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Platinum Priority – Prostate Cancer

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Mapping European Association of Urology Guideline Practice Across Europe: An Audit of Androgen Deprivation Therapy Use Before Prostate Cancer Surgery in 6598 Cases in 187 Hospitals Across 31 European Countries

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Abstract

Background: Evidence-practice gaps exist in urology. We previously surveyed European Association of Urology (EAU) guidelines for strong recommendations underpinned by high-certainty evidence that impact patient experience for which practice variations were suspected. The recommendation "Do not offer neoadjuvant androgen deprivation therapy (ADT) before surgery for patients with prostate cancer" was prioritised for further investigation. ADT before surgery is neither clinically effective nor cost effective and has serious side effects. The first step in improving implementation problems is to understand their extent. A clear picture of practice regarding ADT before surgery across Europe is not available.

Objective: To assess current ADT use before prostate cancer surgery in Europe.

Design, setting, and participants: This was an observational cross-sectional study. We retrospectively audited recent ADT practices in a multicentre international setting. We used nonprobability purposive sampling, aiming for breadth in terms of low- versus high-volume, academic, versus community and public versus private centres.

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Outcome measurements and statistical analysis: Our primary outcome was adherence to the ADT recommendation. Descriptive statistics and a multilevel model were used to investigate differences between countries across different factors (volume, centre type, and funding type). Subgroup analyses were performed for patients with low, intermediate, and high risk, and for those with locally advanced prostate cancer. We also collected reasons for nonadherence.

Results and limitations: We included 6598 patients with prostate cancer from 187 hospitals in 31 countries from January 1, 2017 to May 1, 2020. Overall, nonadherence was 2%, (range 0–32%). Most of the variability was found in the high-risk subgroup, for which nonadherence was 4% (range 0–43%). Reasons for nonadherence included attempts to improve oncological outcomes or preoperative tumour parameters; attempts to control the cancer because of long waiting lists; and patient preference (changing one's mind from radiotherapy to surgery after neoadjuvant ADT had commenced or feeling that the side effects were intolerable). Although we purposively sampled for variety within countries (public/private, academic/community, high/low-volume), a selection bias toward centres with awareness of guidelines is possible, so adherence rates may be overestimated.

Conclusions: EAU guidelines recommend against ADT use before prostate cancer surgery, yet some guideline-discordant ADT use remains at the cost of patient experience and an additional payer and provider burden. Strategies towards discontinuation of inappropriate preoperative ADT use should be pursued.

Patient summary: Androgen deprivation therapy (ADT) is sometimes used in men with prostate cancer who will not benefit from it. ADT causes side effects such as weight gain and emotional changes and increases the risk of cardiovascular disease, diabetes, and osteoporosis. Guidelines strongly recommend that men opting for surgery should not receive ADT, but it is unclear how well the guidance is followed. We asked urologists across Europe how patients in their institutions were treated over the past few years. Most do not use ADT before surgery, but this still happens in some places. More research is needed to help doctors to stop using ADT in patients who will not benefit from it.

1. Introduction

Numerous examples highlight that adherence to urology clinical practice guidelines (CPGs) is suboptimal [1–9]. It is known that such evidence-practice gaps hamper high-quality health care provision [10,11]. Fortunately, there is a body of empirical and theoretical work dedicated to understanding behaviours such nonadherence to CPGs and how to facilitate guideline-adherent behaviour [12–14]. To prioritise which implementation problems in the European urological setting should be investigated further, the Impact Assessment of Guidelines Implementation and Education (IMAGINE) group reviewed the European Association of Urology (EAU) guidelines for strong recommendations with level 1a evidence to identify recommendations with little scope for nonadherence, while acknowledging that there may very occasionally be justifiable clinical or patient preference reasons for nonadherence. We then surveyed EAU guideline panels to nominate recommendations for which there was known/suspected heterogeneity in practice and for which addressing this heterogeneity would have significant a benefit in terms of patient outcomes and experience or the economic burden. Using this prioritisation method, we chose an oncology recommendation to investigate further: Do not offer neoadjuvant androgen deprivation therapy (ADT) before surgery for patients with prostate cancer (PCa) [15].

Evidence demonstrates that ADT before radical prostatectomy (RP) for PCa has no benefits in terms of strong clinical endpoints [16] but has significant side effects (eg, hormonal changes, cardiovascular disease, diabetes, osteoporosis), as well as hidden and real costs associated with administration and management of these side effects. Therefore, neoadjuvant ADT meets the Choosing Wisely campaign definition of "low-value care" (care with little or no benefit, and potential harm and cost) [17].

Both European and American guidelines recommend against neoadjuvant ADT before surgery, yet this practice appears to remain. For instance, an Italian study showed that guideline-discordant ADT use ranged from 20% to 60% across the country [4]. US studies have also demonstrated that ADT is used in patients who are unlikely to benefit and may experience harm [18,19]. For example, one US study estimated that 20% of prostatectomy patients inappropriately received neoadjuvant ADT [20] and another noted that approximately one in eight men received ADT discordant with guidance, with an estimated economic impact of low-value ADT of approximately $42 000 000 per year in the US setting [21]. What is clear from these estimates is that ADT overuse has been variable and is problematic for patients and health care systems internationally. However, a clear contemporary picture of ADT use across Europe is not readily available. To address this, we aimed to survey European urology departments to assess current ADT use patterns.

The objective of the study was to describe adherence to the EAU guidelines on ADT use before surgery for prostate cancer in European countries.

2. Patients and methods

2.1. Design, setting, and participants

This was an observational cross-sectional study using a retrospective audit of recent ADT practices in a multicentre international setting across 31 European countries.

We used nonprobability purposive sampling deployed via collaborating centres in the IMAGINE network, which represents national societies in EU member states plus Norway, Russia, Serbia, Switzerland, Turkey, the UK, and Ukraine. We asked collaborating centres to audit 20 or 40 eligible patients (depending on whether the centre had a high or low case volume, as defined below) and eight or 16 sites according to population size in that country (countries with a population >35 million were asked to contribute 16 sites). First, we asked about differences between EAU and national guidelines and for a description of the differences. We also asked how ADT is reimbursed in the country. The data collection period was from March 1, 2020 to October 31, 2021. The retrospective audit included patients treated from January 1, 2017 to May 1, 2020. The recommendation to refrain from administering neoadjuvant ADT is from the EAU guideline on prostate cancer and remained the same during the study period. It has been endorsed by the EAU, the European Society for Radiotherapy and Oncology (ESTRO), and the International Society of Geriatric Oncology (SIOG) since 2016. The European Society of Urogenital Radiology (ESUR) added endorsement in 2017 and the European Association of Nuclear Medicine (EANM) added endorsement in 2019. For brevity and because of widespread use and understanding of the term, we refer to these iterations as the EAU guideline throughout the manuscript.

2.2. Sampling

We anticipated that practice patterns may differ between high- and low-volume centres, academic and community hospitals, and public and private hospitals, so we sought to purposively sample for a range of hospitals. There is no agreed definition of high and low case volume in the literature [22–25] so our definition was based on consensus agreed by our clinical expert steering group (all co-authors of the paper). We used a pragmatic cutoff of >50 prostatectomy cases per year as a practical proxy for high-volume centres and <50 for low-volume centres. We asked the national society representatives in each country to fulfil the sampling criteria within their country.

A bespoke online data collection platform was created. The local user at each site had a unique user identity and password. Users were able to log and see their own data only and did not have access to data from other sites. No identifiable personal participant or patient information was collected, the hospitals reviewed data for their own patients, and no personal data were transferred to or processed by IMAGINE, so the study fell outside the General Data Protection Regulation requirements. Therefore, this audit was classified as a service evaluation and did not require review of sponsorship and ethics. The data were encrypted and stored on secure ISO27001-compliant servers located in Europe. To retain anonymity, we used numerical codes for each country in the results.

We used the two following inclusion criteria for the audit: (1) patients with histologically proven adenocarcinoma of the prostate and (2) patients undergoing RP with curative intent. We excluded RP in patients with metastatic disease (any T any N M1) and salvage RP for recurrent PCa after radiotherapy or another active therapeutic option besides radiotherapy (eg, cryotherapy, high-intensity focused ultrasound).

We used a random date generator inbuilt in the audit software to mitigate against selection biases. This generated random dates at each site (excluding weekends and national holidays). Participants were asked to select the first eligible patient undergoing RP on the date suggested by the random date generator. If no eligible patients underwent RP on that day, excluding salvage RPs, participants chose the next date on which an eligible patient underwent RP.

2.3. Outcome measures and statistical analysis

Our primary outcome was the proportion of patients treated with guideline-adherent or -nonadherent practice. Specifically, adherence to the guideline recommendation was defined as no ADT prescription. Adherence rates were described by country, and differences in the adherence rate within countries were compared across three factors (academic vs community hospital; public vs private hospital; low-volume vs high-volume centre) using χ^2 tests.

Patients who received ADT because they had originally opted for external beam radiotherapy (EBRT) but subsequently changed their mind and opted for surgery are retained in the analysis and considered to have been treated in nonadherence to the guideline because in practice they received ADT before surgery. This is addressed further in the discussion section.

A global test was performed to analyse whether there were differences in adherence rate between the different hospital types by fitting a multilevel model with nesting of hospitals in countries using nested random effects. Type of hospital, funding, and case volume were included as covariates.

A priori subgroup analyses focussed on localised PCa (categorised as low, intermediate, or high risk) and locally advanced cancer. The following definitions were used: low risk, prostate-specific antigen (PSA) <10 ng/ml and Gleason <7 (International Society of Urological Pathology [ISUP] grade group 1) and stage *c*T1–2a; intermediate risk, PSA 10–20 ng/ml or Gleason 7 (ISUP grade group 2/3) or stage *c*T2b; high risk, PSA >20 ng/ml or Gleason >7 (ISUP grade group 4/5) or stage *c*T2c; and locally advanced PCa, any PSA, any GS (any ISUP grade group), and stage *c*T3–4 or cN+.

3. Results

Our audit included 6598 patients from 187 hospitals in 31 countries. Most centres included were public hospitals (166/187, 89%) and most had a high case volume (148/187, 79%; Supplementary Table 1). All participating sites used either the EAU guidelines concerning ADT before surgery or had national guidelines that did not differ from the EAU on this recommendation (Supplementary Table 1). Approximately two-thirds (21/31) of the participating countries fully reimburse ADT via their public health system either without conditions or on application by the urologist/oncologist and approval by an external physician. In the remaining countries there is partial reimbursement by the public health care system (Supplementary Table 1).

Adherence to the guideline was very high, with 98% of patients (6466/6598) treated in accordance with the guideline. In total, 68% of the centres had a guideline adherence rate of 100%. The median adherence rate was 100%, with a 25th percentile of 98% and a minimum of 69% (Fig. 1).

3.1. Adherence in different hospital types across all countries

The differences in adherence rate across different subgroups among all countries in a multivariable model are shown in Table 1. The odds of adhering to the guideline was 1.42 times higher for public than for private hospitals, although

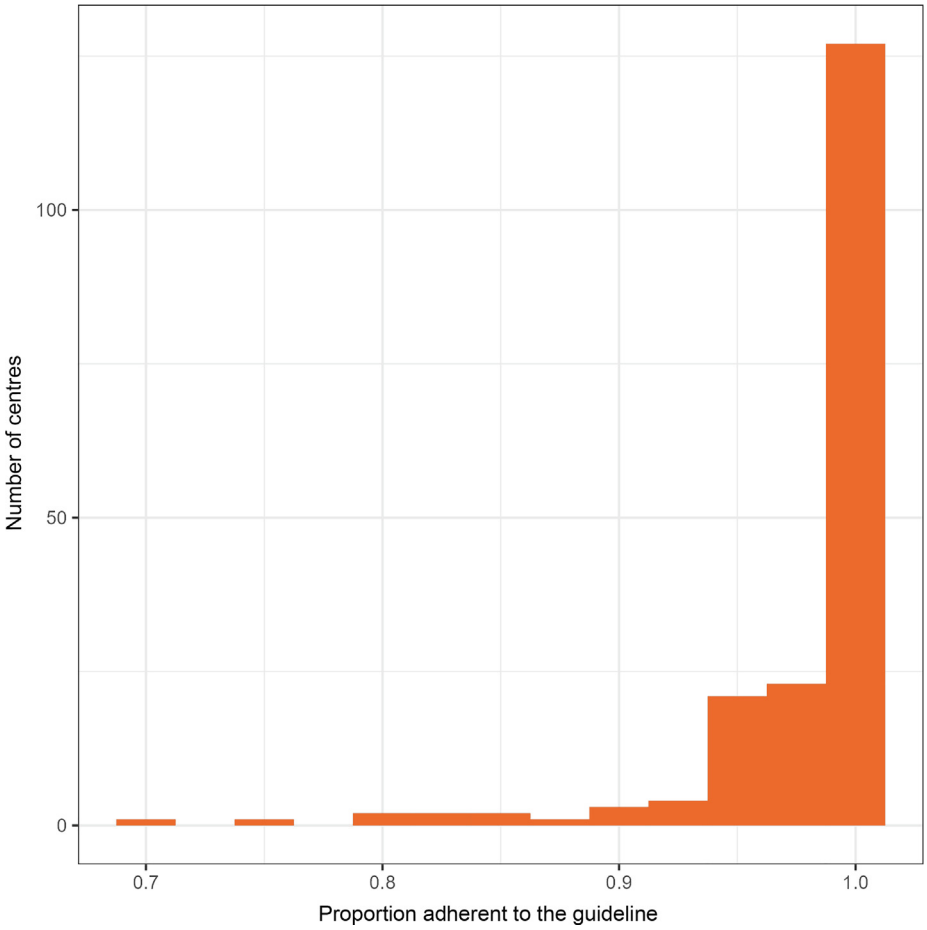

Fig. 1 – Distribution of the adherence rate across centres.

Table 1 – Odds ratios for nonadherence to the recommendation to not give androgen deprivation therapy before surgery for prostate cancer by funding, setting, and volume across all countries included in the study

Characteristic	Odds ratio (95% CI)	*p* value
Funding (public vs private)	1.42 (0.48–4.17)	0.5
Setting (community vs academic)	1.41 (0.62–3.20)	0.4
Case volume (low vs high)	0.56 (0.22–1.43)	0.2

CI = confidence interval.

this difference is statistically nonsignificant and the 95% confidence interval (CI) indicates imprecision and uncertainty, ranging from roughly halving the odds to quadrupling them (95% CI 0.48–4.17). Likewise, the odds of adhering to the guideline was higher in the community than in the academic setting, but the estimate is imprecise and not statistically significant (adds ratio [OR] 1.41, 95% CI 0.62–3.20). The odds of adhering to the guideline was lower for low-volume than for high-volume hospitals, but this finding is not statistically significant, and the estimate is imprecise (OR 0.56, 95% CI 0.22–1.43).

3.2. *Adherence in different hospital settings within countries*

There were no statistically significant differences in adherence between high-volume and low-volume hospitals (Fig. 2A) or between public and private hospitals (Fig. 2B). There was a statistically significant difference in adherence rate between academic and community hospitals in country 60 (81% vs 98%; Fig. 2C).

3.3. *Subgroup analyses*

There were 56 patients with stage T2 PCa for whom it was unclear if they had low-risk or intermediate-risk disease. These patients were excluded from further analyses.

3.3.1. *Low-risk PCa*

Across the 31 countries, 1057 patients had low-risk PCa, of whom 99.5% (n = 1053) were treated in adherence to the EAU ADT guideline. In total, 98% of the centres had an adherence rate of 100% for the low-risk subgroup; the lowest adherence rate was 50% (Figs. 3 and 4). There were no statistically significant differences in adherence rate across the different categories (volume, funding, and setting) for the low-risk group.

3.4. *Types of ADT given and reasons for nonadherence*

3.4.1. *Intermediate-risk PCa*

There were 3011 patients with intermediate-risk PCa across the 31 countries, of whom 99% (n = 2982) were treated in adherence to the guideline. In total, 88% of the centres had an adherence rate of 100% for the intermediate-risk

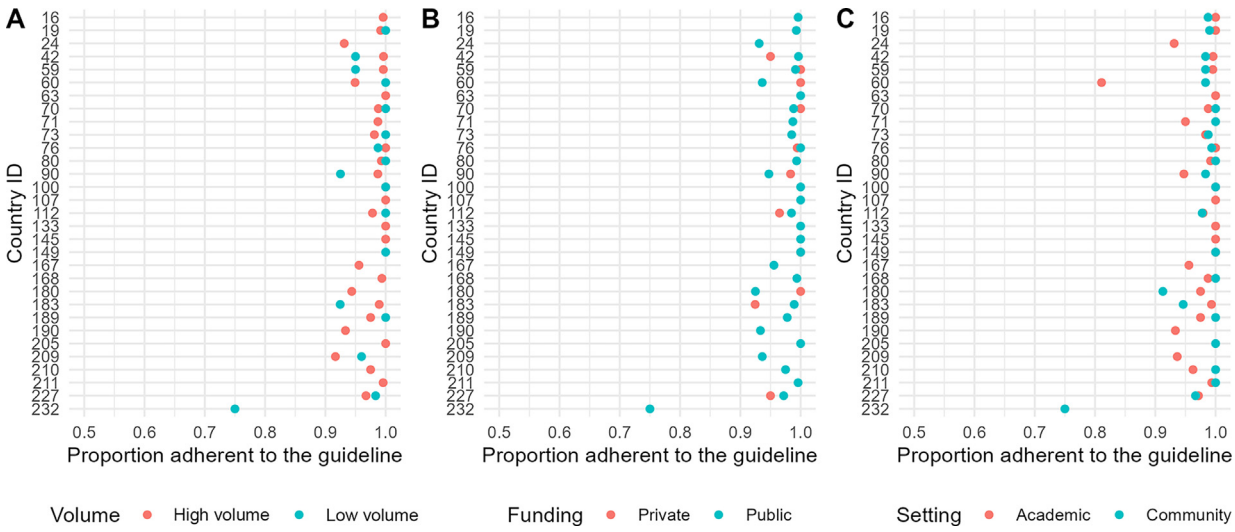

Fig. 2 – Proportion adherent to the guideline for (A) high- and low-volume centres, (B) private and public hospitals, and (C) academic and community centres in each country.

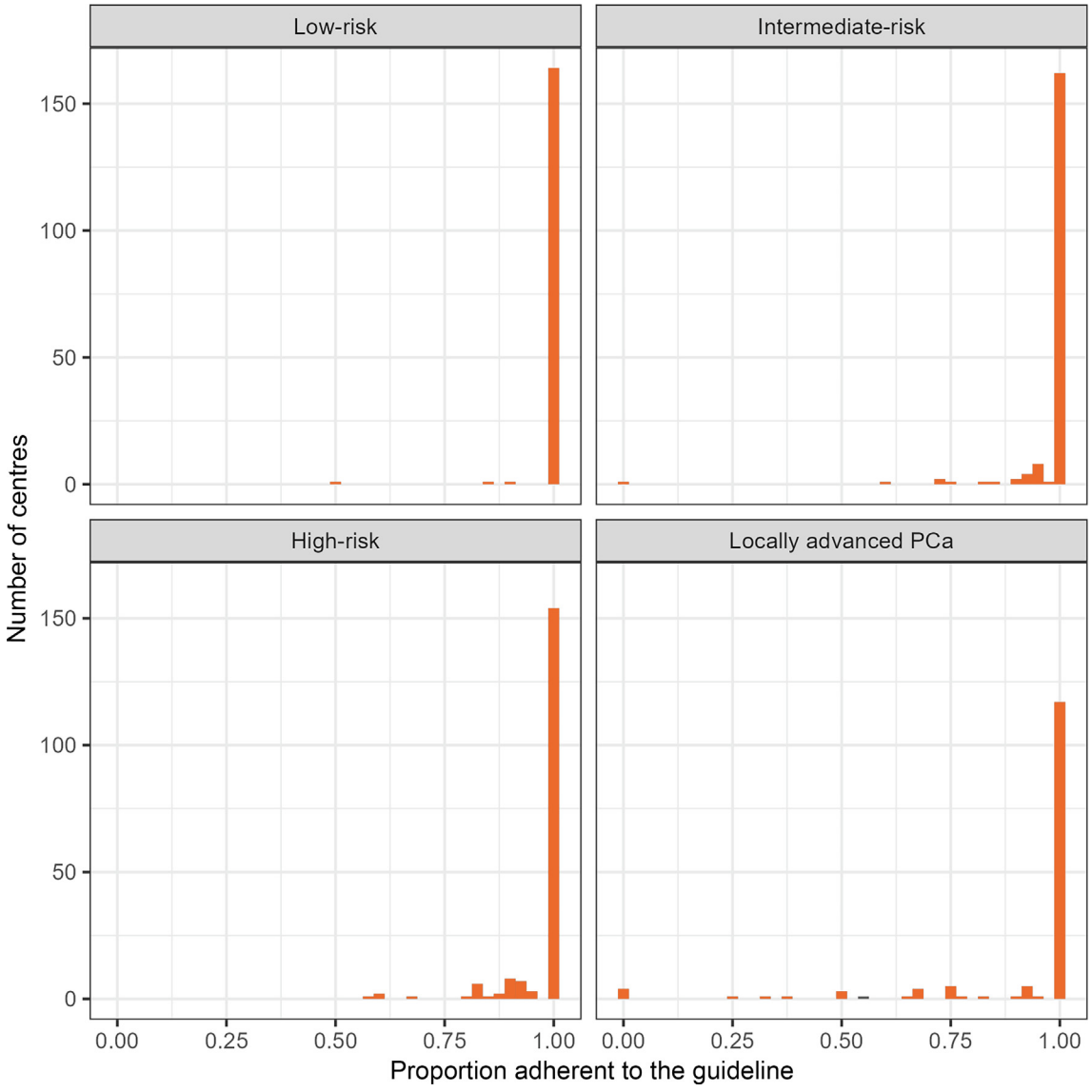

Fig. 3 – Distribution of the proportion patients treated in adherence to the guideline, stratified by risk group. PCa = prostate cancer.

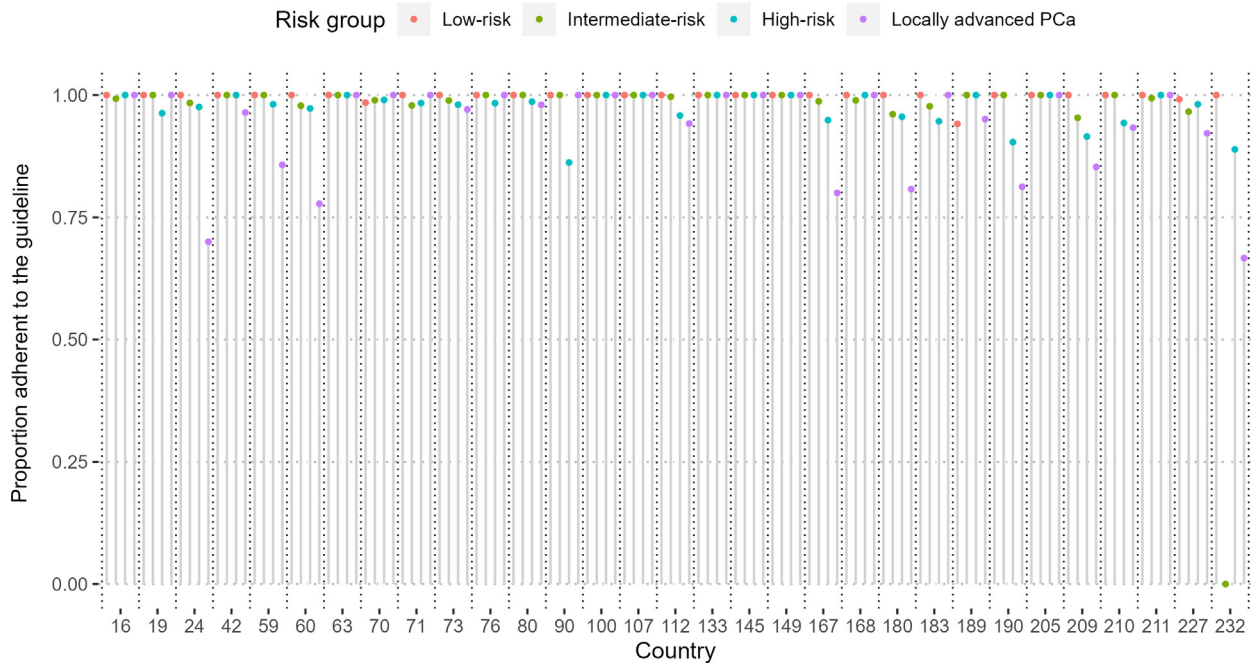

Fig. 4 – Proportion of patients treated in adherence to the guideline in each country, stratified by risk group. PCa = prostate cancer.

group; the lowest adherence rate was 60% (Figs 3 and 4; note that 1 centre with a rate of 0% had no patients with intermediate-risk PCa).

3.4.2. *High-risk PCa*

There were 1706 patients with high-risk PCa across the 31 countries, of whom 97% (1661) were treated in adherence to the guideline. In total, 83% of the centres had an adherence rate of 100% for the high-risk subgroup; the lowest adherence rate was 57%. There were statistically significant differences in country 60 (Figs. 3 and 4).

3.4.3. *Locally advanced PCa*

In total there were 772 patients with locally advanced PCa, of whom 718 (93%) were treated in adherence to the guideline. In total, 80% of the centres had an adherence rate of 100% for the subgroup with locally advanced PCa; the lowest adherence was 0% (Figs. 3 and 4).

Among the 132 patients receiving ADT, 53 (40%) had an antiandrogen, 58 (44%) had a luteinising hormone–releasing hormone (LHRH) agonist, nine (7%) had an LHRH antagonist, ten (8%) had combined LHRH and antiandrogen treatment, and one (0.75%) had surgical castration.

Of the 132 nonadherence instances, no reason was given for 68 (52%), a reason was given for 64 (48%), and more than one reason was given for some cases. The reasons are outlined in Figure 5.

Frequently reported reasons for nonadherence included clinical decisions to try to improve oncological outcomes or parameters such as tumour volume, prostate volume, or the risk of positive margins. There were some instances of a decision change whereby the health care provider had

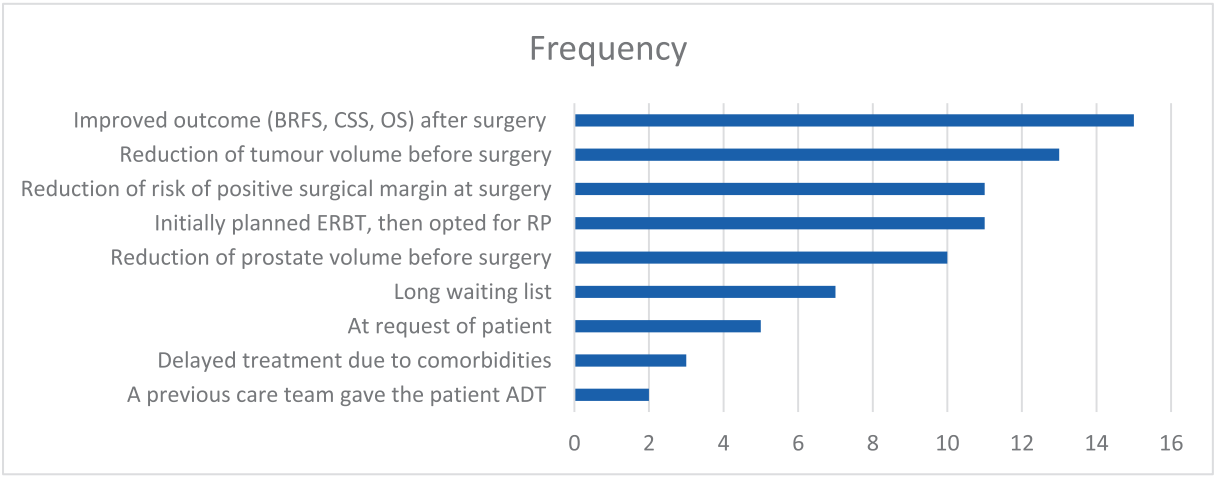

Fig. 5 – Frequency of reasons reported for giving ADT before surgery. BRFS = biochemical recurrence-free survival; CSS = cancer-specific survival; OS = overall survival; ERBT = external beam radiotherapy; RP = radical prostatectomy; ADT = androgen deprivation therapy.

initially planned EBRT but the patient then opted for surgery after neoadjuvant ADT had commenced. In some instances the patient felt that the side effects were intolerable after experiencing or becoming more fully informed about ADT side effects. Other reasons for ADT before surgery included an attempt to control the cancer because of long waiting lists, and ADT initiation by a previous provider.

4. Discussion

This study mapped adherence to EAU guidelines in 6598 patients from 187 hospitals across 31 countries. A network of national societies willing to contribute to guideline audits in association with the EAU was established.

Nonadherence to ADT guidance was variable across sites. Although differences across risk groups were minimal, adherence appeared to be more variable in the high-risk group (ranging from 0% to 43%) but no prespecified or post hoc statistical tests were performed to investigate this issue. No statistically significant differences were found across centre types, and any results derived from the multivariable models should be interpreted with caution because the CIs are imprecise. However, given the strong rating and level 1a evidence for the recommendation to avoid ADT before PCa surgery, our clinically meaningful threshold for nonadherence should be very low. Our results should prompt discussion on what such a threshold should be in settings involving high certainty and a strong recommendation.

Reasons for providing ADT before surgery, such as attempting to reduce the tumour volume before surgery or the risk of positive margins, are somewhat supported by the evidence base but do not translate into better oncological outcomes, and therefore do not warrant nonadherent practice because this may lead to harmful side effects with associated management costs. However, this reasoning does give insight into the belief of some urologists regarding the consequences of ADT use. ADT causes metabolic changes associated with higher risk of cardiovascular disease, stroke, diabetes, and bone fractures [26–29]; changes in psychological function impacting sexual function and relationships, as well as emotional lability, impaired cognition, and depression [30]; and fatigue, which is also associated with anxiety and depression [31]. ADT is also associated with an increase in the risk of Alzheimer's disease [32]. There are additional oncological disadvantages of ADT including false-negative lymph nodes and surgical margins, and postoperative PSA is usually undetectable, so detecting recurrence is impossible for a considerable period.

Additional cost consequences of ADT use, whether appropriate or inappropriate, include medical management [26,33,34]; dietary changes and exercise programmes [35–37] are also not free of cost. The clinical relevance is that in instances of inappropriate ADT use, the consequences for the patient are serious and the implications for the health care provider represent an additional workload; for the payer, the additional treatments and other supervised exercise/dietary interventions have associated costs. Although their results may not be externally valid outside of Canada, the finding by Krahn et al. [38] that management of ADT-associated adverse events increases costs by 100–265% is sobering.

Use of ADT as an interim measure to control PCa because of long waiting lists was one reason for inappropriate ADT use and could just about be justified during disruptive events such as pandemics. However, the recruitment period for our project means that we cannot investigate whether this happened during the COVID-19 pandemic.

A possible explanation for the finding that guideline adherence is high in most countries is that we are seeing the "tail end" of ADT deimplementation. That is, ADT overuse, at least before surgery, was a problem in the past but is now waning. This suggestion is bolstered by reports of higher levels of problematic ADT use from some within-country studies dating from 2002 to 2015, with inappropriate use ranging from 20% to 60% [4,18–21]. A "tail end" characteristic of ADT deimplementation was proposed by Skolarus and colleagues [39] in the US setting, albeit in the context of ADT monotherapy for localised prostate PCa. They found that ADT overuse in that setting has decreased over time, but that some overuse remains; they used qualitative methods to explore patient- and urologist-level barriers and facilitators to stopping such low-value ADT use [40]. They structure their investigation using the theoretical domains framework (a synthesis of >30 theories of behaviour and behaviour change organised in 14 domains) [41] and the capability, opportunity, and motivation-behaviour model of the Behaviour Change Wheel [42]. They found that urologists sometimes find it difficult to advise against ADT when a patient and their relatives request it (something we also found in our study), coupled with the fear that they may lose patients to other providers if they did not agree. A small number of urologists, but still worrying in its implication, prefer to rely on their own experience rather than guidelines and believe that ADT is a reasonable approach. Other facilitators were related to opportunities to avoid prescribing ADT, such as collaborative decision-making and comparison of one's own practice to others in multidisciplinary team meetings (eg, tumour boards). In institutions where such resources are not available, opportunities for appropriate ADT prescription are potentially missed [40].

One of the reasons for ADT before surgery in our audit was that EBRT was initially planned but the patient then opted for surgery. Although we accept that these instances could have been removed from the data set, we felt that it was important, especially for the patient perspective, to retain these cases because in practice such patients still received ADT before surgery and may experience ADT-related adverse events. More research is required to understand this circumstance, but if patient-provider dialogue and decision-making is sufficient, then patients should fully understand the implications of ADT alongside weighing up the side-effect profiles of surgery and radiotherapy and be less likely to change their minds.

Going forward, ADT deimplementation could be addressed via interventions such as education on guidelines and training on evidence-based medicine. Other more tailored interventions could be directed at fostering high-quality decision-making, such as the development of deci-

sions aids with patients and their families to ensure that consent to nonadherent ADT is fully informed, and a top-down approach via formulary restrictions at the organisation level. The latter two suggestions are being researched further in an implementation randomised controlled trial by Skolarus and colleagues [39]. Results from that study will have important relevance for ADT overuse elsewhere and for deimplementation research more generally. Further research to understand patient and provider barriers and facilitators to ADT overuse in the European setting is required.

In brief, any inappropriate ADT use is worrying, is costly for health care systems, and leads to avoidable adverse events for patients. Strategies towards discontinuing inappropriate ADT use should still be pursued.

Finally, while it was not the focus of our study, we recognise that many patients with low-risk disease had radical surgery, which is also discordant with current guideline recommendations; this may be considered for further investigation in a future study. The fact some of those patients with low-risk PCa had both surgery and ADT is worrying.

4.1. Limitations

The coverage within many countries in our sample was minimal and relied on networks of national societies whose membership potentially already indicates awareness of guidelines and collaborative working. Therefore, our sample could have missing harder-to-reach nonreferral institutions, could have a selection bias towards guideline-aware participants, and could have underestimated ADT guideline nonadherence. However, we did try to mitigate against this by asking for inclusion of nonacademic and low-volume centres.

5. Conclusions

Adherence to EAU recommendations for ADT before RP appears to be generally followed for patients with low or intermediate risk. The picture for patients with high-risk PCa is more variable. Although some reasons may appear justifiable, the absolute number of men at risk of harm is worryingly high and the economic impact is alarming. A deeper understanding of the circumstances under which urologists are willing to practice against guidelines warrants further research and may inform strategies to facilitate the discontinuation of inappropriate ADT.

Author contributions: Steven MacLennan 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: MacLennan, Azevedo, Duncan, Dunsmore, Fullwood, Lumen, Plass, Ribal, Roobol, Nieboer, Schouten, Skolarus, Smith, N'Dow, Mottet, Briganti.
Acquisition of data: Azevedo, Schouten, Skolarus, Smith, N'Dow, Briganti.
Analysis and interpretation of data: MacLennan, Azevedo, Lumen, Ribal, Roobol, Nieboer, Skolarus, N'Dow, Mottet, Briganti.
Drafting of the manuscript: MacLennan.
Critical revision of the manuscript for important intellectual content: MacLennan, Azevedo, Duncan, Dunsmore, Fullwood, Lumen, Plass, Ribal, Roobol, Nieboer, Schouten, Skolarus, Smith, N'Dow, Briganti.
Statistical analysis: Roobol, Nieboer.
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Supervision: N'Dow, Briganti.
Other: None.

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Supplementary data

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