Prostate Cancer

Detailed Evaluation of Androgen Deprivation Overtreatment in Prostate Cancer Patients Compared to the European Association of Urology Guidelines Using Long-term Data from the European Randomised Study of Screening for Prostate Cancer Rotterdam

Renée Hogenhout¹*, Ivo I. de Vos¹, Sebastiaan Remmers, Lionne D.F. Venderbos, Martijn B. Busstra, Monique J. Roobol, the ERSPC Rotterdam Study Group

Department of Urology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

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Abstract

Background: Guidelines on androgen deprivation therapy (ADT) for prostate cancer (PCA) arise from a critical appraisal of scientific evidence, which is a costly effort. Despite these efforts and the side effects of ADT, guidelines may not always be adhered to.

Objective: To determine ADT overtreatment in PCA patients compared to the European Association of Urology (EAU) guidelines, and to identify predictors and physicians’ motivations for this overtreatment.

Design, setting, and participants: Men were included from the European Randomised study of Screening for Prostate Cancer (ERSPC) Rotterdam who were diagnosed with PCa between 2001 and 2019, and received ADT < 1 yr after diagnosis. Patients were categorised into the concordant ADT or discordant ADT group following the EAU guidelines. Physicians’ motivations for discordancy were reported. Multivariable logistic regression was performed to identify predictors for guideline-discordant ADT including the non-linear fit of the year of diagnosis.

Results and limitations: Of 3608 PCa patients, 1037 received ADT < 1 yr after diagnosis. Adherence improved gradually over the study period, resulting in overall discordancy of 15%. A patient diagnosed in 2011 had 3.3 times lower risk on guideline-discordant ADT than a patient diagnosed in 2004 (odds ratio [OR] 0.30; 95% confidence interval [CI] 0.18–0.50). The most common reason for discordancy was unwillingness or unfitness for curative treatment of asymptomatic patients. Age (OR 1.19; 95% CI 1.15–1.24) and Gleason score ≥ 4 + 3 (OR 1.70; 95% CI 1.06–2.74) were associated with guideline-discordant ADT.

¹ These authors contributed equally.
* Corresponding author. Department of Urology, Erasmus MC Cancer Institute, Room number NA-1524, Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. Tel. +31 10 70 38145; Fax: +31 10 70 35315.
E-mail address: r.hogenhout@erasmusmc.nl (R. Hogenhout).
1. Introduction

Side effects of androgen deprivation therapy (ADT) for men with prostate cancer (PCa) can lead to reduced quality of life (QoL) [1]. Furthermore, since ADT does not improve overall survival in some patient categories [2], a careful trade-off between harms and benefits must be made when ADT is considered. Guidelines facilitate such decisions in daily clinical practice by promoting effective treatments and discouraging ineffective ones based on scientific research to maintain the quality of health care [3–5].

The European Association of Urology (EAU) guidelines on PCa were first published in 2001 and have since been followed in Dutch daily practice [6]. In general, the guidelines recommend ADT as a primary treatment for metastatic patients and as an adjuvant to radiotherapy (RT) for localised PCa. Previous research has shown that patients with low-risk PCa do not benefit from any form of ADT in terms of overall survival [7]. This is also true for ADT as monotherapy in intermediate-risk and high-risk PCa patients. However, the latter is accepted by the guidelines in patients who are unwilling or unfit to undergo curative treatment, and those who are asymptomatic or with high prostate-specific antigen (PSA) levels or short PSA doubling time (PSADT). In these patients, ADT can be initiated as palliative treatment to improve QoL.

Developing these guidelines is a costly effort, both financially and time-wise. Despite these efforts, several studies have found adherence to the guidelines to be suboptimal [8–11]. However, these studies did not report on the methodology for categorisation into guideline-concordant or guideline-discordant ADT [8,9], while for ADT as monotherapy, the aforementioned conditions should be taken into account according to the EAU guidelines. Furthermore, the physician’s motivation to engage in guideline-discordant behaviour in prescribing ADT remains unclear. Gaining insight into this will be valuable to improve guideline adherence.

Therefore, we assessed the ADT overtreatment in PCa patients compared to the EAU guidelines using detailed clinical data, and we identified predictors and physicians’ motivation for this overtreatment.

2. Patients and methods

2.1. Study population

The European Randomised study of Screening for Prostate Cancer (ERSPC) is a multicentre, randomised controlled trial that investigates the effect of PSA-based screening on PCa mortality. Overall ERSPC Rotterdam study characteristics have been described previously [12]. Eligible men (50–74 yr) were identified from a population register and randomised to an intervention or control arm. Recruitment was initiated in 1993 and lasted until 2000. All participants provided written informed consent. Men in both study arms diagnosed with PCa were included in a study database. At the time of diagnosis, the following information was recorded: date of diagnosis, urinary complaints, PSA level, Gleason score (GS), TNM classification 1992, and initial treatment. During follow-up, PSA level, events of disease progression, and current or change of treatment were monitored and recorded.

For this study, we retrospectively included men from both study arms of the ERSPC Rotterdam who were diagnosed with PCa in all stages. Since the first EAU PCa guideline was published in 2001 [13], we included in our analyses those who were diagnosed with PCa between 2001 and 2019. To quantify the guideline adherence on ADT, all patients who received any form of treatment with ADT within the 1st year after diagnosis were included. This timespan was chosen to prevent missing neoadjuvant ADT treatment to RT or surgery.

2.2. Definitions of ADT use

ADT consisted of luteinising-hormone-releasing hormone (ant)agonists, antiandrogens, or a subcapsular orchietomy as treatment. All uses of ADT were categorised into ADT as monotherapy, ADT combined with RT, ADT before radical prostatectomy (RP), or ADT after failed curative treatment. When ADT was prescribed before or concomitant with RT or RP, it was defined as (neo)adjuvant therapy. ADT as monotherapy for progression during watchful waiting was defined as palliative therapy.

2.3. Risk groups

For categorisation into the guideline-concordant ADT group and the guideline-discordant ADT group, all men with localised PCa and metastatic PCa were identified. Localised PCa was classified using the EAU risk group classification [6]: low-risk disease was defined as PSA ≤10 ng/ml, GS ≤6, or clinical stage T1-2a; intermediate-risk disease was defined as PSA 10–20 ng/ml, GS 7, or clinical stage T2b; and high-risk disease was defined as PSA >20 ng/ml, GS ≥8, or clinical stage T2c. Men in whom GS, PSA, or clinical (c)T stage was missing were classified according to the remaining available clinical factors. Men
diagnosed with PCa in whom information about metastasis (Mx) was missing were considered metastatic if PSA was >100 ng/mL [14]. Men in whom imaging did not show metastasis (M0) were also considered metastatic if PSA was >100 ng/mL, to make an equal assessment among these two groups.

2.4. Classification in guideline-concordant ADT and guideline-discordant ADT

According to the EAU guidelines [15], all uses of ADT for distant metastasis and palliative ADT were considered concordant. In localised PCa, concordant use of ADT included ADT as an adjuvant to RT in intermediate-risk and high-risk groups. For men in whom ADT was started with the intention to combine it with RT, but who refrained from RT later on, the initial treatment proposal was used for the analysis. Any use of ADT in low-risk patients and ADT as an adjuvant to RP in any risk group was classified as guideline-discordant. We considered ADT after curative treatment (ie, RT or RP) as guideline-concordant, since these patients may have had biochemical recurrence (BCR) or persistent PSA after surgery. ADT due to disease progression after initial watchful waiting was also considered as guideline-concordant since the risk classification had changed compared to the baseline risk.

The EAU guidelines allow for ADT as monotherapy in patients with intermediate-risk or high-risk (including locally advanced) PCa under certain conditions. However, some conditions changed over time (Supplementary Table 1). Since these were only minor changes, mostly for a short period, we maintained the most commonly used combination of conditions stated in the guidelines: ADT as monotherapy for intermediate-risk to high-risk PCa patients was considered guideline-concordant if one was unwilling or unfit for local treatment when either being symptomatic or asymptomatic with PSADT <12 mo or PSA >25 ng/ml in or before 2010 and PSA >50 ng/ml after 2010 (Fig. 1). In patients with lymph node metastasis, ADT as monotherapy was unconditionally allowed until 2010, and thus we considered monotherapy as guideline-concordant in patients diagnosed before 2011. Thereafter, we maintained the aforementioned conditions.

“Symptomatic” is not defined by the EAU guidelines [6]. The full-text guidelines refer to the European Organisation for Research and Treatment of Cancer study that established criteria for initiating ADT, including description of symptoms [7]. Based on this study, we scored evidence of ureteric obstruction (ie, hydronephrosis), urethral obstruction with severe consequences (ie, urinary retention), or local rectal obstruction (ie, paradoxical diarrhoea) caused by the primary tumour as “symptomatic”. Since lower urinary tract symptoms (LUTS) are quite common among men in the same age category as the study population due to causes other than PCa (eg, benign prostatic hyperplasia), this condition was not classified as “symptomatic”. “Unwilling” or “unfit” was positively scored (Fig. 1) when it was explicitly reported in the medical record. When not explicitly reported, unfit was scored based on the reported medical history. When none of the conditions could be extracted from the medical record, we considered the prescription for guideline-discordant ADT as not motivated.

2.5. Medical record review

Details concerning symptomatic disease, unfitness or unwillingness, and the physician’s rationale to deviate from the guideline were retrospectively collected by a medical record review. A flowchart was used for a standardised assessment in patients with intermediate-risk and high-risk PCa who received ADT monotherapy (Fig. 1). Chart reviews were independently performed by two authors who are medical doctors with experience in PCa care. Cases without agreement were discussed to reach a consensus.

2.6. Statistical analysis

To assess guideline adherence on ADT and the physician’s rationale to deviate from the guidelines, descriptive statistics were quantified with continuous variables, presented as median (interquartile range), and categorical variables, presented as proportions (%). Multivariable logistic regression was performed to assess the relation between guideline-discordant ADT and the age of diagnosis, the binary transformation of PSA at diagnosis, cT stage (cT1, cT2), GS (3 + 3, 3 + 4, and 4 + 3), and the year of diagnosis since 2001. Missing values were imputed. Non-linearity of the predictor “years of diagnosis” was taken into account using restricted cubic splines and was quantified as the difference between the 75th percentile and the 25th percentile. For this analysis, only those at risk of guideline-discordant ADT were included (ie, men with localised PCa without disease progression or BCR, regardless of whether they were prescribed ADT). We assumed that men not treated with ADT were treated correctly compared to the guideline. All statistical analyses were performed using R version 4.1.0 [16].
3. Results

3.1. Patient characteristics

Between 2001 and 2019, a total of 3608 men were diagnosed with PCa (Table 1). Within the 1st year after diagnosis, 1037 (29%) men received ADT. Most of these men were diagnosed with high-risk PCa (49%).

3.2. Guideline discordancy and rationale

Of all men enrolled, 159 (15%) received guideline-discordant ADT (Tables 1 and 2). In every risk group, most were diagnosed with high-risk PCa (49%).

3.3. Multivariable logistic regression

Multivariable logistic regression showed that patients who were older or had GS ≥4 + 3 were significantly more likely to receive guideline-discordant ADT (Table 3). The nonlinear relation between the year of diagnosis and discordancy showed an increase in the risk of discordancy in the first 4 yr and a decrease in the years thereafter (Fig. 3). To elaborate, a patient diagnosed in 2011 (75th percentile) had a 3.3 times lower risk of guideline-discordant ADT than a patient with the same risk diagnosed in 2004 (25th percentile).

Table 1 – Patient characteristics and given treatment

|                      | All men at risk for discordant ADT | Concordant | Discordant | SMD (95% CI) |
|----------------------|------------------------------------|------------|------------|--------------|
| No. of patients, n   | 2743                               | 648        | 159        |              |
| Not assessable, n    | 30                                 | NA         | NA         |              |
| Age (yr), median (IQR) | 73.0 (68.7–76.5)   | 75.6 (71.5–80.0) | 79.1 (75.1–81.6) | –0.428 (–0.60, –0.26) |
| PSA (ng/ml) overall, median (IQR) | 7.7 (4.4–14.4) | 32.0 (12.6–111.3) | 18.1 (8.1–31.6) | 0.364 (0.19, 0.53) |
| Year of diagnosis, median (IQR) | 2007 (2004–2011) | 2008 (2004–2012) | 2008 (2004–2012) | 0.123 (–0.05, 0.29) |
| Clinical stage, n (%) |                                    |            |            |              |
| ≤T1C                 | 1695 (62)                          | 172 (20)   | 70 (44)    | –0.53 (–0.69, –0.35) |
| T2A                  | 482 (18)                           | 81 (9.6)   | 34 (21)    | –0.33 (–0.50, –0.16) |
| T2B                  | 141 (5.1)                          | 66 (7.8)   | 12 (7.5)   | –0.01 (–0.16, 0.18) |
| T2C                  | 76 (2.8)                           | 58 (6.8)   | 9 (5.7)    | –0.05 (–0.12, 0.22) |
| T3A                  | 201 (7.3)                          | 203 (24)   | 16 (10)    | 0.38 (0.21, 0.55) |
| T3B                  | 94 (2.8)                           | 138 (16)   | 11 (6.9)   | 0.30 (0.13, 0.47) |
| T4                   | 25 (0.9)                           | 99 (12)    | 5 (3.1)    | 0.33 (0.16, 0.5) |
| TX                   | 29 (1.1)                           | 31 (3.7)   | 2 (1.3)    | 0.16 (–0.01, 0.32) |
| Nodal stage, n (%)    |                                    |            |            |              |
| N0                   | NA                                 | 316 (37)   | 45 (28)    | 0.19 (0.02, 0.36) |
| N1                   | NA                                 | 121 (14)   | 10 (6.3)   | 0.27 (0.10, 0.43) |
| Nx                   | NA                                 | 411 (48)   | 104 (65)   | –0.34 (–0.52, –0.18) |
| Metastatic, n (%)     |                                    |            |            |              |
| M0                   | NA                                 | 358 (42)   | 80 (50)    | –0.16 (–0.33, 0.01) |
| M1                   | NA                                 | 309 (36)   | NA         | 1.07 (0.89, 1.25) |
| Nx                   | NA                                 | 181 (21)   | 79 (50)    | –0.62 (–0.79, 0.45) |
| Gleason score, n (%)  |                                    |            |            |              |
| ≤3 + 3               | 1631 (59)                          | 111 (13)   | 53 (33)    | –0.50 (–0.67, –0.33) |
| 3 + 4                | 476 (17)                           | 158 (19)   | 34 (21)    | –0.05 (–0.22, 0.12) |
| 4 + 3                | 184 (6.7)                          | 115 (14)   | 19 (12)    | 0.07 (–0.10, 0.24) |
| 4 + 4                | 302 (13)                           | 383 (45)   | 44 (28)    | 0.43 (0.26, 0.60) |
| Unknown              | 90 (3.3)                           | 81 (9.6)   | 9 (5.7)    | 0.15 (–0.02, 0.32) |
| Risk groups, n (%)    |                                    |            |            |              |
| Low risk             | 1191 (43)                          | 10 (1.2)   | 31 (19)    | –0.63 (–0.80, –0.46) |
| Intermediate risk    | 717 (26)                           | 77 (9.1)   | 27 (17)    | –0.24 (–0.41, –0.07) |
| High risk            | 835 (30)                           | 393 (46)   | 91 (57)    | –0.22 (–0.39, –0.05) |
| Lymph node metastasis| NA                                 | 59 (7.0)   | 10 (6.3)   | 0.03 (–0.14, 0.20) |
| Distant metastasis   | NA                                 | 309 (36)   | 0 (0)      | 1.07 (0.89, 1.25) |
| Treatment, n (%)     |                                    |            |            |              |
| ADT monotherapy      | 205 (7.5)                          | 426 (50)   | 144 (91)   | –0.98 (–1.16, 0.81) |
| Adjuvant ADT with RT | 380 (14)                           | 382 (45)   | 8 (5.0)    | 1.04 (0.87, 1.22) |
| Adjuvant ADT with RP | 7 (0.3)                            | 0 (0)      | 7 (4.4)    | –0.47 (–0.30, –0.13) |
| ADT after curative treatment | NA | NA | NA | |
| ADT due to disease progression | NA | 21 (2.5) | 0 (0) | 0.23 (0.06, 0.40) |
| No ADT               | 2151 (78)                          | NA         | NA         | NA |

ADT = androgen deprivation therapy; CI = confidence interval; IQR = interquartile range; NA = not available; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; SMD = standardised mean difference.

*All men with localised PCa regardless of whether they were prescribed ADT.

* SMD between concordant and discordant.
adherence is suboptimal according to previous studies [8–11]. To our knowledge, this is the first study that investigated ADT overtreatment compared to the EAU guidelines over a long period (ie, 19 yr) and by using detailed data on patient preferences and symptoms. This study is also unique as it is the first to report the physicians’ rationale for guideline-discordant prescription of ADT in the cohort in question.

We found that adherence to the EAU guidelines gradually improved over the study period, resulting in overall overtreatment of 15%, mostly because of unjustified ADT as monotherapy. The most frequently reported motivation for guideline-discordant ADT was unwillingness or unfitness of patients for curative treatment without having symptoms or other reasons such as high PSA level or short PSADT. This is remarkable given that these conditions for justified ADT prescription were described by the guidelines. One way to potentially accelerate the guideline adherence could be a visual structured presentation of these criteria, for example, in flowcharts, as was done for this study (Fig. 1), instead of text boxes to avoid the conditions being neglected unconsciously. A possibly more effective way to improve guideline adherence could be obtained through the emerging clinical decision support systems [17]. These knowledge-based systems enable the integration of guidelines into the electronic health record, eliminating continuous guideline consultation in everyday practice. However, despite promising examples, individualised tailoring is so far limited by the rigid algorithms of these systems.

Unfitness as the most commonly reported motivation for guideline-discordant ADT prescription is reflected by a higher age that was found to be significantly related to ADT overtreatment, which is also reported by previous research [8]. In addition, in line with our findings, Morgia et al. [9] did not find PSA to be predictive for guideline-discordant ADT according to the EAU guidelines, possibly because in some men ADT prescription is justified by high PSA levels. For higher GSs (≥4 + 3), we found a significant relation to ADT overtreatment compared to GS 3 + 3. This could be explained by the fact that in low-risk men, prescription of any ADT is always discordant, whereas ADT for intermediate-risk and high-risk patients is discordant under conditions mentioned earlier. This conditional justification of ADT prescription poses a risk for guideline-discordant behaviour, especially when these conditions are not clearly presented by the guidelines or need to be actively searched for (ie, outside the electronic health record).

Besides PSA, Morgia et al. [9] did not find a relation with the year of diagnosis. However, this study had a relatively short study period (ie, <2 yr). We were able to explore the guideline adherence over a longer period since we included patients between 2001 and 2019. After the first 4 yr, patients were more likely to receive guideline-concordant ADT when diagnosed more recently. An explanation for this could be the time and effort it takes before a new guideline becomes widely known, and subsequently, common practice, emphasising the importance of dissemination of guidelines at, for example, national and international conferences. In addition to the implementation of the guidelines in daily clinical practice, rising awareness of the side effects of ADT over the past decades might have also influenced guideline adherence over time. Around 2002, the negative impact of ADT on cognition came to the attention [18]. In 2006, an increased risk of diabetes and cardiovascular disease was found [19,20] and confirmed by subsequent studies [21]. In addition, more recent studies showed an increased risk of dementia [22]. Other, better known side effects of ADT are sexual dysfunction, gynaecomastia, fatigue, hot flashes, and anaemia [19]. They all potentially decrease the QoL and should, therefore, not be ignored.

Given the broad spectrum of side effects, the remedy can be worse than the disease, especially in asymptomatic men. Therefore, the guidelines allow for ADT as monotherapy in men with localised PCa only when having symptoms, high PSA levels or short PSADT [15]. LUTS, which is common among these men, could be one of those symptoms, especially at a locally advanced PCa stage. There is no specific mention of this issue in the EAU guidelines. However, regardless of whether LUTS should be classified as symptomatic, sometimes less invasive options for treating LUTS could be considered, such as alpha-blockers, 5-alpha-reductase inhibitors (palliative), transurethral resection of

### Table 2 – Frequency of guideline-concordant versus guideline-discordant ADT according to the EAU guidelines stratified by risk group (n = 1037)

| Condition                                | Concordant 848 (82%) | Discordant 159 (15%) |
|------------------------------------------|----------------------|----------------------|
| Low-risk PCa, n (%)                      | 10 (12)              | 31 (19)              |
| ADT monotherapy                          | NA                   | 21 (68)              |
| Adjuvant ADT with RT                      | NA                   | 8 (26)               |
| Adjuvant ADT with RP                      | NA                   | 2 (6.5)              |
| ADT after curative treatment              | 5 (50)               | NA                   |
| ADT due to progression of disease         | 5 (50)               | NA                   |
| Intermediate-risk PCa, n (%)              | 77 (9.1)             | 27 (17)              |
| ADT monotherapy                          | 2 (3.9)              | 25 (93)              |
| Adjuvant ADT with RT                      | 63 (82)              | NA                   |
| Neoadjuvant ADT with RP                   | NA                   | 2 (7.4)              |
| ADT after curative treatment              | 5 (6.5)              | NA                   |
| ADT due to progression of disease         | 7 (9.1)              | NA                   |
| High-risk PCa, n (%)                      | 393 (46)             | 91 (57)              |
| ADT monotherapy                          | 70 (18)              | 88 (97)              |
| Adjuvant ADT with RT                      | 309 (79)             | NA                   |
| Neoadjuvant ADT with RP                   | NA                   | 3 (3.3)              |
| ADT after curative treatment              | 8 (2.0)              | NA                   |
| ADT due to progression of disease         | 7 (1.8)              | NA                   |
| Lymph node metastasis, n (%)              | 57 (7.0)             | 10 (6.3)             |
| ADT monotherapy                          | 48 (81)              | 10 (100)             |
| Adjuvant ADT with RT                      | 9 (15)               | NA                   |
| Neoadjuvant ADT with RP                   | NA                   | 0 (0)                |
| ADT after curative treatment              | 1 (1.7)              | NA                   |
| ADT due to progression of disease         | 1 (1.7)              | NA                   |
| Distant metastasis, n (%)                 | 309 (37)             | NA                   |
| Not assessable, n (%)                     | 30 (3.5)             | NA                   |

ADT = androgen deprivation therapy; EAU = European Association of Urology; PCa = prostate cancer; RP = radical prostatectomy; RT = radiotherapy.

### 4. Discussion

The benefit of ADT for men with PCa in terms of treatment of symptoms and improving survival must be balanced against its side effects. Although evidence-based clinical practice guidelines assist in these decisions, guideline adherence is suboptimal according to previous studies [8–11]. To our knowledge, this is the first study that investigated ADT overtreatment compared to the EAU guidelines over a long period (ie, 19 yr) and by using detailed data on patient preferences and symptoms. This study is also unique as it is the first to report the physicians’ rationale for guideline-discordant prescription of ADT in the cohort in question.

We found that adherence to the EAU guidelines gradually improved over the study period, resulting in overall overtreatment of 15%, mostly because of unjustified ADT as monotherapy. The most frequently reported motivation for guideline-discordant ADT was unwillingness or unfitness of patients for curative treatment without having symptoms or other reasons such as high PSA level or short PSADT. This is remarkable given that these conditions for justified ADT prescription were described by the guidelines. One way to potentially accelerate the guideline adherence could be a visual structured presentation of these criteria, for example, in flowcharts, as was done for this study (Fig. 1), instead of text boxes to avoid the conditions being neglected unconsciously. A possibly more effective way to improve guideline adherence could be obtained through the emerging clinical decision support systems [17]. These
the prostate, or (self-)catheterisation. The same applies to volume reduction to enable RT, which was a common rationale for guideline-discordant prescription of ADT in combination with RT in this study.

The present study has some limitations. First, the EAU guidelines changed over time, which made the assessment difficult. However, no major changes occurred. Some changes were included in the analysis (eg, ADT monotherapy in lymph node metastasis before 2010), but taking into account the subtle changes would have significantly increased the complexity of the analysis without clinically relevant consequences. Additionally, the assessment of the physician’s motivation for discordancy was retrospectively collected. Since the arguments to prescribe ADT were not always explicitly or consistently reported by the physicians in the medical records, some assessments were subject to interpretation. For example, for 25% (39/159) of men who received guideline-discordant ADT, motivation for subscription was not reported by the physician (Fig. 2) but might have been discussed orally with the patient. Furthermore, the analysis is partly based on assumptions (ie, definition of symptomatic, metastatic if PSA >100 ng/ml, and concordance in men who were not prescribed ADT). However, to
create consistency and minimise subjectivity, we standardised the assessment using a flowchart. Besides, all medical records were independently assessed by two authors, and a consensus was reached by face-to-face discussions. Another aspect to keep in mind is that even though this was a multicentre study, our cohort consisted mainly of patients from Rotterdam and surrounding areas. Since previous research found geographical areas to be predictive of guideline-discordant ADT [9], our findings may not reflect guideline adherence in other regions of the Netherlands or Europe. Additionally, we only assessed overtreatment with ADT compared to the guidelines among PCa patients. Another interesting aspect to focus on would be undertreatment, and to distinguish between intermittent ADT and continuous ADT. Therefore, we await the results of the ongoing comprehensive EAU Guidelines Office IMAGINE project, which maps ADT practice patterns in a more extensive way across Europe to improve guideline adherence [23].

5. Conclusions

In a Dutch cohort, slow adaptation of the EAU guidelines on androgen deprivation therapy for prostate cancer patients resulted in overall overtreatment of 15% between 2001 and 2019. Reasons for overtreatment with androgen deprivation therapy were unfitness or unwillingness of the patient for curative treatment, high PSA levels, or short PSA doubling time, pending radical prostatectomy, and prostate volume reduction prior to radiotherapy. Clear, structured flowcharts in guidelines or, more promising, integration of these tailored guidelines into the electronic health record is needed to accelerate the adaptation of future guidelines.

Author contributions: Renée Hogenhout had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hogenhout, de Vos, Remmers, Venderbos, Busstra, Roobol.
Acquisition of data: Hogenhout, de Vos, ERSPC Rotterdam Study Group.
Analysis and interpretation of data: Hogenhout, de Vos, Remmers.
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Critical revision of the manuscript for important intellectual content: Hogenhout, de Vos, Remmers, Venderbos, Busstra, Roobol.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.06.004.

References

[1] Dacal K, Sereika SM, Greenspan SL. Quality of life in prostate cancer patients taking androgen deprivation therapy. J Am Geriatr Soc 2006;54:85–90.
[2] Gupta M, Patel HD, Schwen ZR, Tran PT, Partin AW. Adjuvant radiation with androgen-deprivation therapy for men with lymph node metastases after radical prostatectomy: identifying men who benefit. BJU Int 2019;123:252–60.
[3] Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical practice guidelines and critical pathways. J Clin Oncol 2001;19:2886–97.
[4] Smith TJ, Hillner BE. Ensuring quality cancer care by the use of clinical practice guidelines and critical pathways. J Clin Oncol 1999;17:307–10.
[5] Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 1993;342:1317–22.
[6] Mottet N, Cornford P, van den Bergh RCN, et al. https://uroweb.org/guideline/prostate-cancer/.
[7] Studer UE, Collette L, Whelan P, et al. Using PSA to guide timing of androgen deprivation in patients with T0–4 N0–2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). Eur Urol 2008;53:941–9.
[8] Kuykendal AR, Hendrix LH, Saloum RG, Godley PA, Chen RC. Guideline-discordant androgen deprivation therapy in localized prostate cancer: patterns of use in the Medicare population and cost implications. Ann Oncol 2013;24:1338–43.
[9] Morgia G, Russo GI, Tubaro A, et al. Patterns of prescription and adherence to European Association of Urology guidelines on androgen deprivation therapy in prostate cancer: an Italian multicentre cross-sectional analysis from the Choosing Treatment for Prostate Cancer (CHOICE) study. BJU Int 2016;117:867–73.
[10] Lyckén M, Drevin L, Garmo H, et al. Adherence to guidelines for androgen deprivation therapy after radical prostatectomy: Swedish population-based study. Scand J Urol 2020;54:208–14.
[11] Dell’Oglio P, Abou-Haidar H, Leyh-Bannurah SR, et al. Assessment of the rate of adherence to international guidelines for androgen deprivation therapy with external-beam radiation therapy: a population-based study. Eur Urol 2016;70:429–35.
[12] Roobol MJ, Kerkels WJ, Schröder FH. Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam, the Netherlands). BJU Int 2003;92(Suppl 2):48–54.
[13] Aus G, Abbou CC, Pach D, et al. EAU guidelines on prostate cancer. Eur Urol 2001;40:97–101.
[14] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320–8.
[15] Mottet N, Bellmunt J, Briers E, et al. EAU – ESTRO – ESUR – SIOG guidelines on prostate cancer. Presented at the EAU Annual Congress Amsterdam 2020. Arnhem, The Netherlands: EAU Guidelines Office.
[16] R Core Team. R: a language and environment for statistical computing. ed. 4.1.0. Vienna, Austria: R Foundation for Statistical Computing; 2021.
[17] Teufel A, Binder H. Clinical decision support systems. Visc Med 2021;37:491–8.
[18] Green HJ, Pakenham KI, Headley BC, et al. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: a randomized controlled trial. BJU Int 2002;90:427–32.
[19] Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol 2015;67:825–36.
[20] Keating NL, O’Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–56.
[21] Melloni C, Nelson A. Effect of androgen deprivation therapy on metabolic complications and cardiovascular risk. J Cardiovasc Transl Res 2020;13:451–62.
[22] Sari Motlagh R, Qbal F, Mori K, et al. The risk of new onset dementia and/or Alzheimer disease among patients with prostate cancer treated with androgen deprivation therapy: a systematic review and meta-analysis. J Urol 2021;205:60–7.
[23] Cornford P, Smith EJ, MacLennan S, et al. IMAGINE-IMPact assessment of guidelines implementation and education: the next frontier for harmonising urological practice across Europe by improving adherence to guidelines. Eur Urol 2021;79:173–6.