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Androgen deprivation monotherapy usage in non-metastatic prostate cancer: results from eight European countries

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Introduction The aim of this study was to investigate the attitudes towards use of androgen deprivation therapy (ADT) as monotherapy for localized or locally advanced prostate cancer (PC).
Material and methods A survey using a 28-item, structured, quantitative questionnaire about the management of patients with PC was conducted in eight European countries between February and May 2018. Survey recipients were selected from a private database of healthcare providers.
Results Overall, 375 physicians completed the survey (response rate, 58%). Participants were urologists (71.2%) or medical oncologists (28.8%), with a mean practice duration of 19.9 years and with university hospital or cancer center (41.6%), non-teaching hospital (38.4%) or private-sector clinic (20.0%) affiliations. Median proportions of physicians considering ADT as monotherapy to treat patients with PC in different risk groups varied between countries, but overall were: high/very high-risk, 60%; intermediate-risk, 30%; low-risk, 7.5%. The use of ADT monotherapy in the different risk groups also varied by medical specialty and type of affiliation. Proportions of participants applying different target thresholds for testosterone (T) levels also varied by country, but overall were: <50 ng/dL, 29.9%; <32 ng/dL, 4.8%; <20 ng/dL, 54.3%; castration but no specific target, 11%. More than half of participants (58.7%) determined target T levels only when prostate-specific antigen level was increased.
Conclusions Our multinational survey provides evidence that PC management varies across European countries and with clinical context, and frequently diverges from European Association of Urology (EAU) – European Society for Radiotherapy and Oncology (ESTRO) – European Society of Urogenital Radiology (ESUR) – International Society of Geriatric Oncology (SIOG) guidelines. Strategies for effective implementation of evidence-based recommendations in clinical practice may be needed to optimize patient outcomes.

Key Words: prostate cancer ‹› androgen deprivation therapy ‹› castration levels ‹› European Association of Urology guidelines ‹› testosterone

INTRODUCTION

Androgen deprivation therapy (ADT) is fundamental to the management of advanced and/or metastatic prostate cancer (PC), with consistent, long-term benefits for quality of life and survival observed [1–5]. The use of ADT as monotherapy in non-metastatic, localized forms of PC is, however, controversial [1, 4], with little benefit observed in low- or intermediate-risk patients (cT1–cT2b, Gleason score 2–7, prostate-specific antigen (PSA) <20 ng/mL) [4]. Although ADT as combination therapy is reported to delay progression in high-risk patients, there may be advantages in deferring treatment in asymptomatic patients [4, 5, 6]. It is not yet clear whether ADT administered postoperatively, either preemptively or as a strategy for biochemical relapse, improves patient outcomes [4, 7]. When ADT is indicated,

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the importance of monitoring testosterone (T) levels to ensure that adequate castration thresholds are being met is increasingly recognized, with a target threshold of T <20 ng/dL currently recommended [2, 5].

Evidence-based treatment guidelines for PC, such as those recently published jointly by the European Association of Urology (EAU), the European Society for Radiotherapy and Oncology (ESTRO), the European Society of Urogenital Radiology (ESUR) and the International Society of Geriatric Oncology (SIOG) [5], are key determinants of treatment practices in patients with PC. However, the management of PC in clinical practice often diverges from current recommendations [8–12]. For example, although ADT as monotherapy is recommended for high-risk patients, it is sometimes used relatively early in the course of PC [1, 8], despite serious adverse effects such as cardiovascular disease, diabetes and skeletal complications associated with short- and long-term ADT [1, 4]. Reasons for divergence from treatment guidelines may include physicians' assessment of risk, patient age, comorbidities and PSA levels [9]. There is also evidence that the increase in expectant management approaches relative to radiation therapy or surgery over the last decade may be driven partly by increased uptake of active surveillance among low- and intermediate-risk patients [10].

The aim of the present study was to survey physicians across eight European countries to investigate their attitude to different treatment options in the management of different stages of PC and to relate the findings to current EAU-ESTRO-ESUR-SIOG guidelines [5]. This first publication from the study presents the results from the sections of the survey related to the attitudes towards use of ADT as monotherapy for localized or locally advanced PC.

MATERIAL AND METHODS

A survey using a 28-item, structured, qualitative questionnaire (Supplement S1) was conducted in eight European countries (Czech Republic, Greece, Hungary, Latvia, Lithuania, Poland, Romania and Sweden) between February and May 2018. The questionnaire was distributed to physicians in participating countries by Ipsos (Prague, Czech Republic).

Survey recipients were selected from a private database held by Ipsos and comprised healthcare providers who had participated in activities related to the treatment of PC. Potential participants were then contacted by telephone and the purpose of the survey and their role was explained. Those who were willing to participate gave informed consent and completed the questionnaire online or during a face-to-face interview. The questionnaire covered amongst others, general respondent information, ADT use at different disease stages, target castration T levels and frequency of estimating T levels. Areas not presented in this publication included attitudes to combination use of ADT and docetaxel, anti-androgen therapy, radical prostatectomy, radiotherapy, use of orchiectomy, second line treatment and ADT formulation preference.

Normally distributed variables were expressed as mean (standard deviation), while variables with skewed distribution were expressed as median (interquartile range [IQR]). Qualitative variables were expressed as absolute and relative frequencies. For the comparison of proportions between study groups, the chi-squared and Fisher's exact tests were used. The

Table 1. *Physician characteristics*

	Total sample (N = 375)	Czech Republic (N = 50)	Greece (N = 100)	Hungary (N = 50)	Latvia (N = 18)	Lithuania (N = 15)	Poland (N = 61)	Romania (N = 50)	Sweden (N = 31)
Primary medical specialty, n (%)									
Urologist	267 (71.2)	20 (40.0)	80 (80.0)	50 (100.0)	18 (100.0)	15 (100.0)	61 (100.0)	0 (0.0)	23 (74.2)
Oncologist	108 (28.8)	30 (60.0)	20 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	50 (100.0)	8 (25.8)
What type of practice do you mainly work in? n (%)									
University hospital or cancer center	156 (41.6)	34 (68.0)	25 (25.0)	15 (30.0)	10 (55.6)	14 (93.3)	21 (34.4)	21 (42.0)	16 (51.6)
Non-teaching hospital	144 (38.4)	10 (20.0)	28 (28.0)	35 (70.0)	5 (27.8)	1 (6.7)	30 (49.2)	21 (42.0)	14 (45.2)
Private sector	75 (20.0)	6 (12.0)	47 (47.0)	0 (0.0)	3 (16.7)	0 (0.0)	10 (16.4)	8 (16.0)	1 (3.2)
How many years of experience do you have?									
Mean years (SD)	19.9 (10.2)	21.1 (8.8)	18.9 (9.2)	28 (11.4)	19.6 (12.4)	12.5 (9.4)	17.7 (10.5)	18.8 (7.9)	18.2 (8.6)

SD – standard deviation; N – number

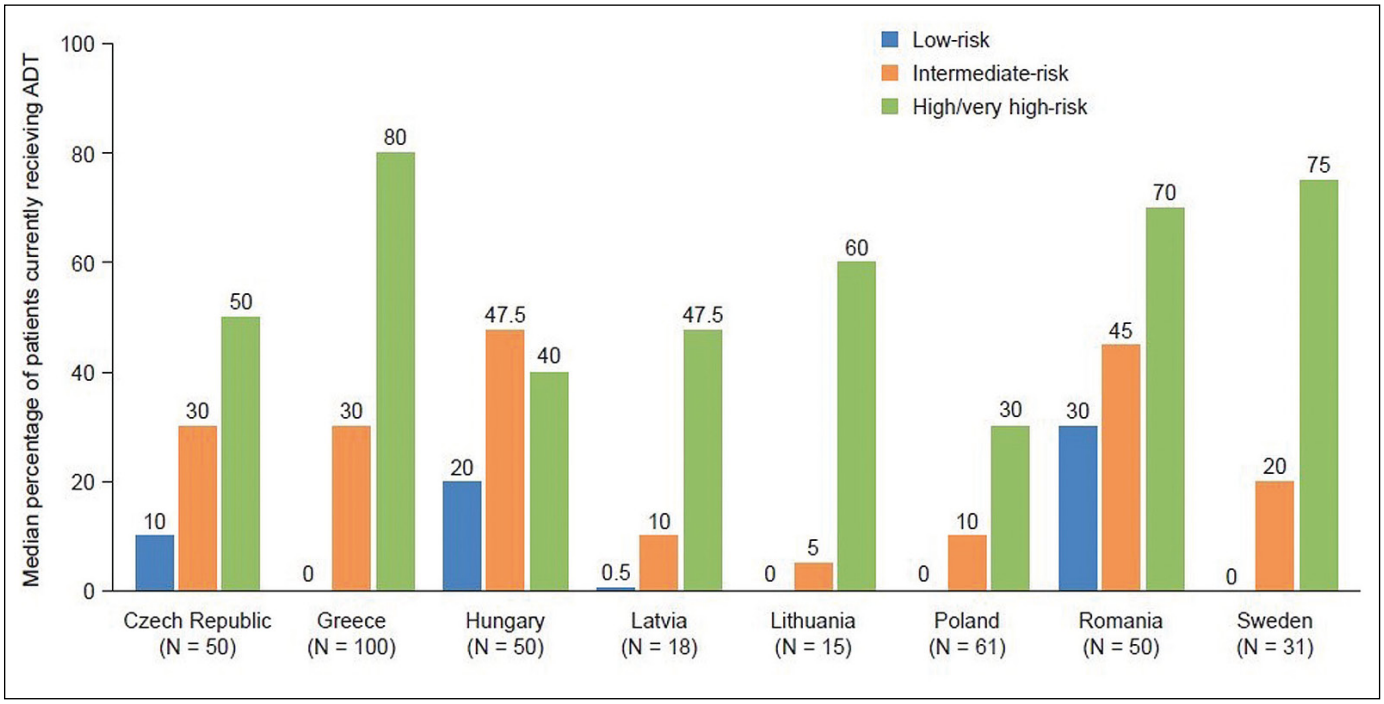

Figure 1. *Patients receiving androgen deprivation therapy (ADT) by country and risk group. Data refer to the management of patients with localized, low-, moderate- or high-risk disease. Physicians were asked to indicate the proportion of patients in each risk group receiving ADT and so proportions in each category do not add up to 100%.*

Mann–Whitney U test was used for the comparison of continuous variables between two groups, and the Kruskal–Wallis test was used for the comparison of means of continuous variables among more than two groups. Bonferroni correction was used in the case of multiple testing in order to control for type I error. All reported p values are two-tailed. Statistical significance was set at $p < 0.05$ and analyses were conducted using SPSS statistical software (version 22.0).

RESULTS

In total, 375 physicians completed the survey, representing an overall response rate of 58%. Of these, 71.2% were urologists and 28.8% were medical oncologists. In Romania, all participants were oncologists, while in Hungary, Latvia, Lithuania and Poland, all were urologists. The overall mean length of clinical experience was 19.9 years, ranging from 12.5 years (Lithuania) to 28.0 years (Hungary). Physicians' affiliations were with university hospitals or cancer centers (41.6%), non-teaching hospitals (38.4%) or private-sector clinics (20.0%) (Table 1). The demographic characteristics of physicians differed significantly between the countries ($p < 0.001$ for all comparisons).

Overall, the use of ADT as monotherapy (median; IQR) considered as an option for localized or locally advanced PC was highest for high/very high-risk patients (60%; 30–90%), followed by intermediate-risk patients (30%; 10–50%) and low-risk patients (7.5%; 0–30%). Between-country ADT as monotherapy use varied significantly for each disease stage (Figure 1; $p < 0.001$ for each risk group [low, intermediate and high]). For low-risk patients, the proportion of physicians using ADT was highest in Romania (30.0%) and lowest in Greece, Lithuania, Poland and Sweden (all 0%). For intermediate-risk patients, the proportion was highest in Hungary (47.5%) and lowest in Lithuania (5.0%). For high-risk patients, the proportion was highest in Greece (80.0%) and lowest in Poland (30.0%).

The number of respondents who considered use of ADT as monotherapy for localized or locally advanced disease varied by medical specialty and type of affiliation. Oncologists considered ADT as monotherapy for significantly higher proportions of patients of all risk types than urologists ($p < 0.001$ for all comparisons). Oncologists and urologists considered ADT as monotherapy for 20% versus 2% of their low-risk patients, 40% versus 20% of their intermediate-risk patients and 70% versus 50% of their high-very high-risk patients. Affiliation did not differ significantly in low- and intermediate-risk patients ($p = 0.063$ and $p = 0.651$, respectively) but differed significantly in high-very high-risk patients ($p = 0.014$; after

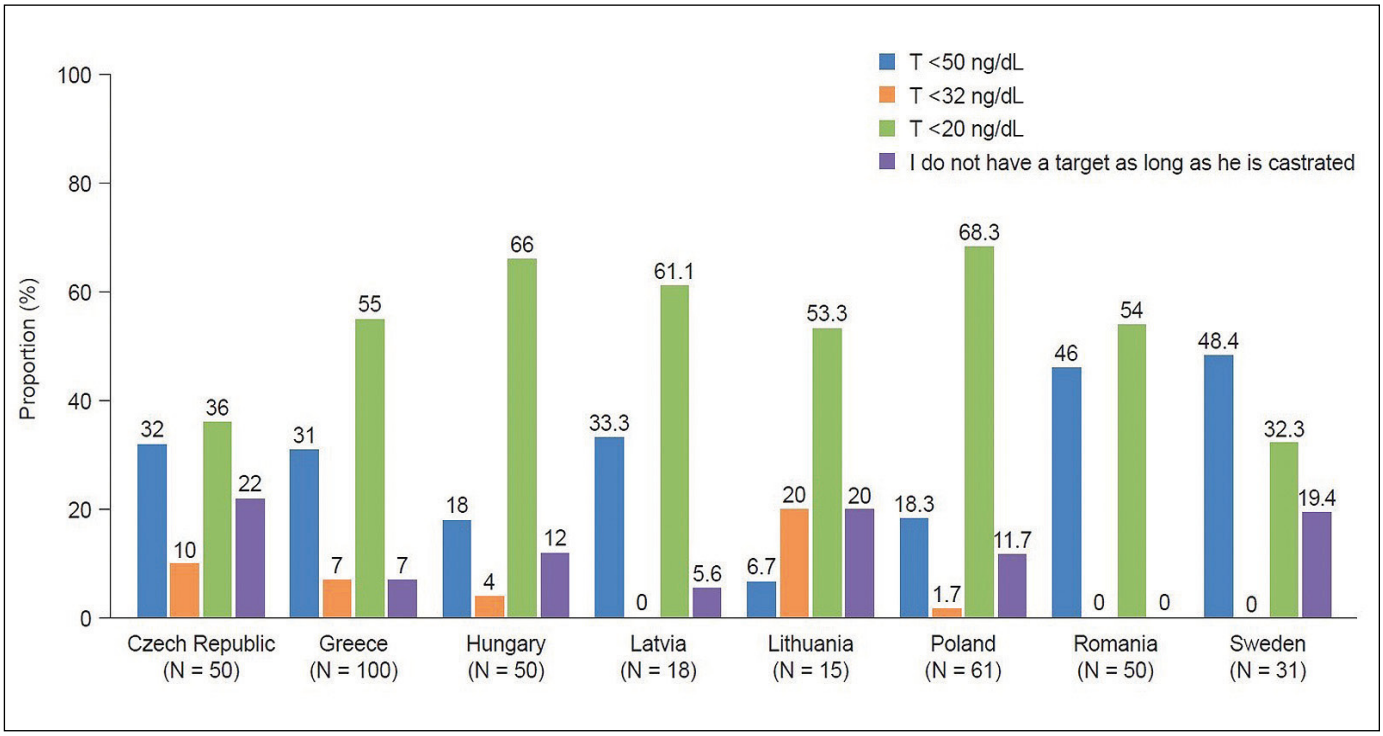

Figure 2. *Physicians treating to different testosterone nadir (T) level castration targets, by country. Data refer to the management of patients with any disease stage (localized or metastatic). Categories of castration target T levels were not mutually exclusive; here, we show the proportion of physicians in each country by T level used.*

Bonferroni correction). Physicians in non-teaching hospitals considered ADT as monotherapy for 50% of their patients in the high-very high-risk group compared with physicians in university hospitals and the private sector, who considered it for 70% of patients.

Across all countries, the proportions of physicians who applied the various target castration T levels were: T <50 ng/dL, 29.9%; T <32 ng/dL, 4.8%; T <20 ng/dL, 54.3%; and "I do not have a target as long as he is castrated", 11.0%. Target T levels differed significantly between countries (p <0.001). The proportion of physicians who considered the optimum T level to be T <50 ng/dL was highest in Sweden (48.4%), T <32 ng/dL was highest in Lithuania (20.0%), and T <20 ng/dL was highest in Poland (68.3%) (Figure 2). Target castration T levels differed significantly between urologists and oncologists (p = 0.045), with a target of T <50 ng/dL being more commonly observed for the oncologists and a target of T <20 ng/dL more commonly observed for the urologists (Table 2).

In the overall sample, more than half (58.7%) of physicians stated they measured T levels when an increase in PSA level was observed (Table 3). In total, 19.7% of physicians stated they only measure T lev-

Table 2. *Target castration T level by medical specialty and practice affiliation*

	Primary medical specialty		Practice affiliation		
	Urologist (N = 267)	Oncologist (N = 108)	University hospital or cancer center (N = 156)	Non-teaching hospital (N = 144)	Private sector (N = 75)
Target castration T level, n (%)					
T <50 ng/dL	69 (25.9)	43 (39.8)	44 (28.2)	52 (36.1)	16 (21.6)
T <32 ng/dL	15 (5.6)	3 (2.8)	11 (7.1)	3 (2.1)	4 (5.4)
T <20 ng/dL	153 (57.5)	50 (46.3)	84 (53.8)	74 (51.4)	45 (60.8)
"I do not have a target as long as he is castrated"	29 (10.9)	12 (11.1)	17 (10.9)	15 (10.4)	9 (12.2)

Data refer to the management of patients with any disease stage (localized or metastatic). Categories of target T levels were not mutually exclusive; here, we show the proportion of physicians in each testosterone target level category by physician's specialty or affiliation
T– nadir testosterone

els in connection to a PSA increase and 6.9% stated they only measure T levels before initiation of ADT. Attitudes towards measurements of T levels differed significantly among the countries studied ($p < 0.001$ for measurement before initiation of luteinizing hormone-releasing hormone analogs [LHRH-a]; $p = 0.045$ for measurement within 3 months of LHRH-a initiation; $p < 0.001$ for measurement regularly during LHRH-a treatment; $p < 0.001$ for measurement every time that PSA is measured; $p < 0.001$ for measurement when an increase in PSA level is observed) (Table 3). The proportion of physicians measuring T levels before LHRH-a initiation was highest in Romania, the proportions of those measuring T levels within 3 months of LHRH-a initiation, regularly during LHRH-a or every time that PSA is measured were most common in Hungary (44.0%, 60.0% and 48.0%, respectively), and the proportion of those measuring T levels when an increase in PSA was observed was highest in Lithuania (93.3%; Table 3).

There were significant differences in T-level measurement practices between urologists and oncologists (Table 3). The proportion of oncologists who stated they measured T levels before LHRH-a initiation was significantly higher than that of urologists (55.6% vs 27.0%, respectively; $p < 0.001$). In contrast, the proportions of oncologists who stated they measured T levels regularly during LHRH-a treatment, or following an increase in PSA level, were significantly lower than the proportions of urologists (26.9% vs 38.6%, $p = 0.031$, and 44.4% vs 64.4%, $p < 0.001$, respectively). The proportions of physicians who stated they measured T levels every time that the PSA level was measured differed significantly between practice affiliations ($p = 0.031$), with the highest proportion being observed at non-teaching hospitals (29.9%).

DISCUSSION

This European multinational survey revealed considerable variation among physicians in the use of ADT as monotherapy for localized or locally advanced PC. Discrepancies from current EAU–ESTRO–ESUR–SIOG guidelines were found in several key treatment practices, including the use of ADT in patients with localized low- or intermediate-risk prostate cancer, the use of T thresholds that are higher than those recommended, and a lack of a coherent strategy for measuring T levels to assess ADT success, all of which may have implications for patient health. The observed variability in approach and divergence from evidence-based recommendations is generally consistent with previous findings [8–15].

Table 3. *Testosterone level measurement practice by specialty, affiliation and country*

Measurement practice	Total sample (N = 375)	Urologist (N = 267)	Oncologist (N = 108)	University hospital* (N = 156)	Non-teaching hospital (N = 144)	Private sector (N = 75)	Czech Republic (N = 50)	Greece (N = 100)	Hungary (N = 50)	Latvia (N = 18)	Lithuania (N = 15)	Poland (N = 61)	Romania (N = 50)	Sweden (N = 31)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
In your prostate cancer patients that are currently receiving ADT, do you measure testosterone levels:														
before LHRH-a initiation	132 (35.2)	72 (27.0)	60 (55.6)	51 (32.7)	52 (36.1)	29 (38.7)	18 (36.0)	37 (37.0)	26 (52.0)	1 (5.6)	1 (6.7)	11 (18.0)	36 (72.0)	2 (6.5)
within 3 months of LHRH-a initiation	120 (32.0)	93 (34.8)	27 (25.0)	42 (26.9)	56 (38.9)	22 (29.3)	16 (32.0)	38 (38.0)	22 (44.0)	3 (16.7)	2 (13.3)	22 (36.1)	11 (22.0)	6 (19.4)
regularly during LHRH-a treatment	132 (35.2)	103 (38.6)	29 (26.9)	51 (32.7)	54 (37.5)	27 (36.0)	26 (52.0)	33 (33.0)	30 (60.0)	5 (27.8)	1 (6.7)	24 (39.3)	10 (20.0)	3 (9.7)
every time PSA is measured	62 (16.5)	43 (16.1)	19 (17.6)	20 (12.8)	33 (22.9)	9 (12.0)	11 (22.0)	9 (9.0)	24 (48.0)	2 (11.1)	0 (0.0)	8 (13.1)	8 (16.0)	0 (0.0)
when PSA increase is observed	220 (58.7)	172 (64.4)	48 (44.4)	92 (59.0)	82 (56.9)	46 (61.3)	23 (46.0)	73 (73.0)	26 (52.0)	11 (61.1)	14 (93.3)	33 (54.1)	13 (26.0)	27 (87.1)

*and cancer centers. Data refer to the management of patients with any disease stage (localized or metastatic). Categories of testosterone measurement practices were not mutually exclusive. This table shows the proportion of physicians in each country by testosterone measurement practice

ADT – androgen deprivation therapy; LHRH-a – luteinizing hormone-releasing hormone analog; PSA – prostate-specific antigen; N – number

According to the EAU–ESTRO–ESUR–SIOG guidelines, ADT may be used in high-risk patients with PC, although monotherapy should not be used in asymptomatic individuals with high-risk, localized disease [5]. In the present study, across medical contexts and countries, the number of physicians who considered use of ADT as monotherapy was greatest in high-risk, localized disease. An international online survey has shown that key drivers for clinicians choosing continuous use of ADT included PSA levels (65% of respondents), Gleason score (52%) and guideline recommendations (48%). The average rate of ADT use in patients with non-metastatic disease was 38% overall in the above survey, although there was considerable variation across the 19 countries (in the range 25–99%), with the highest rates being observed in Eastern Europe [9]. In the present study, profound variation in the use of ADT by country was found in high-risk patients: the median overall rate was 60%, ranging from 30% in Poland to 80% in Greece.

In patients with low-risk of PC, ADT monotherapy is not recommended by the EAU–ESTRO–ESUR-SIOG guidelines, active surveillance is recommended as an alternative to immediate active treatment [5]. Accordingly, a recent US survey of patients with localized PC reported that expectant management increased between 2004 and 2013 relative to radiation therapy and radical prostatectomy [10]. While our data suggest that the majority of physicians' decisions generally reflect current guidelines, the use of ADT in low-risk (7.5%) and intermediate-risk (30%) groups of patients was not insignificant. The early use of ADT was also observed in a US observational study of 7195 patients with PC that reported a marked increase between 1989 and 2001 in the use of primary ADT among low-risk (increase of 4.6% to 14.2%) and intermediate-risk (increase of 8.9% to 19.7%) patient groups. The authors suggested that the advent of PSA screening had enabled earlier disease detection and, thereby, facilitated earlier intervention [8], an argument that may contribute to the present observations. Additionally, patient demand for active treatment in combination with early detection could also contribute to the current findings.

The present data suggest that physician characteristics have an effect on adherence to the EAU-ESTRO-ESUR-SIOG guidelines. Physicians affiliated with a university hospital or cancer center were more likely to adhere to the EAU-ESTRO-ESUR-SIOG guidelines with regard to use of ADT than those affiliated to a non-teaching hospital. Furthermore, urologists were less likely than oncologists to use ADT in all risk groups of patients. These findings are consistent with a study involving >82,000 patients with PC from the Surveillance, Epidemiology and End Results (SEER)-Medicare database [16]. ADT use for localized disease was found to be higher in non-teaching than in teaching hospitals; indeed, higher ADT use was found to be significantly correlated with a lack of an academic affiliation [16]. Similarly, in a separate study involving almost 62,000 patients, ADT use was more strongly associated with physician characteristics (22.56%) than with tumor classification (9.71%) or patient characteristics (4.29%) [17].

Increased survival and delayed progression to castration-resistant PC correlate with lower T levels [2, 18]. The EAU-ESTRO-ESUR-SIOG guidelines acknowledge 50 ng/dL as the official T level for achieved castration used by authorities and in clinical studies but advocate the use of the lower level of 20 ng/dL, a value in line with the effect achieved by surgical procedure (15 ng/dL) [5]. Indeed, this T level was widely achieved in a pooled analysis of nine prospective studies of patients with PC treated with triptorelin depot formations (1-, 3- and 6-month doses) [19], while triptorelin resulted in significantly lower T levels than subcapsular orchidectomy in a randomized controlled trial [20]. In the present study, more than half of physicians (54.3%) used the EAU-recommended level of T <20 ng/dL, although one-third targeted higher levels and 11% used no target T level at all. Urologists were more likely than oncologists to use the target T <20 ng/dL, as were private clinicians, compared with those who were university affiliated or who worked outside of academic institutions. These variations in target T level thresholds could reflect differences in awareness of current recommendations, access to measurement tools or time and cost pressures.

ADT, though effective, cannot be considered a proxy for low T levels. While many patients are likely to achieve levels of T <20 ng/dL, a significant minority (estimated as 13–38%) will not, and up to 24% of patients may experience temporary surges of T >50 ng/dL [5]. Hence, regular T-level monitoring is essential to optimize patient outcomes; in spite of this, the proportion of physicians who monitored T levels regularly during LHRH-a treatment was <10% in some countries and only 35.2% overall. Although rising PSA levels and/or clinical progression are potential indicators of castration resistance, T-level measurements should not be limited to these events. The EAU-ESTRO-ESUR-SIOG guidelines note that timings of T level measurements are not clearly defined but suggest a three to six month assessment to ensure castration level is achieved and maintained. If castration level is not achieved it is recommended to switch to another substance or to recommend orchiectomy [5]. Nevertheless, 6.9%

of physicians stated they only measure T levels before ADT initiation and 19.7% of physicians stated they measured serum T levels only when a rise in PSA level was observed, meaning 26.9% never ensure that their patients are biochemically castrated. In Canada, where consensus guidance recommends a target castrate level of 0.7 nmol/L (20.2 ng/dL) and regular (3–6 monthly) monitoring of T and PSA levels during ADT [18], a wide variability in monitoring approach has been reported. In a survey of Canadian physicians, 42.5% of respondents indicated that they monitor 'regularly', 28.8% 'always' and 5.2% 'never' [18]. The lack of a strong evidence base for monitoring frequency may contribute to the observed variability, with physicians prioritizing the limited time and resources available to the patients that they consider to be most at risk.

The present evidence of physicians' divergence from guidelines reflects a Spanish study that found that only just over half of physicians (52.1%) followed recommendations considered to be 'controversial' [14]. The study results suggest that Spanish urologists may draw on their own real-world clinical experience as well as formal guideline recommendations when making therapeutic management decisions in routine care [14]. It is also possible that different definitions of 'high-risk' and outcome parameters may underlie some of the observed variability of some findings [3]. One possible solution to support the integration of evidence-based strategies into PC management is the use of clinical pathways. A study exploring the utility of a clinical pathway for managing ADT-induced side effects found improvements in the implementation of guidelines and, more importantly, in patient outcomes [21].

This study has potential limitations. The respondents chose different scenarios for hypothetical situations and this might not reflect an actual treatment decision. The respondents were chosen from an existing database and not randomly selected. The response rate was 58% which is below the golden standard of 80% for generalizing the result. Since no data were collected without a consent, the specialty and affiliation of the non-responders is not known, and it is difficult to know how this affected the results. The specialty of the respondents differed between the countries which should be considered when interpreting the inter-country comparisons.

The EAU-ESTRO-ESUR-SIOG guidelines were chosen as the standard for this study. A comparison to e.g. the European Society for Medical Oncology's (ESMO) guidelines might have given another result.

CONCLUSIONS

This survey highlights divergences from the EAU-ESTRO-ESUR-SIOG guidelines that may affect patient outcomes, but the data should be interpreted in light of the following caveats. The present study does not provide insight into individual treatment decisions, and while certain practices were inconsistent with the EAU-ESTRO-ESUR-SIOG guidelines, they may be appropriate for a given patient. As demonstrated by the variability in responses between physicians of different medical disciplines and affiliations, within-country data should not be considered homogenous. Finally, the present survey depended on physician recall and estimation of quantitative information that may be prone to error.

Further research is required to add to the understanding of the reasons for divergence from current evidence-based guidelines, and to identify tools and strategies needed to support physicians in implementing critical treatment choices. This may include utilizing the potential of registries that incorporate patients with a broader spectrum of sociodemographic, comorbidity and risk-factor characteristics, all of which may be key factors in clinicians' treatment decisions [22].

CONFLICTS OF INTEREST

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AUTHOR CONRTIBUTIONS

TS and VM were involved in the conception and design of the study and the acquisition, analysis and interpretation of data. DM, MH and PC were involved in analysis and interpretation of data. All authors were involved in drafting the manuscript and revising it critically for important intellectual content. All authors approved the final version of the manuscript.

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