Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial

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Summary

Background Whether the addition of radiation therapy (RT) improves overall survival in men with locally advanced prostate cancer managed with androgen deprivation therapy (ADT) is unclear. Our aim was to compare outcomes in such patients with locally advanced prostate cancer.

Methods Patients with: locally advanced (T3 or T4) prostate cancer (n=1057); or organ-confined disease (T2) with either a prostate-specific antigen (PSA) concentration more than 40 ng/mL (n=119) or PSA concentration more than 20 ng/mL and a Gleason score of 8 or higher (n=25), were randomly assigned (done centrally with stratification and dynamic minimisation, not masked) to receive lifelong ADT and RT (65–69 Gy to the prostate and seminal vesicles, 45 Gy to the pelvic nodes). The primary endpoint was overall survival. The results presented here are of an interim analysis planned for when two-thirds of the events for the final analysis were recorded. All efficacy analyses were done by intention to treat and were based on data from all patients. This trial is registered at controlledtrials.com as ISRCTN24991896 and Clinicaltrials.gov as NCT00002633.

Results Between 1995 and 2005, 1205 patients were randomly assigned (602 in the ADT only group and 603 in the ADT and RT group); median follow-up was 6·0 years (IQR 4·4–8·0). At the time of analysis, a total of 320 patients had died, 175 in the ADT only group and 145 in the ADT and RT group. The addition of RT to ADT improved overall survival at 7 years (74%, 95% CI 70–78 vs 66%, 60–70; hazard ratio [HR] 0·77, 95% CI 0·61–0·98, p=0·033). Both toxicity and health-related quality-of-life results showed a small effect of RT on late gastrointestinal toxicity (rectal bleeding grade >3, three patients (0·7%) in the ADT only group, two (0·3%) in the ADT and RT group; diarrhoea grade >3, four patients (0·7%) vs eight (1·3%); urinary toxicity grade >3, 14 patients (2·3%) in both groups).

Interpretation The benefits of combined modality treatment—ADT and RT—should be discussed with all patients with locally advanced prostate cancer.

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Introduction

913 000 new cases of prostate cancer and 215 000 deaths occurred worldwide in 2008.1 In the USA prostate cancer is the most frequently diagnosed cancer in men and is second only to lung cancer as a cause of cancer deaths.2 Whether the addition of radiation therapy (RT) improves overall survival in men with locally advanced prostate cancer is unclear. Our aim was to compare outcomes in such patients with locally advanced prostate cancer.
with a Gleason score of more than 8. Additional criteria were an Eastern Cooperative Oncology Group performance status of 0–2, and age less than 80 years. Pelvic lymph nodes were not imaged unless the planned radiation area was to the prostate only and was negated for nodal involvement. Surgical staging was allowed, but if done pelvic nodes had to be histologically confirmed free of disease. Previous treatment for prostate cancer was not allowed, with the exception of neoadjuvant ADT in the 12 weeks before randomisation. No central histological review was done. The appropriate national and local regulatory and ethical approvals were obtained, and all patients provided written informed consent.

**Randomisation and masking**

All randomisation was done centrally by computer with stratification by dynamic minimisation. Patients were randomly assigned to receive ADT only, or ADT and RT. Patients were stratified by institution, PSA concentration at diagnosis, type of ADT (orchiectomy or luteinising hormone-releasing hormone [LHRH] agonist), neo-adjuvant ADT, lymph node staging, and Gleason score. Participating North American centres were randomly assigned to use one of the two quality-of-life instruments, either the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3) with the PR13 prostate-specific module, or Functional Assessment of Cancer Therapy–Prostate (FACT-P). All participating MRC UK centres used FACT-P. Patients and investigators were not masked.

**Procedures**

All patients received lifelong ADT before randomisation; patients chose between bilateral orchiectomy or LHRH agonist (initially given with 2 weeks of antiandrogens, which could be continued at the investigator’s discretion). RT was started within 8 weeks of randomisation and delivered with a four-field box technique. The pelvic target volume (45 Gy given in 25 fractions over 5 weeks) included the whole pelvis, the prostate, seminal vesicles, and external and internal iliac lymph nodes. The prostate target volume (20–24 Gy given in 10–12 fractions over 2–2.5 weeks, at the investigator’s discretion) encompassed the prostate gland with known periprostatic tumour extension. The dose was specified at the intersection of the beam axes according to International Commission on Radiation Units guidelines. Patients with histologically negative lymph nodes and those for whom the treating physician judged that pelvic RT was inappropriate were treated to the prostate volume (65–69 Gy).

The trial’s primary outcome measure of overall survival was defined as survival from time of randomisation to date of death from any cause or censored at the date of last follow-up. The secondary outcome measures were disease-specific survival, time to disease progression, symptomatic local control measured by the rates of surgical interventions necessary for symptomatic local disease, and health-related quality of life (HRQoL). Toxicity was reported with the the National Cancer Institute of Canada Clinical Trials Group expanded common toxicity criteria.

Cause of death was defined by the investigator. Disease progression was defined as the first of: biochemical relapse, local progression, distant metastatic spread, or death from prostate cancer. Biochemical relapse was defined as a PSA concentration of more than 10 ng/mL in two consecutive samples if a minimum PSA concentration of less than 4 ng/mL was reached at any time, or if serum PSA was never less than 4 ng/mL, a PSA concentration of both more than 10 ng/mL and 20% higher than the minimum value. Local progression was defined as either ureteral obstruction or progressive disease accompanied by a biopsy sample showing tumour. Distant metastases were assessed by routine imaging.

**Statistical analysis**

The original design assumed a 10-year survival of 35% for patients with T3, N0, M0 prostate cancer treated with ADT-only. To detect a 10% improvement in 10-year survival (with a hazard ratio [HR] of 0.76), with 80% power by a one-sided 5% threshold test, a sample size of 650 eligible patients was needed. In September, 2002, after 688 patients had been recruited, only 46 events (deaths) were reported. The trial design was then amended to assume a 10-year survival of 57% in the ADT-only group (on the basis of data from the EORTC 22863 study), with the same target HR and power. The primary test was changed to have a two-sided 5% significance threshold, and the sample size was increased to 1200 patients. After adjustment for two planned interim analyses, a minimum of 421 events was calculated to be needed for the final analysis.

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**Figure 1: Trial profile**

ADT=androgen depletion therapy. RT=radiation therapy.
Overall survival was assessed with the Kaplan-Meier product limit method and compared with a log-rank test stratified by the minimising factors at randomisation. HRs and CIs were estimated with the Cox model. Event rates were calculated with Kaplan-Meier or cumulative incidence estimates. The Gray test\textsuperscript{12} was used to test the difference in the cumulative cause-specific incidences. All efficacy analyses were done by intention to treat and used data from all patients. SAS software (version 9.1) was used for the statistical analyses.

Two interim analyses were prospectively planned for when a third and two-thirds of the events for the final analysis were recorded. The first interim analysis was done in March, 2006, with a stopping guideline \( p \) value of 0·001 or less. The data safety monitoring committee (DSMC) reviewed the results and recommended that the study continue. The second interim analysis was done in August, 2009, with 320 deaths, with a stopping guideline \( p \) value of less than 0·02 based on the Lan-Demets error spending function with O’Brien-Fleming-type boundaries.\textsuperscript{13} The DSMC reviewed the data and noted that although the results did not meet the protocol criteria for early discontinuation on the basis of the test of significance, an effect was present, which was consistent with the previous interim analysis in the subgroups for overall survival and with other efficacy endpoints (time to progression and disease-specific survival), as well as with the results of a phase 3 trial of similar design.\textsuperscript{14} On the basis of these observations, the DSMC recommended external disclosure of the study results. The results of the second interim analysis form the basis of this report. The protocol-specified final analysis is planned for when at least 421 deaths are reported.

HRQoL questionnaires were scored according to EORTC (core questionnaire and PR-13 prostate-cancer module) and Functional Assessment of Chronic Illness Therapy standards.\textsuperscript{7,15} For this interim analysis, the HRQoL analysis focused on the hypothesis that treatment groups would differ in mean HRQoL scores for measures relevant to pelvic RT, tested by comparing mean score change from baseline without adjustment for missing data.\textsuperscript{16} A mean score change of 7 (FACT-P) or 10 (EORTC) was judged clinically important.\textsuperscript{15,16} The trial statistician was masked to what treatment the patients received.

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

This trial is registered at controlledtrials.com as ISRCTN24991896 and Clinicaltrials.gov as NCT00002633.

Results
Between March, 1995, and August, 2005, 1205 patients entered the study and were randomly assigned to receive ADT only or ADT and RT (figure I). At the time

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**Table 1: Patients’ baseline characteristics at study entry**

| Patient characteristics               | Androgen deprivation therapy (n=602) | Androgen deprivation therapy and radiation therapy (n=603) |
|----------------------------------------|--------------------------------------|----------------------------------------------------------|
| **Region of recruitment**              |                                      |                                                          |
| North America                          | 180 (30%)                            | 181 (30%)                                                |
| UK                                     | 422 (70%)                            | 422 (70%)                                                |
| **Prostate-specific antigen**          |                                      |                                                          |
| <20 ng/mL                              | 224 (37%)                            | 220 (36%)                                                |
| 20–50 ng/mL                            | 228 (38%)                            | 228 (38%)                                                |
| >50 ng/mL                              | 150 (25%)                            | 155 (26%)                                                |
| Median (IQR)                           | 28 (13·9–49·8)                       | 27 (14·1–53·3)                                          |
| **Gleason score**                      |                                      |                                                          |
| Not available                          | 6 (1%)                               | 3 (<1%)                                                  |
| <8                                     | 489 (81%)                            | 489 (81%)                                                |
| ≥9                                     | 107 (18%)                            | 111 (18%)                                                |
| **Previous hormone therapy**           |                                      |                                                          |
| No                                     | 347 (58%)                            | 347 (58%)                                                |
| Yes                                    | 255 (42%)                            | 256 (42%)                                                |
| **Age at allocation**                  |                                      |                                                          |
| <65 years                              | 134 (22%)                            | 132 (22%)                                                |
| ≥65 years                              | 468 (78%)                            | 471 (78%)                                                |
| Median (IQR)                           | 69·7 (65·5–73·5)                     | 69·7 (65·5–74·0)                                         |
| **Performance status (ECOG)**          |                                      |                                                          |
| 0                                      | 474 (79%)                            | 469 (78%)                                                |
| 1                                      | 119 (20%)                            | 126 (21%)                                                |
| 2                                      | 9 (1%)                               | 8 (1%)                                                   |
| **Clinical stage**                     |                                      |                                                          |
| Missing                                | 0 (0%)                               | 2 (<1%)                                                  |
| T2                                     | 76 (13%)                             | 70 (12%)                                                |
| T3                                     | 499 (83%)                            | 501 (83%)                                                |
| T4                                     | 27 (4%)                              | 30 (5%)                                                  |
| **Lymph node staging**                 |                                      |                                                          |
| Clinical or radiological               | 477 (79%)                            | 475 (79%)                                                |
| Not done                               | 113 (19%)                            | 111 (18%)                                                |
| Surgical                               | 12 (2%)                              | 17 (3%)                                                  |
| **Health-related quality-of-life scores** |                                        |                                                          |
| FACT-P, global assessment*             | 55 3 (1·4)                           | 58 1 (1·4)                                               |
| EORTC, global assessment*              | 77 8 (1·9)                           | 77 4 (1·9)                                               |
| FACT-P, physical function*             | 90 7 (0·5)                           | 90 3 (0·6)                                               |
| EORTC, physical function*              | 92 5 (1·2)                           | 91 4 (1·7)                                               |
| EORTC, bowel or rectum†               | 3 6 (1·2)                            | 3 3 (0·9)                                                |
| EORTC, diarrhoea†                      | 4 3 (1·1)                            | 5 8 (1·9)                                                |
| EORTC, urinary† [n=180]               | 9 7 (1·7)                            | 11 2 (1·7)                                               |
| FACT-P, urinary† [n=835]               | 28 8 (1·4)                           | 29 7 (1·4)                                               |

Data are n (%) or mean (SE). EORTC=European Organisation for Research and Treatment of Cancer, quality-of-life questionnaire and the PR-13 prostate module. *High scores represent a high quality of life. †High scores represent a high symptom burden. FACT-P=Functional Assessment of Cancer Therapy-Prostate Module.
of analysis (data cutoff Dec 31, 2008) the median follow-up from randomisation was 6·0 years (IQR 4·4–8·0), with a maximum of 13·3 years. Because of the interim nature of this analysis, 103 patients were incompletely followed up for at least 2 years (42 participants in the ADT only group, 61 participants in the ADT and RT group).

Table 1 shows the baseline characteristics of the patients. Of the 603 patients randomised to receive ADT and RT, 13 did not receive RT, and data are unavailable for four; 560 (96%) received 64–69 Gy, 17 (3%) received less than 64 Gy, and 12 (2%) received more than 69 Gy. 419 (72%) of patients received RT to the prostate and pelvic lymph nodes and 167 (28%) were treated to the prostate alone. Nine patients randomised to ADT only received RT as part of their initial management (defined as RT more than 50 Gy to the prostate and pelvis given within 1 year of randomisation with no evidence of relapse). LHRH agonists were used as ADT in 1105 patients (92%), and orchiectomy was done in 93 (8%).
with much the same numbers in both treatment groups (555 vs 45 in the ADT group, and 550 vs 48 in the ADT and RT group).

At the time of this analysis, a total of 320 patients had died, 175 in the ADT only group and 145 in the ADT and RT group (figure 2). The addition of radiation to ADT resulted in significantly improved survival (HR 0·77, 95% CI 0·61–0·98, p=0·03). Overall survival at 7 years was 74% (95% CI 70–78) in the ADT plus RT group compared with 66% (60–70) in the ADT only group (figure 2).

Prostate cancer was the cause of death in 140 patients (44%); 89 (51%) in the ADT only group and 51 (35%) in ADT and RT group. The addition of radiation to ADT reduced the risk of death from prostate cancer (HR 0·54, 0·27–0·78, p=0·0001; figure 2). The 7-year cumulative disease-specific deaths were 9% for patients receiving ADT and RT, and 19% for patients receiving ADT only (p=0·001; Gray test; figure 2). The incidence of death from other causes did not differ significantly between groups (figure 2; p=0·734).

A total of 346 patients developed progressive disease—251 in the ADT only group and 95 in the ADT and RT group. The median time to progression in the ADT only group was 6·8 years (IQR 3·4–not reached) and not reached (IQR 8·2–not reached) in the ADT and RT group (estimated HR 0·30, 95% CI 0·23–0·39, p=0·0001). Biochemical relapse was the first reported evidence of relapse in 160 (46%) patients (119 in the ADT only group and 41 in the ADT and RT group), and local progression was the first reported type of relapse in 111 (32%) patients (97 in the ADT only group and 14 in the ADT and RT group). 58 patients in the ADT only group whose local disease progressed were given RT at the time of relapse.

Severe late side-effects higher than grade 3 were uncommon in both groups (table 2). As expected, grade 1 and 2 gastrointestinal toxicity (manageable diarrhoea and rectal bleeding) increased in the ADT and RT group. Baseline HRQoL scores for the measures most relevant to prostate RT are shown in table 1. Compliance was high at baseline (1031 patients, 89%) and was still high for both EORTC and FACT-P at 36 months (>86% at all time points). Table 2 shows the mean change in scores for measures relevant to prostate RT at 6 months and 36 months. Similar to toxicity scores, genitourinary-specific measures were high at baseline (presumably because of disease-related symptoms). Gastrointestinal-specific measures were captured only by the EORTC PR-13, revealing short-term (6 month) but not long-term (36 month) differences between groups. Figure 3 shows the mean scores over time for symptom measures, indicating the between-group differences in symptoms and early overall quality of life (EORTC). Overall quality of life and physical function scores show a general deterioration of physical function in both groups, consistent with ADT suppression (webappendix p I).

The interim analysis only addressed survival, toxicity, and quality of life, therefore the analysis of the rates of surgical intervention was deferred until the final analysis, when more data would be available.
Discussion
This trial shows a greater benefit of combined modality therapy—RT and ADT—than of treatment with ADT alone in the management of patients with locally advanced prostate cancer. Combined modality treatment resulted in a reduction in overall mortality and disease-specific mortality. The addition of RT also reduced disease progression and the rate at which local disease progression presented. The side-effects of RT were modest clinically, and the frequency of serious toxicity was low.

As in this study, the SPCG-7 study showed an improved outcome with the addition of RT to hormonal therapy in patients with non-metastatic prostate cancer (panel). Although both studies addressed the issue of effect of RT on survival, important differences between them exist; patients in the SPCG-7 trial had a more favourable prognosis than patients in this study. In the SPCG-7 trial 20% of patients had intermediate-risk disease, the maximum allowable PSA concentration was 70 ng/mL, patients with PSA concentrations higher than 11 ng/mL were surgically staged, and those with positive pelvic nodes were excluded from the trial. By contrast, in our trial, patients had much more advanced disease—all were high-risk and fewer than 5% had their pelvic nodes surgically assessed. The two trials also had some differences in the treatment. In the SPCG-7 study, total androgen blockade was given for the first 3 months, then antiandrogen monotherapy until progression or death; in our study, hormonal treatments were continuous androgen deprivation therapy and radiotherapy on overall survival, important differences between them exist; patients in the SPCG-7 trial had a more favourable prognosis than patients in this study. In the SPCG-7 trial 20% of patients had intermediate-risk disease, the maximum allowable PSA concentration was 70 ng/mL, patients with PSA concentrations higher than 11 ng/mL were surgically staged, and those with positive pelvic nodes were excluded from the trial. By contrast, in our trial, patients had much more advanced disease—all were high-risk and fewer than 5% had their pelvic nodes surgically assessed. The two trials also had some
with a median follow-up of 6 years, serious long-term genitourinary or gastrointestinal toxicity from RT was uncommon. These findings are supported by patient-reported outcomes, which show that the negative effect of RT on bowel function was modest clinically, with recovery of scores by 36 months tending to match those who did not have RT. These results are consistent with temporary RT toxicity and suggest that concerns about the side-effects of RT are not a reason to withhold treatment. As expected for patients receiving ADT, a decrease in global and physical function was evident in both groups. Neither the recorded conventional toxicity data nor the patient-reported HRQoL data show between-group differences in long-term genitourinary toxicity, although the FACT-P scores show a small increase in genitourinary symptom scores at 6 months in patients receiving RT.

Our trial used continuous ADT, which is consistent with the prevailing view in the early 1990s of duration of therapy. However, although the optimum duration of ADT in locally advanced disease still needs to be defined, all available data suggest that long-term use is associated with an improved outcome. The long-term morbidity and possibly mortality of ADT should be included in the risk–benefit ratio when considering long-term combined modality treatment. Loss of bone density, increased fragility fractures, problems with cognition, increased risk of diabetes, and increased cardiac morbidity and mortality with ADT have been reported in addition to fatigue, hot flushes, decreased libido, and erectile dysfunction.

Although our study and interim analysis have strengths—randomisation and a large sample size—we note some limitations. Cause of death was assessed by the local investigator and some bias could have been introduced into the disease-specific survival endpoint because the treatment allocation was not masked. Another limitation was that data for skeletal adverse events were not obtained—at the time of the study’s inception the importance of bone health in patients treated with ADT was not appreciated. Data for cardiovascular complications of ADT were obtained but not analysed in this interim analysis; however, they will be published in the final study report. The criteria for PSA concentration progression were those used in the original protocol designed in 1993—biochemical progression results obtained with the Phoenix–ASTRO criteria will be reported in the final analysis. In our final analysis we intend to calculate multivariable risk scores for all patients to verify that risk is much the same between the two treatment

Panel: Research in context
Systematic review
Whether the addition of radiation therapy improves overall survival in men with locally advanced prostate cancer receiving androgen deprivation therapy is unclear. We searched PubMed for phase 3 trials, guidelines, meta-analyses, randomised controlled trials, and reviews, using the MeSH terms “prostatic neoplasms”, “radiotherapy”, and “hormonal therapy”. The search was restricted to reports published in English up to April 18, 2011. Additional papers identified by PW and MM were also included. We identified two randomised trials that have addressed this issue and had conflicting results—one showed improved survival (a large study of a favourable subset of patients with locally advanced disease) and the other (a small underpowered trial) showed no change in survival.

Interpretation
In our randomised study with an unselected cohort of 1205 patients the addition of radiation therapy to androgen deprivation therapy improved overall survival. This trial was the first study powered to assess the effect of androgen-deprivation therapy and radiotherapy on overall survival compared with androgen deprivation therapy alone in a locally advanced prostate cancer (with eligibility not restricted on the basis of prognostic factors). No clinically important adverse effects on late treatment toxicity were recorded. This trial provides convincing evidence that local control of disease in the prostate improves survival in patients with locally advanced prostate cancer.
groups. We will also do an exploratory analysis to test whether any difference in outcomes exist when patients are stratified by baseline level of risk. The dose of RT used in this trial (65–69 Gy) is low by modern standards. However, this dose was the standard of care in the 1990s when the trial was started. In the past 15 years the development of new RT techniques has allowed for a 20–25% increase in RT dose while keeping an acceptable morbidity in patients who would have been eligible for this trial. Randomised trials of dose escalation in low-to-intermediate risk patients, treated with and without ADT, have shown improved local control and freedom from recurrence with minimum toxicity, and furthermore, the improvement in survival with the addition of RT to ADT recorded in this trial could be increased again with modern RT dose fractionation schemes. In our study, elective treatment of the pelvic lymph nodes was done in most cases but the possible benefit of this approach is still controversial. Future analyses will explore the relation between the use of pelvic nodal radiation and disease-related outcomes in the study population. However, such data can apply only to outcomes from the modest doses of pelvic nodal irradiation that we delivered in the time before intensity-modulated RT (IMRT) became available. Higher doses can be safely delivered with IMRT than with previous techniques, and the continuing randomised trials re-examining pelvic nodal radiation and disease-related outcomes are the only way to address this issue with current technology.

That clinicians’ and patients’ preferences have an important role in the selection of treatment for patients with locally advanced prostate cancer is not surprising in view of the absence of good quality evidence of the effectiveness of alternative treatment approaches. This lack of evidence is shown in the wide variation in current practice patterns, with noticeable geographic differences in the use of curative treatment approaches. Furthermore, the use of ADT alone as primary management has increased in the past 20 years, a practice not supported by the use of ADT alone as primary management has increased in the past 20 years, a practice not supported by the use of curative treatment approaches. Furthermore, the use of ADT alone as primary management has increased in the past 20 years, a practice not supported by curative treatment approaches. 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Burton-upon-Trent); F Mickina (Eastbourne Hospital, Eastbourne); I Syndikus (Southport & Formby District General Hospital, Southport); J Glaholm (Good Hope Hospital, Sutton Coldfield), Russia—O Kariakine (MRRC RAMS, Obninsk), Russia—G Zietman (MD Anderson, Houston), USA—T Howdeshell (UCLA), USA—A Abratt (Groote Schuur Hospital, Cape Town).

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