Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial

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Summary

Background The aim of this trial was to compare dose-escalated conformal radiotherapy with control-dose conformal radiotherapy in patients with localised prostate cancer. Preliminary findings reported after 5 years of follow-up showed that escalated-dose conformal radiotherapy improved biochemical progression-free survival. Based on the sample size calculation, we planned to analyse overall survival when 190 deaths occurred; this target has now been reached, after a median 10 years of follow-up.

Methods RT01 was a phase 3, open-label, international, randomised controlled trial enrolling men with histologically confirmed T1b–T3a, N0, M0 prostate cancer with prostate specific antigen of less than 50 ng/mL. Patients were randomly assigned centrally in a 1:1 ratio, using a computer-based minimisation algorithm stratifying by risk of seminal vesicle invasion and centre to either the control group (64 Gy in 32 fractions, the standard dose at the time the trial was designed) or the escalated-dose group (74 Gy in 37 fractions). Neither patients nor investigators were masked to assignment. All patients received neoadjuvant androgen deprivation therapy for 3–6 months before the start of conformal radiotherapy, which continued until the end of conformal radiotherapy. The coprimary outcome measures were biochemical progression-free survival and overall survival. All analyses were done on an intention-to-treat basis. Treatment-related side-effects have been reported previously. This trial is registered, number ISRCTN47772397.

Findings Between Jan 7, 1998, and Dec 20, 2001, 862 men were registered and 843 subsequently randomly assigned: 422 to the escalated-dose group and 421 to the control group. As of Aug 2, 2011, 236 deaths had occurred: 118 in each group. Median follow-up was 10·0 years (IQR 9·1–10·8). Overall survival at 10 years was 71% (95% CI 66–75) in each group (hazard ratio [HR] 0·99, 95% CI 0·77–1·28; p=0·96). Biochemical progression or progressive disease occurred in 391 patients (221 [57%] in the control group and 170 [43%] in the escalated-dose group). At 10 years, biochemical progression-free survival was 43% (95% CI 38–48) in the control group and 55% (50–61) in the escalated-dose group (HR 0·69, 95% CI 0·56–0·84; p=0·0003).

Interpretation At a median follow-up of 10 years, escalated-dose conformal radiotherapy with neoadjuvant androgen deprivation therapy showed an advantage in biochemical progression-free survival, but this advantage did not translate into an improvement in overall survival. These efficacy data for escalated-dose treatment must be weighed against the increase in acute and late toxicities associated with the escalated dose and emphasise the importance of use of appropriate modern radiotherapy methods to reduce side-effects.

Funding UK Medical Research Council.

Introduction

External beam radiotherapy is one of the standard curative options for men with localised prostate cancer and is particularly appropriate for men with intermediate-risk or high-risk disease.[1,2] Improved radiotherapy techniques, such as conformal radiotherapy, allow high treatment doses to be given safely[3,4] and several phase 3 randomised controlled trials of dose escalation have reported improved biochemical progression-free survival.[5–10] The Medical Research Council (MRC) RT01 trial is the largest of these trials to have reported results, and since its initial report of results dose-escalated conformal radiotherapy has been the standard of care in the UK since 2008.[1] The trial mandated the use of short-course neoadjuvant androgen deprivation therapy (ADT); neoadjuvant ADT has since been shown to improve overall and cancer-specific survival in patients with advanced localised disease.[11–14]

The aim of the RT01 trial was to assess the effect of dose-escalation on overall survival, biochemical progression-free survival, and toxicity, by comparing doses of 74 Gy and 64 Gy delivered by use of conformal radiotherapy techniques. 64 Gy in 32 fractions was chosen as the radiotherapy schedule for the control group in our randomised trial, because that was the standard

dose at the time the trial was designed. We initially reported findings of the trial with a 5-year median follow-up and now update these results with a median follow-up of 10 years, because the target number of deaths for analysis of overall survival has been reached. Treatment-related side-effects have been reported previously.[7,15,16]

Methods

Study design and participants

RT01 was a phase 3, open-label, international, randomised controlled trial comparing dose-escalated conformal radiotherapy with control-dose conformal radiotherapy. It was preceded by a pilot study at the Royal Marsden Hospital.[5] Patients were registered, initiated on neoadjuvant ADT, and then randomly assigned to receive either control or escalated radiotherapy using conformal radiotherapy techniques. Men 18 years or older with histologically confirmed T1b–T3a, N0, M0 prostate cancer and prostate-specific antigen (PSA) of less than 50 ng per mL, with no contraindications for radical radiotherapy were included in the trial. All patients gave written informed consent. The trial was overseen by a trial management group and reviewed on three occasions by an independent data-monitoring committee. No formal stopping rules were specified. At each review, the Data Monitoring and Ethics Committee recommended that the trial could continue. This study was done in compliance with the Declaration of Helsinki, and the protocol was approved by the appropriate Research Ethics Committees.

Randomisation and masking

Consenting patients were randomly assigned in a 1:1 ratio to control or escalated-dose conformal radiotherapy centrally at the MRC clinical trials unit (CTU) using a computer-based minimisation algorithm, stratifying for risk of seminal vesicle invasion and centre. Sites phoned MRC CTU to randomise patients. Neither participants nor investigators were masked to the allocated treatment because blinding was not practicable. The random allocation list was created by the MRC CTU.

Procedures

As reported previously, androgen deprivation was achieved using injections of luteinising-hormone-releasing hormone agonists every 4 weeks and was accompanied by antiandrogen therapy to prevent flare events.[7] Neoadjuvant ADT was given for 3–6 months before commencement of conformal radiotherapy and continued until the end of conformal radiotherapy.

Men were randomised to receive either a control-dose schedule (64 Gy in 32 fractions; control group) schedule, or an escalated-dose schedule (74 Gy in 37 fractions). All radiotherapy treatments used three-dimensional conformal techniques as previously described.[7,11,17] The radiotherapy phase 1 target volume included the prostate and all or part of the seminal vesicles, depending on the

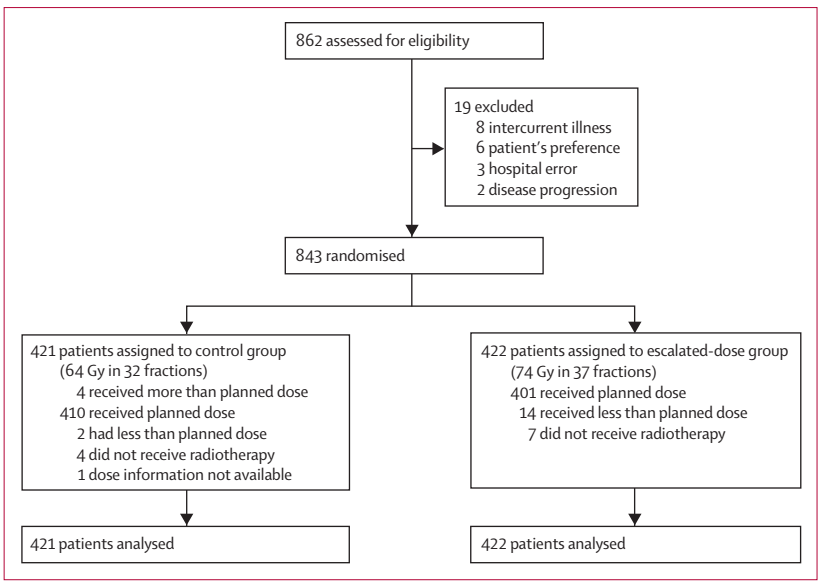

Figure 1: **Trial profile**

	Control group (N=421)	Escalated-dose group (N=422)
Age (years)		
Median (range)	67 (46–80)	67 (48–80)
T stage		
T1b/T1c	106 (26%)	103 (25%)
T2a/T2b	236 (57%)	239 (57%)
T3a/T3b	71 (17%)	76 (18%)
Not known	8	4
Gleason score*		
6 or lower	261 (62%)	249 (59%)
7	105 (25%)	117 (28%)
8 or higher	52 (12%)	54 (13%)
Not known	3	2
Prehormone PSA (ng/mL)		
Median (IQR)	12·8 (8·4–20·0)	12·8 (7·8–20·2)
Mean (SD)	15·6 (10·0)	15·2 (9·6)
Risk group for involvement of seminal vesicles		
Low	137 (33%)	138 (33%)
Moderate	284 (67%)	284 (67%)
NCCN risk group*		
Low	79 (19%)	81 (19%)
Intermediate	159 (38%)	152 (36%)
High	178 (43%)	184 (44%)
Unobtainable	5	5

Data are n (%) unless otherwise specified. Percentages exclude missing data. Some percentages do not total 100% because of rounding. PSA=prostate-specific antigen. NCCN=National Comprehensive Cancer Network. *If Gleason score was missing, WHO differentiation was used in the following way: well, moderate, or poor differentiation is classified as Gleason score of 6, 7, or 8, respectively.

Table 1: **Baseline characteristics**

risk of seminal vesicle invasion.[18] All patients were treated to a dose of 64 Gy in 32 fractions over 6·5 weeks using a standard three-field plan (anterior field and left and right lateral or posterior oblique fields) with a 1·0 cm margin. Patients randomised to the escalated-dose group had a phase 2 boost to the prostate alone using a six-field technique (left and right anterior oblique, left and right posterior oblique, and left and right lateral fields) with no margin added. The boost radiotherapy followed the phase 1 treatment. All doses were prescribed to the isocentre. Beam shaping was with multileaf collimators or customised shaped blocks and treatment was delivered with 6–10 MV photons. No dose constraints for normal tissues were specified. Verification was with daily and then weekly port films and images.

Men were followed-up throughout radiotherapy at 6 monthly intervals up to 2 years, and annually thereafter. Acute and late treatment-related side-effects were collected using Radiation Therapy Oncology Group[19] and Late Effects of Normal Tissues-Subjective Objective Management Analytic scales[20] and timed from the start of radiotherapy. Disease assessments were PSA, digital rectal examination, and symptoms. Technetium-99m bone scans, CT, or MRI were done as clinically indicated. The design, objectives, eligibility criteria for patients, treatment methods, and statistical considerations are detailed elsewhere.[7,17]

Outcomes

The coprimary outcome measures were overall survival and biochemical progression-free survival. Overall

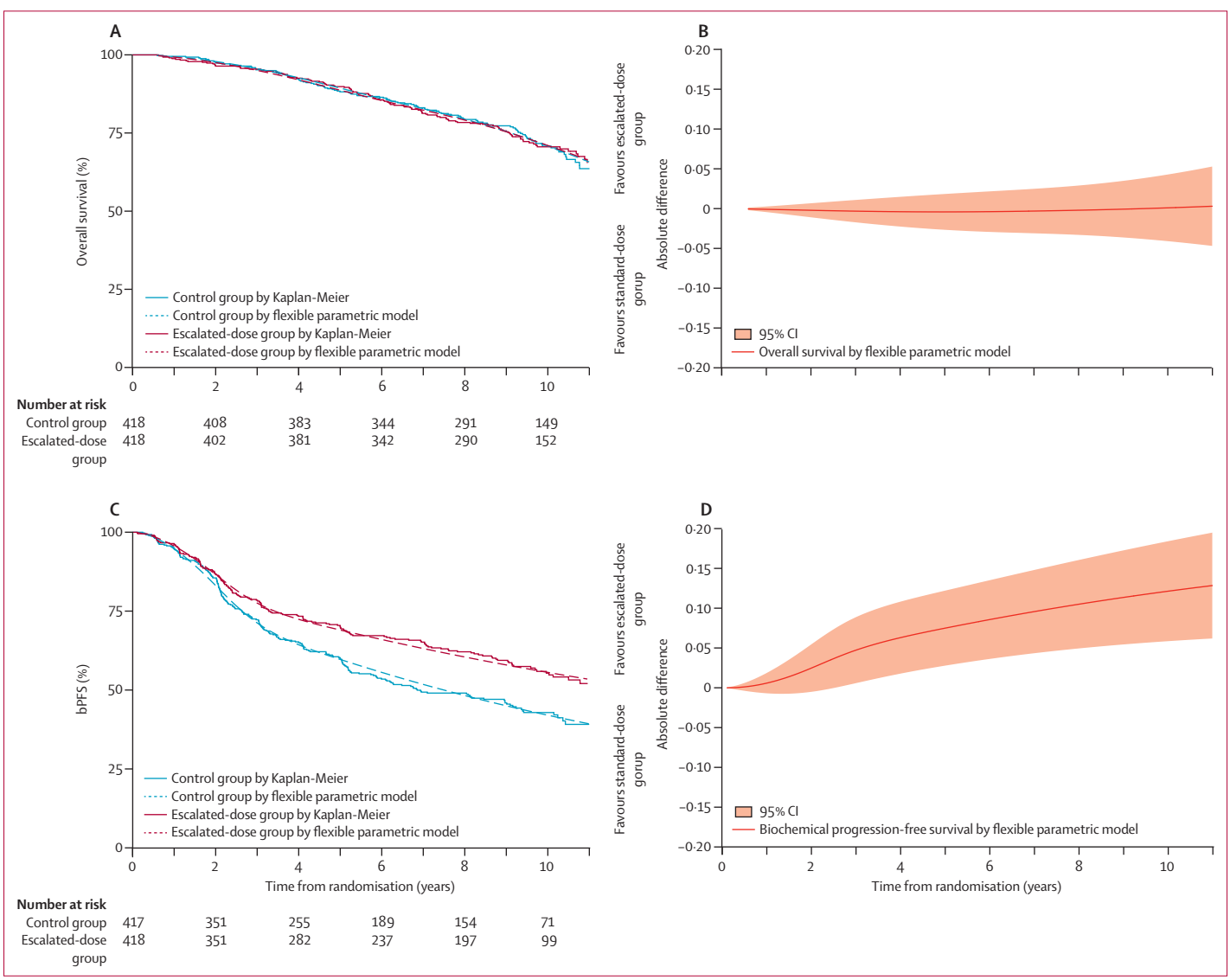

Figure 2: **Primary analysis of overall survival and biochemical progression-free survival**
(A) Overall survival, predicted from Kaplan-Meier function and flexible parametric model. (B) Absolute difference in overall survival, from flexible parametric model. (C) Biochemical progression-free survival, predicted by Kaplan-Meier function and flexible parametric model. (D) Absolute difference in biochemical progression-free survival, from flexible parametric model.

survival was defined as time from randomisation to death from any cause or censoring at date of last contact. Biochemical progression-free survival was defined as time from randomisation to biochemical failure, death from prostate cancer, or development of local, nodal, or metastatic disease, whichever occurred first.

Additional outcome measures were biochemical failure (an increase in PSA concentration to 50% above nadir and above 2 ng/mL 6 months or more after the start of radiotherapy); progression-free survival (excluding PSA failure); initiation of long-term salvage ADT; development of metastases; death from prostate cancer; and metastases-free survival (time to development of any metastases or death from prostate cancer). Cause of death was reviewed by pairs of clinicians from a panel of five individuals who were masked to treatment allocation.

The original protocol specified five primary outcome measures (biochemical progression-free survival [named as "biochemical control" in the protocol, freedom from local progression, metastases free survival, overall survival, and late toxicity); with sample size calculations included for local control and overall survival. During the course of the trial, the Trial Management Group, Independent Data Monitoring Committee, and Trial Steering Committee agreed from external evidence that biochemical progression-free survival was a more important outcome measure than local control. Therefore, the trigger for intermediate and long-term analyses has been biochemical progression-free survival and overall survival. All outcome measures are reported.

Statistical analysis

We estimated that inclusion of about 800 patients would meet the targets for the numbers of patients in the subgroups at low-risk and intermediate-risk of seminal vesicle involvement.[17] We assumed that survival at 5 years would be 50% in patients in the control group, and the trial aimed to achieve a 15% increase in survival at 5 years in the escalated-dose group. Assuming proportional hazards, this improvement corresponds to a hazard ratio (HR) of 0·62. With 90% power and a 5% two-sided significance level, we established that about 194 deaths were needed for this analysis of overall survival.

We did all analyses on an intention-to-treat basis, with patients analysed according to allocated treatment group. We used a two-sided 5% significance level for all analyses. All analysed outcome measures are presented in this report.

We used standard survival analysis methods to investigate time from randomisation to the first reported event for each outcome measure, except for time to death from prostate cancer. Patients who have not yet reported the relevant event are censored at the date of last contact. Median follow-up time was established with the reverse Kaplan-Meier method. The assumption of proportionality of hazards was tested. Hazard ratios (HR) were estimated with Cox models, adjusted for seminal vesicle risk group.[18] We applied the restricted mean survival time method to overall survival and biochemical progression-free survival, as an additional method of estimating difference between the treatments, with the restriction time being 10 years. We used flexible parametric modelling to estimate restricted mean survival time. All comparisons are expressed relative to the control group; therefore, an HR of less than 1·0 indicates a decreased risk in the escalated-dose group.

We did a competing-risk analysis for prostate cancer death because the number of deaths from causes other than prostate cancer exceeded the prespecified level of 20%. For this analysis, time to prostate cancer death is presented with cumulative incidence function rather than survival function; sub-HR is presented with 95% CI and p value. We used the method of Fine and Gray[21] to estimate sub-HR. Cause-specific HRs are presented for both prostate cancer and non-prostate-cancer deaths.

We did pre-planned, exploratory subgroup analyses to examine consistency of effect across seminal vesicle risk group (low *vs* moderate) and National Comprehensive Cancer Network (NCCN) risk group (low *vs* intermediate *vs* high).[2] This analysis uses χ^2 tests for heterogeneity of interaction or trend when appropriate, and examines overall survival and biochemical progression-free survival. A health economic analysis is planned.

We used Stata (version 12.1) for analyses. This trial is registered, number ISRCTN47772397.

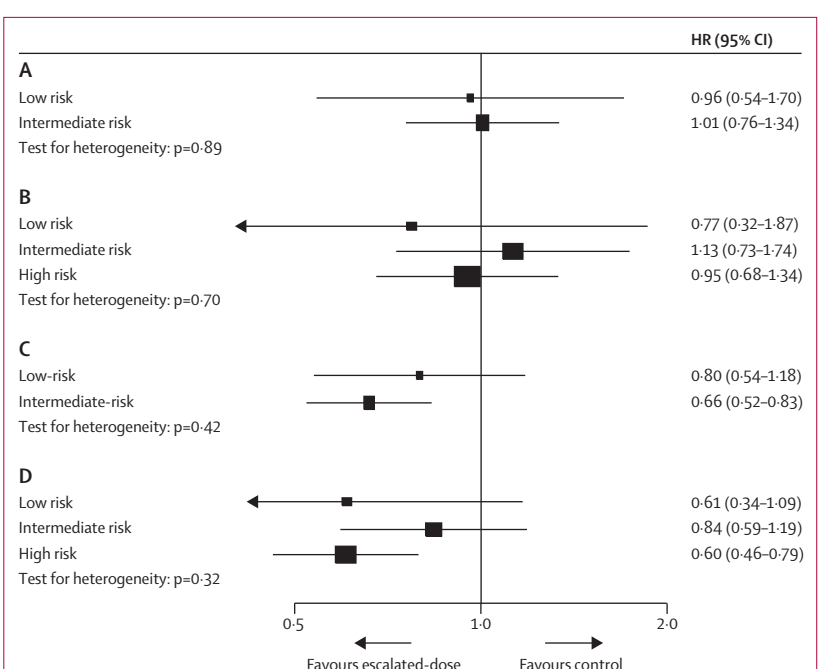

Figure 3: **Subgroup analyses of overall survival and biochemical progression-free survival**
(A) Overall survival and risk of seminal vesicle involvement. (B) Overall survival and National Comprehensive Cancer Network risk group. (C) Biochemical progression-free survival and risk of seminal vesicle involvement. (D) Biochemical progression-free survival and National Comprehensive Cancer Network risk group. HR=hazard ratio.

Role of the funding source

The trial was sponsored by UK Medical Research Council and conducted by the MRC Clinical Trials Unit (from August, 2013, part of University College London). MRC employees were central to the conduct of the trial and the development of this report. The sponsor of the trial had no role in trial design, data analysis, or data interpretation. MRS and GJ had access to raw data. MRS had access to all data in the trial and had final responsibility for the decision to submit for publication.

Results

Between Jan 7, 1998, and Dec 20, 2001, 862 men were registered and 843 subsequently randomised: 422 to the escalated-dose group and 421 to the control group (figure 1).

Table 1 shows characteristics of the patients at baseline; the groups were balanced. Overall, median age was 67 years (IQR 63–71), and presenting median PSA was 12·8 (IQR 8·1–20·0). 209 (25%) of 831 patients had T1 stage cancers, 475 (57%) had T2 stage, and 147 (18%) had T3 cancers; T stage was unavailable for 12 patients. Analyses of biopsy specimens were reported by local histopathologists, and showed Gleason scores of 6 or lower in 510 (61%) of the 838 enrolled patients, a score of 7 in 222 (26%) of patients, and a score 8 of or higher in 13% (106) of patients; Gleason score was not available for five patients. 160 (19%) of 833 patients had low-risk disease according to NCCN criteria, 311 (37%) had intermediate-risk disease, and 362 (43%) had high-risk disease; unavailability of T-stage or histological grading precluded ascertainment of risk group in ten patients. 275 (33%) of 843 patients had a low risk of seminal vesicle involvement; 568 (67%) had intermediate or high risk. Median follow-up was 10·0 years (IQR 9·1–10·8; range 0·6–13·4). Overall, 117 patients were alive at 11 years and 30 at 12 years.

See Online for appendix

As of Aug 2, 2011, 236 deaths had been reported, 118 in each group, triggering the overall survival analysis. There was no difference in 10 year overall survival between groups: 10 year overall survival was 71% (95% CI 66–75) in both groups (HR 0·99, 95% CI 0·77–1·28, p=0·96, figure 2). Mean overall survival, using the flexible parametric model and when restricted to 10 years, was 9·30 years (95% CI 9·08–9·52) for the control group and 9·28 years (9·06–9·50) for the escalated-dose group. There was no evidence of a difference between restricted mean survival: –0·02 years (95% CI –0·34 to 0·29; p=0·88).

For patients who had not yet reported a biochemical progression event, adherence to PSA testing was 90% complete at 5 years and 76% complete at 10 years. Adherence patterns were much the same in the two randomised groups (appendix). 391 biochemical progression events occurred: 221 (57%) in the control group and 170 (43%) in the escalated-dose group. Biochemical progression-free survival was better in the escalated-dose group, being 43% at 10 years (95% CI 38–48) in the control group and 55% (50–61) in the escalated-dose group (HR 0·69, 95% CI 0·56–0·84; p=0·0003, figure 2). Mean biochemical progression-free survival, when time of analysis was restricted to 10 years, was 7·33 years (95% CI 6·87–7·80) in the control group and 8·01 years (7·60–8·40) in the escalated-dose group, leading to an improvement in restricted mean survival of 0·69 years with escalated-dose radiotherapy (95% CI 0·08–1·30; p=0·03). This finding represents a relative improvement of about 10% in the escalated-dose group compared to the control group.

	HR (Escalated *vs* Control)	95% CI	p value	Control group events	Escalated-dose group events	Control group at 10 years (% [95% CI])	Escalated-dose group 10 years (% [95% CI])
Primary							
Overall survival	0·99	0·77–1·28	0·96	118	118	71% (66–75)	71% (66–75)
Biochemical progression-free survival*	0·69	0·56–0·84	0·0003	221	170	43% (38–48)	55% (50–61)
Additional							
Biochemical failure†	0·67	0·55–0·83	0·0003	208	157	45% (40–51)	58% (53–64)
Initiation of ADT	0·76	0·58–0·99	0·04	123	97	68% (63–73)	74% (69–79)
PFS‡	0·76	0·60–0·97	0·03	148	120	61% (56–66)	69% (64–74)
Any metastases	0·94	0·62–1·42	0·76	46	44	88% (84–91)	88% (84–91)
MFS§	0·94	0·67–1·32	0·72	67	65	82% (77–86)	83% (78–87)
Time to prostate cancer death	1·07¶	0·71–1·61	0·75	..	..	..	..
Prostate cancer death	1·06‖	0·70–1·60	0·79	44	47	11% (9–14)	11% (9–13)
Non-prostate cancer death	0·96‖	0·69–1·32	0·78	74	71	18% (15–21)	18% (15–21)

The assumption of proportional hazards was tested and there was no evidence of non-proportionality for any of the outcome measures; therefore, HR is an appropriate summary measure. HR=hazard ratio. ADT=androgen deprivation therapy. PFS=progression-free survival. MFS=metastases-free survival. *Defined as PSA failure or PFS event. †Defined as PSA greater than 2 ng/mL, 6 months or more after commencement of radiotherapy and PSA rising from nadir concentration by 50% or more. ‡Defined as local progression, lymph node, bone or other metastases, prostate-cancer-related death, or restart of ADT. §Defined as bone or other metastases or prostate-cancer-related death. ¶Sub-HR. ‖Cause-specific HR.

Table 2: **Outcome measures**

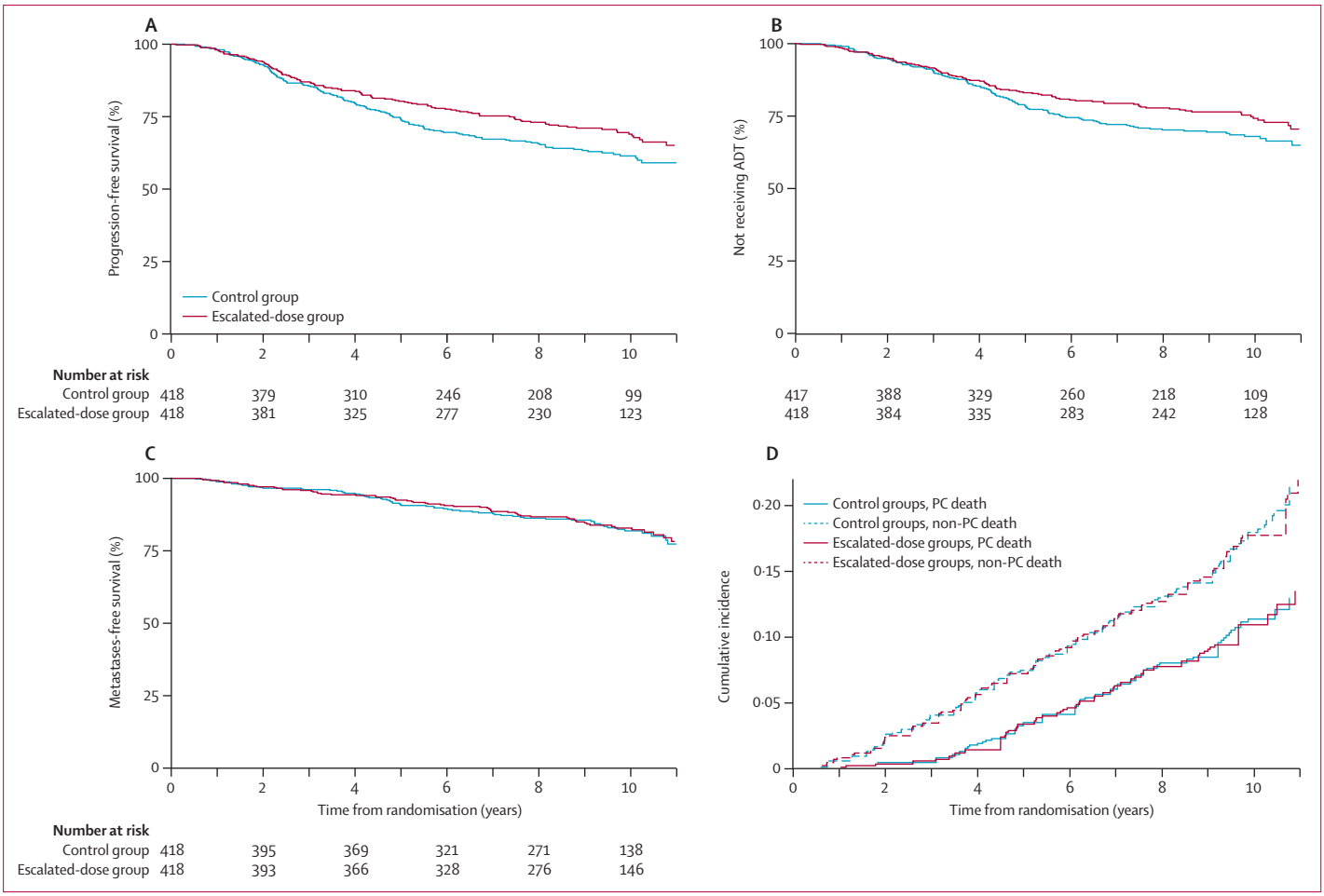

Figure 4: **Additional outcome measures**
(A) Progression-free survival, Kaplan-Meier plot. (B) Initiation of ADT, Kaplan-Meier plot. (C) Metastases-free survival, Kaplan-Meier plot. (D) Cumulative incidence of PC deaths and non-PC deaths. ADT=androgen deprivation therapy. PC=prostate cancer.

Figure 3 shows subgroup analyses by seminal vesicle involvement and NCCN risk group. We identified no difference in the treatment effect across these subgroups in overall survival and biochemical progression-free survival. Progression-free survival, biochemical failure, and delayed commencement of salvage ADT were all significantly better in the escalated-dose group compared to the control group (table 2, figure 4). Of patients who had biochemical progression, a lower proportion (67 [30%] of 221 patients) in the control group had metastases, or died from prostate cancer compared to the escalated-dose group (65 [38%] of 170 patients). Notably, of the 391 patients who developed PSA failure or progressive disease, only 220 (56%) reported commencing long-term salvage ADT (123 in the control group, 97 in the escalated-dose group). Of 268 men who had clinical evidence of progressive disease, 132 (49%) developed metastases or died from prostate cancer (67 in the control group, 65 in the escalated-dose group).

According to the central, blinded review of deaths, 91 of 236 (39%) deaths were from prostate cancer (44 in the control group, 47 in the escalated-dose group), 132 (56%) were from other causes (68 in the control group *vs* 64 in the escalated-dose group), and for 13 (6%) patients there were insufficient data for the reviewers to assign cause of death (six control *vs* seven escalated dose): for ten, the investigator defined causality as not prostate cancer (which was accepted), and for the other three, no evidence of recurrent prostate cancer had been recorded. Therefore, 91 patients were deemed to have died from prostate cancer and 145 from other causes. Overall concordance between the investigators and clinical review was good (199 of 236, 84%; κ statistic 0·71).

We did a competing-risk analysis for prostate cancer death because 145 (61%) of 236 deaths were from causes other than prostate cancer, which exceeded the prespecified level of 20%. The competing-risk analysis showed no evidence of a difference in death from prostate

cancer. The sub-HR for the comparison of cumulative incidences is 1·07 (95% CI 0·71–1·61; p=0·75) in favour of the control group with a cause-specific HR for prostate cancer deaths of 1·06 (95% CI 0·70–1·60; p=0·79) and for other deaths of 0·96 (0·69–1·32; p=0·78).

NCCN risk group was available for 90 of the 91 patients who died from prostate cancer. NCCN risk group was clearly related to the probability of dying from prostate cancer. Only one of 160 (1%) men with low-risk disease died from prostate cancer compared with 21 of 311 (7%) with intermediate-risk disease and 68 of 362 (19%) with high-risk disease. As a proportion of total deaths, for low-risk disease, one (control group) of 20 (5%) were from prostate cancer compared with 21 (nine control *vs* 12 escalated-dose) of 81 (26%) for intermediate-risk disease and 68 (34 control *vs* 34 escalated-dose) of 133 (51%) for high-risk disease. We identified no evidence of heterogeneity of effect of dose escalation between these subgroups.

Discussion

The previously reported advantage of escalated-dose conformal radiotherapy treatment compared to control-dose conformal radiotherapy in biochemical progression-free survival after a median follow-up of about 5 years was maintained in the present study with more mature data and a median follow-up of 10 years. Using the HR, there was an absolute 13% (95% CI 6–19) increase in biochemical progression-free survival at 10 years from 43%. This improvement in biochemical control of disease has not translated into an advantage for metastases-free survival, prostate-cancer-specific survival, or overall survival. We identified no evidence of heterogeneity of treatment effect between low, intermediate, and high-risk groups.

We recorded a significant delay in the reported time to initiation of long-term, salvage ADT in the escalated-dose group; using the HR there was an absolute improvement of 7% (95% CI 0–12) at 10 years from 45%. This advantage of reducing or delaying the initiation of long-term ADT, which is associated with well-documented andropausal side-effects,[22] must be balanced against the known small increase in bowel side-effects from the five extra treatments in the escalated-dose group, which we and others have reported.[5,6,8,10,16,23]

Why has the difference in PSA control not translated into an advantage for metastasis-free survival and prostate-cancer-specific survival? Several factors might be involved. First, it is likely that there were more indolent recurrences confined to the prostate in the control group: a lower proportion of patients in the control group had metastases or died from prostate cancer than those in the escalated-dose group. Moreover, of patients who developed PSA failure or progressive disease, only 56% reported commencing long-term salvage ADT, and only 49% of patients who had clinical evidence of progressive disease developed metastases or died from prostate cancer. We now know that some men with indolent local disease do not necessarily need treatment, for example men with low-risk disease or older than 65 years do not benefit from radical prostatectomy,[24,25] and active surveillance has become a standard of care for patients with a favourable outlook.[26]

Second, there is a long time from commencement of salvage ADT to death. In an international trial of intermittent or continuous salvage androgen suppression,[22] time from salvage ADT to death was estimated at about 9 years, but with only about 17% of patients dying of prostate cancer after 7 years. In the control group of RT01, 25% of patients had a biochemical progression-free survival event by 2·6 years after randomisation, but it was 5·7 years from randomisation before 25% of patients had reported initiation of salvage ADT; median times for these outcome measures have not been reached. Moreover, our results clearly show that NCCN risk group was related to the probability of dying from prostate cancer.

The lower bound of the 95% CI for overall survival was 0·77, and therefore our results cannot rule out some improvement in overall survival. More prolonged follow-up might show a difference in prostate-cancer mortality. After 14 years of follow-up, the small pilot study (N=126) which recruited before the start of RT01 suggested an overall survival advantage for the escalated-dose group (74 Gy) with HR 0·59, but with only 19 prostate cancer deaths the 95% CIs were wide (0·23–1·49).[5]

Our trial was designed in 1997 and launched in 1998 before the Phoenix definition[27] for biochemical recurrence became established, but our chosen definition of PSA failure with 2 ng/mL has much the same specificity and sensitivity.[28] Our results are in alignment with reported data from other studies of dose-escalated external beam radiotherapy (table 3), which have shown absolute advantages in PSA failure-free survival of 6–19% for dose-escalated treatments.

Even in trials with a high proportion of patients with poor prognostic factors and long follow-up, none have yet reported prostate-cancer-specific mortality of greater than 15%. When designing the RT01 trial, we anticipated that most patients would die of the disease. However, overall survival was much better than predicted and death from non-prostate-cancer causes was a major competing risk. A meta-analysis with the other randomised trials would provide a larger number of events from patients with high-risk disease to assess the effect of dose-escalation on death from prostate cancer.

Our findings draw attention to two issues for future trials. First, prostate-cancer-specific survival has become a difficult outcome measure for localised prostate cancer trials to report in a reasonable timescale. Survival-based outcome measures must remain of paramount importance, but there are implications for recruiting centres, trials units, and funding bodies in collecting long-term data. The potential value of high-quality, electronically linked, routinely collected

	N	Accrual period	Total radiation dose (Gy/number of fractions)		NAADT	NCCN risk		Median age (years)	Data last reported	Median follow-up (years)	PSA failure (N [%])	Absolute reduction in PSA failure in dose escalated group	Survival in escalated-dose group	Prostate cancer deaths (N [%])	Non-prostate-cancer deaths (N [%])
			Control	Escalated		Intermediate	High								
MRC RT01	843	1998–2001	64/32	74/37	All	37%	43%	67	2012	10·0	365 (43%)	13% (10 year)	70% (10 year)	91 (11%)	145 (17%)
NKI[9]	664	1997–2003	68/34	78/39	22%	27%	55%	69	2013	9·2	329 (50%)	6% (10 year)	67% (10 year)	88 (13%)	117 (18%)
PROG 95-09[8]	393	1996–99	70·2/39	79·2/44	No	37%	4%	67	2010	8·9	83 (21%)	16% (10 year)	83% (NS)	6 (1·5%)	55 (14%)
MDACC[6]	301	1993–98	70/35	78/39	No	46%	34%	69	2008	8·7	61 (20%)	19%* (8 year)	79% (8 year)	10 (3%)	70 (23%)
ICR-RMH[5]	126	1995–97	64/32	74/37	All	27%	53%	67	2013	13·7	64 (51%)	8% (12 year)	About 60% (14 year)	19 (15%)	32 (25%)
GETUG 06[10]	306	1999–2002	70/35	80/35	No	NS	29%	67	2011	5·1	85 (28%)	8·5% (5 year)	(NS)	10 (3·3%)	16 (5·2%)
Total	2633	..	..	..	..	..	..	..	..	..	987	..	..	224	435

N=number of patients randomised. NAADT=short course neoadjuvant androgen deprivation therapy. NCCN=National Comprehensive Cancer Network. PSA=prostate-specific antigen. NS=not stated. *Freedom from biochemical (PSA) or clinical failure.

Table 3: **Data from randomised controlled trials of dose-escalated external beam radiotherapy for prostate cancer**

outcome data needs to be explored. Second, it is particularly important to minimise treatment-related side-effects in groups of patients who are expected to live for a long time. We have previously reported our comparative side-effect data, which we planned to collect only to 5 years,[7,15,16] and a limitation of the present report is that no 10-year patient-reported outcome data are available.

By contrast with the dose-escalation trials, phase 3 studies assessing the addition of neoadjuvant ADT to radical prostate radiotherapy have shown clear evidence of improved overall survival and cause-specific survival in meta-analysis.[29,30] Review of additional trial results[11–14] shows that survival benefits become apparent about 3–5 years after randomisation. One interpretation is that, in addition to short-course ADT having an effect on local control of disease,[11] 6 months of ADT also has a direct effect on eradication of micrometastatic disease. These trials have been in patients given modest doses of radiotherapy by present standards (equivalent to 70 Gy or lower) but large institutional US series have suggested much the same benefits of neoadjuvant ADT in patients given doses of 76–81 Gy.[31,32]

What are the relative merits of dose escalation and combined modality treatment with neoadjuvant ADT? Dose escalation leads to excellent local disease control using either external beam radiotherapy or brachytherapy[33] in lower risk disease. In more advanced NCCN intermediate-risk or high-risk localised disease neoadjuvant ADT seems to improve both local control and reduce distant metastases. By use of a biopsy sample obtained 2 years after treatment as a gold standard method[34] to detect local recurrence, a 3-month period of neoadjuvant ADT given with modest-dose or high-dose radiotherapy reduced positive biopsy findings from 46% to 10%.[35] In a preplanned substudy of the RT01 trial, only six (6%) of 97 men in the escalated-dose group who agreed to have a biopsy 2 years after treatment had positive histology (unpublished). The gain of further dose escalation when given with neoadjuvant ADT might therefore be limited. The use of neoadjuvant ADT, however, must be balanced against the usually short-lasting increase in morbidity from

Panel: **Research in context**

Systematic review

Radiotherapy dose is limited by treatment-related side-effects. Advancing radiotherapy techniques using conformal radiotherapy had been shown to reduce the occurrence of side-effects.[3] Dose-escalation therefore became feasible with the hypothesis that higher radiation doses would lead to improved outcomes.[5,37–39]

Interpretation

As far as we are aware, this study is the largest dose-escalation trial to have reported long-term efficacy results. Other dose-escalation trials[5,6,8–10] in prostate cancer have shown an improvement in disease outcome assessed by biochemical progression-free survival. However, none of these trials have convincingly shown a positive effect on overall or prostate-cancer-specific survival after 10 years of follow-up. Dose escalation improves intermediate disease outcomes and reduces the use of salvage hormonal treatment, but at the cost of a modest increase in treatment-related side-effects. Further improvements in radiotherapy techniques have been shown to reduce the effect of dose-escalation on side-effects[4,40,41] and should be used to maintain the reported advantages of dose-escalation while minimising treatment sequelae.

short-term ADT.[36] Clinical trials that are in progress, including EORTC study 22991 (NCT00021450), will more completely define the role of combined modality treatment and high-dose radiotherapy.

Since we designed our trial using conformal radiotherapy methods, technology advances have led to the widespread introduction of intensity-modulated, image-directed, and image-guided techniques including the combined use of external beam radiotherapy with high-dose or low-dose rate brachytherapy, which have enabled high-dose treatment to be given with a reduced prevalence of side-effects using conventional or hypofractionated schedules (panel).[4,40,41] High-quality treatments are essential to maintain the potential advantages of dose-escalated treatment in improving disease control and avoiding salvage therapy, while maintaining low levels of treatment-related side-effects.

In conclusion, we have shown a clear and maintained advantage in biochemical (PSA) assessment of disease control, which has translated into a modest reduction in salvage ADT, but no evidence of a benefit in survival-based outcome measures with a median follow-up of 10 years. These efficacy data must be weighed against the increase in acute and late toxicities associated with escalated dose.

Contributions

DPD was chief investigator and Trial Management Group chair. DPD, IS, JDG, DB, CCJ, JLM, JMR, and CDS were principal investigators. DPD, GJ, JDG, EGA, CM, and MRS were Trial Management Group members. DPD designed the trial and did the scientific literature search. MRS and CM did trial coordination. GJ and MRS did data analysis. All authors collected data. DPD, IS, JG, RAC, and VK reviewed deaths. DPD, GJ, and MRS wrote the report. All authors were involved in data interpretation, manuscript review, and approval of the final manuscript.

Declaration of interests

MRS, MKBP, GJ, CM are employees of the sponsor at the Medical Research Council, Clinical Trials Unit at UCL, London, UK. The other authors declare that they have no competing interests.

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References

1 NICE. Prostate cancer: diagnosis and treatment. 2014. http://guidance.nice.org.uk/CG175 (accessed Feb 11, 2014).
2 Mohler J, Bahnson RR, Boston B, et al. NCCN clinical practice guidelines in oncology: prostate cancer. *J Natl Compr Canc Netw* 2010; **8:** 162–200.
3 Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 1999; **353:** 267–72.
4 Dearnaley D, Syndikus I, Sumo G, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *Lancet Oncol* 2012; **13:** 43–54.
5 Creak A, Hall E, Horwich A, et al. Randomised pilot study of dose escalation using conformal radiotherapy in prostate cancer: long-term follow-up. *Br J Cancer* 2013; **109:** 651–57.
6 Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M D Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; **70:** 67–74.
7 Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007; **8:** 475–87.
8 Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol* 2010; **28:** 1106–11.
9 Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. *Radiother Oncol* 2013; published online Nov 15. DOI:10.1016/j.radonc.2013.09.026.
10 Beckendorf V, Guerif S, Le Prise E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys* 2011; **80:** 1056–63.
11 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.
12 D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA* 2008; **299:** 289–95.
13 Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011; **365:** 107–18.
14 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.
15 Dearnaley DP, Sydes MR, Langley RE, et al. The early toxicity of escalated versus standard dose conformal radiotherapy with neo-adjuvant androgen suppression for patients with localised prostate cancer: results from the MRC RT01 trial (ISRCTN47772397). *Radiother Oncol* 2007; **83:** 31–41.
16 Syndikus I, Morgan RC, Sydes MR, Graham JD, Dearnaley DP. Late gastrointestinal toxicity after dose-escalated conformal radiotherapy for early prostate cancer: results from the UK Medical Research Council RT01 trial (ISRCTN47772397). *Int J Radiat Oncol Biol Phys* 2010; **77:** 773–83.
17 Sydes MR, Stephens RJ, Moore AR, et al. Implementing the UK Medical Research Council (MRC) RT01 trial (ISRCTN 47772397): methods and practicalities of a randomised controlled trial of conformal radiotherapy in men with localised prostate cancer. *Radiother Oncol* 2004; **72:** 199–211.
18 Roach M 3rd. The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. *J Urol* 1993; **150:** 1923–24.
19 Pilepich MV, Asbell SO, Krall JM, et al. Correlation of radiotherapeutic parameters and treatment related morbidity—analysis of RTOG Study 77-06. *Int J Radiat Oncol Biol Phys* 1987; **13:** 1007–12.
20 LENT SOMA scales for all anatomic sites. *Int J Radiat Oncol Biol Phys* 1995; **31:** 1049–91.
21 Fine J, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Soc* 1999; **94:** 496–509.
22 Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012; **367:** 895–903.
23 Al-Mamgani A, van Putten WL, Heemsbergen WD, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; **72:** 980–08.
24 Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012; **367:** 203–13.
25 Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011; **364:** 1708–17.
26 Klotz L. Active surveillance: the Canadian experience with an "inclusive approach". *J Natl Cancer Inst Monogr* 2012; **45:** 234–41.

27 Roach M 3rd, Hanks G, Thames H Jr, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006; **65:** 965–74.

28 Fitch DL, McGrath S, Martinez AA, Vicini FA, Kestin LL. Unification of a common biochemical failure definition for prostate cancer treated with brachytherapy or external beam radiotherapy with or without androgen deprivation. *Int J Radiat Oncol Biol Phys* 2006; **66:** 1430–39.

29 Bria E, Cuppone F, Giannarelli D, et al. Does hormone treatment added to radiotherapy improve outcome in locally advanced prostate cancer?: meta-analysis of randomized trials. *Cancer* 2009; **115:** 3446–56.

30 Shelley MD, Kumar S, Wilt T, Staffurth J, Coles B, Mason MD. A systematic review and meta-analysis of randomised trials of neo-adjuvant hormone therapy for localised and locally advanced prostate carcinoma. *Cancer Treat Rev* 2009; **35:** 9–17.

31 Zumsteg ZS, Spratt DE, Pei X, et al. Short-term androgen-deprivation therapy improves prostate cancer-specific mortality in intermediate-risk prostate cancer patients undergoing dose-escalated external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2013; **85:** 1012–17.

32 Castle KO, Hoffman KE, Levy LB, et al. Is androgen deprivation therapy necessary in all intermediate-risk prostate cancer patients treated in the dose escalation era? *Int J Radiat Oncol Biol Phys* 2013; **85:** 693–99.

33 Morris WJ, Keyes M, Spadinger I, et al. Population-based 10-year oncologic outcomes after low-dose-rate brachytherapy for low-risk and intermediate-risk prostate cancer. *Cancer* 2013; **119:** 1537–46.

34 Crook JM, Malone S, Perry G, et al. Twenty-four-month postradiation prostate biopsies are strongly predictive of 7-year disease-free survival: results from a Canadian randomized trial. *Cancer* 2009; **115:** 673–79.

35 Zelefsky MJ, Leibel SA, Gaudin PB, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998; **41:** 491–500.

36 Stephens RJ, Dearnaley DP, Cowan R, Sydes M, Naylor S, Fallowfield L. The quality of life of men with locally advanced prostate cancer during neoadjuvant hormone therapy: data from the Medical Research Council RT01 trial (ISRCTN 47772397). *BJU Int* 2007; **99:** 301–10.

37 Leibel SA, Zelefsky MJ, Kutcher GJ, et al. The biological basis and clinical application of three dimensional conformal external beam radiation therapy in carcinoma of the prostate. *Semin Oncol* 1994; **21:** 580–97.

38 Sandler HM, McLaughlin PW, Ten Haken RK, Addison H, Forman J, Lichter A. Three dimensional conformal radiotherapy for the treatment of prostate cancer: low risk of chronic rectal morbidity observed in a large series of patients. *Int J Radiat Oncol Biol Phys* 1995; **33:** 797–801.

39 Pollack A, Zagars GJ, Starkschall G et al. Conventional vs. Conformal radiotherapy for prostate cancer: preliminary results of dosimetry and acute toxicity. *Int J Radiat Oncol Biol Phys* 1996; **34:** 555–64.

40 Spratt DE, Pei X, Yamada J, Kollmeier MA, Cox B, Zelefsky MJ. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2013; **85:** 686–92.

41 Zaorsky NG, Doyle LA, Yamoah K, et al. High dose rate brachytherapy boost for prostate cancer: a systematic review. *Cancer Treat Rev* 2014; **40:** 414–25.