TITLE

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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KEYWORDS: Prostate cancer; Androgen Deprivation Therapy; Guidelines; Implementation Science

ABSTRACT

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

Methods: This was an observational cross-section design. We retrospectively audited recent ADT practices in a multi-centre international setting. We used non-probability purposive

sampling, aiming for breadth in terms of low/high volume, academic/community and public/private centres. 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 and funding type). Subgroup analyses were performed according to low, intermediate, and high risk, and locally advanced prostate cancer. We also collected reasons for non-adherence.
Results: We included 6598 patients with prostate cancer from 187 hospitals in 31 countries from January 1st 2017 to May 1st 2020. Overall, non-adherence was 2%, (range 0% to 32%). Most of the variability was found in the high-risk subgroup, where non-adherence was 4% (range 0% - 43%). Reasons for non-adherence included attempts to improve oncological outcomes; attempts to improve pre-surgery 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 non-adherence rates may be overestimated.
Discussion and 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 additional payer and provider burden. Strategies toward discontinuing inappropriate ADT use pre-surgery 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, emotional changes, increased risk of cardiovascular disease, diabetes, and osteoporosis. Guidelines strongly recommend that men opting for surgery should not get ADT but it is unclear how well that guidance is followed. We decided to try and find out if it is followed by asking urologists across Europe how patients in their institutions were treated over the past few years. We found that most do not use ADT before surgery but it still happens in some places so we think that more research is needed to help clinicians stop using ADT in patients who will not benefit from it.

TAKE HOME MESSAGE

Adherence to EAU guidelines to not give neoadjuvant ADT before prostate cancer surgery is variable, more so in high-risk subgroups. Inappropriate ADT use may cause serious harm for patients and the consequences are burdensome and costly for health care providers and payers.

BACKGROUND

Numerous examples highlight that adherence to urology Clinical Practice Guidelines (CPG) is sub-optimal. [1-9] It is known that such evidence-practice gaps hamper high-quality healthcare provision. [10, 11] Fortunately, there is a body of empirical and theoretical work dedicated to understanding behaviours such non-adherence 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, we, the IMpact Assessment of Guidelines ImplementatioN and Education (IMAGINE) group, reviewed EAU guidelines for 'strong' recommendations with level 1a evidence, to identify recommendations with little scope for non-adherence, whilst acknowledging that there may very occasionally be justifiable clinical or patient-preference related reasons for non-adherence. Then, we surveyed EAU guideline panels to nominate recommendations for which there was known/suspected heterogeneity in practice and where addressing this would have significant benefit on patient outcome and experience or economic burden. Using this prioritisation method, an oncology recommendation was chosen to investigate further: Do not offer neoadjuvant androgen deprivation therapy (ADT) before surgery for prostate cancer patients. [15]

Evidence demonstrates that androgen deprivation (ADT) before radical prostatectomy for prostate cancer (PCa) has no benefits on strong clinical endpoints, [16] while having significant side effects (e.g., hormonal changes, cardiovascular disease, diabetes, osteoporosis), as well as having hidden and real costs associated with administration and management of side effects. Therefore, it meets the Choosing Wisely campaigns' definition of "Low-value care" (care with little or no benefit, potential harm, and cost). [17]

Both European and American guidelines recommend against neoadjuvant ADT prior to surgery yet these practices appear to remain. For instance, an Italian study showed guideline discordant ADT use ranged from 20% to 60% across the country.[4] US studies also demonstrate ADT is used in patients who are unlikely to benefit and may experience harm[18, 19]. For example, one US study estimated 20% prostatectomy patients inappropriately received neoadjuvant ADT, [20] whereas another noted around one in eight men received ADT discordant with guidance with an estimated economic impact of low value ADT of around $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 healthcare 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.

OBJECTIVE

To describe adherence to the EAU's guidelines on ADT use before surgery for prostate cancer in European countries.

METHODS

DESIGN, SETTING AND PARTICIPANTS

This was an observational cross-section design using a retrospective audit of recent ADT practices in a multi-centre international setting across 31 European countries.

We used non-probability purposive sampling deployed via collaborating centres in our IMAGINE group National Societies Network which represents EU member states plus Norway, Russia, Serbia, Switzerland, Turkey, the UK and Ukraine. We asked collaborating centres to audit 20 or 40 eligible patients (based on centre high or low-volume as defined below) and eight or 16 sites based on country population size (those with 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 their country. The data collection period was from March 1st 2020 to 31st October 2021. The retrospective audit included patients treated from January 1st 2017 to May 1st 2020. This recommendation belongs to the Guidelines on Prostate Cancer and has remained the same during the study period. It was 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 as the EAU guidelines throughout.

Sampling

We anticipated practice patterns may differ between high- and low-volume centres, academic and community hospitals, and public and private hospitals so sought to purposively sample for a range of hospitals. There is no agreed definition of high and low volume in the literature [22-25] so our definition was based on consensus among our clinical expert steering group (all co-authors of the paper). We used a pragmatic cut-off of >50 (prostatectomy cases per year) as a practical proxy for a high-volume centre 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. Each site's local user had a unique ID and password. They were able to log and see their own data only and did not have access to other sites' data. No identifiable personal participant or patient information was collected, the hospitals reviewed data on their own patients and no personal data was transferred to or processed by IMAGINE, taking the study outside of the provisions of GDPR. Therefore, this audit was classified as service evaluation and did not require sponsorship and ethical review. The data were encrypted and stored on secure ISO27001 compliant servers located in Europe. To retain anonymity, we use 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 radical prostatectomy with curative intent. We excluded radical prostatectomy in metastatic patients (anyT anyN M1) and salvage radical prostatectomy for recurrent prostate cancer after radiotherapy or another active therapeutic option outside radiotherapy (e.g. cryotherapy, HIFU).

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 receiving a radical

prostatectomy on the date suggested by the random date generator. If there were no eligible patients receiving a radical prostatectomy on that day, excluding salvage prostatectomies, participants chose the next date with an eligible patient receiving a radical prostatectomy.

OUTCOME MEASURES AND STATISTICAL ANALYSIS

Our primary outcome was the proportion of patients treated with guideline adherent or non-adherent practices. Specifically, adherence to guideline recommendation was defined as 'no ADT prescription.' Adherence rates were described by country, subsequently differences in adherence rates within countries across different factors (academic vs community hospital; public vs private hospital; low volume vs high volume) were tested using Chi-square tests.

Patients who received ADT because they had originally opted for EBRT but subsequently changed their mind and opted for surgery are retained in the analysis and considered to have been treated in non-accordance with the guidelines because in practice they received ADT prior to surgery. This is unpacked further in the discussion.

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

A priori subgroup analyses focussed on localised (split in to low, intermediate and high risk) and locally advanced cancer. The following definitions were used: Low-risk group: PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a; Intermediate-risk: PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b; High-risk: PSA>20 ng/mL or GS>7 (ISUP grade 4/5) or cT2c; Locally advanced: any PSA, any GS (any ISUP grade), cT3-4 or CN+.

RESULTS

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

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

[FIGURE 1 AROUND HERE]

[NOTE TO EDITOR – we have inserted the legends within the manuscript. The figures are shown in line here in the track-change version to aid review and are submitted also as .png files]

Figure 1: Distribution of adherence rates across centres

Adherence in different hospital types across all countries

The differences in adherence rates across different subgroups using all countries in a multivariable model is shown in table 1. The odds of adhering to the guidelines is 1.42 higher in public hospitals compared to private hospitals, although this difference is statistically non-significant and the confidence intervals indicate 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 guidelines is higher in community vs academic settings but the estimate is imprecise and not statistically significant (OR 1.41, 95% CI 0.62, 3.20). The odds of lower volume hospitals adhering to guidelines was reduced compared to higher volume hospitals, but this finding is not statistically significant, and the estimate is imprecise (OR 0.56, 95% CI 0.22, 1.43).

[Table 1 ABOUT HERE]

Table 1: Odds Ratios for non-adherence to the recommendation 'do not give ADT before surgery' comparing funding, setting and volume across all included countries

Adherence in different hospital settings within countries

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

[FIGURE 2 ABOUT HERE]

Figure 2: A) Proportion adherent to guidelines in high and low volume centres in each country; B) Proportion adherent to guidelines in private and public hospitals in each country; C) Proportion adherent to guidelines in academic and community centres in each country

Subgroup analyses

There were 56 patients with T-stage T2 for which it was unclear if they were low-risk or intermediate-risk. These were removed from further analyses.

Low risk

Across, the 31 countries, there were 1057 low-risk patients, of which 99.5% (1053) were treated adherently according to EAU ADT guidelines. In total 98% of the centres had a 100% adherence rate in the low-risk patient subgroup with the lowest adherence rate 50% (figure

3 & 4). There were no statistically significant differences in adherence rates across the different categories (volume, funding, and setting) for the low-risk group.

[FIGURE 3 ABOUT HERE]

Figure 3: Distribution of proportion patients treated in adherence with guidelines stratified by risk group

[FIGURE 4 ABOUT HERE]

Figure 4: Proportion of patients treated in adherence with guidelines in each country stratified by risk group

Types of ADT given and reasons for non-adherence

Intermediate risk

There were 3011 intermediate-risk patients across the 31 countries of which 99% (2982) were treated adherently. In total 88% of the centres had a 100% adherence with the lowest adherence rate 60% (Figure 3 & 4) (Note: one centre with 0% had 0 intermediate risk patient).

High risk

There were 1706 high-risk patients across the 31 countries of which 97% (1661) were treated adherently. In total 83% of the centres had a 100% adherence rate in the high-risk patient subgroup with the lowest adherence rate 57%. There were statistically significant differences in country 60 (Figure 3 & 4).

Locally advanced

In total there were 772 locally advanced patients, of which 718 (93%) were treated adherently. In total, 80% of the centres had 100% adherence in the locally advanced subgroup and the lowest adherence was 0% (Figure 3 & 4).

In the 132 cases receiving ADT, 53 (40%) had anti-androgen, 58 (44%) had an LHRH agonist, nine (7%) had LHRH antagonist, 10 (8%) had combined LHRH and anti-androgen, and one (0.75%) had surgical castration.

Of 132 non-adherence instances, 68 (52%) did not give a reason, 64 (48%) did, and some gave more than one reason. These are outlined in Figure 7

[FIGURE 5 ABOUT HERE]

Figure 5. The frequency of reasons reported for giving ADT before surgery

Frequently reported reasons for non-adherence included clinical decisions to try to improve oncological outcomes, to improve parameters such as tumour volume, prostate volume or

the risk of positive margins. In some instances, healthcare provider decision changes were that EBRT was initially planned, but then the patient opted for surgery after neoadjuvant ADT had commenced, in some instances the patient felt that the side-effects were intolerable after experiencing them or becoming more fully informed about side-effects. Other reasons for ADT before surgery included an attempt to control the cancer because of long waiting lists, or that a previous provider had initiated ADT.

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.

Non-adherence to ADT guidance was variable across sites, and although differences across risk groups were minimal, adherence appears more variable in the high-risk group (ranging from 0% to 43%) but no pre-specified or post-hoc statistical tests were done to investigate this. No statistically significant differences were found across centre types and any results derived from the multivariate models should be regarded with caution because the confidence intervals are imprecise. However, given then strong rating and 1a evidence for the ADT before surgery recommendation, our clinically meaningful threshold for non-adherence should be very low. Our results should prompt discussion on what such a threshold should be in 'high-certainty and strong recommendation' settings.

Reasons for providing ADT before surgery such as attempting to reduce the tumour volume before surgery, reduce the risk of positive margins are somewhat supported by the evidence base but do not translate into better oncological outcomes, and therefore do not mandate practicing against the guideline because it may cause impactful side effects with associated costs to manage those. However, this reasoning does give insight into some urologists' beliefs about the consequences of ADT use. Nonetheless, ADT causes: metabolic changes which are associated with increased risk of cardiovascular disease, stroke, diabetes, and bone fractures [26-29]; psychological functional changes impacting sexual function and relationships as well as emotional lability, impaired cognition, and depression [30]; fatigue, which is associated patient experience outcome and it too is associated with anxiety and depression [31]. ADT is also associated with an increased risk of Alzheimer's disease [32]. There are additional oncological disadvantages of ADT including: false negative lymph nodes and surgical margins and is usual that postoperative PSA is undetectable so detecting recurrence is impossible for a considerable period.

Additional cost consequences of appropriate and inappropriate ADT-use include medical management [26, 33] [34] as well as dietary changes and exercise programmes [35-37], but are not free of cost. The clinical relevance is that in those instances where ADT is used inappropriately, the consequences for the patient are serious and the implications for healthcare provider are additional workload, and for the payer the additional treatments and other supervised exercise/dietary interventions have associated cost. Although their findings may not be externally valid outside of Canada, Krahn et al's finding that managing ADT associated adverse events increases costs by 100% - 265%, is sobering. [38].

Using ADT as an interim measure to control the cancer because of long waiting lists was one reason for inappropriate ADT use and could be just about 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 de-implementation. That is, ADT overuse, at least before surgery, was a problem in the past but is now waning. That suggestion is bolstered by findings of some of the older within country studies on this topic, dating from 2002-2015 reporting higher levels of problematic ADT use, with inappropriate use ranging from 20% to 60% [4, 18-21] Moreover, characterisation of the "tail end" of ADT deimplementation was proposed by Skolarus and colleagues in the US setting, though in the context of ADT monotherapy for localised prostate cancer. [39] They found ADT overuse in that setting has decreased over time, but that some overuse remains and explored patient and urologist level barriers and facilitators to stopping such low-value ADT use using qualitative methods. [40] Their investigation was structured using the theoretical domains framework (TDF – a synthesis of over 30 theories of behaviour and behaviour change organised in 14 domains) [41] and the Behaviour Change Wheel's 'Capability, Opportunity and Motivation – Behaviour' (COM-B) model. [42] They found that urologists sometimes find it difficult to advise against ADT when a patient and their relatives request it (something we found in our study too), and this was 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, preferred to rely on their own experience rather than guidelines and believed ADT is a reasonable approach. Other facilitators related to opportunities to not prescribe ADT, such as collaborative decision-making and comparing one's own practice to others in multidisciplinary team meetings (e.g. 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 dataset, 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 de-implementation 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, e.g. the development of decisions aids with patients and their families to make sure consent for non-adherent ADT is fully informed, or top-down through formulary restrictions at the organisation level. The latter two suggestions are being researched further in an implementation RCT by Skolarus and colleagues. [39] The results of that study will have important relevance for ADT overuse elsewhere and for deimplementation research more

generally. Further research in the European setting to understand patient and provider barriers and facilitators to ADT overuse is required

In brief, any inappropriate ADT use is worrying, costly for healthcare systems and importantly creates avoidable adverse events for patients. Strategies toward discontinuing inappropriate ADT use should still be pursued.

Finally, whilst 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 and that this may be considered for further investigation in a future study. That some of those low-risk patients had surgery *and* ADT is worrying.

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 be missing harder to reach non-referral institutions, could have a selection bias toward guideline-aware participants and as such could have underestimated ADT guideline non-adherence. However, we did try to mitigate against this by asking for non-academic and low volume centres to be included.

CONCLUSIONS

Adherence to EAU recommendations for ADT before surgery appear to be generally followed for low and intermediate risk patients. The picture in high-risk patients becomes more variable and although some reasons may appear justifiable, the absolute numbers of men at risk of harm are worryingly high and the economic impacts 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.

Acknowledgements
We are grateful to the EAU Research Foundation for funding the project

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