RESEARCH ARTICLE

Prevalence study of intermittent hormonal therapy of Prostate Cancer patients in Spain [version 1; peer review: 1 approved, 1 approved with reservations]

Xavier Bonfill-Cosp¹⁻³, Ariadna Auladell-Rispau ¹, Ignasi Gich¹⁻³,
Javier Zamora^{2,4,5}, Luis Carlos Saiz⁶, Jose Ignacio Pijoan^{2,7}, Iratxe Urreta ^{2,8},
José Antonio Cordero ⁹

¹Iberoamerican Cochrane Centre, Biomedical Research Institute Sant Pau (IIB Sant Pau), Barcelona

²CIBER of Epidemiology and Public Health (CIBERESP), Madrid

³Autonomous University of Barcelona, Barcelona

⁴Clinical Biostatistics Unit, Hospital Universitario Ramón y Cajal, Madrid

⁵Institute of Metabolism and System Research, University of Birmingham, UK, Birmingham

⁶Unit of Innovation and Organization, Navarre Health Service, Pamplona

⁷Clinical Epidemiology Unit, Hospital Universitario Cruces/BioCruces-Bizkaia Health Research Institute, Barakaldo

⁸Clinical Epidemiology and Research Unit, University Hospital of Donostia, Donostia

⁹School of Health Sciences Blanquerna, University Ramon Llull, Barcelona

V1 First published: 21 Oct 2021, 10:1069
<https://doi.org/10.12688/f1000research.53875.1>
Latest published: 21 Apr 2022, 10:1069
<https://doi.org/10.12688/f1000research.53875.2>

Abstract

Background: Although intermittent androgen deprivation therapy was introduced many years ago to improve patients' quality of life with the same carcinologic efficiency as continuous hormonal therapy, recent data suggest that those patients could be overtreated. This study aims to estimate the prevalence of prostate cancer patients receiving intermittent androgen deprivation therapy in Spain.

Methods: A retrospective, longitudinal study was conducted using electronic drug dispensation data from four Spanish autonomous communities, which encompass 17.23 million inhabitants (36.22% of the total population in Spain). We estimated intermittent androgen therapy use (%IAD) and the prevalence of patients under intermittent androgen therapy (P_{IAD}) overall and stratified by region. Other outcome variables included the pharmaceutical forms dispensed and the total direct annual expenditure on androgen deprivation therapy-associated medications.

Results: A total of 863,005 dispensations corresponding to a total of 65,752 men were identified, treated with either luteinizing hormone-releasing hormone (LHRH) analogues (353,162) administered alone or in combination with anti-androgens (509,843). Overall, the mean ($\pm$ SD) age of the patients was 76.9 ($\pm$ 10.4) years. Results revealed that the mean annual P_{IAD} along the study was 6.6% in the total population

Open Peer Review

Approval Status

	1	2
version 2		
(revision)
21 Apr 2022
version 1
21 Oct 2021

1. **Helena Colom Codina** , University of Barcelona, Barcelona, Spain

2. **Philipp Dahm**, University of Minnesota, Minneapolis, USA

Any reports and responses or comments on the article can be found at the end of the article.

studied, and the overall %IAD during the five-year study period was 5.6%. The mean cost of hormonal therapy per year was 25 million euros for LHRH analogues and 6.3 million euros for anti-androgens.

Conclusions: An important proportion of prostate cancer patients in Spain could benefit from intermittent androgen therapy during the study period while avoiding overtreatment harms associated with continuous hormonal therapy.

Keywords

intermittent androgen deprivation therapy (IAD), LHRH analogues, prostate cancer, appropriateness

This article is included in the **Oncology** gateway.

Corresponding author: José Antonio Cordero (joseantonioocr1@blanquerna.url.edu)

Author roles: **Bonfill-Cosp X:** Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Auladell-Rispau A:** Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **Gich I:** Data Curation, Formal Analysis, Methodology; **Zamora J:** Writing – Review & Editing; **Saiz LC:** Writing – Review & Editing; **Pijoan JI:** Writing – Review & Editing; **Urreta I:** Writing – Review & Editing; **Cordero JA:** Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by Instituto de Salud Carlos III under the project number PI15/00886 (co-funded by the European Regional Development Fund/European Social Fund, “Investing in your future”).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2021 Bonfill-Cosp X *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Bonfill-Cosp X, Auladell-Rispau A, Gich I *et al.* **Prevalence study of intermittent hormonal therapy of Prostate Cancer patients in Spain [version 1; peer review: 1 approved, 1 approved with reservations]** F1000Research 2021, 10:1069 <https://doi.org/10.12688/f1000research.53875.1>

First published: 21 Oct 2021, 10:1069 <https://doi.org/10.12688/f1000research.53875.1>

Abbreviations

ADT: Androgen Deprivation Therapy
 ATC: Anatomic Therapeutic Code
 CAD: Continuous Androgen Deprivation therapy
 ELD: Effect duration of the Last Dose
 GPC: Clinical Practice Guideline
 IAD: Intermittent Androgen Deprivation therapy
 %IAD: Percentage of time off treatment
 IntT: Interval Time
 LHRH analogue: Luteinizing Hormone-Releasing Hormone analogue
 PCa: Prostate Cancer
 P_{IAD}: Prevalence of Intermittent Androgen Deprivation therapy
 PIIT: Potentially Intermittent Interval Time
 PSA: Prostate Specific Antigen

Introduction

Androgen deprivation therapy (ADT) is the most used therapeutic approach to treat patients with Prostate Cancer (PCa) who experience a biochemical relapse after radical prostatectomy. Reduction of circulating levels of androgen hormones can be achieved either with drugs, such as luteinizing hormone-releasing hormone analogues (LHRH) or with orchiectomy, which is irreversible. Nevertheless, ADT is associated with a wide array of adverse effects¹ ranging from the well-known hot flushes, loss of libido, gynecomastia, or erectile dysfunction up to midterm consequences such as bone fractures, depression, diabetes, and hematologic² and cardiovascular events.^{3,4} Importantly, all of these undesirable effects increase with the duration of ADT.⁵

In the 1990s, as a response to minimise these negative outcomes, intermittent androgen deprivation therapy (IAD) emerged as an alternative to continuous androgen deprivation therapy (CAD) but not without controversy regarding its feasibility.⁶ Over the years, it has been shown that IAD can improve patients' quality of life by reducing toxicity,⁷ reduce costs⁸ and potentially delay the onset of resistance to chemical castration.⁹ Recent strong evidence from randomized clinical trials^{10–14} and systematic reviews,^{15,16} as well as favourable recommendations included in recently updated clinical guidelines,^{17–19} highlight the potential benefits of IAD, supporting its use as an alternative treatment.

Despite the potential advantages of IAD, in a previous study we detected a low use of this approach in Catalonia (Spain)²⁰ compared to recent evidence of IAD utilization in Canada.²¹ We conducted the current study to assess the prevalence of IAD with real-world data from four Spanish autonomous communities.

Methods

Study design and setting

An observational, longitudinal study was conducted using electronic drug dispensation data from four Spanish autonomous communities: Catalonia, Madrid, Basque Country and Navarra (population: 16.05%, 14.17%, 4.63%, and 1.37% of the total population in Spain respectively, representing overall 36.22% of the total population in Spain, which was about 47 million inhabitants in 2020).

Data sources

Data used for this study were obtained from the health government agencies from each of the four territories in Spain: CatSalut in Catalonia, Servicio Madrileño de Salud in Madrid, Osakidetza in the Basque Country and Servicio Navarro de Salud-Osasunbidea in Navarra. We received all relevant dispensation data from the four respective agencies for the period between 1 January 2011 and 31 December 2016. Databases contained anonymised patient codes, date of birth, dispensing date, prescriber code (anonymised), drug name and anatomic therapeutic code (ATC), total dose per pharmaceutical form, number of dispensed drug units and the corresponding cost. The dispensation of each of the following LHRH analogues was identified: leuporelin (L02AE02), triptorelin (L02AE04), goserelin (L02AE03), buserelin (L02AE0), histrelin (H01CA0), nafarelin (H01CA02), and the following antiandrogen drugs: bicalutamide (L02BB03) and flutamide (L02BB0), in any pharmaceutical form or dose registered in Spain. We selected ≥ 18 -year-old male patients with at least one dispensation of LHRH analogues. We excluded individuals under age 18 based on the high likelihood that LHRH dispensations in this subgroup would be associated with precocious puberty, which was not within our interest. Given the specificity of ADT, we assumed that all other men $\geq$ age 18 were prescribed these drugs as PCa treatment.

The requested data were provided under the requirements of the Spanish data protection laws and no personal data was available to the investigators.

Exposure parameters

To distinguish between the CAD and IAD regimens, we identified all the periods during which patients received no LHRH analogue or Potentially Intermittent Interval Times (PIIT). We first identified all interval times (IntT), defined as the period between any two consecutive dispensations for each patient, together with the effect of the last dose (ELD), identified as the time period during which the patient was covered by the medication, as shown in Figure 1. Further details about the methods followed can be consulted in our previous publication.²⁰ Table 1 summarizes the type of LHRH analogue used, the total dose of the commercially available formulation, and the corresponding total duration of action of each dose. Although an intermittency gap usually starts after a minimum of six months of continuous hormonal treatment to reconfirm patient castration (PSA < 4 ng/mL), in our study, we considered three months as the minimum potential gap in order to have a conservative approach in IAD estimation.

Data analyses

One of the two key study variables created to estimate the use of intermittence was the percentage of time off treatment (%IAD). This percentage was calculated by dividing the sum of all the off periods (in patients with ≥ 1 intermittent interval time) by the sum of all interval times on any LHRH analogue regimen (i.e., the sum of periods between the first and the last dispensation dates for each patient in the study). The %IAD was calculated overall and for each region along the study period. The other key variable to estimate the number of patients under intermittency was the prevalence of IAD (P_{IAD}), calculated as the number of patients with ≥ 1 PIIT per year, divided by the total number of patients treated

IAD: Intermittent Androgen Deprivation Regimen; **CAD**: Continuous Androgen Deprivation Regimen;
IntT: Interval Time; **ELD**: Effect duration of the Last Dose; **PIIT**: Potentially Intermittent Interval Time; **a**: Assessment

Yellow: LHRH Analogue Injection

Red: STOP of LHRH Analogue Injections

Green: Re-Start of LHRH Analogue Injections

Note: The parameters include the time interval between two consecutive dispensations (IntT), the effect duration of the last dose (ELD), and the potential intermittent interval time (PIIT).

Figure 1. Representation of the parameters needed to identify the intermittent periods in a 36-month scenario.

Table 1. LHRH analogue sustained-release formulations used, including dose and expected duration of action.

	Dose, mg												
	≤2	3.30	3.60	3.75	6.60	7.50	9.90	10.80	11.25	22.5	30	45	50
Busereline	1 d*	1 m*	-	-	2 m	-	3 m	-	-	-	-	-	-
Gosereline	-	-	-	-	-	-	-	3 m	-	-	-	-	-
Histreline	-	-	1 m	-	-	-	-	-	-	-	-	-	12 m
Leuproreline	1 d	-	-	1 m	-	2 m	-	-	3 m	6 m	6 m	6 m	-
Triptorelin	1 d	-	-	1 m	-	-	-	-	3 m	6 m	-	-	-
Nafarelin	1 d	-	-	-	-	-	-	-	-	-	-	-	-

*Exposition measure: d = day/s, m = month/s.

with LHRH analogues in the same year. Nevertheless, it should be noted that the P_{IAD} for the first year of data (2011) was underestimated due to the prior three-month intermittency requirement (e.g., patients in the intermittent period in January 2011 could not be identified as such until the next off period). Because of that, the data from 2011 was not included in the specific analysis of intermittency. We present the costs of hormonal treatment, including LHRH analogues and anti-androgenic therapeutic groups, per drug, year, and autonomous community. We excluded the Basque Country for the calculation of the annual expenditure because of its lack of complete 2011 data. To compare the cost between communities, we normalised the data as euros per dispensation. We expressed baseline characteristics, as mean $\pm$ standard deviation for continuous variables and frequency (%) for categorical variables with the corresponding 95% confidence interval (95%CI). Calculations were performed using SPSS version 26.0 software (IBM, Armonk, NY).

Results

For the full study period (2011-2016), a total of 863,005 dispensations corresponding to a total of 65,752 men, including either LHRH analogues administered alone (353,162) or in combination with anti-androgens (509,843), were made in Catalonia, Madrid, Basque Country and Navarra. Previously, 309 males under the age 18 were excluded together with 7,731 subjects that were dispensed only with antiandrogens, because complete castration was not guaranteed. Additionally, 2012 data from the Basque Country were considered inconsistent (likely incomplete electronic system introduction in this area) and were also excluded from the analysis. Finally, a total of 44,264 PCa patients were included in the study, as summarized in [Figure 2](#). Overall, the mean ($\pm$ SD) age of the patients was 76.9 ($\pm$ 10.4) years, although 81% were older than 70 years and 47% older than 80 years.

Of the total men (44,264) finally included in the study and taking LHRH analogues alone, 36,775 (83%) were under CAD therapy and 7,489 (17%) under IAD therapy, considering the full five-year period of the study. However, this value of global prevalence represents an overestimation of the actual annual prevalence of IAD, as can be observed in [Figure 3](#). For example, among the ten patient profiles simulated, only five profiles (6 to 10) fulfilled IAD requirements at least once (5/10 cases where “Potential IAD = Yes”), when considering the six years globally. Then, the global IAD prevalence was of 50%. However, when considering each year separately, the annual prevalence varied from 0 to 50%, with a mean annual prevalence of 24%. The age distribution of the patients according to the treatment regimen (IAD vs CAD) is

Figure 2. Patient distribution flowchart.

Figure 3. Simulation of 10 putative subject profiles in terms of CAD or IAD.

shown in Figure 4. Patients on the IAD regimen were somewhat older compared to the total patients under continuous hormonal therapy. The proportion of octogenarians and older patients under IAD therapy (56.7%) was higher compared to those under CAD (45.1%).

The five-year prevalence (P_{IAD}) of patients under an IAD regimen was 6.6% in the total population studied. The global prevalence of intermittency slightly increased from 8.2% in 2012 to 8.4% in 2013, but later decreased to 3.6% in 2016. We also calculated the %IAD during the five-year study period with a total %IAD value of 5.6%, which is rather consistent with the P_{IAD} figure reported earlier.

Among the four Spanish regions, the P_{IAD} shows that in 2012 Madrid had the highest prevalence of IAD therapy (10.7%), followed by Navarra (8.2%) and Catalonia (5.8%). Peak values obtained were up to 14.2% [2014] in Madrid, 8.5% [2013] in Navarra, 8.4% [2013] in Catalonia, and 3.8% [2015] in the Basque Country; thereafter, the use of intermittent treatment decreased to 4.3% by 2016 in Madrid, 4.0% in Catalonia, 3.4% in Navarra and 2.5% in the Basque Country. Table 2 shows the total P_{IAD} distributed per community per year, as well as %IAD for each community.

Figure 4. Age distribution of prostate cancer patients under IAD or under CAD.

Table 2. Estimations of hormonal treatment prevalence.

Autonomous community	N° PCa under hormonal treatment	Hormonal treatment prevalence # (%)	%IAD	P _{IAD}					Total
				2012	2013	2014	2015	2016	
Catalonia	33650	1.35	5.2 (5.2-5.2)	5.8% (5.4-6.2)	8.4% (7.8-8.9)	6.6% (6.1-7.0)	6.1% (5.7-6.6)	4.0% (3.6-4.3)	6.2% (6.1-6.4)
Madrid	21718	1.02	11.4 (11.3-11.4)	10.7% (10.0-11.3)	8.3% (7.8-8.9)	14.2% (13.4-14.9)	6.7% (6.2-7.3)	4.3% (3.9-4.8)	8.9% (8.6-9.2)
Basque Country	7095	0.88	1.7 (1.7-1.7)	-	0.3% (0.1-0.8)	1.3% (1.0-1.8)	3.8% (3.2-4.5)	2.5% (2.0-3.0)	2.4% (2.2-2.7)
Navarra	3289	1.44	4.3 (4.3-4.3)	8.2% (6.7-9.8)	8.5% (7.0-10.2)	6.8% (5.5-8.3)	4.9% (3.8-6.2)	3.4% (2.5-4.5)	6.4% (5.8-7.0)
Global	65752	1.18	5.6	8.2	8.4	7.2	5.4	3.6	6.6

#In reference to male inhabitants older than 20 years of each Autonomous Community in 2016.

Note: IAD prevalence (CI 95%) based on annual PIAD and %IAD.

Abbreviations: **IAD** Intermittent Androgen Deprivation therapy; **P_{IAD}** Prevalence of Intermittent Androgen Deprivation therapy; **%IAD** percentage of time off treatment.

Figure 5. Total cost of LHRH analogues per year from 2011 to 2016 in Spain.

We found that the most representative non-treatment period lasted for a median of six months (ranging from 3 to 58 months) considering all four areas. In Madrid and Catalonia, the median of the PIIT intervals was 6.2 months with an IQR of 7.1 and 9.2 months respectively, while in the Navarra and Basque Country the PIIT intervals were shorter and less variable: 5.1 months (IQR 4 months) and 4.0 months (IQR 3.1 months), respectively. In the four areas the global tendency was to increase the duration of the “off” period from four (2012) up to six months (2016).

The most prescribed drug in all four communities during the five-year study period was leuprorelin, followed by triptorelin and goserelin (representing globally a 51.72%, 34.72%, and 12.33%, respectively) of the total LHRH analogues dispensed.

The global mean cost of hormonal therapy per year was 25 million euros for LHRH analogues and 6.3 million euros for anti-androgens for the four regions. Along the study period, the total expenditure in Catalonia, Madrid and Navarra decreased from 34.7 million euros [2011] down to 25.3 million euros [2016]. Figure 5 plots the changes in total cost for each specific LHRH analogue per year. The global mean ($\pm$ SD) cost per dispensation was 214.6 ± 33.5 euros in 2011, then decreased to 201.7 ± 31.9 euros in 2014, and increased again up to 213.9 ± 26.3 euros in 2016.

Discussion

We conducted a study that estimates the prevalence of IAD in four Spanish autonomous communities (17 million people), based on electronic dispensation information from 2011 to 2016. Our results show that, taking either the mean P_{IAD} (6.6%) or the %IAD (5.6%) as reference, IAD use was in the range of 6%. These results are in agreement with our previous estimations from Catalonia (2008-2012): $P_{IAD} = 4.2\%$ and %IAD = 1.7%²⁰ and confirm a low global utilisation of IAD in Spain. Even worse, the IAD utilisation rate has evolved in a progressively decreasing manner along the current study period, ranging from 8.4% (2013) to 3.6% (2016). Among the four Spanish regions, the %IAD showed that Madrid had the highest prevalence of intermittency (11.4%), followed by Catalonia (5.2%), Navarra (4.3%) and the Basque Country (1.7%). The P_{IAD} showed a decreasing trend along the study period until 2016 in Madrid (4.3%), Catalonia (4.0%), Navarra (3.4%) and the Basque Country (2.5%). Based on the obtained data, we interpret that the well-known role of intermittent treatment in hormonal therapy, based on sound evidence from randomised controlled trials^{10–14} and systematic reviews,^{15,16} does not appear to be influencing actual clinical practice in a significant proportion of cases. It seems that the necessary trade-off between benefits and adverse effects could be much improved in those situations where IAD is as effective as CAD, since adverse effects of IAD should be lower for a broad range of morbidities.^{4,13,16,22–24} An international survey conducted in 19 countries asking 441 physicians currently treating PCa patients, showed that 23% of non-metastatic patients treated with gonadotropin-releasing hormone analogues were using IAD. Additionally, the same authors agree with our results that the CAD and IAD use in Spain among men with non-metastatic prostate cancer, was of 35.7% and 6.9%, respectively.²⁵ Reference countries like France, Italy or Germany showed higher IAD use than Spain (9.1, 13.9 and 14.3%, respectively), still based on physicians opinions. Further evidence suggesting that the use of IAD is low in Spain, comes from data collected in Manitoba (Canada), where 74% (447/601 nonmetastatic hormone-sensitive PCa patients) were using IAD for the management of their relapse.²¹

When analysing the data related to the duration of the “off” periods, or halted medication periods, we observed that the median duration varied between 4 and 6,2 months in all four regions (ranging from 3 to 13 months). These off-treatment periods are concordant with the corresponding values reported by Crook *et al.*, that ranged from approximately 20 months

in the first non-treatment interval, down to three months in the 6th interval.¹³ Globally, there was also a tendency to increase the median duration of the pause period between 2012 (three to four months) and 2016 (five to six months). This may suggest that prescribers using IAD are progressively more confident with the risk/benefit balance of this therapeutic strategy. This is in agreement with the fact that patient-reported outcomes were significantly better in IAD versus CAD at 20 and 38 months of treatment, based on validated quality of life questionnaires in Japan.²⁶

We calculated that the total cost of hormonal therapy in the four autonomous communities was 31.3 million euros per year (25 million corresponding to LHRH analogues and 6.3 to anti-androgens), which represents a mean of 214 euros per dispensation. The fact that the mean cost per dispensation declined from 214.6 euros in 2011 to 201.7 euros in 2014 could be related to the fact that in 2012, the Spanish health authorities introduced restrictive measures for the sustainability of the National Health System (Royal Decree 16/2012)²⁷ and all kind medication were reduced in the whole country by as much as 12 million per month.²⁸ However, thereafter the cost increased again up to 213.9 euros per dispensation in 2016. Obviously, the efforts to enhance the use of IAD would produce important cost savings due to the reduction in expensive drug consumption, which some authors estimate in the range of one-third of CAD.¹¹ In the population studied, we would be talking of around half a million savings per million inhabitants per year.

If PCa patients are to be actively involved in their decision process related to hormonal therapy medications, as current clinical guidelines suggest, they should know the existing sound evidence that shows similar overall survival of both CAD and IAD users, but the broader span of morbidities associated to CAD. From the physicians' point of view, the PSA levels (54%), patient request (48%), desire to maintain sexual function (40%), patient age and comorbidities (38%) were reported as the most frequent reasons for IAD use.²⁵

The main strength of our study is the capacity to analyse all public health systems electronic dispensations data from the selected Spanish regions, which eliminates any potential selection bias. They constitute a very large sample size, which favours the representativeness of the whole Spanish population. Also, the reliability of the database reduces information bias and missing data problems as previously observed by other authors.²⁹

Due to the administrative nature of our data sources, our study is not able to estimate whether patients identified under IAD are clinically appropriate or not. However, taking into account the conservative approach that we used and compared to the real-world utilization in Canada²¹ and 19 other countries,²⁵ we could say that the use of IAD in Spain could be significantly increased, leading to the consequent improvement in patients' quality of life and significant savings for the National Health Service. We plan to conduct an audit in a sample of the electronic records of PCa patients who were potential IAD candidates, to assess if they fulfilled the clinical criteria for having eventually stopped the hormonal therapy.

Conclusions

We conclude that the IAD use in Spain was relatively low during the study period, although enough time has passed since the related international recommendations were published. As a consequence, an important proportion of hormone-sensitive prostate cancer patients could be currently overtreated with CAD, which would produce a significant number of avoidable adverse effects on their quality of life, apart from the important repercussion that this expense has on the health budget in times of crisis. The population-based method to estimate the IAD prevalence seems to be a quite consistent approach and opens the door to comparable international data to set up reference standards on adequate IAD utilisation.

Data availability

Underlying data

Project Datasphere: Intermittent hormonal therapy of prostate cancer patients in Spain: a prevalence study, <https://doi.org/10.34949/fzzk-ye57>. This project contains the following underlying data:

- CEIC_PROTOCOLO_Ca prostat.pdf (Study protocol)
- IAD_CRF_v1.docx
- DataDescription_v1.xlsx
- BBDD_Spain_IAD_v4.xlsx (Dispensation data)

Data are available under the terms of the PDS [Data Sharing Agreement](#). Any individuals who wish to access the data will need to register for an account on Project Datasphere.

Acknowledgments

We are grateful to those who facilitated the data for this study: Public Data Analysis Program for Research and Innovation in Healthcare in Catalonia held by the Health Quality and Assessment Agency (AQuAS, Catalonia), Carmen Marina Meseguer Barros (Pharmaceutical Information Systems Area, Madrid Health Service), Javier Gorricho Mendivil (Planning, Evaluation and Management Service, Pamplona) and Begoña San Jose Ruiz (Hospital Pharmacy Department, Hospital de Cruces, Bilbao).

References

- Bourke L, Kirkbride P, Hooper R, *et al.*: **Endocrine therapy in prostate cancer: time for reappraisal of risks, benefits and cost-effectiveness?** *Br. J. Cancer.* 2013; **108**(1): 9–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Grossmann M, Zajac JD: **Hematological changes during androgen deprivation therapy.** *Asian J. Androl.* 2012; **14**(2): 187–192.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Jespersen CG, Nørgaard M, Borre M: **Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study.** *Eur. Urol.* 2014; **65**(4): 704–709.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Nguyen PL, Alibhai SM, Basaria S, *et al.*: **Adverse effects of androgen deprivation therapy and strategies to mitigate them.** *Eur. Urol.* 2015; **67**(5): 825–836.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Krahn MD, Bremner KE, Luo J, *et al.*: **Health care costs for prostate cancer patients receiving androgen deprivation therapy: treatment and adverse events.** *Curr. Oncol.* 2014; **21**(3): e457–e465.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Sato N, Gleave ME, Bruchovsky N, *et al.*: **Intermittent androgen suppression delays progression to androgen-independent regulation of prostate-specific antigen gene in the LNCaP prostate tumour model.** *J. Steroid Biochem. Mol. Biol.* 1996; **58**(2): 139–146.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Tucci M, Leone G, Buttigliero C, *et al.*: **Hormonal treatment and quality of life of prostate cancer patients: new evidence.** *Minerva Urol. Nefrol.* 2018; **70**(2): 144–151.
[Publisher Full Text](#)
- Rosario DJ, Bourke L: **Reply: Endocrine therapy in prostate cancer: time for reappraisal of risks, benefits and cost-effectiveness?** *Br. J. Cancer.* 2013 May 28; **108**(10): 2194.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bruchovsky N, Rennie PS, Coldman AJ, *et al.*: **Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma.** *Cancer Res.* 1990; **50**(8): 2275–2282.
[PubMed Abstract](#)
- Schulman C, Cornel E, Matveev V, *et al.*: **Intermittent Versus Continuous Androgen Deprivation Therapy in Patients with Relapsing or Locally Advanced Prostate Cancer: A Phase 3b Randomised Study (ICELAND).** *Eur. Urol.* 2016; **69**(4): 720–727.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Hussain M, Tangen CM, Berry DL, *et al.*: **Intermittent versus continuous androgen deprivation in prostate cancer.** *N. Engl. J. Med.* 2013; **368**(14): 1314–1325.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Crook JM, O'Callaghan CJ, Duncan G, *et al.*: **Intermittent androgen suppression for rising PSA level after radiotherapy [published correction appears in N Engl J Med. 2012 Dec 6;367(23):2262].** *N. Engl. J. Med.* 2012; **367**(10): 895–903.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Casas F, Henríquez I, Bejar A, *et al.*: **Intermittent versus continuous androgen deprivation therapy to biochemical recurrence after external beam radiotherapy: a phase 3 GICOR study.** *Clin. Transl. Oncol.* 2017; **19**(3): 373–378.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Calais da Silva FE, Bono AV, Whelan P, *et al.*: **Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Urological Group.** *Eur. Urol.* 2009; **55**(6): 1269–1277.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Niraula S, Le LW, Tannock IF: **Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials.** *J. Clin. Oncol.* 2013 Jun 1; **31**(16): 2029–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Magnan S, Zarychanski R, Pilote L, *et al.*: **Intermittent vs Continuous Androgen Deprivation Therapy for Prostate Cancer: A Systematic Review and Meta-analysis.** *JAMA Oncol.* 2015; **1**(9): 1261–1269.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mottet N, Cornford P, van den Bergh RCN, *et al.*: **EAU Guidelines 2019.** Accessed November 11, 2020.
[Reference Source](#)
- NICE: **Guidance - Prostate cancer: diagnosis and management: © NICE (2019) Prostate cancer: diagnosis and management.** *BJU Int.* 2019; **124**(1): 9–26.
[Publisher Full Text](#)
- Carroll PH, Mohler JL: **NCCN Guidelines Updates: Prostate Cancer and Prostate Cancer Early Detection.** *J. Natl. Compr. Cancer Netw.* 2018; **16**(55): 620–623.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Cordero JA, Sancho G, Bonfill X: **Population-based estimate of the use of intermittent androgen deprivation therapy in prostate cancer patients in Catalonia, Spain.** *Pharmacoeconom. Drug Saf.* 2019; **28**(6): 796–803.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Janzen BW, Ong A, Penner M, *et al.*: **Population-based Assessment of Intermittent Androgen Deprivation Therapy Utilization for Relapsed, Nonmetastatic, Hormone-sensitive Adenocarcinoma of the Prostate.** *Am. J. Clin. Oncol.* 2020; **43**(12): 865–871.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Cherrier MM, Higano CS: **Impact of androgen deprivation therapy on mood, cognition, and risk for AD.** *Urol. Oncol.* 2020; **38**(2): 53–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Tsai HT, Pfeiffer RM, Phillips GK, *et al.*: **Risks of Serious Toxicities from Intermittent versus Continuous Androgen Deprivation Therapy for Advanced Prostate Cancer: A Population Based Study.** *J. Urol.* 2017; **197**(5): 1251–1257.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Higano CS: **New developments in the treatment of castration-resistant prostate cancer.** *J. Natl. Compr. Cancer Netw.* 2014; **12**(5 Suppl): 773–776.
[Publisher Full Text](#)
- Liede A, Hallett DC, Hope K, *et al.*: **Editorial on an international survey of androgen deprivation therapy (ADT) for non-metastatic prostate cancer in 19 countries.** *Ann Oncol.* 2016 [cited 2021 Jan 31]; **1**: e000040.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Yokomizo A, Koga H, Ito K, *et al.*: **Patient-reported outcomes following neoadjuvant endocrine therapy, external beam radiation, and adjuvant continuous/intermittent endocrine therapy for locally advanced prostate cancer: A randomized phase III trial.** *Cancer Med.* 2021 May [cited 2021 May 3]; **10**: 3240–3248.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Real Decreto-ley 16/2012, de 20 de abril, de medidas urgentes para garantizar la sostenibilidad del Sistema Nacional de Salud y mejorar la calidad y seguridad de sus prestaciones: **Boletín Oficial del Estado (BOE) 2012.** Accessed November 11, 2020.
[Reference Source](#)
- Farmaindustria: **Boletín de Coyuntura del Mercado del Medicamento en España. No 113.** Accessed September 2, 2020.
[Reference Source](#)
- Acezat OJ: **«Impacta el uso de las TICs en el gasto farmacéutico? Incorporación de la receta electrónica.» [Impact of the use of ICT on pharmacy costs. The incorporation of the electronic prescription].** *Aten. Primaria.* 2013; **45**(3): 139–140.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:

Version 1

Reviewer Report 13 January 2022

<https://doi.org/10.5256/f1000research.57300.r100495>

© 2022 Dahm P. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Philipp Dahm

Department of Urology, Minneapolis VAMC, University of Minnesota, Minneapolis, MN, USA

1. Abstract, Background: I don't think the first sentence makes logical sense ("although IADT was introduced...recent data suggest that those patients could be overtreated"). I think what you are trying to say is that it is being underutilized.
2. Abstract, Methods: Please clarify the denominator. Here I have the impression it is the entire (male?) population but I'd assume it to be patients with advanced/metastatic PCA.
3. In alignment with the study results I'd say that few patients use IADT; secondarily you can state that this likely represents underuse.
4. Introduction: I would state that metastatic disease is the main indication (not biochemical recurrence after radical prostatectomy which is also unnecessarily narrow).
5. Reference 20 seems to represent a similar study. You should discuss what this study will add/how it differs?
6. The first part of the discussion appears repetitive. If you present the results clearly, you do not need to repeat them here. Please focus on the big picture take-away points.
7. The RCTs and SRs you cite are likely overlapping bodies of evidence. Citing one recent high quality SR would suffice. Citing relevant guidelines would be even more compelling.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: evidence-based medicine, clinical practice guidelines, prostate cancer, urology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 13 Apr 2022

José Antonio Cordero Rigol

Thanks Dr. Dahm for your comments and support.

Let me answer step by step:

1. *"Abstract, Background: I don't think the first sentence makes logical sense ("although IADT was introduced...recent data suggest that those patients could be overtreated"). I think what you are trying to say is that it is being underutilized".* **Agree. Will be corrected in next version.**
2. *"Abstract, Methods: Please clarify the denominator. Here I have the impression it is the entire (male?) population but I'd assume it to be patients with advanced/metastatic PCA."* **It is correct. The prevalence estimation was referred (denominator) to the total number of patients under hormonal treatment.**
3. *"In alignment with the study results I'd say that few patients use IADT; secondarily you can state that this likely represents underuse."* **Agree. Will be corrected in next version.**
4. *"Introduction: I would state that metastatic disease is the main indication (not biochemical recurrence after radical prostatectomy which is also unnecessarily narrow)."* **Agree. Will be corrected in next version.**
5. *"Reference 20 seems to represent a similar study. You should discuss what this study will add/how it differs?"* **Agree. Basically, extension of the same method of prevalence estimation to other 3 Spanish autonomous communities confirming the same tendency previously observed in the first region (Catalonia). Will be added in next version.**

6. "The first part of the discussion appears repetitive. If you present the results clearly, you do not need to repeat them here. Please focus on the big picture take-away points." **Agree. The first sentence in the discussion will be removed.**

7. "The RCTs and SRs you cite are likely overlapping bodies of evidence. Citing one recent high quality SR would suffice. Citing relevant guidelines would be even more compelling." **Agree. The older SRs will be deleted.**

Competing Interests: No competing interests were disclosed.

Reviewer Report 06 December 2021

<https://doi.org/10.5256/f1000research.57300.r97868>

© 2021 Codina H. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Helena Colom Codina

Department of Pharmacy and Pharmaceutical technology and Physical-Chemistry, Faculty of Pharmacy and Food sciences, University of Barcelona, Barcelona, Spain

This is a very interesting study to estimate the prevalence of IAD in four Spanish autonomous communities based on electronic dispensation information from 2011 to 2016. The paper is well written; clear and appropriate in its methods and results. A very high number of data have been recorded so that very consistent results have been obtained.

To complete the results I would suggest to perform statistical comparisons of the prevalence values between communities and between the years of follow-up. The study has fulfilled the aims, i.e. to estimate the prevalence values of IAD in different Spanish communities from 2011 to 2016; however, I would have appreciated some discussion about the reasons why the prevalence of IAD in Spain is low.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My expertise area is biopharmaceutics pharmacokinetic-pharmacodynamic data analysis and statistics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 13 Apr 2022

José Antonio Cordero Rigol

Thanks Dr. Colom for your comments and support.

As for your suggestion "*To complete the results I would suggest to perform statistical comparisons of the prevalence values between communities and between the years of follow-up.*" Agree. The statistical comparison will be added to the version 2 but very significant differences ($p < 0.001$) among communities and years of follow-up will be expected due to the big size of the sample analysed. We therefore concentrated on comparing the magnitude of the differences summarised in table 2.

With respect to your comment that "*I would have appreciated some discussion about the reasons why the prevalence of IAD in Spain is low*". Agree. This result is quite surprising and we only have conjectures to explain that e.g., Liede *et al.* reported important differences in IAD use among European countries due to "clinicians devise individualised treatment courses of optimal length based on patient characteristics while accounting for associated risks and benefits of ADT. This individualised clinical approach is represented in the variation of survey responses as it can become difficult to compartmentalise patients when deciding on treatment strategies." The fact that in Spain we have 4 physicians/1000 inhabitants may explain some extra healthcare pressure than in France, Italy or UK with >4.5 physicians/1000 inhabitants. In any case, the data are fairly consistent when it comes to demonstrating this weak use of IAD therapy in Spain.

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research