation therapy, *RP + ADT* ADT after RP user group, *RT + ADT* RT combine with ADT, *SD* standard deviation

mostly comprised patients with RP alone, with predominantly localized or early-stage PC. Therefore, differences in HRQoL decreased after excluding the stage IV population with metastatic PC. Patients with metastatic PC likely have poorer HRQoL compared with those with non-metastatic PC. An observational study indicated that QoL was poorer among patients with metastatic PC compared with localized PC and the all-stages population [24].

However, in our study, participants with metastatic PC showed deterioration in HRQoL in the ADT alone group. The ADT alone group consistently reported the worst HRQoL, even when excluding the stage IV population. Furthermore, differences among the ADT after RP group, RT combined with ADT group, and ADT alone group were similar for the two subgroup analyses, except for pain, which could be explained by excluding participants with metastases [25].

Besides the cancer stage, the ADT alone group may have had poor QoL due to frequent symptoms reported and poor functioning as most items reached clinical significance. ADT duration was longer in the ADT alone group than the other two groups, which may have led to increased adverse effects and stress.

The cost of RP or ADT after RP is the lowest among other therapies, although Drummond et al. suggested otherwise [26] and a study by Bach et al. [27] indicated similar costs for surgery. The discrepancies in these findings are likely due to differences in the health insurance system, health literacy, and health access barriers. Interestingly, participants who underwent RP for localized PC tended to have a higher educational level than those with advanced stage PC, suggesting that education affects health literacy as well as a possible increased awareness of health status and routine health examinations. Consequently, diseases may be detected and treated at earlier stages.

Our results for sexual activity and sexual functioning among the different treatment groups differ from other studies. Participants undergoing RP or ADT after RP did not show the poorest sexual activity and sexual function among other treatment groups; however, overall sexual activity and sexual functioning in our study appeared to be lower than other studies [15, 28, 29].

Table 4 HRQoL among subgroups of stage I to III ADT user group

	RP + ADT ($n=21$)	RT + ADT ($n=34$)	ADT alone ($n=13$)	p value
QLQ-C30, mean (SD)				
QoL	76.67 (18.85)	73.28 (14.62)	68.59 (17.73)	0.3970
Physical functioning	93.33 (8.65)	84.51 (20.08)	79.49 (21.68)	0.0769
Role functioning	99.17 (3.73)	89.22 (24.23)	89.74 (19.88)	0.1780
Emotional functioning	98.33 (4.36)	95.83 (8.52)	80.13 (24.89)	0.0114
Cognitive functioning	93.33 (16.58)	93.14 (12.39)	88.46 (19.70)	0.6048
Social functioning	95.83 (10.64)	93.63 (12.98)	88.46 (15.79)	0.2786
Fatigue	16.11 (16.71)	17.32 (22.09)	19.66 (24.49)	0.8946
Nausea and vomiting	0.83 (3.73)	0.00 (0.00)	5.13 (12.52)	0.0285
Pain	4.17 (9.17)	8.82 (13.13)	19.23 (32.52)	0.0618
Dyspnea	13.33 (19.94)	7.84 (14.35)	10.26 (28.50)	0.6053
Insomnia	15.00 (22.88)	19.61 (29.72)	33.33 (33.33)	0.1933
Appetite loss	6.67 (20.52)	0.00 (0.00)	15.38 (25.88)	0.0053
Constipation	6.67 (17.44)	9.80 (19.30)	28.21 (32.90)	0.0316
Diarrhea	6.67 (13.68)	2.94 (9.60)	0.00 (0.00)	0.1740
Financial difficulties	0.00 (0.00)	1.96 (7.96)	10.26 (16.01)	0.0074
QLQ-PR25, mean (SD)				
Sexual activity	6.67 (13.68)	3.92 (10.10)	3.85 (9.99)	0.6566
Sexual functioning ($n=6$)	33.33 (0.00)	22.22 (4.81)	50.00 (18.37)	0.0191
Urinary symptoms	19.37 (13.60)	18.14 (13.25)	24.36 (13.49)	0.3652
Bowel symptoms	0.42 (1.86)	2.94 (4.98)	8.97 (13.38)	0.0065
Hormonal treatment-related symptoms	11.95 (9.75)	6.54 (7.42)	9.83 (13.25)	0.1244
Incontinence aid ($n=14$)	41.67 (31.91)	0.00 (0.00)	66.67 (38.49)	0.0102

ADT androgen deprivation therapy, *HRQoL* health-related quality of life, *n* number, *QLQ-C30* Quality of Life Questionnaire Core 30, QoL global quality of life, *QLQ-PR25* Quality of Life Questionnaire-Prostate, *RP* radical prostatectomy, *RT* radiation therapy, *RP + ADT* ADT after RP user group, *RT + ADT* RT combine with ADT, *SD* standard deviation

Overall, functioning and symptoms of ADT patients were significantly and clinically significant among different therapies; however, while QoL was the poorest for the ADT group, this was not significant or clinically significant among other therapies. A systematic review also revealed similar findings [30]. This may be due to the level of the functioning and symptom burden. While functioning in the ADT group was the poorest, it was still good (80–90 points). There were similar findings for symptoms, which were low for the ADT group, but still low-level. These findings for functioning and symptoms burden level are in agreement with those of Duchesne et al. [29], but not hugely different from the findings of Drummond et al. [26] who reported poor functioning for ADT patients. Some of our findings are different from those described by Lehto et al. [31], who reported that the effect on sexual activity and urinary symptoms were related to decreased QoL. However, these differences may be attributed to differences in the methodology and HRQoL assessment tools used. Lehto et al. used a questionnaire purposely designed for their study, while our study used the EORTC QLQ-C30 and QLQ-PR25 questionnaires.

The study results showed that age and comorbidities might not be key determinants associated with deterioration of HRQoL. Furthermore, role functioning appears to have had a positive effect on HRQoL; in that better role functioning was associated with better QoL. Higher role functioning scores indicate that patients are more independent in their daily life in work and leisure activities. A previous study also implied similar findings in cancer patients [32], as participants with longer disease duration showed better HRQoL. This suggests that patients may become accustomed to the disease condition with longer disease duration.

Our cross-sectional survey of HRQoL using EORTC QLQ-C30 and QLQ-PR25 questionnaires has clinical implications for PC treatment and provides valuable decision-making information for health care providers and patients. Treatment for PC varies according to the disease stage. Health care providers and patients need to be aware of the benefits and risks of different treatments in addition to survival outcome. While survival outcome is important in localized and locally advanced PC, it is necessary to understand how treatments may affect daily life. While ADT may

Table 5 Multivariable analysis of associations for QoL life in stage I to IV population

Variable	Estimate (SE)	*p* value	95% Confidence Interval	
			Lower 95%	Upper 95%
Age	−0.04 (0.19)	0.8149	−0.42	0.33
Duration	0.43 (0.62)	0.4891	−0.79	1.65
ADT user	−1.24 (4.45)	0.7814	−10.03	7.56
Active treatment	−3.37 (3.74)	0.3691	−10.76	4.02
Relapse	−3.08 (3.73)	0.4107	−10.45	4.30
GS				
Grade 1 (GS = 6)	1			
Grade 2 (GS = 3+4)	−1.58 (4.45)	0.7234	−10.38	7.22
Grade 3 (GS = 4+3)	1.38 (4.54)	0.7618	−7.61	10.37
Grade 4 (GS = 8)	−2.55 (4.18)	0.5435	−10.81	5.72
Grade 5 (GS ≥ 9)	1.63 (4.27)	0.7029	−6.81	10.07
PSA at diagnosis (ng/mL)				
< 10	1			
10–19	0.68 (3.70)	0.8546	−6.63	7.99
≥ 20	−1.84 (3.81)	0.6305	−9.38	5.70
Stage				
I	1			
II	−2.84 (6.78)	0.6758	−16.24	10.56
III	−0.87 (7.40)	0.9070	−15.51	13.78
IV	0.26 (7.87)	0.9739	−15.31	15.83
Marital status				
Single	1			
Married	23.45 (8.41)	0.0061	6.82	40.08
Widowed	39.32 (10.48)	0.0003	18.59	60.05
Role functioning	0.28 (0.08)	0.0006	0.12	0.43
Nausea and vomiting	−0.55 (0.16)	0.0005	−0.86	−0.25
Insomnia	−0.14 (0.05)	0.0033	−0.23	−0.05

R-square 38.76%

Controlling variables: ADT user, age, duration, ADT user, active treatment, relapse, GS, stage

ADT androgen deprivation therapy, *GS* Gleason score, *PSA* prostate-specific antigen, *QoL* global quality of life, *SE* standard error

worsen QoL, this is not significant in patients with localized and locally advanced PC (stages I–III). Furthermore, symptoms like nausea, vomiting, and insomnia are the main factors that affect HRQoL, while work and leisure activities improve QoL.

One of the strengths of our study is that this cross-sectional study is the largest study to evaluate the HRQoL in PC patients in Taiwan. Furthermore, we demonstrated HRQoL among all disease stages, not only metastatic diseases, and evaluated various therapies for PC. We evaluated HRQoL using QLQ-C30 and PR-25 questionnaires, which were specifically designed for PC. However, there are also some limitations to the study. First, this study was conducted in two hospitals in southern Taiwan and this might limit generalization. Second, family members were allowed to accompany the participants when completing the questionnaires. This may mean that participants have not always responded accurately to some items, especially regarding sexual activity and sexual functioning. Furthermore, some questionnaires were completed with the help of family members or researchers. Additionally, some participants with long disease duration may have changed the type of ADT. However, these limitations were equal across the analyzed groups.

Conclusion

Our findings improve our understanding of HRQoL in PC patients across all disease stages using different treatments. QoL in PC patients with all-stages differed significantly between the ADT and non-ADT groups and was poorer for the ADT group. However, while QoL was poorer for the ADT group than the non-ADT group among stages I–III patients, this was not significantly different. Symptoms are

key determinants of QoL, and patients and health care providers need to be aware of these when deciding on treatment.

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References

1. Ministry of Health and Welfare. Death statistics annual report. 2017. https://www.mohw.gov.tw/lp-3961-2.html. Accessed 23 July 2018.
2. Ministry of Health and Welfare. 2015 Taiwan Cancer Registry. https://www.hpa.gov.tw/EngPages/Detail.aspx?nodeid=1061&pid=6071. Accessed 29 Jan 2015.
3. National Cancer Institute. Cancer stat facts: prostate cancer. 2016; https://seer.cancer.gov/statfacts/html/prost.html (2018). Accessed 12 Jan 2018.
4. Namiki S, Arai Y. Health-related quality of life in men with localized prostate cancer. Int J Urol. 2010;17(2):125–38.
5. Chen RC, Basak R, Meyer AM, Kuo TM, Carpenter WR, Agans RP, et al. Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. JAMA. 2017;317(11):1141–50.
6. Namiki S, Kwan L, Kagawa-Singer M, Tochigi T, Ioritani N, Terai A, et al. Sexual function following radical prostatectomy: a prospective longitudinal study of cultural differences between Japanese and American men. Prostate Cancer Prostatic Dis. 2008;11(3):298–302.
7. Cella DF. Measuring quality of life in palliative care. Semin Oncol. 1995;22(2 Suppl 3):73–81.
8. Barocas DA, Chen V, Cooperberg M, Goodman M, Graff JJ, Greenfield S, et al. Using a population-based observational cohort study to address difficult comparative effectiveness research questions: the CEASAR study. J Comp Eff Res. 2013;2(4):445–60.
9. Shields AL, Hao Y, Krohe M, Yaworsky A, Mazar I, Foley C, et al. Patient-Reported Outcomes in Oncology Drug Labeling in the United States: A Framework for Navigating Early Challenges. Am Health Drug Benefits. 2016;9(4):188–97.
10. Smith-Palmer J, Takizawa C, Valentine W. Literature review of the burden of prostate cancer in Germany, France, the United Kingdom and Canada. BMC Urol. 2019;19(1):19.
11. Adamowicz K. Assessment of quality of life in advanced, metastatic prostate cancer: an overview of randomized phase III trials. Qual Life Res. 2017;26(4):813–22.
12. Osoba D. Health-related quality of life and cancer clinical trials. Ther Adv Med Oncol. 2011;3(2):57–71.
13. Murasawa H, Sugiyama T, Matsuoka Y, Okabe T, Hino A, Tanaka N, et al. Health utility and health-related quality of life of Japanese prostate cancer patients according to progression status measured using EQ-5D-5L and FACT-P. UQual Life Res. 2019. https://doi.org/10.1007/s11136-019-02184-y.
14. Lopez-Calderero I, Lopez-Fando L, Rios-Gonzalez E, Maisonobe P, Hernández-Yuste E, Sarmiento-Jordán M, et al. Impact of locally advanced or metastatic prostate cancer on the quality of life. Actas Urol. Esp. 2017;41(6):368–75.
15. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. The New England journal of medicine. 2016;375(15):1425–37.
16. Hashine K, Azuma K, Koizumi T, Sumiyoshi Y. Health-related quality of life and treatment outcomes for men with prostate cancer treated by combined external-beam radiotherapy and hormone therapy. Int J Clin Oncol. 2005;10(1):45–50.
17. Chie W-C, Yu C-C, Yu H-J. Reliability and validity of the Taiwan Chinese Version of the EORTC QLQ-PR25 in assessing quality of life of prostate cancer patients. Urol Sci. 2010;21(3):118–25.
18. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 scoring manual (3rd edition). European Organisation for Research and Treatment of Cancer; 2001.
19. Potosky AL, Haque R, Cassidy-Bushrow AE, Ulcickas Yood M, Jiang M, Tsai HT, et al. Effectiveness of primary androgen-deprivation therapy for clinically localized prostate cancer. J Clin Oncol. 2014;32(13):1324–30.
20. Health Promotion Administration Ministry of Health and Welfare Taiwan. Cancer registry annual report, 2015 Taiwan. https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=269&pid=8084. Accessed 27 Dec 2017.
21. National Health Research Institutes. Guideline for clinical diagnosis and treatment of prostate cancer. 2010; 2010:120.
22. National Comprehensive Cancer Network. National Cancer Institute Cancer Stat Facts: Prostate Cancer (Version 2.2017). 2017; https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 8 Jan 2018.
23. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int. 2013;111(5):753–60.
24. Bergius S, Torvinen S, Muhonen T, Roine RP, Sintonen H, Taari K. Health-related quality of life among prostate cancer patients: real-life situation at the beginning of treatment. Scand J Urol. 2017;51(1):13–9.
25. Mendez LC, Raman S, Wan BA, da Silva JLP, Moraes FY, Lima KMLB, et al. Quality of life in responders after palliative radiation therapy for painful bone metastases using EORTC QLQ-C30 and EORTC QLQ-BM22: results of a Brazilian cohort. Ann Palliat Med. 2017;6(Suppl 1):S65–s70.
26. Drummond FJ, Kinnear H, O'Leary E, Donnelly, Gavin A, Sharp L. Long-term health-related quality of life of prostate cancer survivors varies by primary treatment. Results from the PiCTure (Prostate Cancer Treatment, your experience) study. J Cancer Surviv. 2015;9(2):361–72.
27. Bach P, Doring T, Gesenberg A, Mohring C, Goepel M. Quality of life of patients after retropubic prostatectomy—pre- and postoperative scores of the EORTC QLQ-C30 and QLQ-PR25. Health Qual Life Outcomes. 2011;9:93.
28. Adam S, Feller A, Rohrmann S, Arndt V. Health-related quality of life among long-term (>/=5 years) prostate cancer survivors by primary intervention: a systematic review. Health Qual Life Outcomes. 2018;16(1):22.
29. Duchesne GM, Woo HH, King M, Bowe SJ, Stockler MR, Ames A, et al. Health-related quality of life for immediate versus delayed androgen-deprivation therapy in patients with asymptomatic, non-curable prostate cancer (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol. 2017;18(9):1192–201.
30. Adam S, Feller A, Rohrmann S, Arndt V. Health-related quality of life among long-term (>/=5 years) prostate cancer survivors by primary intervention: a systematic review. Health Qual Life Outcomes. 2018;16(1):22.

31. Lehto US, Tenhola H, Taari K, Aromaa A. Patients' perceptions of the negative effects following different prostate cancer treatments and the impact on psychological well-being: a nationwide survey. Br J Cancer. 2017;116(7):864–73.
32. Hung HY, Wu LM, Chen KP. Determinants of quality of life in lung cancer patients. J Nurs Scholarsh. 2018;50(3):257–64.