High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial

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Summary

Background The optimum duration of androgen deprivation combined with high-dose radiotherapy in prostate cancer remains undefined. We aimed to determine whether long-term androgen deprivation was superior to short-term androgen deprivation when combined with high-dose radiotherapy.

Methods In this open-label, multicentre, phase 3 randomised controlled trial, patients were recruited from ten university hospitals throughout Spain. Eligible patients had clinical stage T1c–T3b N0M0 prostate adenocarcinoma with intermediate-risk and high-risk factors according to 2005 National Comprehensive Cancer Network criteria. Patients were randomly assigned (1:1) using a computer-generated randomisation schedule to receive either 4 months of androgen deprivation combined with three-dimensional conformal radiotherapy at a minimum dose of 76 Gy (range 76–82 Gy; short-term androgen deprivation group) or the same treatment followed by 24 months of adjuvant androgen deprivation (long-term androgen deprivation group), stratified by prostate cancer risk group (intermediate risk *vs* high risk) and participating centre. Patients assigned to the short-term androgen deprivation group received 4 months of neoadjuvant and concomitant androgen deprivation with subcutaneous goserelin (2 months before and 2 months combined with high-dose radiotherapy). Anti-androgen therapy (flutamide 750 mg per day or bicalutamide 50 mg per day) was added during the first 2 months of treatment. Patients assigned to long-term suppression continued with the same luteinising hormone-releasing hormone analogue every 3 months for another 24 months. The primary endpoint was biochemical disease-free survival. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT02175212.

Findings Between Nov 7, 2005, and Dec 20, 2010, 178 patients were randomly assigned to receive short-term androgen deprivation and 177 to receive long-term androgen deprivation. After a median follow-up of 63 months (IQR 50–82), 5-year biochemical disease-free survival was significantly better among patients receiving long-term androgen deprivation than among those receiving short-term treatment (90% [95% CI 87–92] *vs* 81% [78–85]; hazard ratio [HR] 1·88 [95% CI 1·12–3·15]; p=0·01). 5-year overall survival (95% [95% CI 93–97] *vs* 86% [83–89]; HR 2·48 [95% CI 1·31–4·68]; p=0·009) and 5-year metastasis-free survival (94% [95% CI 92–96] *vs* 83% [80–86]; HR 2·31 [95% CI 1·23–3·85]; p=0·01) were also significantly better in the long-term androgen deprivation group than in the short-term androgen deprivation group. The effect of long-term androgen deprivation on biochemical disease-free survival, metastasis-free survival, and overall survival was more evident in patients with high-risk disease than in those with low-risk disease. Grade 3 late rectal toxicity was noted in three (2%) of 177 patients in the long-term androgen deprivation group and two (1%) of 178 in the short-term androgen deprivation group; grade 3–4 late urinary toxicity was noted in five (3%) patients in each group. No deaths related to treatment were reported.

Interpretation Compared with short-term androgen deprivation, 2 years of adjuvant androgen deprivation combined with high-dose radiotherapy improved biochemical control and overall survival in patients with prostate cancer, particularly those with high-risk disease, with no increase in late radiation toxicity. Longer follow-up is needed to determine whether men with intermediate-risk disease benefit from more than 4 months of androgen deprivation.

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Introduction

Several randomised trials done during the past two decades have shown a significant improvement in biochemical control and overall survival with the combination of androgen deprivation and conventional-dose radiotherapy (≤70 Gy) in patients with high-risk[1–7] and intermediate-risk prostate cancer.[8,9] Similarly, advances in external beam radiotherapy have enabled dose escalation with substantial improvements in biochemical outcome.[10–15] Because randomised trials showing a significant clinical benefit with androgen deprivation and radiotherapy use exclusively conventional dose levels of 65–70 Gy, the optimum duration of androgen deprivation to use in combination with high-dose radiotherapy remains unresolved.[16] Thus,

we aimed to determine whether long-term androgen deprivation was superior to short-term androgen deprivation for patients receiving high-dose radiotherapy.

Methods

Study design and participants

In this open-label, multicentre, phase 3 randomised controlled trial, patients were recruited from ten university hospitals throughout Spain (appendix). Patients aged 18 years or older with histologically confirmed clinical stage T1c–T3b adenocarcinoma of the prostate, N0, M0 with intermediate-risk and high-risk factors according to National Comprehensive Cancer Network criteria, serum PSA concentration less than 100 ng/mL, a Karnofsky performance score of 70 or greater, and a life expectancy of more than 5 years were eligible for inclusion. Patients with T4 tumours, regional lymph-node involvement, distant metastatic disease, previous pelvic radiotherapy or surgery, neoadjuvant hormonal treatment for more than 3 months, or concomitant use of chemotherapy were excluded from the trial. Severe psychiatric or medical conditions that could hamper both treatment and follow-up and major malignancies were also considered exclusion criteria. Patients with a previous history of cancer that had been controlled for 5 years or more and patients with cutaneous basal cell or squamous-cell carcinoma were not excluded. Pretreatment evaluation included a digital rectal examination, transrectal ultrasound, abdominal-pelvic CT, and bone scan. Review of pathology specimens was not centralised.

The study was approved by the independent review board at each participating centre and conducted according to the provisions of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent before participating in the trial. The full study protocol can be viewed online.

Randomisation and masking

Before randomisation, patients were screened to verify the study selection criteria and stratified based on prostate cancer risk subgroups (intermediate risk: T1–T2 with a Gleason score of 7, or PSA concentration of 10–20 ng/mL, or both; high risk: T3 with Gleason score of 8–10, or PSA concentration of >20 ng/mL, or both) and the participating centre.

Patients were randomly assigned (1:1) to receive 4 months of neoadjuvant and concomitant androgen deprivation combined with three-dimensional conformal radiotherapy (short-term androgen deprivation group) or the same treatment followed by 24 months of adjuvant androgen deprivation (long-term androgen deprivation group). Randomisation was centralised at the Health Research Institute of Hospital Universitario de la Princesa (Madrid, Spain). After eligibility screening, the research coordinator assigned eligible patients using a randomisation schedule generated by means of the SAS programme (version 9.1) and an interactive web response system. The research coordinator then faxed the investigator of the participating centres, reported the number, and informed the investigator about the assigned treatment. No blocks were used. Neither the participants nor the investigators were masked to treatment allocation, because blinding was not feasible.

Procedures

See Online for appendix

Radiotherapy was administered with three-dimensional conformal radiotherapy techniques done with a six-field isocentric beam setup based on a CT scan. The target volume included the prostate and the seminal vesicles. In view of the controversy regarding the role of prophylactic pelvic radiotherapy and the absence of definitive data, elective pelvic radiotherapy was left to the criteria of each participating centre. The radiation dose was specified at the intersection of the beam axes (isocentre) according to the guidelines of the International Commission on Radiation Units.[17] Treatment was provided in daily 2 Gy fractions at a minimum dose of 76 Gy (range 76–82 Gy). The median isocentre radiation dose to the prostate was 78 Gy for both groups, and the corresponding dose to the seminal vesicles was 56 Gy. Beams were shaped with multileaf collimators or customised shaped blocks, and treatment was delivered with 6–18 MV photons. Dose constraints for normal tissues have been described elsewhere.[18] Treatment was verified with electronic portal image devices according to the quality assurance protocols at each centre.

The hormone therapy regimen was based on that used in the RTOG 9202 trial[4] and on the usual clinical practice in Spain. Patients assigned to the short-term androgen deprivation group received 4 months of neoadjuvant and concomitant androgen deprivation with subcutaneous goserelin (in both groups, goserelin was given subcutaneously at 3·6 mg; after 1 month, it was given subcutaneously at 10·8 mg subcutaneously every 3 months). Treatment started 2 months before high-dose radiotherapy, and was then given for 2 months combined with radiotherapy. Anti-androgen therapy (flutamide 750 mg per day or bicalutamide 50 mg per day) was added during the first 2 months of treatment. Patients assigned to long-term suppression continued with the same luteinising hormone-releasing hormone analogue every 3 months for another 24 months.

For the **protocol** see http://www.gicor.es/invest003/resumen.pdf

Follow-up visits were at intervals of 3 months after radiotherapy during the first year, every 6 months for 5 years, and yearly thereafter. PSA concentrations, serum testosterone concentration, and a complete blood count were obtained at every visit. Specifically, 12 PSA measurements were obtained during the first 5 years of follow-up to enable systematic assessment of the lowest PSA value achieved (PSA nadir) after completion of treatment. Imaging (abdominal-pelvic CT and bone scan) was repeated in cases in which clinical or biochemical progression was suspected. Decisions on salvage therapy

	STAD (n=178)	LTAD (n=177)
Age (years)	72 (54–85)	71 (56–82)
Risk subgroup		
Intermediate	81 (45%)	85 (48%)
High	97 (55%)	92 (52%)
T stage		
T1	42 (24%)	38 (21%)
T2	103 (58%)	100 (57%)
T3	33 (18%)	39 (22%)
PSA (ng/mL)	11·0 (3·4–66)	11·1 (3·1–72)
<10	74 (42%)	80 (45%)
10–20	64 (36%)	61 (35%)
>20	40 (22%)	36 (20%)
Gleason score		
≤6	30 (17%)	21 (12%)
7	103 (58%)	110 (62%)
8–10	45 (25%)	46 (26%)
Positive biopsy samples	4 (1–16)	4 (1–13)
Duration of androgen deprivation before randomisation (months)	2·2 (0·3–7·7)	2·2 (0·5–7·8)
Prostate radiotherapy dose (Gy)	78·0 (64·0–82·2)	78·0 (30·6–88·4)
<78	51 (29%)*	43 (25%)†
≥78	122 (71%)	128 (75%)
Pelvic radiotherapy		
Yes	28 (16%)	20 (12%)
No	145 (84%)*	148 (86%)†
Missing	0	3 (2%)
Pelvic radiotherapy by risk group		
Intermediate risk	2 (7%)	2 (10%)
High risk	26 (93%)	18 (90%)
Pelvic radiotherapy dose (Gy)	46·0 (34·7–56·0)	46·0 (30·6–46·0)
Salvage treatment		
Androgen deprivation	14 (8%)	8 (5%)
Other treatments	1 (1%)	0
Time from randomisation to salvage treatment (months)	25·9 (7·1–71·4)	54·7 (41·6–66·0)

Data are n (%) or median (range). Intermediate-risk disease was defined as a clinical stage of T1 to T2 with a Gleason score of 7, or a PSA concentration of 10–20 ng/mL, or both. High-risk disease was defined as a clinical stage of T3, Gleason score of 8–10, PSA concentration of more than 20 ng/mL, or both. STAD=short-term androgen deprivation. LTAD=long-term androgen deprivation. PSA=prostate-specific antigen. *173 evaluable patients. †171 evaluable patients.

Table 1: **Patient baseline clinical and treatment characteristics**

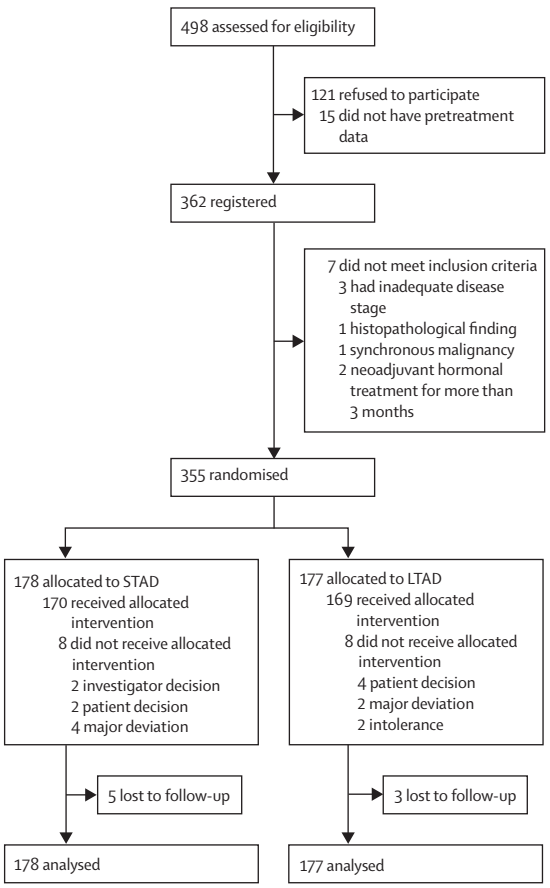

Figure 1: **Trial profile**
STAD=short-term androgen deprivation. LTAD=long-term androgen deprivation.

were based on the criteria of each participating centre. Baseline and annual or every 2 year bone mineral densitometry was recommended but not mandatory. Radiation-related complications were assessed with EORTC/RTOG radiation morbidity scoring criteria.[19]

Outcomes

The primary endpoint was biochemical disease-free survival, defined as the time from randomisation to progression of biochemical disease, or death from any cause, or censoring at the date of the last contact. The RTOG-ASTRO Phoenix Consensus Conference definition[20] (an increase in the PSA concentration of ≥2 ng/mL above the nadir) was used to define biochemical failure. Secondary endpoints included overall survival, distant metastasis-free survival, and cause-specific survival. Overall survival was defined as the time from randomisation to death from any cause or censoring at the date of the last contact. Metastasis-free survival was defined as the time from randomisation to the occurrence of metastatic disease (documented by imaging studies) or death from any cause, and patients who received salvage therapy were censored. Cause-specific survival included all deaths from prostate cancer or treatment complications, and deaths from unknown causes in patients with either active cancer or a previously documented relapse. Cause of death was recorded by the treating physician and was subject to central independent review.

Statistical analysis

On the basis of previous studies, we estimated that biochemical disease-free survival at 5 years in the

short-term androgen deprivation group would be 60% in the high-risk group and 70% in the intermediate-risk group. The addition of 2 years of androgen deprivation was expected to increase this to 75% in the high-risk group and 85% in the intermediate-risk group. Assuming that the risks between the two groups were proportional and accepting a two-tailed α risk of 0·05 with a power (1–β) of 0·80, we estimated that we would need to enrol 307 patients, roughly equally distributed between the two subgroups. Assuming a loss to follow-up of 15%, the estimated required sample size to be 350 patients. All analyses were done on an intention-to-treat basis, with patients analysed according to the treatment group. No formal stopping rules were specified in the protocol.

The χ^2 test was used to evaluate differences in toxicities and the overall worst degree of toxicity. Survival analyses were done with Kaplan-Meier curves[21] and the log-rank (Mantel-Cox) test was used to compare survival between groups.[22]

Univariate analysis was done to assess the relation between potential prognostic factors with biochemical progression-free survival. Variables included in the analysis were patient age, T stage (T3 *vs* T1–2), pretreatment PSA (>20 ng/mL *vs* ≤20 ng/mL), Gleason score (>7 *vs* ≤7), number of positive prostate biopsies, treatment group (short-term *vs* long-term androgen deprivation), radiation dose, pelvic radiotherapy (yes or no), and PSA nadir. Patient age, radiation dose, and PSA nadir were analysed as continuous variables. PSA nadir was treated as a time-dependent covariable. Variables with a statistical significance less than 0·25 were taken into account in a multivariate Cox regression analysis.[23] The Wald forward method was used to select variables in the Cox proportional hazard model. All hazard ratios (HRs) were calculated with Cox proportional hazard models and expressed relative to the control group.

We did a planned subgroup analysis of the efficacy endpoints within the prostate risk categories used in stratification—ie, intermediate-risk and high-risk prostate cancer. A forest plot was generated to explore the treatment effects across risk groups.

Analyses were done with SPSS for Windows version 19. This trial is registered with ClinicalTrials.gov, number NCT02175212, and the EU Clinical Trials Register, number 2005-000417-36.

Role of the funding source

AZ was the sponsor of the trial, because in 2004 GICOR still had no legal entity. Further funding was provided by the Spanish National Health Investigation Fund and AstraZeneca. Neither of these funding bodies had a role in trial design, data collection, statistical analysis, or

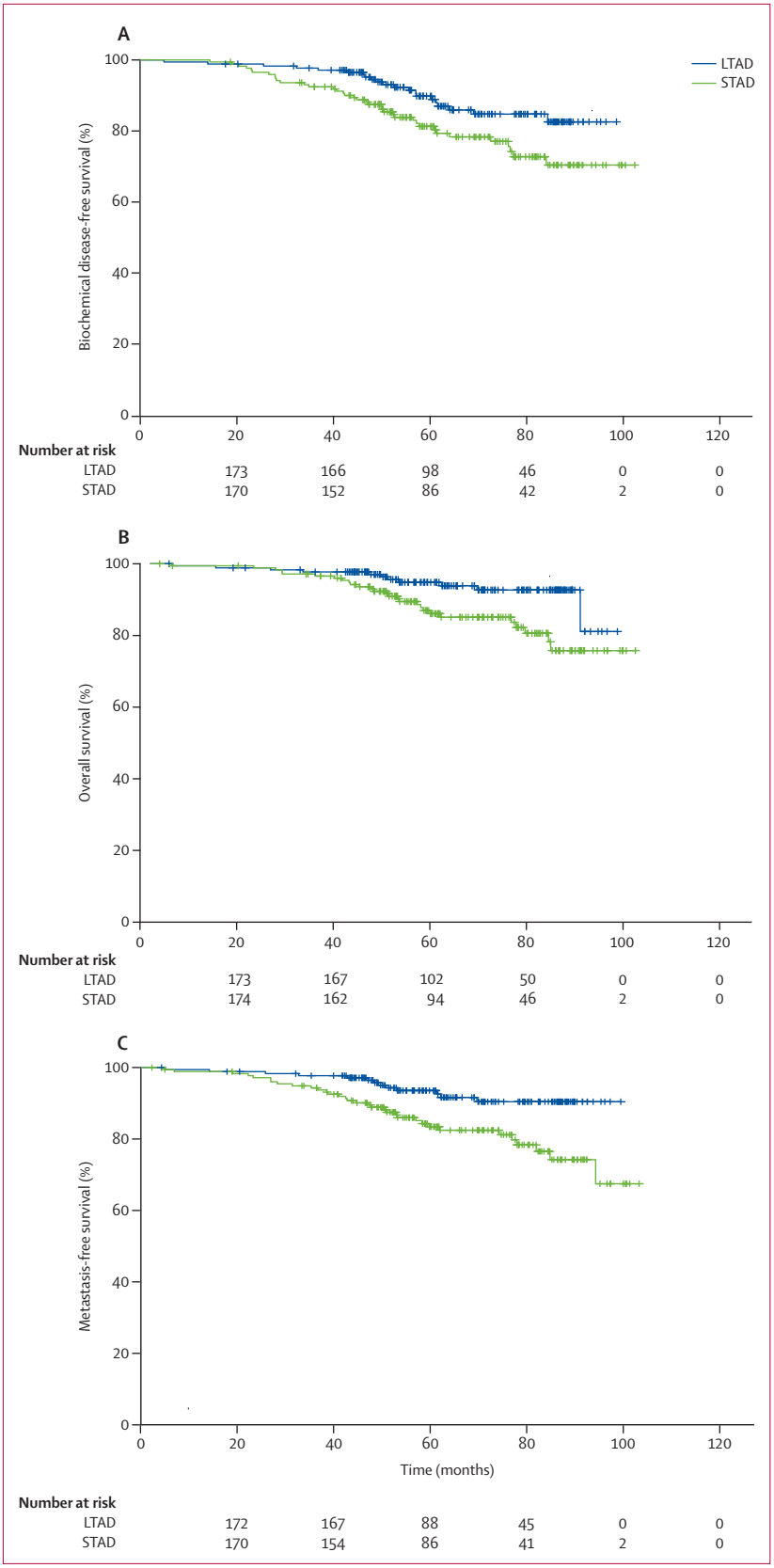

***Figure 2*: Kaplan-Meier estimates of biochemical disease-free survival (A), overall survival (B), and metastasis-free survival (C)**
STAD=short-term androgen deprivation. LTAD=long-term androgen deprivation.

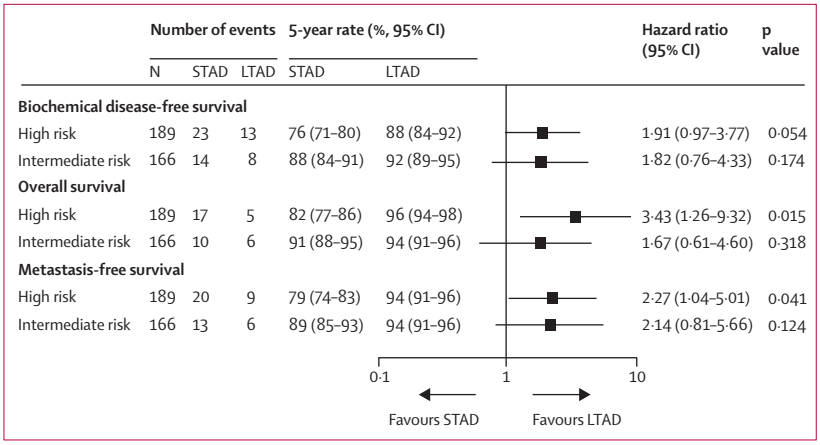

Figure 3: **Effects of duration of androgen deprivation stratified by risk group**
STAD=short-term androgen deprivation. LTAD=long-term androgen deprivation.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Patient age	0·946 (0·907–0·988)	0·012	0·941 (0·900–0·985)	0·008
Treatment group (STAD *vs* LTAD)	1·881 (1·101–3·215)	0·021	2·171 (1·178–4·002)	0·013
Radiation dose	0·950 (0·902–1·000)	0·051	0·943 (0·899–0·988)	0·014
PSA nadir	6·211 (2·296–16·799)	<0·001	5·123 (1·399–18·757)	0·014
Pelvic radiotherapy	0·734 (0·380–1·419)	0·35	0·953 (0·414–2·197)	0·91
T stage (T3 *vs* T1–2)	1·243 (0·681–2·270)	0·47	1·552 (0·699–3·445)	0·28
Pre-treatment PSA (>20 ng/mL *vs* ≤20 ng/mL)	1·794 (1·037–3·105)	0·037	1·841 (0·809–4·187)	0·14
Gleason score (>7 *vs* ≤7)	1·287 (0·731–2·267)	0·38	1·398 (0·626–3·120)	0·41
Number of positive biopsy samples	1·064 (0·967–1·172)	0·21	1·067 (0·966–1·179)	0·19

HR=hazard ratio. STAD=short-term androgen deprivation. LTAD=long-term androgen deprivation. PSA=prostate-specific antigen.

Table 2: **Univariate and multivariate analysis of biochemical progression-free survival**

interpretation of the results. The drugs were not supplied by the manufacturer. AZ had full access to the data and responsibility for the decision to submit for publication.

Results

Between Nov 7, 2005, and Dec 20, 2010, 498 men were screened (121 refused to participate and 15 did not have pretreatment data), and 362 patients were registered. Of these, seven did not meet the inclusion criteria because of inadequate disease stage (three patients), histopathology findings (one patient), synchronous malignancies (one patient), and patient refusal of allocated treatment (two patients). The final trial population thus consisted of 355 men, of whom 178 were randomly assigned to the short-term androgen deprivation group and 177 to the long-term androgen deprivation group. The treatment groups were well balanced in terms of demographic, tumour-related, and treatment characteristics (table 1). Adherence to the treatment protocol was confirmed in 170 (96%) patients in the short-term androgen deprivation group and in 169 (95%) in the long-term androgen deprivation group (figure 1).

Median follow-up was 63 months (IQR 50–82)—61 months (IQR 50–81) for the short-term androgen deprivation group, and 64 months (IQR 49–83) for the long-term androgen deprivation group. 5-year biochemical disease-free survival was 90% (95% CI 87–92) for patients receiving long-term androgen deprivation compared with 81% (78–85) for those receiving short-term androgen deprivation (HR 1·88, 95% CI 1·12–3·15; p=0·01; figure 2A). In the subgroup analysis by prostate cancer risk, the benefit in 5-year biochemical disease-free survival was more evident in the high-risk population than in the intermediate-risk population (figure 3).

5-year overall survival with long-term androgen deprivation was 95% (95% CI 93–97) compared with 86% (83–89) with short-term androgen deprivation (HR 2·48 [95% CI 1·31–4·68]; p=0·009; figure 2B). In the subgroup analysis by prostate cancer risk, the benefit in overall survival with long-term deprivation was more evident for patients with high-risk disease, but not for those with intermediate-risk disease (figure 3). 5-year metastasis-free survival was 94% (95% CI 92–96) in the long-term androgen deprivation group compared with 83% (80–86) in the short-term androgen deprivation group (HR 2·31 [95% CI 1·23–3·85]; p=0·01; figure 2C). This benefit in metastasis-free survival was greater in patients with high-risk disease than in those with intermediate-risk disease (figure 3).

The results of the multivariate analysis showed that the independent prognostic factors affecting biochemical failure were patient age, radiation dose, PSA nadir, and treatment group (table 2).

At the date of analysis, 38 (11%) of 355 patients had died; 27 in the short-term androgen deprivation group and 11 in the long-term androgen deprivation group. The cause of death was prostate cancer in only five patients, all of whom were in the short-term androgen deprivation group. 17 patients died of cancer, but not of the prostate (14 [8%] in the short-term group *vs* three [2%] in the long-term group), eight of cardiac failure (three [2%] *vs* five [3%]), and eight of other causes (five [3%] *vs* three [2%]).

61 cardiovascular events occurred: 36 (20%) in 177 patients in the long-term androgen deprivation group and 25 (14%) in 178 in the short-term group, but only eight (2%) were fatal (five [3%] in the long-term group and three [2%] in the short-term group). Late rectal toxicity of grade 2 or worse occurred in 21 (12%) of 177 patients in the long-term androgen deprivation group and 15 (8%) of 178 in the short-term group; late urinary toxicity of grade 2 or worse occurred in 18 (10%) patients in the long-term group and in 17 (10%) in the short-term group (table 3). Three (2%) patients in the long-term androgen deprivation group and two (1%) patients in the

short-term androgen deprivation group had grade 3 late rectal complications, whereas five (3%) in the long-term group and five (3%) in the short-term group had grade 3–4 late urinary complications (table 3). We did not note significant differences in rectal complications (p=0·54) or urinary complications (p=1·00) between the treatment groups.

Discussion

The results of this trial show that long-term androgen deprivation, in combination with high-dose radiotherapy, significantly improved biochemical disease-free survival for men with localised prostate cancer compared with short-term androgen deprivation and high-dose radiotherapy. Subgroup analyses suggest that the greatest clinical benefit with long-term androgen deprivation was in the high-risk subgroup of patients. This benefit was accompanied by a significant improvement in the secondary endpoints of overall survival and metastasis-free survival, with no significant increase in late radiation toxicity (panel). Although the results of our trial are encouraging, whether high-dose radiotherapy is necessary to prolong survival in men with high-risk prostate cancer given long-term androgen deprivation remains to be determined.

Although it is common practice for patients with high-risk prostate cancer to receive 2–3 years of adjuvant androgen deprivation and for patients with intermediate-risk prostate cancer to receive 4–6 months of adjuvant androgen deprivation, the optimum duration of androgen deprivation, especially in the setting of high-dose radiotherapy at 76 Gy or higher, has not been established. Furthermore, results from non-randomised studies assessing the role and optimum duration of androgen deprivation alongside high-dose radiotherapy have been mixed (table 4).

Our findings indicate that the effect of long-term androgen deprivation on biochemical disease-free survival and overall survival was more evident in patients with high-risk disease than in those with low-risk disease. The role of androgen deprivation in the management of intermediate-risk disease is more controversial in the context of dose-escalated radiotherapy,[29,31] at least in part because of the heterogeneous nature of the patient population in this group. Further stratification of patients with intermediate-risk disease may go some way to clarifying the situation. We believe that longer follow-up and more events will enable us to provide more information about the effect of long-term versus short-term androgen deprivation in patients with intermediate-risk prostate cancer. Nevertheless, larger sample sizes will be needed to show significant benefits in unfavourable intermediate-risk prostate cancer. Several ongoing randomised trials (GETUG 14, EORTC 22991, and RTOG 0815) are investigating the role of short-term androgen deprivation combined with high-dose radiotherapy in patients with intermediate-risk disease.[24,32,33]

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
LTAD (n=177)					
Rectal	39 (22%)	18 (10%)	3 (2%)	0	0
Urinary	32 (18%)	13 (7%)	3 (2%)	2* (1%)	0
STAD (n=178)					
Rectal	35 (20%)	13 (7%)	2 (1%)	0	0
Urinary	31 (17%)	12 (7%)	4 (2%)	1* (<1%)	0

Data are n (%). All complications were resolved except two cases of urethral stenosis (one in the LTAD group and one in the STAD group) and one case of urinary incontinence in the STAD group. LTAD=long-term androgen deprivation. STAD=short-term androgen deprivation. *Urethral stenosis.

Table 3: **Chronic late radiation toxicity**

Panel: Research in context

Systematic review

We searched PubMed and Medline between Jan 1, 1988, and Dec 30, 2003, using the search terms "randomized trial", "androgen deprivation therapy", "androgen suppression therapy", "hormone therapy", "dose escalation radiotherapy", and "conformal radiotherapy". Only English language articles were included.

Several randomised trials done during the past two decades have shown that androgen deprivation combined with conventional-dose radiotherapy improves overall survival, mainly in patients with intermediate-risk and high-risk prostate cancer.[1,7] Similarly, clinical outcomes have also improved substantially with high-dose radiotherapy.[10] However, in view of the absence of specific randomised trials, the optimum duration of androgen deprivation remained unresolved in the era of dose-escalated radiotherapy.[16,24]

Interpretation

To our knowledge, this is the first randomised trial to report that long-term androgen deprivation is superior to short-term androgen deprivation in patients given high-dose radiotherapy in terms of biochemical control and overall survival, particularly in men with high-risk prostate cancer. The optimum duration of androgen deprivation in intermediate-risk disease remains to be defined. Further follow-up is needed to determine the effect of long-term androgen deprivation in this subgroup.

An unexpected finding of our trial was that almost five times as many patients died of cancers other than of the prostate in the short-term androgen deprivation group than in the long-term androgen deprivation group. We cannot provide a satisfactory explanation for this finding, although we do recognise its potential effect on the interpretation of the results. An association between the hormonal environment, immune tolerance, and the immune response to cancer cannot be excluded.

At the time that this study was designed, we felt that the decision to use pelvic radiotherapy should be based on the criteria of the participating institution. Evidence

	Number of patients	Patients	Androgen deprivation therapy	Radiotherapy dose	Outcome
Phase 3 trials of ADT and conventional-dose radiotherapy					
RTOG 92–02[4]	1554	T2c–4 N0–1 M0	4 months NAD with or without 2 years LHRHa	65–70 Gy	ADT for 2 years improved overall survival only in patients with a Gleason scoreof 8–10 (31·9% *vs* 45·1%; p=0·006)
EORTC 22961[5]	970	T1c–2ab N1 M0; T2c–4 N0–1 M0	6 months NAD with or without 2·5 years LHRHa	70 Gy	ADT for 6 months provides worse overall survival compared with 3 years
Nabid et al[6] (NCT00223171)	630	T3–4, N0 PSA >20 ng/mL, or Gleason >7	36 months *vs* 18 months adjuvant LHRHa	70 Gy	No significant differences in overall survival
Retrospective studies of ADT and HDRT					
Zelefsky et al[25]	1980	T1–T3 N0	3–6 months LHRHa	64·8–86·4 Gy	HDRT and ADT for 6 months improved biochemical disease-free and metastasis-free survival, but not overall survival
Nguyen et al[26]	741	NCCN criteria	295 ADT for 2 or more years (range 2–18)	Median 70 Gy (range 60–79)	ADT and HDRT had a positive effect on overall survival (p=0·003)
Zapatero et al[27]	306	NCCN criteria	231 patients, 28 months LHRHa; 59 patients, 6 months; 16 patients, no hormones	Median 78 Gy (range 66–84)	ADT for 28 months and >78 Gy improved overall survival; 96–89% at 5–10 years
Feng et al[28]	234	NCCN criteria	No ADT, 48; STAD (<1 year), 84; LTAD (≥1 year), 102	Median 77 Gy (range 75–79)	Long-term ADT improved overall survival (p=0·001)
Krauss et al[29]	262	NCCN criteria	40% ADT duration not specified, 60% no ADT % no ADT	EBRT 75·6 Gy, or brachytherapy, or EBRT plus b brachytherapy	No benefit with the addition of ADT
Tendulkar et al[30]	585	NCCN criteria	95% 6 months LHRHa, 5% no ADT	Median 78 Gy (range 74-80)	No benefit with the addition of ADT

NAD=neoadjuvant androgen deprivation. ADT=androgen deprivation therapy. LHRHa=luteinising hormone-releasing hormone analogue. PSA=prostate-specific antigen. NCCN=National Comprehensive Cancer Network. STAD=short-term androgen deprivation. LTAD=long-term androgen deprivation. HDRT=high-dose radiation therapy. EBRT=external beam radiation therapy.

Table 4: **Studies addressing the duration of androgen deprivation combined with conventional-dose and high-dose radiotherapy in high-risk prostate cancer**

from randomised trials showing a significant benefit in overall survival with pelvic radiotherapy was absent, and the use of pelvic radiotherapy was a controversial issue. The results of our univariate and multivariate analyses did not show a significant difference in biochemical disease-free survival between patients who were or were not given pelvic radiotherapy. Nevertheless, the clinical effect of pelvic radiotherapy in the context of combined treatment with androgen suppression remains highly controversial, and we await the results of the RTOG 0924 trial to confirm whether there is any benefit of pelvic radiotherapy in a high-risk population.

The incidence of late grade 2 or higher rectal or urinary complications in our study was acceptably low in both treatment groups. Despite the use of higher radiation doses, our results compare favourably with those of RTOG 9202. However, we should be cautious when comparing these two trials because of relevant differences in technique (conventional *vs* three-dimensional conformal radiotherapy) and treatment volume.

We recognise the limitations inherent in our study—namely, the fairly short follow-up, the low number of events, and the small sample size. We intend to report 10-year outcomes in due course. These limitations also affect the power of the subgroup analyses and the analysis of late grade 3 radiation toxicity.

In conclusion, our results show that long-term androgen deprivation plus high-dose radiotherapy is superior to short-term androgen deprivation plus high-dose radiotherapy in terms of biochemical disease-free survival and overall survival, particularly in patients with high-risk prostate cancer. Longer follow-up is required to confirm these results and to determine the effect of long-term androgen deprivation in patients with intermediate-risk prostate cancer.

Contributors

AZ was the sponsor and chief investigator. AZ developed the protocol and wrote the report. FAC coordinated the study. APdH did the statistical analysis. All the investigators enrolled the patients, did the literature search, and were involved in the interpretation of data and the review of the report. All investigators approved the final version of the report for publication.

Declaration of interests

All authors declare no competing interests.

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