Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis

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Summary

Background Randomised trials have investigated various androgen deprivation therapy (ADT) intensification strategies in men receiving radiotherapy for the treatment of prostate cancer. This individual patient data meta-analysis of relevant randomised trials aimed to quantify the benefit of these interventions in aggregate and in clinically relevant subgroups.

Methods For this meta-analysis, we performed a systematic literature search in MEDLINE, Embase, trial registries, the Web of Science, Scopus, and conference proceedings to identify trials with results published in English between Jan 1, 1962, and Dec 30, 2020. Multicentre randomised trials were eligible if they evaluated the use or prolongation of ADT (or both) in men with localised prostate cancer receiving definitive radiotherapy, reported or collected distant metastasis and survival data, and used ADT for a protocol-defined finite duration. The Meta-Analysis of Randomized trials in Cancer of the Prostate (MARCAP) Consortium was accessed to obtain individual patient data from randomised trials. The primary outcome was metastasis-free survival. Hazard ratios (HRs) were obtained through stratified Cox models for ADT use (radiotherapy alone *vs* radiotherapy plus ADT), neoadjuvant ADT extension (ie, extension of total ADT duration in the neoadjuvant setting from 3–4 months to 6–9 months), and adjuvant ADT prolongation (ie, prolongation of total ADT duration in the adjuvant setting from 4–6 months to 18–36 months). Formal interaction tests between interventions and metastasis-free survival were done for prespecified subgroups defined by age, National Comprehensive Cancer Network (NCCN) risk group, and radiotherapy dose. This meta-analysis is registered with PROSPERO, CRD42021236855.

Findings Our search returned 12 eligible trials that provided individual patient data (10 853 patients) with a median follow-up of 11·4 years (IQR 9·0–15·0). The addition of ADT to radiotherapy significantly improved metastasis-free survival (HR 0·83 [95% CI 0·77–0·89], p<0·0001), as did adjuvant ADT prolongation (0·84 [0·78–0·91], p<0·0001), but neoadjuvant ADT extension did not (0·95 [0·83–1·09], p=0·50). Treatment effects were similar irrespective of radiotherapy dose, patient age, or NCCN risk group.

Interpretation Our findings provide the strongest level of evidence so far to the magnitude of the benefit of ADT treatment intensification with radiotherapy for men with localised prostate cancer. Adding ADT and prolonging the portion of ADT that follows radiotherapy is associated with improved metastasis-free survival in men, regardless of risk group, age, and radiotherapy dose delivered; however, the magnitude of the benefit could vary and shared decision making with patients is recommended.

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Introduction

Meta-analyses of randomised, controlled trials represent one of the highest levels of evidence for their ability to overcome potential limitations of individual trials. The Early Breast Cancer Trialists' Collaborative Group[1,2] and the Meta-Analysis of Radiotherapy in Carcinomas of Head and Neck Collaborative Group,[3] which are practice-changing, multinational, individual patient data meta-analyses of randomised trials evaluating the benefit of various treatment strategies for breast and head and neck cancers, respectively, are relevant examples. Although prostate cancer is a common cancer, for which data from randomised clinical trials abound, such an international collaborative effort to provide robust treatment effect estimates of the treatment strategies evaluated for

Research in context

Evidence before this study

Several randomised trials have investigated the oncological benefit of adding androgen deprivation therapy (ADT) to definitive radiotherapy for prostate cancer, as well as the benefit of prolonging ADT duration. Our literature search (described in the Methods) found 12 eligible trials that evaluated the use or prolongation (or both) of ADT in men with localised prostate cancer receiving definitive radiotherapy. These multicentre trials were conducted by various cooperative groups over the span of several decades and differed in radiotherapy dose, form of ADT used, duration of ADT, timing of ADT with radiotherapy, and which component (ie, neoadjuvant *vs* adjuvant) of ADT was prolonged. None of the trials, in isolation, was able to quantitate the aggregate benefit of these interventions, nor have they been able to ascertain whether the benefits (if any) are preserved across clinically relevant subgroups.

Added value of this study

This meta-analysis is the first study, to our knowledge, that quantitatively and comprehensively shows the benefit of adding ADT to radiotherapy alone and the benefit to adjuvant ADT prolongation. We also provide high-level evidence that the benefits of both interventions persist across subgroups defined by parameters such as age, National Comprehensive Cancer Network risk group, and radiotherapy dose, which should address the substantial controversies regarding which subgroups of patients these interventions might provide benefit to. This study is also, to our knowledge, the first to conclusively show no clear oncological benefit to neoadjuvant ADT prolongation.

Implications of all the available evidence

Our findings provide the strongest evidence to date for the routine recommendation of the addition of ADT to radiotherapy for men with intermediate-risk and high-risk prostate cancer, regardless of radiotherapy dose. The findings also suggest that prolonging the adjuvant component of ADT offers a significant benefit, regardless of radiotherapy dose, in men with intermediate-risk and high-risk disease—although the absolute benefit is greater in men with high-risk disease. The incorporation of biomarkers will be crucial for tailored recommendations for ADT duration. However, neoadjuvant ADT extension offers no clear benefit and should not be routinely recommended.

localised prostate cancer has not, to the best of our knowledge, taken place yet. Several trials have evaluated the intensification of treatment, from radiotherapy alone to radiotherapy in combination with androgen deprivation therapy (ADT).[4] Additional trials have investigated prolonging the total duration of ADT given with radiotherapy, whereas others have evaluated extending the neoadjuvant portion of ADT only, or prolonging the adjuvant portion of ADT only. The various trials and cooperative groups often differ in studied radiotherapy dose, the form of ADT used, duration of ADT, and the timing of ADT with radiotherapy. However, the aggregate benefit of these interventions is poorly quantified, and real-world evidence suggests that the addition of ADT and prolongation of ADT are both underused in clinical practice, especially when high-dose radiotherapy is delivered.[5,6] This underuse is further driven by concerns from both patients and physicians about the possible adverse events caused by ADT.[7] Quantifying the benefits of these interventions and evaluating whether they are modified by radiotherapy dose, age, or National Comprehensive Cancer Network (NCCN) risk group is crucial to ensure that evidence-based care is provided to patients within the context of shared decision making.

To fulfil this unmet need, the Meta-Analysis of Randomised trials in Cancer of the Prostate (MARCAP) Consortium was formed, in 2020, to serve as a data repository for international trial groups. The primary aim of this MARCAP study was to quantify three clinically relevant questions for men with localised prostate cancer: the oncological effects of the addition of ADT to radiotherapy, the effects of neoadjuvant ADT extension before radiotherapy, and the effects of adjuvant ADT prolongation after completion of radiotherapy.

Methods

Search strategy and selection criteria

The inclusion criteria and analytical plan for overall MARCAP consortium meta-analyses were prespecified in a protocol submitted to PROSPERO, CRD42021236855. To identify all relevant randomised trials for individual patient data request, a literature review was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[8] We performed a systematic literature search of MEDLINE (1966–2020), Embase (1982–2020), trial registries (Cochrane Central Register of Controlled Trials and ClinicalTrials.gov), the Web of Science, Scopus, and major urology and oncology conference proceedings (1990–2020) to retrieve studies published in English between Jan 1, 1962, and Dec 30, 2020 that evaluated the use or prolongation of ADT in men with localised prostate cancer receiving definitive radiotherapy. Controlled vocabulary was used for studies involving humans using the following terms: "randomised AND prostate AND (androgen deprivation OR hormone therapy) AND (radiotherapy OR radiation) AND (neoadjuvant OR adjuvant) NOT prostatectomy". According to our four prespecified exclusion criteria, we excluded trials that: did not collect distant metastasis or survival data; used only non-steroidal anti-androgen

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See Online for appendix

For the **protocol** see https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=236855

therapy without ADT; were single-centre in nature; or used lifelong ADT.

The rationale for these inclusion criteria was as follows. First, the prespecified primary oncological endpoint of interest for our study was metastasis-free survival, which is a known surrogate endpoint for overall survival in men with localised prostate cancer.[4,9] Second, the use of non-steroidal anti-androgen therapy without ADT has not, to date, been shown to improve oncological outcomes in any study in localised prostate cancer, and is not recommended as a standard approach.[10] Third, we decided to exclude single-centre trials because previous studies have suggested that the treatment effects reported in single-centre randomised trials will be systematically larger than in similar multicentre studies.[11,12] Finally, we chose to exclude trials using lifelong ADT because this practice is no longer recommended as a standard option in the definitive management of prostate cancer with radiotherapy.[13] As such, all forms of ADT studied were pharmacological. The search was done by a single investigator (AUK) and verified by another (DES). Data sharing agreements were submitted to data governance bodies representing the Radiation Therapy Oncology Group (now NRG Oncology), the European Organisation for Research and Treatment of Cancer (EORTC), the Trans-Tasman Radiation Oncology Group (TROG), the Ireland Cooperative Oncology Research Group, the Prostate Cancer Study group, and the Grupo de Investigación Clínica en Oncología Radioterápica. Individual patient data were collected for all eligible trials identified.

The requirement for ethics approval was waived by the University of California Los Angeles and University Hospitals institutional review boards. The protocol is available online.

Data analysis

All analyses were prespecified in the analysis plan. Data extraction and preparation for each individual study was performed by the relevant governing body. The data requested for all patients were age, T category in the TNM staging system, tumour grade (as per Gleason score), prostate-specific antigen (PSA) concentration at enrolment, performance status, and allocated treatment. Outcome data requested included time-to-event information and event status for biochemical failure, local failure, regional failure, distant failure, death, and cause of death. Updated survival status and time to last follow-up were requested from the trialist groups. After institutional review board approval, individual patient data were shared with the co-principal investigators (AUK and DES) and statisticians (YS, TR, and XW) of the MARCAP consortium (secured at the UH Seidman Cancer Center, Case Western Reserve University, Cleveland, OH, USA, and at the University of California Los Angeles, Los Angeles, CA, USA). Data for each individual trial were checked for consistency with the trial protocol and published or presented results.

Three treatment intensification strategies were reported across the 12 identified trials: ADT use (*vs* radiotherapy alone), neoadjuvant ADT prolongation (total duration of ADT prolonged entirely in the neoadjuvant setting from short [3–6 months] to extended [6–9 months]), and adjuvant ADT prolongation (total duration of ADT prolonged entirely in the adjuvant setting from short-term ADT [4–6 months] to long-term ADT [18–36 months]). Exceptionally, for the purposes of the neoadjuvant ADT meta-analysis, the 6-month duration of ADT in the TROG 96.01 study[14] was considered as extended therapy, and the 3-month duration was considered as short neoadjuvant ADT; conversely, 6 months of ADT for the adjuvant ADT meta-analysis was used in the short-term ADT groups of EORTC 22961 and TROG RADAR.[15,16] Metrics for inter-trial heterogeneity were calculated and are summarised in the appendix (p 3). Publication bias was examined by Egger's test and evaluated graphically with funnel plots (appendix pp 4, 8–10).

Outcomes

The primary endpoint of each meta-analysis (ADT use, neoadjuvant ADT prolongation, and adjuvant ADT prolongation) was to determine the oncological effects of treatment intensification on metastasis-free survival.[4,9] At the time the analytical plan was developed, the median follow-up period for each trial was unknown, so metastasis-free survival was chosen as the primary endpoint over overall survival (because effects on metastasis-free survival will manifest earlier than on overall survival).

The secondary outcomes were to assess the effects of each treatment intensification method on the rates of biochemical recurrence, distant metastasis, and overall survival. All endpoints were defined by the respective trials, and consisted most commonly of time from randomisation until the event of interest. Biochemical recurrence was determined according to the Phoenix definition for all trials, except for EORTC 22863 and EORTC 22961 (in which it was defined as a PSA concentration of >1·5 ng/mL with at least two consecutive rises), and for RTOG 8610 (in which it was defined as a PSA concentration of >1·0 ng/mL at any point ≥1 year after randomisation). Distant metastasis in all trials was defined by extrapelvic disease assessed by clinical or radiographical examination.

Statistical analysis

A statistical plan was created before data pooling and analysis. All analyses were performed on an intention-to-treat basis. Median follow-up time and IQR were calculated using the reverse Kaplan-Meier method.[17] Baseline characteristics were compared by treatment group using the Mann-Whitney *U* test for age and the

χ^2 test for all other baseline characteristics. Inter-trial heterogeneity was assessed using a two-stage approach: in stage one, the effect sizes and standard errors were calculated in each trial and, in stage two, these aggregated data were analysed with a random effects model. We used a one-stage approach for this individual patient data meta-analysis, wherein data from all patients receiving a similar treatment were pooled and the hazard ratios (HRs) were estimated using univariable Cox regression models stratified by trial.[18] For example, for the ADT use meta-analysis, all patients receiving radiotherapy alone across trials were pooled together to form one group, and those receiving radiotherapy plus ADT across trials were pooled together to form the comparator group. Metastasis-free survival and overall survival were reported using the HR and 95% CIs from Cox regression models, along with absolute differences in Kaplan-Meier event probability estimates.[19,20] The Grambsch-Therneau test was used to identify violation of the proportionality assumption of the Cox regression models. For cumulative incidence of biochemical recurrence, distant metastasis, and prostate cancer-specific mortality, the subdistribution HRs with 95% CI was reported from Fine-Gray's competing risk regression models, along with cumulative incidence of events. Death from any cause was considered a competing event for biochemical recurrence and distant metastasis.

We did sensitivity analyses using a cause-specific, additive frailty model with random trial effect and random treatment-by-trial interaction to account for heterogeneity across trials. Non-prostate cancer-related death was considered a competing event for prostate cancer-specific mortality.[21–24] For each treatment group, 10-year restricted mean survival time and 10-year restricted mean time lost were calculated. Restricted mean survival time was determined from the Kaplan-Meier estimate of the survival function, whereas restricted mean time lost was determined from the estimated cumulative incidence function. In a prespecified sensitivity analysis, we repeated the ADT use meta-analysis but excluded the EORTC 22863 trial, which evaluated the addition of 36 months of ADT to radiotherapy alone (a substantially longer duration of ADT than the other five trials of ADT use).

Formal interaction tests between the intervention of interest and oncological outcomes were done for the following subgroups: age (<70 years *vs* ≥70 years), NCCN risk group (intermediate *vs* high),[13] and radiotherapy dose (low [<74 Gy] *vs* high [≥74 Gy]). Notably, risk group classifications were obtained retrospectively on the basis of granular PSA concentration, T category, and Gleason score data. The interactions were assessed in Cox regression and Fine-Gray competing risk regression models stratified by trials. We did a prespecified sensitivity analysis as a formal interaction test between the intervention of interest and metastasis-free survival for radiotherapy dose, defining less than 76 Gy as a low dose (rather than <74 Gy). Absolute risk reductions at 4, 8, 10, or 12 years for biochemical recurrence, distant metastasis, and all-cause mortality events were calculated as the differences in event risks, estimated with the cumulative incidence function (for biochemical recurrence and distant metastasis) and the Kaplan-Meier method (for all-cause mortality) at 4, 8, 10, or 12 years between the treatment groups, correspondingly. The numbers-needed-to-treat to avoid biochemical recurrence, distant metastasis, and all-cause mortality for each treatment intensification strategy were calculated as the inverse of the absolute risk reduction at 10 years.

All analyses were performed in R (version 4.1.1) at a two-tailed level of significance of 0·05.

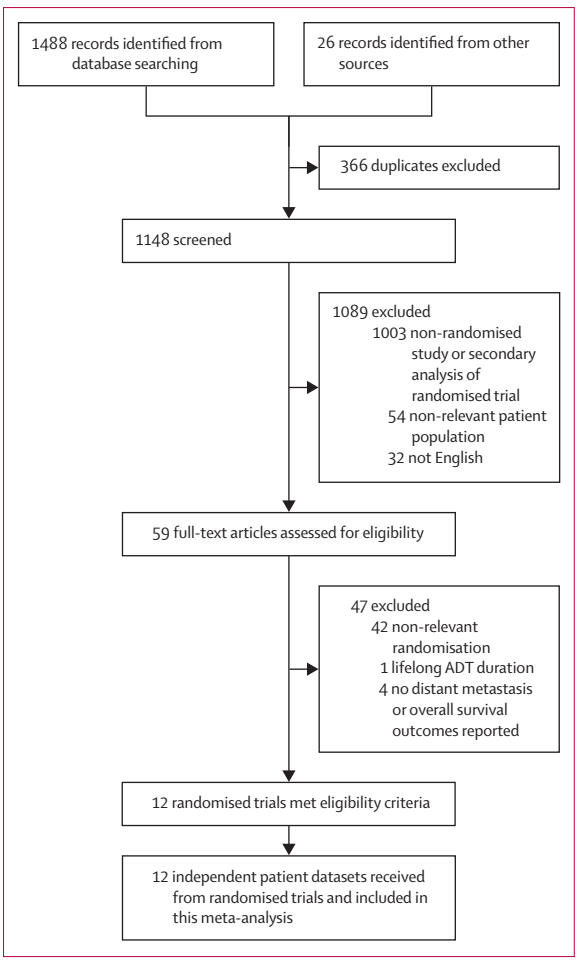

Figure 1: **Trial profile**
Full details on included and excluded trials (and reason for exclusion) are provided in table 1 and in the appendix (pp 5,6). ADT=androgen deprivation therapy.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Our search returned 18 trials, 12 of which met all eligibility criteria. Individual patient data were available for 12 randomised trials including 10 853 patients (figure 1, appendix pp 5–6) with a median follow-up of 11·4 years (IQR 9·0–15·0). Details of the included trials are shown in table 1.[14–16,25–33] Patient characteristics were well balanced within each group of each of the three treatment effects meta-analysed (table 2). Assessment of inter-trial heterogeneity and funnel plots are shown in the appendix (pp 3–4, 8–10). Significant heterogeneity was found for metastasis-free survival across all treatment categories, though no significant publication bias was seen. Our full heterogeneity findings can be found in the appendix (p 3). Trial-specific estimates are reported in the appendix for ADT use (appendix p 13), neoadjuvant ADT prolongation (appendix pp 15), and adjuvant ADT prolongation (appendix p 17).

Seven randomised comparisons across six trials[14,25–29] evaluated the addition of ADT to radiotherapy (5136 patients, median follow-up 12·9 years [IQR 10·9–16·9]). Notably, two comparisons from TROG 96.01 were made: 2 months of ADT followed by 1 month of radiotherapy plus ADT versus radiotherapy alone (first comparison), and 5 months of ADT followed by 1 month of radiotherapy plus ADT versus radiotherapy alone (second comparison). The median duration of additional ADT was 6 months (IQR 4–6) with the inclusion of EORTC 22863, and 5 months (4–6) with the exclusion of EORTC 22863. The addition of ADT to radiotherapy significantly improved metastasis-free survival (HR 0·83, 95% CI 0·77–0·89; p<0·0001), corresponding to a 10-year absolute benefit of 8·6% (95% CI 5·8–11·4; figures 2A, 3A). ADT use also significantly improved biochemical recurrence, distant metastasis, and overall survival (figure 3A).

	Patient population	Study period	Intervention group	Control group	Radiotherapy dose, Gy*	Participants, n	Controls, n	Metastasis-free survival, HR (95% CI)
ADT use								
RTOG 8610[25]	Stages T2c–T4; tumour size ≥25cm²; node-positive allowed if below common iliac station	1987–91	2 months of ADT followed by 2 months of radiotherapy plus ADT	Radiotherapy	70·0	226	230	0·80 (0·65–0·98)
EORTC 22863[26]	Stages T1–T2; WHO grade 3, T3–T4	1987–95	Radiotherapy plus 36 months of ADT	Radiotherapy	70·0	207	208	0·50 (0·38–0·65)
RTOG 9408[27]	Stages T1b–T2b; PSA ≤20 ng/mL	1994–2001	2 months of ADT followed by 2 months of radiotherapy plus ADT	Radiotherapy	66·6	987	992	0·94 (0·66–1·05)
TROG 96.01[14] (first comparison)	Stages T2b–T4	1996–2000	2 months of ADT followed by 1 month of ADT plus radiotherapy	Radiotherapy	66·0	265	270	0·84 (0·66–1·05)
TROG 96.01[14] (second comparison)	Stages T2b–T4	1996–2000	5 months of ADT followed by 1 month of ADT plus radiotherapy	Radiotherapy	66·0	267	270	0·59 (0·46–0·75)
PCS III[28]	NCCN intermediate risk	2000–10	4 months of ADT followed by 2 months of radiotherapy plus ADT	Radiotherapy	76·0	200	200	0·90 (0·67–1·21)
EORTC 22991[29]	(1) Stages T1b–T2a, PSA >10 ng/mL, and Gleason score ≥7; (2) stages T2b–T4 and PSA up to 12·5-times ULN	2001–08	Radiotherapy plus 6 months of ADT	Radiotherapy	70·0, 74·0, and 78·0	410	409	0·77 (0·57–1·04)
Neoadjuvant ADT prolongation								
TROG 96.01[14]	Stages T2b–T4	1996–2000	5 months of ADT followed by 1 month of radiotherapy plus ADT	2 months of ADT followed by 1 month of radiotherapy plus ADT	66·0	267	265	0·71 (0·55–0·92)
ICORG 97-01[30]	Stages T3–T4; PSA >20 ng/mL; Gleason score ≥7	1997–2001	8 months of ADT, with radiotherapy added in last month	4 months of ADT, with radiotherapy added in last month	70·0	124	129	1·68 (1·16–2·43)
RTOG 9910[31]	(1) Stages T1b–T4; Gleason score 2–6; PSA >10 ng/mL ≤100; (2) stages T1b–T4; Gleason score 7; PSA <20 ng/mL; (3) stages T1b–T1c; Gleason score 8–10; PSA <20 ng/mL	2000–04	7 months of ADT followed by 2 months of radiotherapy plus ADT	2 months of ADT followed by 2 months of radiotherapy plus ADT	70·2	737	752	0·96 (0·80–1·15)

(Table 1 continues on next page)

	Patient population	Study period	Intervention group	Control group	Radiotherapy dose, Gy*	Participants, n	Controls, n	Metastasis-free survival, HR (95% CI)
(Continued from previous page)								
Adjuvant ADT prolongation								
RTOG 9202[32]	Stages T2c–T4; PSA <150 ng/mL	1992–95	2 months of ADT followed by radiotherapy and an additional 26 months of ADT	2 months of ADT followed by 2 months of radiotherapy plus ADT	65·0–70·0	758	762	0·87 (0·77–0·97)
EORTC 22961[15]	Stages T1c–T2b pN1-N2 or T2c–T4 N0–N2, with PSA <40-times ULN	1997–2001	Radiotherapy plus 36 months of ADT	Radiotherapy plus 6 months of ADT	70·0	487	483	0·60 (0·47–0·76)
DART–GICOR[33]	Stages T1c–T3b, with NCCN intermediate or high risk and PSA <100 ng/mL	2000–04	2 months of ADT followed by radiotherapy and an additional 26 months of ADT	2 months of ADT followed by 2 months of radiotherapy plus ADT	78·0	177	178	0·45 (0·24–0·83)
TROG RADAR[16]	Stages T2b–T4 (T2a if Gleason score ≥7 and PSA ≥10 ng/mL)	2003–07	5 months of ADT followed by 13 months of radiotherapy plus ADT	5 months of ADT followed by 1 month of radiotherapy plus ADT	66·0, 70·0, and 74·0; 46·0 plus 19·5 via brachytherapy	535	536	0·92 (0·82–1·04)

ADT=androgen deprivation therapy. DART–GICOR=DART trial from the Grupo de Investigación Clínica en Oncología Radioterápica. EORTC=European Organisation for Research and Treatment of Cancer. ICORG=Ireland Cooperative Oncology Research Group. MFS=metastasis-free survival. PCS=Prostate Cancer Study. PSA=prostate-specific antigen. RTOG=Radiation Therapy Oncology Group. TROG=Trans-Tasman Radiation Oncology Group. ULN=upper limit of normal. *Refers to prostate dose. EORTC 22991 and TROG RADAR allowed different, prespecified dose levels. DART–GICOR required a minimum dose of 76·0 Gy, and the reported dose is the median dose. PCS III was a three-group trial; the relevant comparison for this meta-analysis used 76·0 Gy in both groups. RTOG 9202 had a dose range for the prostate primary tumour depending on clinical T category in the Tumour, Node, Metastasis staging system of the lesion.

Table 1: **Trials included in this meta-analysis**

	Total	ADT use		Neoadjuvant ADT prolongation		Adjuvant ADT prolongation	
		Experimental group (radiotherapy plus ADT)	Control group (radiotherapy alone)	Experimental group (6–9 months of ADT)	Control group (3–4 months of ADT)	Experimental group (18–36 months of ADT)	Control group (4–6 months of ADT)
Number of patients	10 853	2557	2579	1103	1110*	1900	1874
Median follow-up (IQR), years	11·4 (9·0–15·0)	12·9 (10·9–16·9)	†	10·3 (8·8–11·2)	†	10·9 (7·0–14·8)	†
Median age (IQR), years	70·0 (65·0–74·0)	70·0 (65·6–74·0)	70·0 (65·2–74·0)	70·0 (65·0–73·8)	69·6 (65·0–73·0)	70·0 (65·0–73·6)	70·0 (65·0–74·0)
Gleason score							
6	4280 (40·3%)	1267 (51·4%)	1230 (49·6%)	369 (33·5%)	360 (32·4%)	578 (30·8%)	590 (31·8%)
7	4452 (41·9%)	870 (35·3%)	933 (37·6%)	600 (54·4%)	599 (54·0%)	790 (42·2%)	775 (41·7%)
8–10	1886 (17·8%)	326 (13·2%)	318 (12·8%)	134 (12·1%)	151 (13·6%)	506 (27·0%)	492 (26·5%)
T category							
1–2	7420 (68·4%)	1993 (78·0%)	2020 (78·4%)	879 (79·7%)	878 (79·1%)	916 (48·3%)	898 (47·9%)
3–4	3428 (31·6%)	563 (22·0%)	558 (21·6%)	224 (20·3%)	232 (20·9%)	982 (51·7%)	975 (52·1%)
Median PSA (IQR), ng/mL	12·2 (7·6–20·6)	10·1 (6·6–16·5)	10·6 (6·9–17·3)	11·5 (7·5–17·4)	11·8 (7·5–17·4)	16·3 (9·8–30·2)	16·6 (10·0–30·0)
NCCN risk group							
Low	1090 (10·1%)	500 (19·9%)	469 (18·6%)	4 (0·4%)	5 (0·5%)	58 (3·1%)	54 (2·9%)
Intermediate	4653 (43·3%)	1197 (47·6%)	1230 (48·7%)	685 (62·1%)	671 (60·5%)	482 (25·4%)	487 (26·0%)
High	5012 (46·6%)	819 (32·6%)	828 (32·8%)	414 (37·5%)	434 (39·1%)	1356 (71·5%)	1332 (71·1%)

Data are n (%) unless otherwise stated. ADT=androgen deprivation therapy. NCCN=National Comprehensive Cancer Network. PSA=prostate-specific antigen. *One patient was excluded from the survival analysis of neoadjuvant ADT extension because he passed away after randomisation but before completing radiotherapy. †Same follow-up duration as the experimental group.

Table 2: **Patient characteristics**

Results were unchanged in the sensitivity analysis that excluded EORTC 22863 (appendix p 11).

Three randomised trials[14,30,31] evaluated neoadjuvant ADT extension (2213 patients, median follow-up 10·3 years [IQR 8·8–11·2]). These trials extended total ADT duration from 3 months to 6 months (TROG 96.01), from 4 months to 8 months (Ireland Cooperative Oncology Research Group 97-01), and from 4 months to

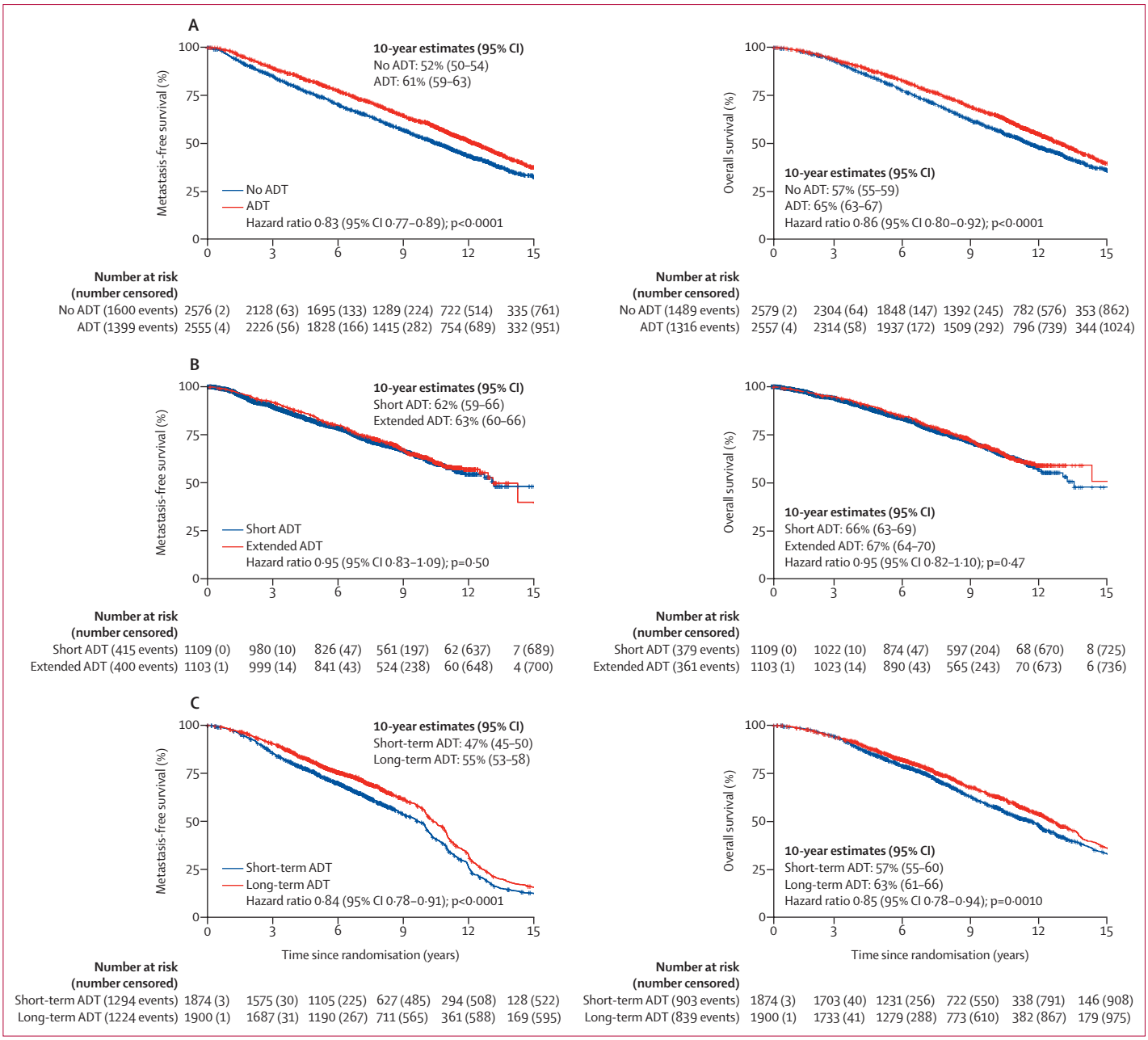

Figure 2: **Metastasis-free survival and overall survival curves for ADT use (A), neoadjuvant ADT extension (B), and adjuvant ADT prolongation (C)**
Five patients did not have information on metastases and were excluded from the metastasis-free survival analysis. ADT=androgen deprivation therapy.

9 months (RTOG 9910); the median total duration of ADT was 4·0 months (IQR 3·5–4·0) in the short neoadjuvant ADT cohort and 8·0 months (7·0–8·5) in the extended neoadjuvant ADT cohort, with a median neoadjuvant ADT prolongation of 4·0 months (3·5–4·5). Neoadjuvant ADT extension was not associated with any improvements in metastasis-free survival (HR 0·95 [95% CI 0·83–1·09], p=0·50; figure 2B). It was also not associated with any improvements in overall survival or biochemical recurrence (figures 2B, 3B).

Four randomised trials[15,16,32,33] evaluated adjuvant ADT prolongation (3774 patients, median follow-up 10·9 years [IQR 7·0–14·8]). These trials extended total ADT duration from 4 months to 28 months (NRG–RTOG 9202 and DART–Grupo de Investigación Clínica en Oncología Radioterápica), from 6 months to 36 months (EORTC 22961), and from 6 months to 18 months (TROG RADAR). The median ADT duration in the short-term ADT cohort was 5·0 months (IQR 4·0–6·0) versus 28·0 months (25·5–30·0) in the

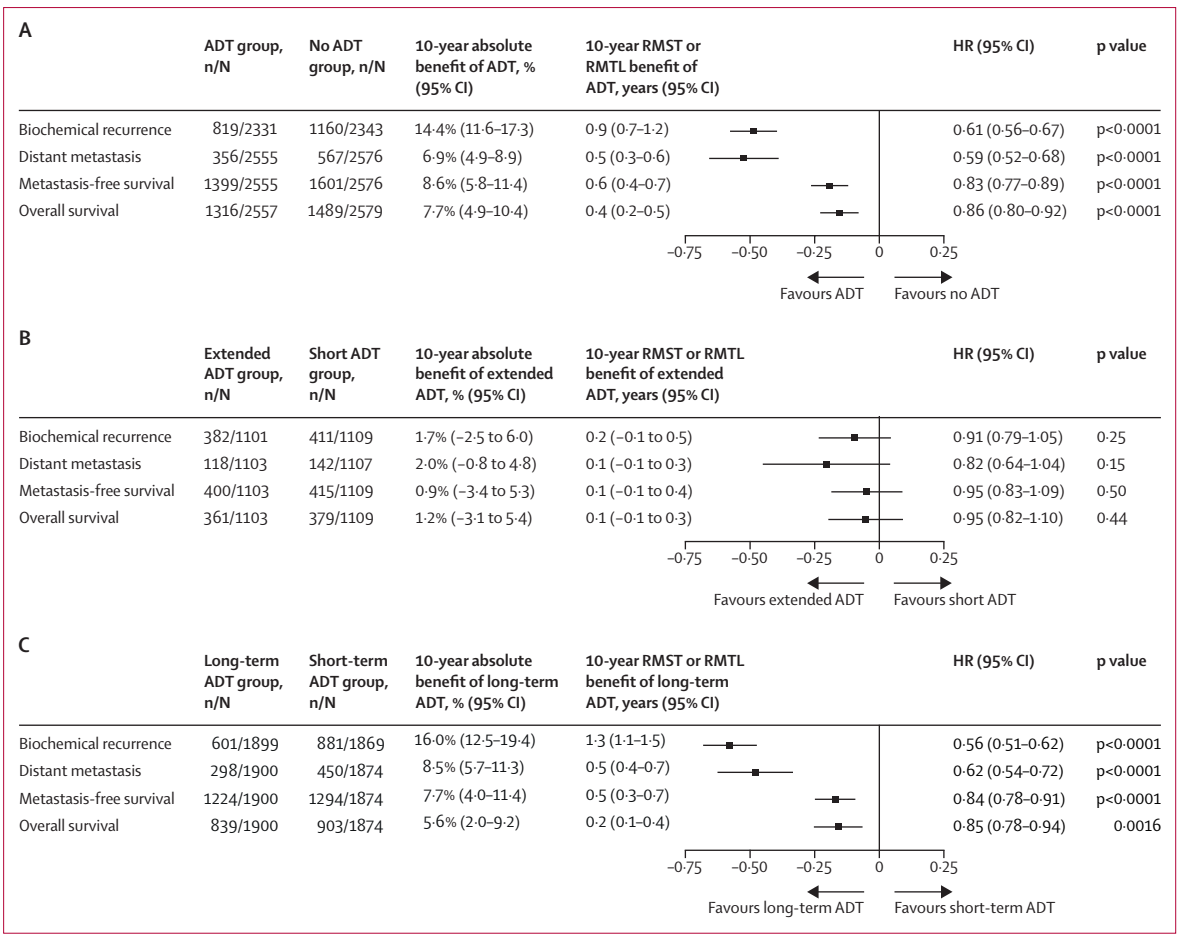

Figure 3: **Forest plots showing effects of ADT use (A), neoadjuvant ADT extension (B), and adjuvant ADT prolongation (C) on biochemical recurrence, distant metastasis, metastasis-free survival, and overall survival**

ADT=androgen deprivation therapy. HR=hazard ratio. RMST=restricted mean survival time. RMTL=restricted mean time lost.

long-term ADT cohort; the median duration of adjuvant ADT prolongation was 24·0 months (21·0–25·5). Adjuvant ADT prolongation was significantly associated with improved metastasis-free survival (HR 0·84 [95% CI 0·78–0·91], p<0·0001), corresponding to a 10-year absolute benefit of 7·7% (4·0–11·4; figures 2C, 3C). Adjuvant ADT prolongation also significantly improved overall survival, biochemical recurrence, and distant metastasis (figures 2C, 3C).

Subgroup effects and p values for interaction tests are shown in table 3 and interaction plots are shown in the appendix (p 18). No significant interaction was seen between radiotherapy dose and the metastasis-free survival benefit of ADT use ($p_{interaction}$ 0·96) or adjuvant ADT prolongation ($p_{interaction}$ 0·41); between NCCN risk group and metastasis-free survival treatment effect from ADT use ($p_{interaction}$ 0·091) or adjuvant ADT prolongation ($p_{interaction}$ 0·72); nor between age and metastasis-free survival treatment effect from ADT use ($p_{interaction}$ 0·088) or adjuvant ADT prolongation ($p_{interaction}$ 0·72). No patients undergoing neoadjuvant ADT extension received high-dose radiotherapy. No significant benefits to metastasis-free survival were seen with neoadjuvant extension in our primary analysis, nor were any metastasis-free survival benefits found in subgroups defined by age or NCCN risk group (table 3). Results were unchanged in our sensitivity analysis in which the threshold for high-dose radiotherapy was changed to at least 76 Gy (appendix p 19).

Notably, when analysing biochemical recurrence and distant metastasis outcomes in the main meta-analyses, we used a Fine-Gray competing risk framework and the results were largely unchanged from the competing risk framework. Because this framework does not isolate the treatment effects on the competing risks (ie, the protective effect of treatment could be indirect and a result of increased subdistribution hazard of death), we repeated analyses using a cause-specific framework for biochemical recurrence and distant metastasis for evaluating the impact of ADT use (appendix p 12), neoadjuvant ADT extension (appendix p 14), and adjuvant ADT prolongation (appendix p 16).

	Number of patients	Hazard ratio (95% CI)	p value	$p_{interaction}$
ADT use				
NCCN risk group	..	..	..	0·091
High	1647	0·72 (0·64–0·82)	<0·0001	..
Intermediate	2427	0·84 (0·75–0·93)	0·0014	..
Radiotherapy dose	..	..	..	0·96
High (≥74 Gy)	1018	0·83 (0·68–1·01)	0·063	..
Low (<74 Gy)	4118	0·83 (0·76–0·89)	<0·0001	..
Age, years	..	..	..	0·088
<70	2419	0·77 (0·69–0·87)	<0·0001	..
≥70	2716	0·88 (0·80–0·97)	0·0080	..
Neoadjuvant ADT extension*				
NCCN risk group	..	..	..	0·92
High	848	0·95 (0·78–1·16)	0·63	..
Intermediate	1356	0·97 (0·81–1·18)	0·79	..
Age, years	..	..	..	0·56
<70	1118	0·98 (0·80–1·21)	0·88	..
≥70	1095	0·91 (0·75–1·09)	0·29	..
Adjuvant ADT prolongation				
NCCN risk group	..	..	..	0·72
High	2688	0·85 (0·77–0·93)	0·0005	..
Intermediate	969	0·81 (0·69–0·94)	0·0058	..
Radiotherapy dose	..	..	..	0·41
High (≥74 Gy)	856	0·90 (0·76–1·06)	0·20	..
Low (<74 Gy)	2918	0·83 (0·76–0·91)	0·0004	..
Age, years	..	..	..	0·72
<70	1841	0·83 (0·74–0·94)	0·0019	..
≥70	1930	0·85 (0·76–0·94)	0·0024	..

ADT=androgen deprivation therapy. NCCN=National Comprehensive Cancer Network. *No patients received high-dose radiotherapy, precluding analysis of a radiotherapy dose interaction effect in this cohort.

Table 3: **Subgroup effects and interaction test results for metastasis-free survival**

For the addition of ADT to radiotherapy for patients with NCCN intermediate-risk disease, the number-needed-to-treat to avert one distant metastasis event at 10 years was 18·0 (95% CI 12·7–30·7); for patients with high-risk disease, the number-needed-to-treat was 8·4 (6·0–13·8; appendix p 7). The number-needed-to-treat with prolonged adjuvant ADT to avert one distant metastasis event at 10 years was 16·1 (9·2–63·7) for patients with intermediate-risk disease and 10·4 (7·6–16·4) for patients with high-risk disease. Numbers-needed-to-treat for biochemical recurrence, distant metastasis, and all-cause mortality for patients with intermediate-risk and high-risk disease are provided in the appendix (p 7). Plots showing the associations between the absolute risk reductions (4-year biochemical recurrence *vs* 8-year distant metastasis and 8-year distant metastasis *vs* 12-year all-cause mortality) for ADT use and adjuvant ADT prolongation are shown in the appendix (p 20). These associations were not further studied for neoadjuvant ADT extension as this intervention was not associated with any significant improvements in biochemical recurrence, distant metastasis, or all-cause mortality.

Discussion

This study from the MARCAP consortium represents, to our knowledge, the first individual patient data meta-analysis of eligible randomised trials evaluating the use and prolongation of ADT with radiotherapy. It provides four novel, clinically relevant insights that were unclear from individual trial results. First, the findings highlight a significant metastasis-free survival and overall survival benefit from the addition of ADT to radiotherapy, and quantify this benefit with a number-needed-to-treat to prevent one distant metastasis event at 10 years of 8–18 patients treated, on the basis of NCCN risk group. Second, adjuvant ADT prolongation to at least 18 months in conjunction with radiotherapy further improves metastasis-free survival and overall survival compared with short-term ADT, with a number-needed-to-treat to prevent one distant metastasis of 10 for patients with high-risk disease. Third, extension of neoadjuvant ADT was not associated with improved biochemical recurrence, distant metastasis, metastasis-free survival, or overall survival, and thus should not be routinely recommended. Finally, the treatment effects of each intensification strategy were not significantly affected by radiotherapy dose, NCCN risk group, or patient age.

The benefit of ADT in intermediate-risk prostate cancer is often questioned, particularly in conjunction with dose-escalated radiotherapy.[34] Our meta-analysis shows that the addition of short-term ADT to radiotherapy has substantial benefits on clinical endpoints, and the effect is similar across radiotherapy doses. This benefit is clinically relevant because some practitioners who prescribe various forms of dose-escalation advocate for the exclusion of ADT with radiotherapy, albeit without evidence from randomised trials to support this practice. Furthermore, we found no significant interaction between age (≥70 years *vs* <70 years) and the metastasis-free survival benefit of ADT use, suggesting that this benefit persists even in older men, who are more likely to have greater competing causes of death. However, heterogeneity exists within any risk group, and because the absolute benefit of adding ADT will be variable within intermediate-risk disease, shared decision making between health-care professionals and patients is essential. On this topic, the NRG GU010 phase 3 trial (NCT05050084) is attempting to identify, via a genomic classifier, patients with unfavourable intermediate-risk prostate cancer that might safely omit ADT.

Intermediate-risk disease is often divided into favourable or unfavourable subgroups.[35] This stratification scheme requires information about the

percentage of biopsy cores that were positive for cancer, which was not uniformly available across the trials included here. However, given that both stage and grade migration have occurred during the past three decades, the patients with intermediate-risk disease in this meta-analysis might be more similar to patients with unfavourable intermediate-risk, or even high-risk, prostate cancer today. The similar relative benefits of ADT use or adjuvant prolongation by NCCN risk groups highlights the need for better prognostic and predictive biomarkers to optimise treatment intensification for each patient. Nonetheless, the results of our meta-analysis suggest that prolonging ADT in the adjuvant setting to reach a total duration of 18–36 months provides a metastasis-free survival benefit to both intermediate-risk and high-risk patients, regardless of radiotherapy dose. The optimal duration, particularly for patients with high-risk disease, will be the subject of a separate meta-analysis from the MARCAP consortium and is the focus of ongoing randomised trials (eg, NRG GU009).[36,37] Ongoing trials, such as NRG GU009 (NCT04513717), are attempting to identify favourable genomic subsets of patients that can safely shorten the duration of ADT to 12 months.

Notably, all studies included in this meta-analysis used conventionally fractionated radiotherapy, except for 237 patients on the TROG RADAR trial who received a brachytherapy boost. The results of our prespecified sensitivity analyses, which restricted inclusion to patients receiving at least 76 Gy and patients who received a brachytherapy boost, suggest that dose escalation does not preclude the benefit of ADT use or prolonging adjuvant ADT. Randomised trials[38–41] have shown that hypofractionated radiotherapy schedules are not superior to conventional fractionation in terms of PSA-based endpoints (ie, biochemical recurrence), much less distant metastasis-based endpoints or overall survival. To date, there are no randomised trial data to support a differential effect of ADT treatment intensification in the setting of alternative fractionation schema, such as moderate hypofractionation or ultrahypofractionation. Until randomised data supporting a difference in ADT duration on the basis of fractionation can be generated, we believe that the findings of our meta-analysis provide justification to recommend the use and adjuvant prolongation of ADT irrespective of fractionation schedule. Similarly, no randomised data exist to support the omission of ADT with a brachytherapy boost.

Our meta-analysis also shows that extension of neoadjuvant ADT does not significantly improve biochemical recurrence, metastasis-free survival, or overall survival. Although it is possible that the duration of extended neoadjuvant ADT (<6 month prolongation) was insufficient—compared with adjuvant ADT prolongation (>12-month prolongation)—our findings might not be solely based on duration. A 2021 meta-analysis of the only two randomised trials that have evaluated sequencing of ADT in relation to radiotherapy, while keeping ADT duration constant, showed that adjuvant ADT led to significantly superior metastasis-free survival than did neoadjuvant ADT.[42] Taken with our findings that extending neoadjuvant ADT offers no clear oncological benefit, we believe there is strong evidence that extending neoadjuvant ADT beyond a 2-month neoadjuvant course should not be used for oncological purposes when total ADT durations of 4–6 months (ie, short-term ADT) are being used. We acknowledge, however, that extended courses could be used for logistical reasons, particularly if treatment is being intentionally delayed for other reasons.[43] Notably, the aforementioned heterogeneity within the intermediate-risk category and our inability to capture this heterogeneity could affect the identification of any benefit to neoadjuvant ADT extension.

The benefits of ADT must be weighed against potential morbidity, including side-effects affecting the reproductive cardiovascular systems, and metabolic, cognitive, and psychiatric consequences.[7] Reassuringly, we found no significant interaction between age and the benefit of ADT use or adjuvant ADT prolongation, given that men aged 70 years and older receiving treatment for prostate cancer are the most likely to have impactful comorbidities and to have a prolonged time to testosterone recovery.[44] However, additional studies focused on quality-of-life metrics are crucial and will be the subject of future study through the MARCAP consortium.

Limitations of this meta-analysis are, first, that the included trials span an accrual period ranging from 1987 to 2010, a 23-year timespan during which there has been Gleason grade migration[45] and stage migration.[46] However, several trials included have patients followed up for longer than 15 years, which allows long-term estimates to be quantified. Given the consistency in results between trial-adjusted and the overall direct meta-analysis presented, this heterogeneity is not likely to have substantially affected our findings. Adjusting for centre within each trial might have added an extra layer of precision; however, data on treatment centre were not available. Two trials that reported overall survival results (but not distant metastasis results) were not eligible for inclusion on the basis of our prespecified inclusion criteria; furthermore, after discussion with the principal investigators of these studies, individual patient data could not be made available for a sensitivity analysis. The first trial evaluated ADT use and reported an overall survival benefit, which is consistent with our results.[47] The second trial evaluated neoadjuvant ADT extension and reported no differences in failure-free survival (which is largely driven by biochemical recurrence events) or overall survival, which is also consistent with our results.[48] Second, within each broad treatment strategy, heterogeneity regarding the specifics of ADT sequencing and duration persists, even among patients receiving prolonged adjuvant

ADT. We believe these differences are a strength of the meta-analysis approach, as was appreciated in the landmark EBCTG[1,2] (breast cancer) and MARCH[3] (head and neck cancer) meta-analyses. Nonetheless, although all relevant and eligible studies were included, the low number of trials for each meta-analysis (six for ADT use, three for neoadjuvant ADT prolongation, and four for adjuvant ADT prolongation) prevents a rigorous assessment of heterogeneity and publication bias, which is an important limitation of our approach. From our attempts to quantify heterogeneity and publication bias we found significant between-trial heterogeneity. Third, a few additional trials identified during our literature searches could not be included in this meta-analysis because they did not collect data on metastasis or survival, and were often small in size. Fourth, although all included trials used luteinising hormone-releasing hormone agonists as the backbone of ADT, the dosing schedule was variable, as was the duration of concomittant first-generation non-steroidal anti-androgen agents (which were used in 11 of the 12 trials). Therefore, these results cannot be extrapolated to second-generation anti-androgen agents, and no conclusions about concomittant androgen blockade with ADT can be drawn from this analysis. Fifth, statistical power can be a limitation of reaching statistical significance of interaction tests, and this point must be considered when interpreting our results, although our sample size and event rates are large. Another limitation of our statistical approach is that Fine-Gray regression does not isolate the treatment effects on the competing risks; that is, the protective effect of treatment on outcomes such as biochemical recurrence or distant metastasis could be indirect and a result of increased subdistribution hazard of death. To mitigate this, we did a sensitivity analysis using a cause-specific framework, which showed no notable differences from the competing risk approach. Finally, other prognostic variables were not collected in many of the included trials, such as percentage of positive cores, and thus alternative risk stratification schemes could not be tested. Most notably, we were unable to determine whether the benefit of ADT use or adjuvant ADT prolongation (or both) would be consistent in patients with favourable versus unfavourable intermediate-risk disease.[35]

In summary, this meta-analysis from the MARCAP consortium is, to our knowledge, the first systematic individual patient data meta-analysis of randomised trials evaluating the use and prolongation of ADT in localised prostate cancer. We provide the strongest level of evidence for the routine recommendation for the addition of ADT to radiotherapy in men with intermediate-risk disease, and the use and prolonged adjuvant ADT for men with high-risk disease, irrespective of radiotherapy dose. However, the strategy of prolongation of neoadjuvant ADT should not be routinely recommended. Given the similar relative treatment effect benefits seen by age or NCCN risk group, more accurate tools for risk stratification are needed to determine which cohorts of men derive clinically meaningful benefits from ADT treatment intensification.

Contributors

AUK, YS, TMP, MB, AN, AS, JWD, FYF, AZ, JGA, AN, JAG, and DES contributed to the idea for the study and data collection. AUK, YS, and DES analysed the data. All authors contributed to manuscript drafting and critical review. AUK and DES have accessed and verified the underlying data. The corresponding authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Individual patient data obtained via data sharing agreements were used in this analysis. Researchers interested in obtaining data from this study can contact the corresponding authors.

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References

1 Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011; **378:** 1707–16.

2 McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; **383:** 2127–35.

3 Lacas B, Bourhis J, Overgaard J, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. *Lancet Oncol* 2017; **18:** 1221–37.

4 Gharzai LA, Jiang R, Wallington D, et al. Intermediate clinical endpoints for surrogacy in localised prostate cancer: an aggregate meta-analysis. *Lancet Oncol* 2021; **22:** 402–10.

5 Wang C, Raldow AC, Nickols NG, et al. Underutilization of androgen deprivation therapy with external beam radiotherapy in men with high-grade prostate cancer. *Eur Urol Oncol* 2021; **4:** 327–30.

6 Falchook AD, Basak R, Mohiuddin JJ, Chen RC. Evaluation of the effectiveness of adding androgen deprivation to modern dose-escalated radiotherapy for men with favorable intermediate-risk prostate cancer. *Cancer* 2016; **122:** 2341–49.

7 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.

8 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6:** e1000097.

9 Xie W, Regan MM, Buyse M, et al. Metastasis-free survival is a strong surrogate of overall survival in localised prostate cancer. *J Clin Oncol* 2017; **35:** 3097–104.

10 McPartlin AJ, Glicksman R, Pintilie M, et al. PMH 9907: long-term outcomes of a randomized phase 3 study of short-term bicalutamide hormone therapy and dose-escalated external-beam radiation therapy for localised prostate cancer. *Cancer* 2016; **122:** 2595–603.

11 Bafeta A, Dechartres A, Trinquart L, Yavchitz A, Boutron I, Ravaud P. Impact of single centre status on estimates of intervention effects in trials with continuous outcomes: meta-epidemiological study. *BMJ* 2012; **344:** e813.

12 Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. *Ann Intern Med* 2011; **155:** 39–51.

13 Schaeffer E, Srinivas S, Antonarakis ES, et al. NCCN guidelines insights: prostate cancer, version 1.2021. *J Natl Compr Canc Netw* 2021; **19:** 134–43.

14 Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. *Lancet Oncol* 2011; **12:** 451–59.

15 Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009; **360:** 2516–27.

16 Denham JW, Joseph D, Lamb DS, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): 10-year results from a randomised, phase 3, factorial trial. *Lancet Oncol* 2019; **20:** 267–81.

17 Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17:** 343–46.

18 Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials* 2005; **2:** 209–17.

19 Cox DR. Regression models and life-tables. *J R Stat Soc B* 1972; **34:** 187–202.

20 Dinse GE, Lagakos SW. Nonparametric estimation of lifetime and disease onset distributions from incomplete observations. *Biometrics* 1982; **38:** 921–32.

21 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94:** 496–509.

22 Korn EL, Dorey FJ. Applications of crude incidence curves. *Stat Med* 1992; **11:** 813–29.

23 Latouche A, Allignol A, Beyersmann J, Labopin M, Fine JP. A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. *J Clin Epidemiol* 2013; **66:** 648–53.

24 Dignam JJ, Zhang Q, Kocherginsky M. The use and interpretation of competing risks regression models. *Clin Cancer Res* 2012; **18:** 2301–08.

25 Roach M 3rd, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol* 2008; **26:** 585–91.

26 Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol* 2010; **11:** 1066–73.

27 Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localised prostate cancer. *N Engl J Med* 2011; **365:** 107–18.

28 Nabid A, Carrier N, Vigneault E, et al. Androgen deprivation therapy and radiotherapy in intermediate-risk prostate cancer: a randomised phase III trial. *Eur J Cancer* 2021; **143:** 64–74.

29 Bolla M, Maingon P, Carrie C, et al. Short androgen suppression and radiation dose escalation for intermediate- and high-risk localised prostate cancer: results of EORTC trial 22991. *J Clin Oncol* 2016; **34:** 1748–56.

30 Armstrong JG, Gillham CM, Dunne MT, et al. A randomized trial (Irish clinical oncology research group 97-01) comparing short versus protracted neoadjuvant hormonal therapy before radiotherapy for localised prostate cancer. *Int J Radiat Oncol Biol Phys* 2011; **81:** 35–45.

31 Pisansky TM, Hunt D, Gomella LG, et al. Duration of androgen suppression before radiotherapy for localised prostate cancer: radiation therapy oncology group randomized clinical trial 9910. *J Clin Oncol* 2015; **33:** 332–39.

32 Lawton CAF, Lin X, Hanks GE, et al. Duration of androgen deprivation in locally advanced prostate cancer: long-term update of NRG Oncology RTOG 9202. *Int J Radiat Oncol Biol Phys* 2017; **98:** 296–303.

33 Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. *Lancet Oncol* 2015; **16:** 320–27.

34 Kollmeier MA, McBride S, Gorovets D, Zelefsky MJ. Role of androgen-deprivation therapy remains uncertain for intermediate-risk patients when using dose-escalated radiotherapy. *J Clin Oncol* 2020; **38:** 3821–22.

35 Zumsteg ZS, Spratt DE, Pei I, et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol* 2013; **64:** 895–902.

36 Kollmeier MA, Zelefsky MJ. What is the role of androgen deprivation therapy in the treatment of locally advanced prostate cancer? *Nat Clin Pract Urol* 2008; **5:** 584–85.

37 Joseph D, Denham JW, Steigler A, et al. Radiation dose escalation or longer androgen suppression to prevent distant progression in men with locally advanced prostate cancer: 10-year data from the TROG 03.04 RADAR trial. *Int J Radiat Oncol Biol Phys* 2020; **106:** 693–702.

38 Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016; **17:** 1047–60.

39 Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol* 2017; **35:** 1884–90.

40 Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet* 2019; **394:** 385–95.

41 Lehrer EJ, Kishan AU, Yu JB, et al. Ultrahypofractionated versus hypofractionated and conventionally fractionated radiation therapy for localized prostate cancer: a systematic review and meta-analysis of phase III randomized trials. *Radiother Oncol* 2020; **148:** 235–42.

42 Spratt DE, Malone S, Roy S, et al. Prostate radiotherapy with adjuvant androgen deprivation therapy (ADT) improves metastasis-free survival compared to neoadjuvant ADT: an individual patient meta-analysis. *J Clin Oncol* 2021; **39:** 136–44.

43 Dee EC, Mahal BA, Arega MA, et al. Relative timing of radiotherapy and androgen deprivation for prostate cancer and implications for treatment during the COVID-19 pandemic. *JAMA Oncol* 2020; **6:** 1630–32.

44 Spiegel DY, Hong JC, Oyekunle T, et al. A nomogram for testosterone recovery after combined androgen deprivation and radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2019; **103:** 834–42.

45 Weiner AB, Etzioni R, Eggener SE. Ongoing Gleason grade migration in localised prostate cancer and implications for use of active surveillance. *Eur Urol* 2014; **66:** 611–12.

46 Fossati N, Passoni NM, Moschini M, et al. Impact of stage migration and practice changes on high-risk prostate cancer: results from patients treated with radical prostatectomy over the last two decades. *BJU Int* 2016; **117:** 740–47.

47 D'Amico AV, Chen MH, Renshaw A, Loffredo M, Kantoff PW. Long-term follow-up of a randomized trial of radiation with or without androgen deprivation therapy for localised prostate cancer. *JAMA* 2015; **314:** 1291–93.

48 Crook J, Ludgate C, Malone S, et al. Final report of multicenter Canadian Phase III randomized trial of 3 versus 8 months of neoadjuvant androgen deprivation therapy before conventional-dose radiotherapy for clinically localised prostate cancer. *Int J Radiat Oncol Biol Phys* 2009; **73:** 327–33.