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

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Article info

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.

Outcome measurements and statistical analysis: 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 nonlinear 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 $\geq 4 + 3$ (OR 1.70; 95% CI 1.06–2.74) were associated with guideline-discordant ADT.

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Conclusions: In a Dutch cohort, slow adaptation of the EAU guidelines on ADT for PCa patients between 2001 and 2019 resulted in overall overtreatment of 15%, mostly in asymptomatic patients who were unfit or unwilling for curative treatment. Clear, structured presentation, or integration of these tailored guidelines into the electronic health record might accelerate the adaptation of future guidelines.

Patient summary: Slow adaptation of the guidelines on hormonal therapy resulted in overtreatment in 15% of prostate cancer patients, mostly in asymptomatic patients who were unfit or unwilling for curative treatment.

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 symptomatic 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 orchiectomy 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 $\leq$10 ng/ml, GS $\leq$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 $\geq$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
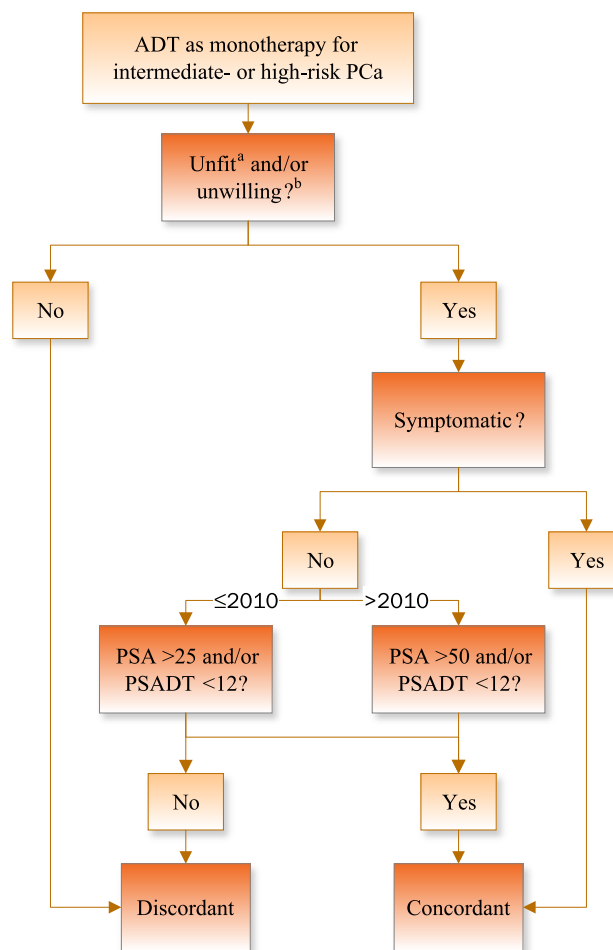
Fig. 1 – Flowchart for the assessment of guideline adherence on androgen deprivation therapy as monotherapy in intermediate-risk and high-risk PCa patients. ADT = androgen deprivation therapy; PCa = prostate cancer; PSA = prostate-specific antigen in ng/ml; PSADT = PSA doubling time in ng/ml/mo. [a] Unfit when explicitly reported in the medical record or based on medical history. [b] Unwilling when explicitly reported in the medical record.

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 discordancy was related to ADT as monotherapy. In 30 (3.5%) patients, adherence could not be evaluated due to missing information in the medical record.

The most frequent reason for guideline-discordant ADT as monotherapy was unfitness for curative treatment in absence of symptoms, PSA >50 ng/ml, or PSADT <12 mo (Fig. 2). In 24%, motivation was not reported or could not be inferred from the medical record. The most frequent reason for ADT prior to RP was pending the scheduled RP, with a most common waiting period of 1 mo (maximum 4 mo). Guideline-discordant ADT adjuvant to RT was mostly prescribed to achieve volume reduction of the prostate.

3.3. Multivariable logistic regression

Multivariable logistic regression showed that patients who were older or had GS $\geq 4 + 3$ 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[a]	Concordant	Discordant	SMD (95% CI)[b]
No. of patients, n	2743	848	159	
Not assessable, n	30	NA	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)
Mx	NA	181 (21)	79 (50)	−0.62 (−0.79, −0.45)
Gleason score, n (%)				
≤3 + 3	1631 (59)	111 (13)	53 (33)	−0.50 (−.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	362 (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	19 (2.2)	0 (0)	0.21 (0.04, 0.38)
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.
[a] All men with localised PCa regardless of whether they were prescribed ADT.
[b] SMD between concordant and discordant.

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

	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 (%)	59 (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)	

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 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 ($\geq 4 + 3$), 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 concordant 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

A

ADT monotherapy (*n* = 144)

B

ADT + RP (*n* = 7)

C

ADT + RT (*n* = 8)
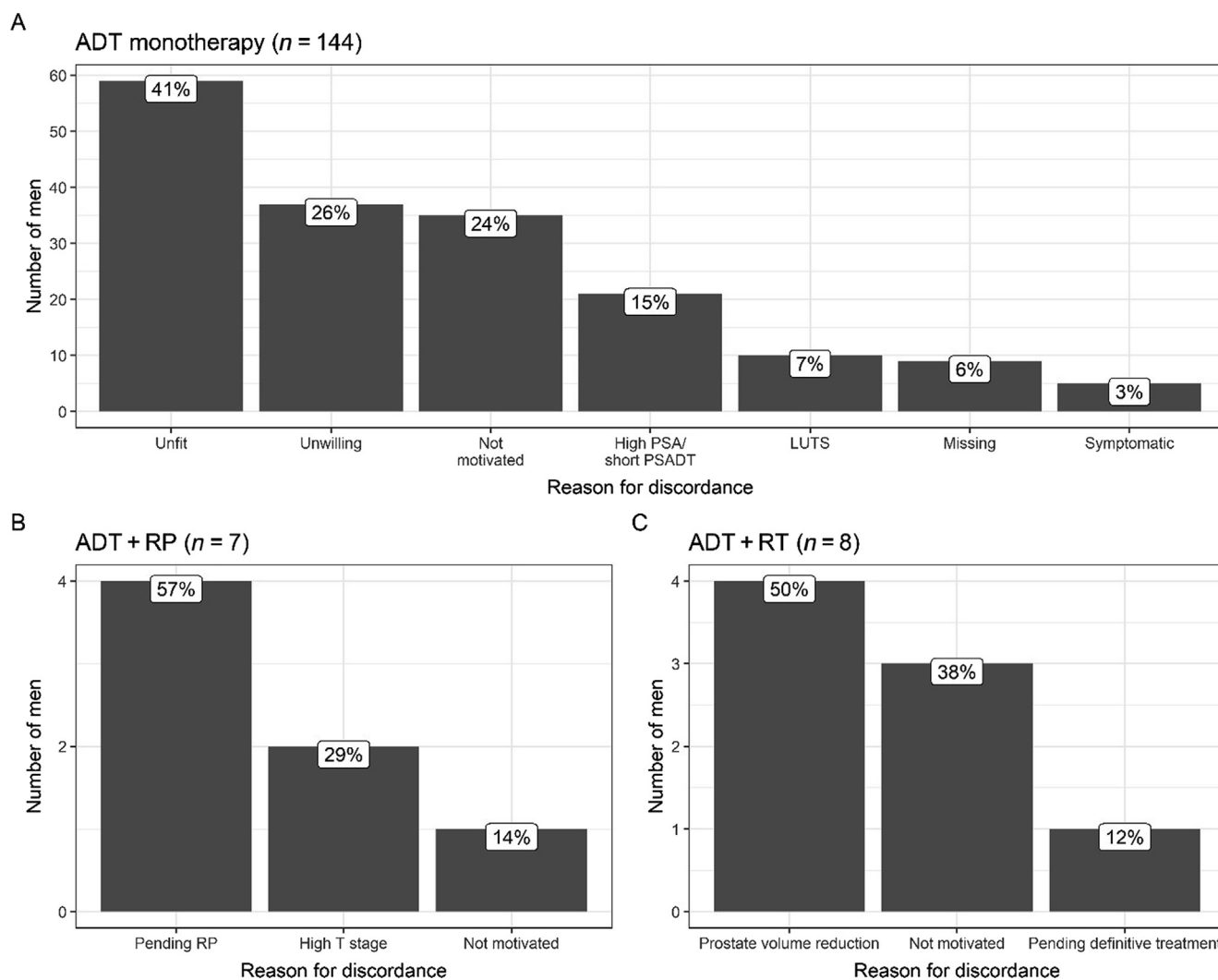
Fig. 2 – Physician's motivations for guideline-discordant androgen deprivation therapy. ADT = androgen deprivation therapy; LUTS = lower urinary tract symptoms; PSA = prostate-specific antigen in ng/ml; PSADT = PSA doubling time in ng/ml/mo; RP = radical prostatectomy; RT = radiotherapy; T stage = tumour stage.

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,

Table 3 – Multivariable logistic regression of guideline-discordant ADT

	OR (95% CI)	*p* value
Age (yr)	1.19 (1.15–1.24)	<0.001
Year of diagnosis		
25th percentile (2004)	Reference	
75th percentile (2011)	0.30 (0.18–0.50)	0.014
Binary transformation of PSA (ng/ml)	1.10 (0.97–1.24)	0.13
T stage		
T1	Reference	
≥T2	1.45 (1.00–2.10)	0.052
Gleason score		
≤6	Reference	
3 + 4	1.43 (0.85–2.40)	0.18
≥4 + 3	1.70 (1.06–2.74)	0.029

ADT = androgen deprivation therapy; CI = confidence interval; PSA = prostate-specific antigen; OR = odds ratio.

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
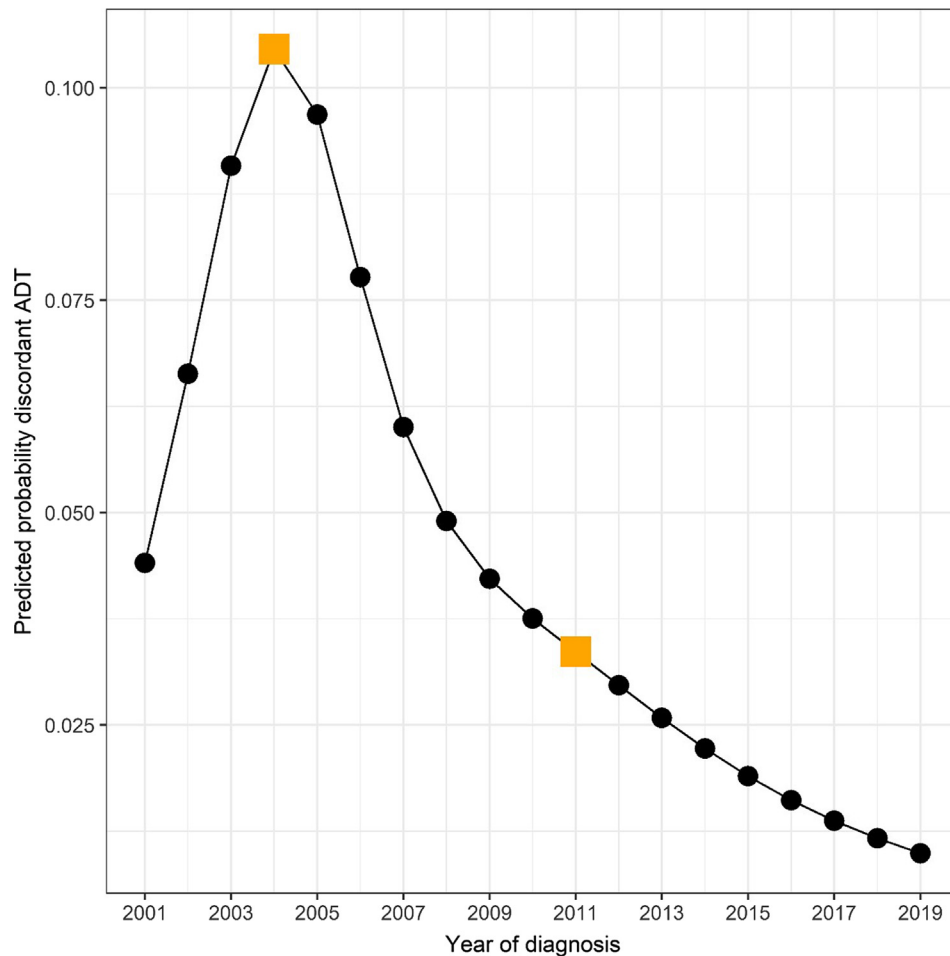
Fig. 3 – Predicted probability of guideline-discordant androgen deprivation therapy per year for a patient with median PSA, median age at diagnosis, cT2, and Gleason score 3 + 4. A patient diagnosed in 2011 (right orange square, 75th percentile) had a 3.3 times lower risk of guideline-discordant ADT than a patient with the same risk diagnosed in 2004 (left orange square, 25th percentile). ADT = androgen deprivation therapy; PSA = prostate-specific antigen.

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 andorgen 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.

Appendix A. Supplementary data

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

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