

Medication utilization evaluation of androgen deprivation therapy for prostate cancer in Taiwan

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Abstract

Prostate cancer is one of the most common cancer in males. Both the incidence and the mortality rates of prostate cancer show an increasing trend. Androgen deprivation therapy (ADT) is the standard treatment for metastatic prostate cancer. The aim of our study was to show the epidemiology of prostate cancer and the proportion of patients utilizing ADT.

This study used Taiwan's National Health Insurance Research Database (NHIRD) and identified the patients who had been diagnosed with prostate cancer (International Classification of Disease (ICD)-10: C61) and followed up between Jan 1, 2008 and Dec 31, 2015. The ADT drugs used by prostate cancer patients were recorded: Gonadotropin-releasing hormone (GnRH) agonists; GnRH antagonist; estrogen analogs and androgen receptor antagonist.

A total of 25,233 patients with newly diagnosed prostate cancer in 2008–2014 were enrolled. The utilization of ADT increased from more than 7,000 person-time in 2008 to more than 50,000 person-time in 2014. Cyproterone acetate was the most commonly used drug in 2008–2015, but its proportion of utilization, which was the highest in stage 2 cancer, dropped from 43% in 2008 to 15% in 2015. Bicalutamide was the second most used drug from 2008 to 2015, but its utilization was not different for different stages.

The incidence rate of prostate cancer increased in the study period and medical expenditure also increased in ADT treatment. Health insurance benefits for various ADT drugs should be further evaluated.

Abbreviations: ADT = Androgen deprivation therapy, CI = confidence interval, GnRH = gonadotropin-releasing hormone, HR = hazard ratio, ICD = International Classification of Disease, NHIRD = National Health Insurance Research Database, PSA = prostate specific antigen.

Keywords: androgen deprivation therapy, medication utilization, prostate cancer

1. Introduction

Other than skin cancer, prostate cancer is the most common cancer in males in America. In Taiwan, more than 4,000 new cases of prostate cancer are diagnosed each year. The age-standardized incidence rate is 29.22/100,000, and in 2015, the mortality rate was 10.5/100,000. Both the incidence and the mortality rates of prostate cancer in Taiwan show an increasing trend year to year.^[1] The treatment of prostate cancer can be divided into four main categories: surgical treatment, radiation therapy, hormone therapy and chemotherapy. The prototypical

oncogene and the product of gene fusions are often elevated throughout the course of prostate cancer progression. The main mechanism of hormone therapy is to reduce the binding of androgen hormones and steroid hormones to their receptors, thus inhibiting the proliferation of cancer cells. Another treatment method that uses drugs or surgery is androgen deprivation therapy (ADT); it is the standard treatment for metastatic prostate cancer.^[2] ADT includes gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, estrogen analogs, androgen receptor antagonists, and orchiectomy. Hormone

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The authors declare no conflict of interest.

Data are available from the National Health Insurance Research Database (NHIRD) published by Taiwan National Health Insurance (NHI) Bureau. Due to legal restrictions imposed by the government of Taiwan in relation to the "Personal Information Protection Act", data cannot be made publicly available. Requests for data can be sent as a formal proposal to the NHIRD (<http://nhird.nhri.org.tw>).

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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therapy may cause some changes in male hormones within the body, leading to some side effects due to resultant hypogonadism. The common side effects of orchiectomy, GnRH antagonists, GnRH agonists are sexual dysfunction, hot flushes, muscle atrophy, weight gain, dyslipidemia, and anemia; long-term ADT may increase the risk of osteoporosis, cardiovascular disease and diabetes.^[3] GnRH agonists may increase the risk of diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death. Orchiectomy has also been found to increase the risk of diabetes. The risk in developing the above diseases is higher for GnRH agonists than for orchiectomy.^[4,5] However, the results of subsequent studies on the correlation between ADT and cardiovascular disease are not consistent.^[6–9] Current studies indicate that ADT side effects include cardiovascular diseases and dementia,^[10–12] but the results of a study on the correlation between ADT and stroke showed that ADT did not increase the risk of stroke (hazard ratio (HR): 1.09; 95% confidence interval (CI): 0.8–1.5). Therefore, the risk of cardiovascular and cerebrovascular diseases resulting from ADT has not yet been clearly elucidated in the published literature.^[13–16]

Information on the epidemiology, medical costs, and side effects of ADT in patients with prostate cancer is insufficient in Taiwan. In particular, in early radical prostatectomy and other treatments, the clinical data for the cost of ADT as an adjuvant therapy is still very limited. Therefore, this study retrieved data for patients with prostate cancer, and based on their medical records, the epidemiology of prostate cancer and the cost of ADT as a postoperative adjuvant drug treatment were evaluated. Based on the prevalence rates and incidence rates for different age groups, the changing trend in the incidence rate was investigated, and the proportion of patients utilizing ADT in different years was recorded. Additionally, the cost of ADT in patients with prostate cancer receiving ADT were investigated.

2. Materials and methods

This study used data retrieved from Taiwan's National Health Insurance Research Database (NHIRD). Details of this population-based database have been published previously.^[17] In this population-based retrospective cohort study, we first identified the patients who had been diagnosed with prostate cancer (International Classification of Disease (ICD)-10: C61) and between Jan 1, 2008 and Dec 31, 2014 and followed up until Dec 31, 2015. The date that the patient was first diagnosed with prostate cancer was the index date. The exclusion criterion for the patients was diagnosis of prostate cancer or other cancers before the index date. For the epidemiological investigation, the number and age distributions of the patients for each year were investigated. For the assessment of ADT drug utilization, the amount of ADT drug utilized each year, the number of claims per year, the annual reported expense, and the average drug cost were analyzed. The ADT drugs used by prostate cancer patients were recorded: the GnRH agonists used included leuprolide, goserelin, triptorelin, buserelin, and degarelix; the androgen receptor antagonists used included flutamide, bicalutamide, and enzalutamide; the estrogen analogs used included cyproterone, medroxyprogesterone, hexoestrol, and diethylstilbestrol; and the antiandrogen was abiraterone. The number of patients in each year (the number of patients diagnosed with prostate cancer in different stages for the first time), the age of the newly diagnosed patient [the number of the patients newly diagnosed with prostate cancer in different age groups (40–49, 50–59, 60–69, 70–79, 80–89, and greater than

90)], the mortality rate (the mortality rate for the patients in different stages), and the survival time (the calculated time from the index date to death) were analyzed. For the surviving patients, the time from the index date to the last day of the follow-up period was recorded and analyzed. Person-time is a measure that incorporates time directly into the person. Person-years of observation take into consideration both the number of persons who were observed and the duration of observation of each person. For example, one person who used ADT drug for 10 years contribute 10 person-years of observation.

2.1. Statistical analysis

The drug use assessment analysis in this study calculated the utilization status of individual drugs during the overall observation period, such as the number of patients utilizing an individual drug / the overall patients included in the study. The Cochran-Armitage test was used to analyze the trends of the utilization of various drugs for each year. A Kaplan–Meier analysis was used to plot survival rates. This study used SAS version 9.4 (SAS Institute Inc., Cary, NC) to extract, debug, and statistically analyze the variables from the NHIRD and the medical center database. The research was approved by the IRB of Kaohsiung Medical University Hospital (KMUHIRB-EXEMPT-20170011).

3. Results

3.1. Epidemiological study of prostate cancer

A total of 25,223 patients with newly diagnosed prostate cancer in 2008–2014 were retrieved from the cancer registration data, and the patients showing unclear cancer staging were excluded. As shown in Table 1, most of the included prostate cancer patients were had stage 2 cancer (a total of 10,521 patients), followed by patients with stage 4 cancer. The number of newly diagnosed patients in each year increased from 2,522 in 2008 to 4,153 in 2014. As shown in Table 2 and Figure 1. In Taiwan, the onset age of 25,223 patients with newly diagnosed prostate cancer was predominantly 70 to 79 years old, and the age proportions of the patients in each stage were similar, with more than 80% of patients in the age range of 60 to 80 years old. ADT is utilized as a first-line preventive therapy for the recurrence of prostate cancer, as shown in Table 3.

According to the proportion of the patients who utilized ADT drugs in each year, the ADT drugs used by patients with stage 2 prostate cancer was the highest proportion, followed by patients with stage 3 prostate cancer (Fig. 2). The observation from 2008 to 2015 showed that the proportions of patients with stages 2 and 4 prostate cancer who utilized ADT drugs decreased, while the

Table 1
Number of patients with different stages of prostate cancer, 2008 to 2014.

Year	Stage 1 (n = 2126)	Stage 2 (n = 10521)	Stage 3 (n = 4341)	Stage 4 (n = 8235)	Total
2008	50	1246	416	810	2522
2009	84	1623	521	963	3191
2010	376	1393	612	1204	3585
2011	411	1504	664	1271	3850
2012	402	1534	685	1231	3852
2013	380	1568	747	1375	4070
2014	423	1653	696	1381	4153

Table 2
Number of patients in different age groups for each prostate cancer stage.

Cancer stage	40–49	50–59	60–69	70–79	80–89	90–99
Stage 1 (n=2126)	20	184	669	811	413	29
Stage 2 (n=10521)	57	871	2872	4320	2243	158
Stage 3 (n=4341)	19	409	1467	1750	664	32
Stage 4 (n=8235)	51	533	1851	3185	2364	251

proportions of patients with stages 1 and 3 prostate cancer increased year to year. In 2008, the number of patients with stage 3 prostate cancer who utilized ADT drugs was smaller than that of patients with stage 4 prostate cancer, but after 2009, patients with stage 3 prostate cancer who utilized ADT outnumbered those with stage 4 prostate cancer. The trend analysis showed that ADT utilization was significantly increased ($P < .0001$).

ADT utilization in 2008–2015 showed a significant change. Cyproterone acetate was the most commonly used drug in 2008–2015, but its proportion of utilization, which was the highest in stage 2 cancer, dropped from 43% in 2008 to 15% in 2015. Bicalutamide was the second most used drug from 2008 to 2015, but its utilization was not different for different stages. Patients who received leuprolide in 2008 mainly had stage 2 and stage 3 prostate cancer, while the number of the patients with stage 2 prostate cancer who utilized leuprolide in 2012 was more than that of patients with stage 3 prostate cancer.

3.2. The utilization and cost of ADT drugs

As shown in Table 4, most ADT drugs showed steady growth in utilization between 2008 and 2015. In particular, the utilization of leuprolide increased from 399 person-time in 2008 to 14,939 person-time in 2015 (approximately 37.5-fold); it was also the

most frequently utilized ADT drug. The next most frequently utilized ADT drug was bicalutamide, which was utilized more than 15,000 person-time in 2014, compared to 1551 person-time in 2008, a 10-fold increase. In 2008, the most frequently used ADT drug was cyproterone, which continued to be utilized, but its utilization showed a decreasing trend year to year after 2012. In addition, the utilization of diethylstilbestrol significantly decreased after 2013, and the data for 2015 showed that its utilization was zero person-time. Based on the above data, the utilization of estrogen analog drugs significantly reduced in recent years, which was highly related with current clinical treatment guidelines and side effects. The average cost per person-time for each ADT drug was shown in Table 5. In addition, the utilization of abiraterone acetate and degarelix, approved in 2014, showed a significant increase in 2015, especially abiraterone, which was utilized 1000 person-time within two years. As shown in Table 6, the declared expense of ADT utilization reported in 2008–2015 increased from 20 million Taiwan Dollars in 2008 to 210 million Taiwan Dollars in 2015.

3.3. ADT treatment mode for prostate cancer

According to the data in Table 7, in 2008–2015, the number of prostate cancer patients who received at least one ADT after the

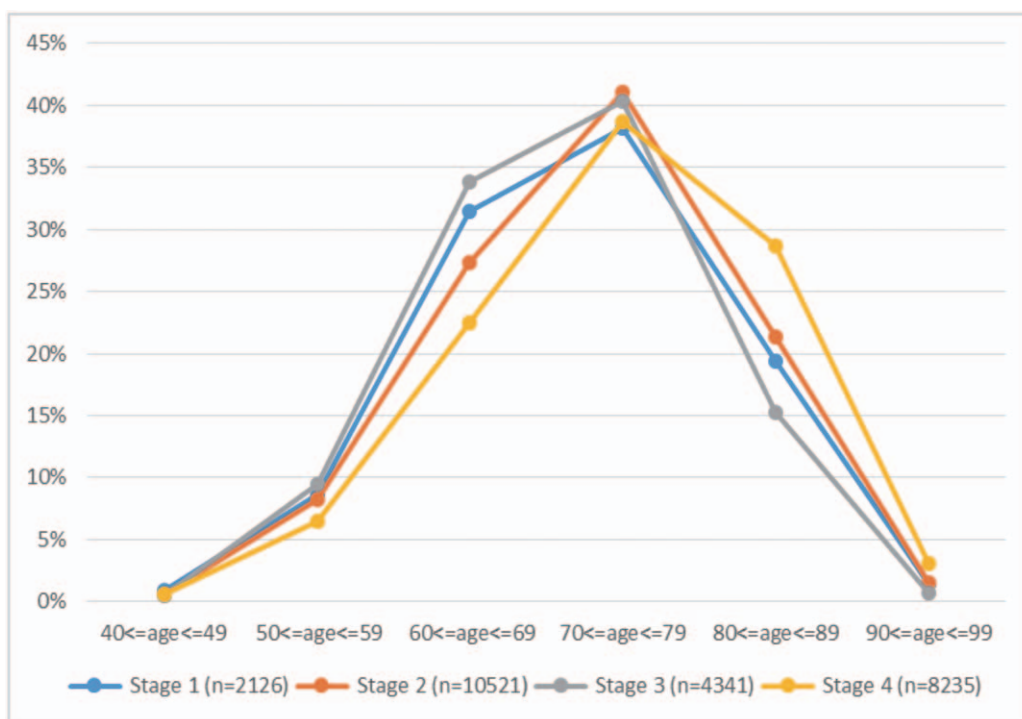


Figure 1. Proportion of prostate cancer patients in each age group for each cancer stage.

Table 3**Number of patients who received androgen deprivation therapy by each prostate cancer stage and for each year.**

Year	e	Stage 2 (n=10521)	Stage 3 (n=4341)	Stage 4 (n=8235)	Total
2008	32	745	261	300	1338
2009	67	1493	580	482	2622
2010	186	1918	922	691	3717
2011	285	2299	1224	793	4601
2012	349	2723	1497	899	5468
2013	360	2996	1768	992	6116
2014	363	3193	1936	1025	6517
2015	311	2767	1739	727	5544

index date was 14,125. The number of patients with stage 2 prostate cancer who used ADT was 6416 (accounting for 60.9% of the patients with stage 2 prostate cancer). The numbers of patients with stage 3 and stage 4 prostate cancer who used ADT were close, but the proportions were different; 75.3% and 44.3% of patients with stage 3 and stage 4 prostate cancer used ADT, respectively. The number of patients with stage 1 prostate cancer who received ADT was relatively small, accounting for approximately 36.8%.

From Table 8, the period from diagnosis to the beginning of ADT was gradually shortened from stage 1 to stage 3 (0.49–0.36 years), and the patients with stage 1 to stage 3 prostate cancer who utilized ADT did so within 6 months after diagnosis. According to the current treatment guidelines for patients with stage 4 prostate cancer, ADT should be applied after chemotherapy. Therefore, the period from diagnosis to beginning ADT was longer, an average of 10 months, for patients with stage 4 prostate cancer than those with other stages of prostate cancer. ADT drugs were utilized immediately after diagnosis in some cases for each stage, and the longest period before utilization was more than 7 years (these patients all showed deterioration or raised prostate specific antigen (PSA)). In addition, based on the data of 14125 patients shown in Figure 3, the period from diagnosis to beginning ADT for 2918 (20.6%) patients was longer than 183 days; for the remaining 11207 patients (79.4%),

the period was less than 183 days and mostly 1 day (the day of diagnosis) or within 7 days after diagnosis. Figure 4 showed the survival analysis for each prostate cancer stage.

4. Discussion

According to the patient and drug epidemiological data for prostate cancer from 2008 to 2015, the incidence rate of prostate cancer increased year to year, with drugs and different treatment methods showing the same upward trend. In our study, the cost of ADT utilized by patients with prostate cancer showed a substantial increase after 8 years. Because prostate-specific antigen screening was implemented in Taiwan, the number of the patients with stages 1 to 3 prostate cancer was higher than that of patients with stage 4 prostate cancer; when detected early, prostate cancer has a high survival rate based on current treatment guidelines. Therefore, there was a significant increase in the utilization of ADT drugs because the incidence increased; however, the mortality rate was low. In addition, the cost of abiraterone acetate became one of the top three drug claims in just 2 years. In fact, if the average cost per person-time for each drug was calculated based on the total person-time and the total cost for each ADT drug, the average cost of abiraterone acetate per person-time was found to be more than 30,000 Taiwan Dollars. In addition, the average cost of triptorelin per person-time

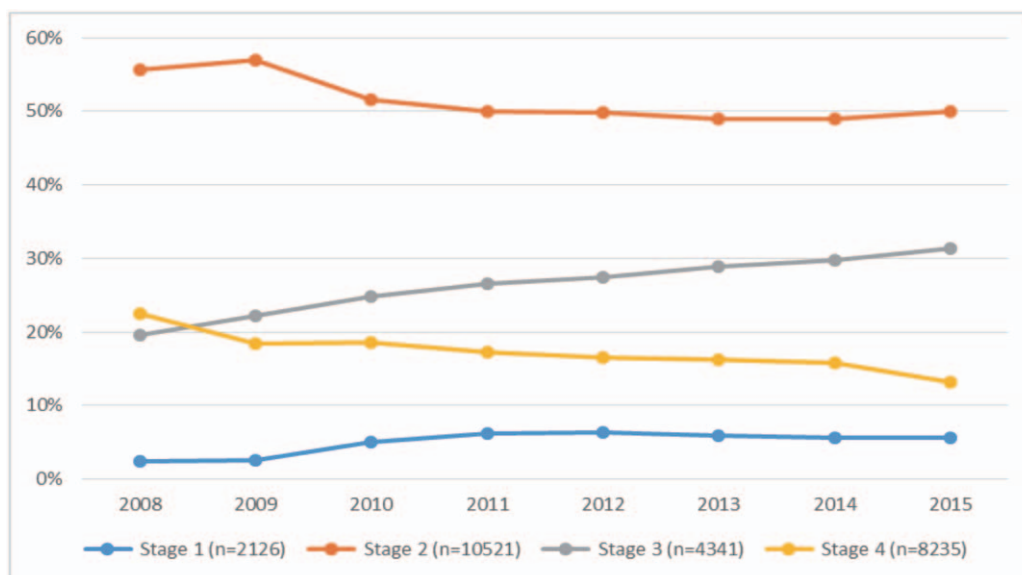
**Figure 2.** Proportion of patients who utilized ADT by different stages for each year.

Table 4
Claims for each androgen deprivation therapy drug (person-time), 2008–2015.

	2015	2014	202013	2012	2011	2010	2009	2008
Cyproterone acetate	8251	11130	1111874	12691	12127	10782	8579	4502
Diethylstilbestrol	0	1	14148	691	741	619	401	189
Medroxyprogesterone	337	294	26268	260	227	117	49	31
Buserelin	0	0	000	0	0	0	0	0
Leuprolide	14939	14956	1111446	8911	6566	4085	2047	399
Goserelin	3837	4962	464638	3398	2097	1325	508	144
Triptorelin	1608	1536	141482	1209	685	276	116	28
Flutamide	1884	2486	282846	2867	2538	1992	1316	520
Bicalutamide	12822	15088	1313670	11201	8779	6176	3898	1551
Enzalutamide	0	0	000	0	0	0	0	0
Aminoglutethimide	0	0	000	0	0	0	0	0
Degarelix	83	0	000	0	0	0	0	0
Abiraterone acetate	1058	5	000	0	0	0	0	0
Total	44819	50458	4646372	41228	33760	25372	16914	7364

was also more than 10,000 Taiwan Dollars. The average cost of the other drugs was less than 6,000 Taiwan Dollars.

In our study, prostate cancer patients started ADT within an average of half a year after diagnosis, especially for patients with stage 1 to stage 3 prostate cancer. The utilization of ADT increases from more than 7,000 person-time in 2008 to more than 50,000 person-time in 2014. The corresponding ADT cost also increased from 50 million Taiwan Dollars in 2008 to 200 million Taiwan Dollars in 2014. Among the individual ADT drugs, some patients with stage 4 prostate cancer gradually tended to utilize new drugs (degarelix and abiraterone acetate) that had a higher unit price but, in recent years, were covered by health insurance, while the patients with stage 1 to stage 3 prostate cancer tended to utilize drugs that were not covered by health insurance (triptorelin/leuprolide/bicalutamide). However, regardless of the stage, the utilization of estrogen analogs decreased significantly after 2012, mainly related to side effects and survival rates.^[18] The survival rate of the patients with prostate cancer in Taiwan showed that patients with stage 4 prostate cancer had a higher mortality rate than the patients with other stages prostate cancer; therefore, early diagnosis is of great importance for prostate cancer. In addition, the patients who utilized ADT were at higher risk than those who did not utilize ADT, leading to a higher mortality rate in patients who utilized

ADT. Regarding treatment mode, more than half of the patients received radiation therapy, prostate-related surgery or ADT. The data also showed that some patients received more than two treatments simultaneously; the patients who received more than two treatments were mostly treated with surgery followed by other treatments (especially ADT).

The treatment algorithms for patients with high-risk nonmetastatic prostate cancer has changed considerably and evolved rapidly over the last few years. ADT alone is potentially inappropriate care for patients with high-risk nonmetastatic disease.^[19] In our study, very few patients received ADT alone, and most patients followed the treatment guidelines for their prostate cancer stage.

Based on the clinical data and the survival curves of patients who utilized ADT and the patients who did not utilize ADT, the survival rate of the patients who did not utilize ADT was higher ($P < .0001$), which was highly related to the disease severity of the patients. Most patients who currently utilize ADT in Taiwan are patients at moderate and high risk with raised PSA levels; therefore, the mortality rate of patients who utilize ADT can be higher than that of those who do not utilize ADT. Even if the patients who utilized ADT were assessed by separate stages, the same trend was observed. If the survival risk of patients who utilize ADT is high, the efficacy of ADT treatment should be

Table 5
Average cost per person-time for each androgen deprivation therapy drug, 2008–2015.

	2015	2014	2013	2012	2011	2010	2009	2008
Cyproterone acetate	2091	2063	2163	2238	2337	2332	2601	2538
Diethylstilbestrol	0	90	64	76	72	74	75	38
Medroxyprogesterone	691	813	818	905	809	765	801	331
Buserelin	0	0	0	0	0	0	0	0
Leuprolide	5266	5059	4875	4676	4875	4721	5368	5754
Goserelin	5390	5886	6227	5641	5536	6409	8042	8201
Triptorelin	11271	11395	10584	9989	8624	7411	6347	6659
Flutamide	1958	1937	1867	1883	1943	2019	2410	1955
Bicalutamide	3210	3294	3546	3668	3602	3577	3502	3244
Enzalutamide	0	0	0	0	0	0	0	0
Aminoglutethimide	0	0	0	0	0	0	0	0
Degarelix	5669	0	0	0	0	0	0	0
Abiraterone acetate	30419	50722	0	0	0	0	0	0
Total	4740	3970	3883	3592	3396	3201	3253	2873

Table 6
Declared expense for each androgen deprivation therapy drug, 2008–2015.

	2015	2014	2013	2012	2011	2010	2009	2008
Cyproterone acetate	17249960	22964962	25681170	28408588	28343178	25144698	22313797	11426183
Diethylstilbestrol	0	90	9476	52278	53488	45906	29978	7258
Medroxyprogesterone	233014	239049	219316	235384	183583	89475	39228	10250
Buserelin	0	0	0	0	0	0	0	0
Leuprolide	78666584	75663707	55798529	41665094	32009869	19283968	10989280	2295891
Goserelin	20680486	29207169	28879505	19168010	11609672	8492472	4085532	1180876
Triptorelin	18124281	17502225	15685027	12076958	5907613	2045464	736287	186444
Flutamide	3688055	4815559	5312698	5397629	4930590	4021323	3171821	1016511
Bicalutamide	41159023	49696028	48467854	41089127	31621655	22094513	13651728	5031520
Enzalutamide	0	0	0	0	0	0	0	0
Aminoglutethimide	0	0	0	0	0	0	0	0
Degarelix	470498	0	0	0	0	0	0	0
Abiraterone acetate	32183720	253612	0	0	0	0	0	0
Total	212455621	200342401	180053575	148093068	114659648	81217819	55017651	21154933

assessed based on the efficacy of different drugs or additional doses. In contrast, the efficacy assessment of ADT treatment in the patients not undergoing surgery showed that the risk of death of patients with stage 1 to stage 3 prostate cancer who utilized ADT was the same as that of the patients who did not utilize ADT; there was no statistically significant difference.

Prostate-specific antigen screening for prostate cancer has gradually improved the early detection of patients with prostate cancer in Taiwan.^[20] However, the results of this study showed that more than 60% of patients who obtained an early diagnosis received ADT drugs, leading to a continuous increase in ADT drugs costs, which is highly relevant for insurance coverage of ADT drugs. Therefore, after eliminating highly suspicious vascular side effects, the health insurance payment specifications relevant to ADT utilization should be reviewed and revised to avoid increasing medical expenses. Impairment in quality of life on ADT is well published, the economic benefit of new drugs should be routinely evaluated, and ADT drugs that are covered by health insurance must undergo a systemic health technology assessment to reduce the continuous increase in medical costs.

However, there are some limitations in our study. The study was based on the NHIRD, we could not further analyze the

factors of diet, smoking and obesity. We also do not have information about family history and gene change. The aim of our study was to conduct a drug utilization research. We used an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines. Some prescribing information probably cannot be matched to primary evidence based and carry a considerable impact on medical cost. We identified the patients who had been diagnosed with prostate cancer and between Jan 1, 2008 and Dec 31, 2014 and followed up until Dec 31, 2015, which is 5 years ago. The changes in prescribing and utilization of ADT have changed significantly over the last 5 years. There has been a large reduction in men undertaking ADT. Moreover, the impact of newer agents such as use of docetaxel, abiraterone from the STAMPEDE trials^[21] in recent years also impacts upon how clinically meaningful these results are.

5. Conclusion

This study investigated the utilization of individual ADT drugs for different years and cancer stages to understand the drug

Table 7
Time from the index date to first utilization of androgen deprivation therapy.

Cancer stage	Number of users	%	Longest period (days)	Shortest period (days)	Average period (years)
1 (n=2126)	784	36.8	2415	0	0.49
2 (n=10521)	6416	60.9	2732	0	0.36
3 (n=4341)	3273	75.3	2578	0	0.34
4 (n=8235)	3652	44.3	2801	0	0.83
Total	14125		2801	0	0.48

Table 8
Time from the index date to first utilization of androgen deprivation therapy for each stage.

Cancer Stage	Number of users	%	Longest period (days)	Shortest period (days)	Average period (years)
1 (n=2126)	784	36.8	2415	0	0.49
2 (n=10521)	6416	60.9	2732	0	0.36
3 (n=4341)	3273	75.3	2578	0	0.34
4 (n=8235)	3652	44.3	2801	0	0.83
Total	14125		2801	0	0.48

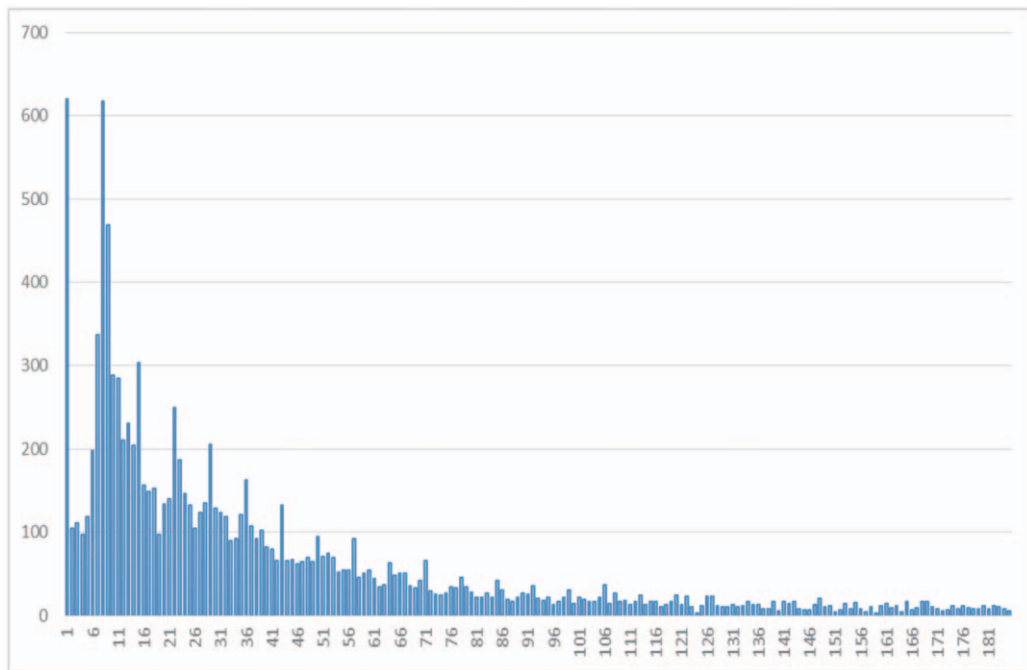


Figure 3. Number of days from the index date to first utilization of ADT.

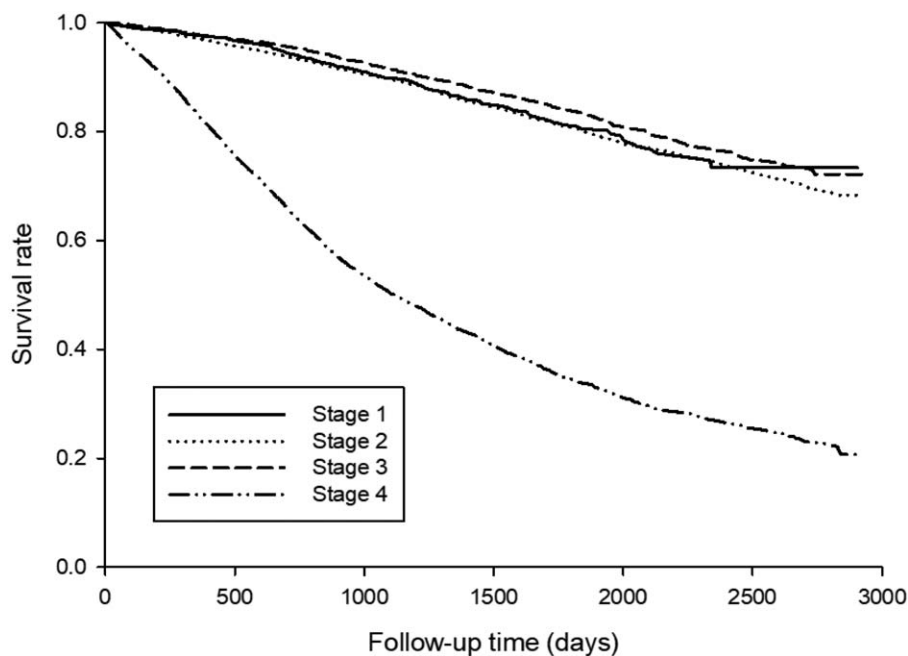


Figure 4. Survival analysis for each prostate cancer stage.

epidemiology of ADT for patients with prostate cancer in Taiwan. The results can provide not only patient epidemiological and drug epidemiological data for prostate cancer in Taiwan but also a reference for relevant clinicians when prescribing ADT drugs. These results should be interpreted cautiously, the study followed up until Dec 31, 2015, which is 5 years ago, new combination study has evolved as the standard of care for metastatic prostate cancer. We may need to perform a follow-up review of high-priced new drugs, combination therapy, and to

assess the use of recently approved drugs. Additionally, health insurance benefits for various ADT drugs should be further evaluated.

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Funding acquisition: Chung-Yu Chen, Ya-Ling Wang.

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Visualization: Chung-Yu Chen.

Writing – original draft: Kuang-Ming Liao, Chung-Yu Chen.

Writing – review & editing: Kuang-Ming Liao, Chung-Yu Chen.

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