External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study

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Summary

Background We did a randomised phase 3 trial assessing the benefit of addition of long-term androgen suppression with a luteinising-hormone-releasing hormone (LHRH) agonist to external irradiation in patients with prostate cancer with high metastatic risk. In this report, we present the 10-year results.

Methods For this open-label randomised trial, eligible patients were younger than 80 years and had newly diagnosed histologically proven T1–2 prostatic adenocarcinoma with WHO histological grade 3 or T3–4 prostatic adenocarcinoma of any histological grade, and a WHO performance status of 0–2. Patients were randomly assigned (1:1) to receive radiotherapy alone or radiotherapy plus immediate androgen suppression. Treatment allocation was open label and used a minimisation algorithm with institution, clinical stage of the disease, results of pelvic-lymph-node dissection, and irradiation fields extension as minimisation factors. Patients were irradiated externally, once a day, 5 days a week, for 7 weeks to a total dose of 50 Gy to the whole pelvis, with an additional 20 Gy to the prostate and seminal vesicles. The LHRH agonist, goserelin acetate (3·6 mg subcutaneously every 4 weeks), was started on the first day of irradiation and continued for 3 years; cyproterone acetate (50 mg orally three times a day) was given for 1 month starting a week before the first goserelin injection. The primary endpoint was clinical disease-free survival. Analysis was by intention to treat. The trial is registered at ClinicalTrials.gov, number NCT00849082.

Findings Between May 22, 1987, and Oct 31, 1995, 415 patients were randomly assigned to treatment groups and were included in the analysis (208 radiotherapy alone, 207 combined treatment). Median follow-up was 9·1 years (IQR 5·1–12·6). 10-year clinical disease-free survival was 22·7% (95% CI 16·3–29·7) in the radiotherapy-alone group and 47·7% (39·0–56·0) in the combined treatment group (hazard ratio [HR] 0·42, 95% CI 0·33–0·55, p<0·0001). 10-year overall survival was 39·8% (95% CI 31·9–47·5) in patients receiving radiotherapy alone and 58·1% (49·2–66·0) in those allocated combined treatment (HR 0·60, 95% CI 0·45–0·80, p=0·0004), and 10-year prostate-cancer mortality was 30·4% (95% CI 23·2–37·5) and 10·3% (5·1–15·4), respectively (HR 0·38, 95% CI 0·24–0·60, p<0·0001). No significant difference in cardiovascular mortality was noted between treatment groups both in patients who had cardiovascular problems at study entry (eight of 53 patients in the combined treatment group had a cardiovascular-related cause of death *vs* 11 of 63 in the radiotherapy group; p=0·60) and in those who did not (14 of 154 *vs* six of 145; p=0·25). Two fractures were reported in patients allocated combined treatment.

Interpretation In patients with prostate cancer with high metastatic risk, immediate androgen suppression with an LHRH agonist given during and for 3 years after external irradiation improves 10-year disease-free and overall survival without increasing late cardiovascular toxicity.

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Introduction

Overall survival of patients with prostate cancer with high metastatic risk has improved with the combined use of long-term androgen suppression and external beam irradiation by comparison with treatment with radiotherapy and deferred androgen deprivation at time of relapse.[1–4] A non-inferiority trial[5] has shown that 6 months of short-term androgen suppression followed by androgen suppression in case of relapse was inferior to 3 years of immediate androgen suppression for patients with locally advanced prostate cancer. Long-term suppression might, however, increase risk of fatal myocardial infarction[6] and bone fractures.[7] We present the 10-year results of European Organisation for Research and Treatment of Cancer (EORTC) 22863, with the aim of confirming whether previously reported improvements in overall survival were sustained and assessing the effect of the treatment on long-term cardiovascular morbidity and bone fractures.

Methods

Patients

EORTC 22863 was an open-label randomised phase 3 trial. Eligible patients were younger than 80 years, with a WHO performance status of 0–2, and had newly diagnosed histologically proven T1–2 prostatic

adenocarcinoma with WHO histological grade 3, or T3–4 prostatic adenocarcinoma of any histological grade (International Union Against Cancer TNM classification system, 1982).[8] Patients with a history of malignant disease, apart from adequately treated basal-cell carcinoma of the skin, or evidence of distant metastases, including involvement of common iliac or para-aortic lymph nodes, were excluded. Clinical assessment was based on bone scan, chest radiograph, ultrasound, or CT scan of the abdomen. Lymph-node evaluation was by CT scan, bipedal lymphangiography, or extraperitoneal lymphadenectomy. Laboratory studies included complete blood count and creatinine, serum testosterone, and prostate-specific antigen (PSA) concentrations assessed by radioimmunometric or immunoenzymatic assays. All patients gave written informed consent. Ethics committee approval was obtained at all centres.

Randomisation and masking

Randomisation was done centrally at EORTC headquarters. Patients were assigned in a 1:1 ratio to receive radiotherapy alone or radiotherapy plus immediate androgen suppression. Randomisation used the minimisation technique,[9] with institution, clinical disease stage (T1–2 WHO grade 3 *vs* T3–4 WHO grade 1–3), results of pelvic-lymph-node dissection (N0 *vs* N1), and irradiation fields extension (extended *vs* limited fields) as minimisation factors. Treatment allocation was open label.

Procedures

External irradiation was not conformal and was delivered with photons of 10 MV and higher. Planning target volume 1 was the whole pelvis and volume 2 encompassed the prostate and the seminal vesicles. A four-field technique was used to irradiate the whole pelvis. The typical lower and upper borders of the pelvic fields were the seat bone and the promontory, although some centres preferred to use the lower end of the sacroiliac joint as the upper border, and some used anorectal blocks in the lateral fields. Planning target volume 2 was irradiated with either the same technique or with three fields. The specification of the dose was given at the intersection of the beam axes according to International Commission on Radiation Units and Measurements report 29.[10] Patients were treated once a day, 5 days a week, for 7 weeks. Planning target volume 1 was irradiated up to 50 Gy, and volume 2 received an additional 20 Gy. The LHRH agonist, goserelin acetate (Zoladex, AstraZeneca, Macclesfield, UK), was administered subcutaneously every 4 weeks starting the first day of pelvic irradiation and continued for 3 years; this mode of administration is now obsolete and a 3-monthly depot is generally used. A steroidal antiandrogen (cyproterone acetate) was given orally for 1 month (Androcur, Schering AG, Berlin, Germany, and Schering GmbH und Co Produktions KG, Weimar, Germany), 50 mg three times a day, starting a week before goserelin, to prevent the flare that results from the testosterone surge occurring after LHRH-agonist administration.

Criteria for local failure, regional failure, and distant metastases have been described, as well as the quality assurance concerning calibration of linear accelerator[1,11] and treatment technique. Data for quality of life were not obtained in this study. Participating centres were retrospectively asked to report on peripheral and vertebral fractures. The primary endpoint was clinical disease-free survival. Secondary outcomes were overall survival, distant metastasis-free survival, cause-specific mortality, and locoregional control.

Statistical analysis

SAS (version 9.2) was used for all analyses. The study was sized to detect a hazard ratio (HR) of 0·65 for clinical disease-free survival with a power of 80% and a type 1

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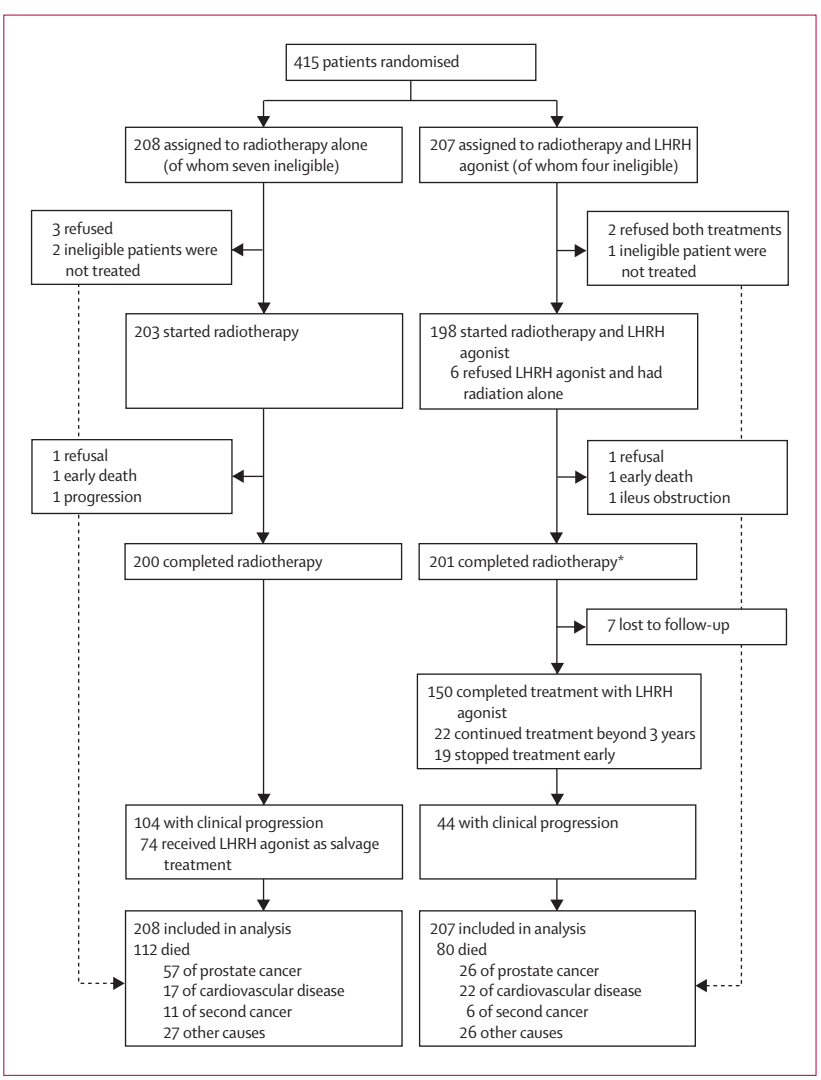

Figure 1: **Trial profile**
LHRH=luteinising-hormone-releasing hormone. *195 patients receiving radiotherapy plus LHRH agonist, six patients on radiotherapy alone.

error probability of 0·05.[12] Distant metastasis-free survival (time to first clinical evidence of distant metastasis progression or death of any cause), clinical disease-free survival (time to first clinical progression or death of any cause), and overall survival were calculated from the date of randomisation to the date of event and have already been defined.[1] Survival curves were estimated with the Kaplan-Meier technique.[13] Survival durations were compared with a two-sided log-rank test.[14] Cumulative incidence curves were used to assess cause-specific mortality and locoregional failure. Cause of death was prospectively documented by the treating physician and was not subjected to central independent review.

Analysis was by intention to treat in all patients randomly assigned to treatment groups, and a sensitivity analysis was done for the stratum with T3–4 any grade disease. This report is an update of previously published results,[1] and the significance level used was 0·05 (two-sided).

This trial is registered with ClinicalTrials.gov, number NCT00849082.

	Radiation only (N=208)	Radiation plus androgen suppression (N=207)
Age (years)	70 (65–75)	71 (67–75)
WHO performance status		
0	164 (79%)	162 (78%)
1	38 (18%)	37 (18%)
2	4 (2%)	7 (3%)
Not documented	2 (1%)	1 (<1%)
Chronic disease		
None	100 (48%)	111 (54%)
Cardiovascular	63 (30%)	53 (26%)
Other	42 (20%)	43 (21%)
Not documented	3 (1%)	0
WHO histopathological grade		
G1	39 (19%)	44 (21%)
G2	96 (46%)	98 (47%)
G3	68 (33%)	63 (30%)
Not documented	5 (2%)	2 (1%)
Gleason total score (central review)		
2–4	16 (8%)	11 (5%)
5–6	40 (19%)	50 (24%)
7–10	71 (34%)	66 (32%)
Not documented	81 (39%)	80 (39%)
T classification (clinical)		
T1	2 (1%)	2 (1%)
T2	20 (10%)	18 (9%)
T3	167 (80%)	167 (81%)
T4	18 (9%)	20 (10%)
Not documented	1 (<1%)	0
T according to grade (stratification)		
T1–2 G3	20 (10%)	20 (10%)
T3–4 any G	188 (90%)	187 (90%)
N classification		
N0	183 (88%)	184 (89%)
N1	5 (2%)	4 (2%)
N2	1 (<1%)	5 (2%)
N4	1 (<1%)	0
NX	18 (9%)	14 (7%)
Baseline PSA concentration*		
<4 µg/L	10 (5%)	16 (8%)
4 to <10 µg/L	23 (11%)	24 (12%)
10 to <20 µg/L	36 (17%)	29 (14%)
20 to <40 µg/L	49 (24%)	47 (23%)
>40 µg/L	67 (32%)	72 (35%)
Not documented	23 (11%)	19 (9%)

Data are number (%) or median (IQR). PSA=prostate-specific antigen. *Upper limit of normal=4 µg/L.

Table 1: **Patient characteristics**

Role of the funding source

AstraZeneca provided goserelin, but study design, data collection, data analysis, and data interpretation were all done by the EORTC in complete independence from AstraZeneca. AstraZeneca had no role in the writing of the report. MB had full access to all the data and had final responsibility for the decision to submit the report for publication.

Results

Between May 22, 1987, and Oct 31, 1995, 415 patients entered the study from 26 centres (21 centres from eight European countries, three sites in Israel, one in Russia, and one in Canada). 208 were assigned to the radiation-alone group and 207 to the combined treatment group (figure 1). At the time of this analysis, the median duration of follow-up was 9·1 years (IQR 5·1–12·6). Of 415 patients, 11 were ineligible (four assigned to combined treatment and seven to radiotherapy alone). Reasons for ineligibility were: incomplete examination before randomisation (one), inadequate disease stage or histopathology (nine), and poor physical condition (one). The characteristics of all patients were well balanced between treatment groups with respect to age, WHO performance status, clinical stages, pelvic-lymph-node status, WHO histological grade, Gleason grade, and baseline PSA concentration (table 1). PSA baseline concentration was defined with respect to the normal value of each PSA determination by immunoenzymatic or radioimmunometric assay.

Figure 1 details compliance to treatment for all patients. In the radiotherapy group, 203 (98%) of 208 patients started treatment, of whom three finished treatment early. Of the 207 patients allocated combined treatment, two refused all treatment, one ineligible patient was not treated, and six refused hormonal therapy, but were irradiated. Three patients stopped irradiation early. Of the 198 patients who started hormonal therapy, 150 (76%) completed their treatment per protocol (of whom 23 stopped before year 3 because of progression or died within 3 years), 22 (11%) continued beyond 3 years of treatment, seven (4%) were

lost to follow-up, and 19 (10%) had less than 3 years of treatment (15 refused to continue or stopped because of toxic effects, four required surgery).

After a median 9·1 years, 104 eligible patients in the radiotherapy group had progressive disease as compared with 44 in the combined treatment group (table 2). In the radiotherapy group, the treatment applied at the time of progression was an LHRH agonist in 74 (71%) patients, 25 patients received another treatment (in general, orchiectomy or antiandrogens), and treatment at relapse was unknown for five patients. Clinical disease-free survival differed significantly between the two groups (HR 0·42, 95% CI 0·33–0·55, p<0·0001; figure 2), with 47·7% (95% CI 39·0–56·0) of patients in the combined treatment group being clinically disease-free at 10 years compared with 22·7% (16·3–29·7) in the radiotherapy group.

Overall survival was significantly better after combined treatment than after radiotherapy alone (HR 0·60, 95% CI 0·45–0·80; p=0·0004); 10-year overall survival was 58·1% (95% CI 49·2–66·0) in the combined treatment group compared with 39·8% (31·9–47·5) in the radiotherapy group (figure 3). Overall, 112 deaths were registered in the radiotherapy group and 80 in the combined treatment group, with 57 deaths in the radiotherapy group and 26 in the combined treatment group due to prostate cancer. Results were similar when analysis was restricted to the cohort of T3–4 patients (90% of the whole sample); those in the combined treatment group had a better 10-year overall survival (58·5%) than did those in the radiotherapy group (37·7%; HR 0·56, 95% CI 0·41–0·75; p=0·0001).

There was a significant reduction in the 10-year cumulative incidence of prostate-cancer mortality with combined treatment (HR 0·38, 95% CI 0·24–0·60; p<0·0001); 10-year prostate-cancer mortality was 30·4% (95% CI 23·2–37·5) for the radiotherapy group versus 10·3% (5·1–15·4) for the combined treatment group (figure 4). These results were similar when analysis was restricted to the T3–4 stratum (data not shown). With respect to cardiovascular mortality, no significant difference was noted between treatment groups in patients who presented with cardiovascular disease at study entry (eight of 53 patients in the combined treatment group died from cardiovascular-related causes *vs* 11 of 63 patients in the radiotherapy group; p=0·60; figure 5A) or in those who reported no such disease at study entry (14 of 154 *vs* six of 145; p=0·25; figure 5B).

As reported previously, locoregional control was significantly improved in the combined treatment group compared with the radiotherapy alone group (HR 0·21, 95% CI 0·12–0·40; p<0·0001). At 10 years, the cumulative locoregional failure rate was 23·5% (95% CI 17·2–29·9) with radiation only, and 6·0% (2·1–9·9) in the combined treatment group. Equally apparent was a significant difference in favour of the combined treatment group in terms of the distant-metastasis-free survival (HR 0·50,

	Radiation only (N=208)	Radiation plus androgen suppression (N=207)
Any clinical progression	104 (50%)	44 (21%)
Local	19 (9%)	9 (4%)
Local and regional	3 (1%)	0
Distant progression	58 (28%)	31 (15%)
Local and distant	20 (10%)	4 (2%)
Local, regional, and distant	4 (2%)	0

Data are number (%).

Table 2: **Sites of disease progression**

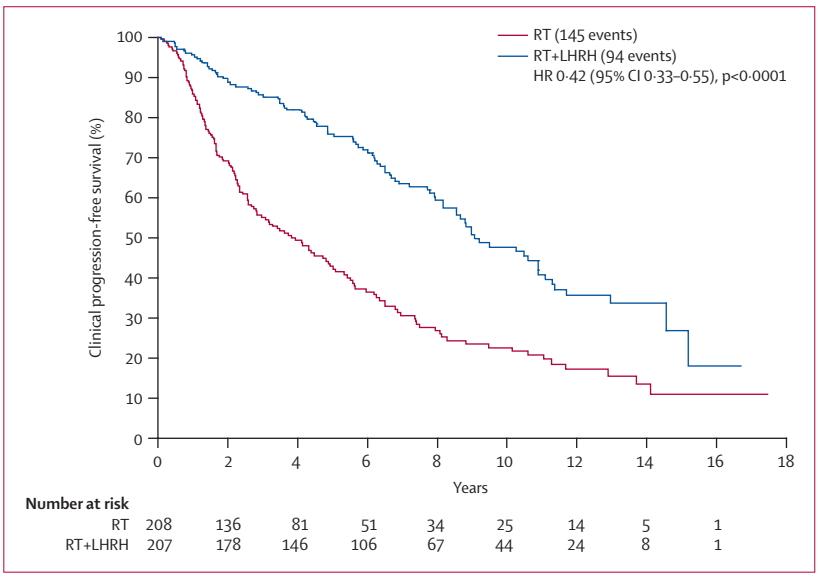

Figure 2: **Clinical progression-free survival**
RT=radiotherapy. LHRH=luteinising-hormone-releasing hormone.

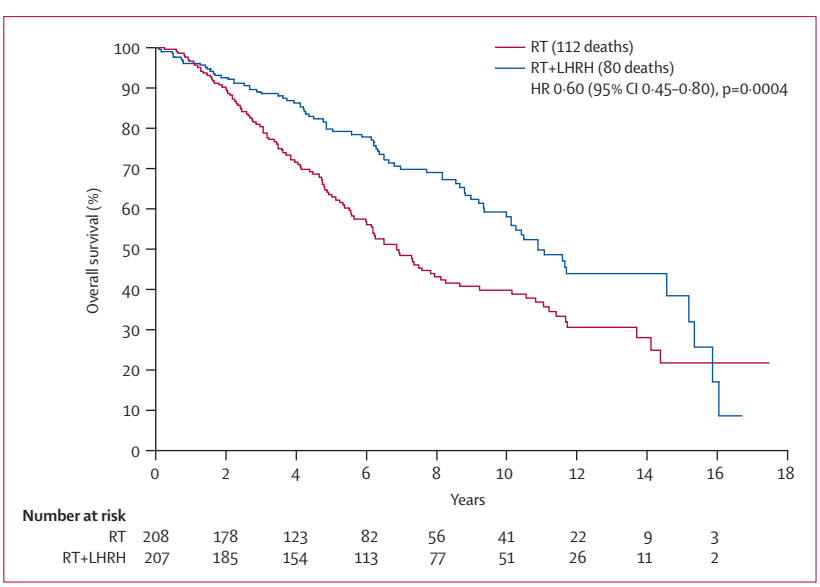

Figure 3: **Overall survival**
RT=radiotherapy. LHRH=luteinising-hormone-releasing hormone.

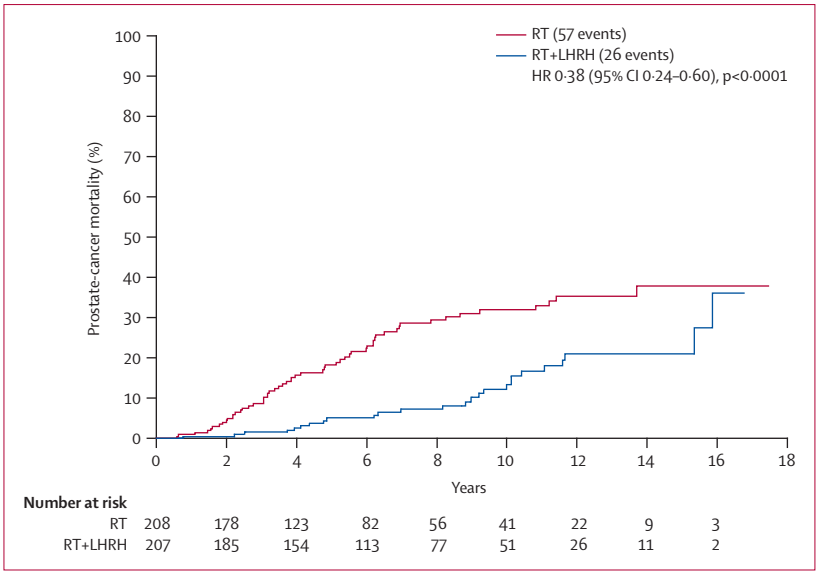

Figure 4: **Prostate-cancer mortality**
RT=radiotherapy. LHRH=luteinising-hormone-releasing hormone.

95% CI 0·38–0·65); 10-year distant-metastasis-free survival was 51% (95% CI 42·3–59·1) in the combined treatment group versus 30·2% (23·1–37·6) in the radiotherapy group (p<0·0001).

Two fractures were reported in the combined treatment group, at 7·2 and 9·9 years after the start of treatment. The number of second cancers did not differ between groups—18 (9%) patients had a second cancer after radiation only and 14 (7%) after combined treatment.

Discussion

EORTC 22863 showed that in patients with prostate cancer with high metastatic risk, radiotherapy plus 3 years of androgen suppression significantly improved overall survival[1] compared with initial therapy with radiation alone. The 10-year results of this study confirm that the benefit is maintained. Androgen suppression probably contributes to elimination of occult systemic disease while also potentiating external irradiation by an additive, perhaps even supra-additive, effect on local control through induction of apoptosis.[15,16] These results are in line with those of RTOG 85-31, in which patients were randomly assigned to either radiotherapy alone, with goserelin at relapse, or to radiotherapy and adjuvant goserelin given indefinitely or until disease progression. At 10 years, absolute survival was significantly better for the goserelin group than for the control group (49% *vs* 39%; p=0·002).[4] Table 3 lists all trials addressing the use or duration of androgen suppression and the dose of irradiation as combined modality of adjuvant treatments of prostate cancer.

Our trial has raised criticism linked to the absence of a group receiving endocrine treatment alone. When our study was initiated, LHRH agonists were fairly new and data for the long-term antitumour effects of goserelin were scarce. Widmark and colleagues[17] have since shown that the radiotherapy component of the combined treatment is necessary. Protocol SPCG-7/SFUO-3 included 875 patients with locally advanced prostate cancer who were randomly assigned to androgen suppression alone (3 months of total androgen blockade followed by continuous endocrine treatment with flutamide) or to the same endocrine treatment combined with local radiotherapy; addition of radiotherapy to endocrine treatment halved the 10-year prostate-specific mortality and substantially decreased overall mortality.[17] One of the remaining questions was whether the duration of androgen suppression, 3 years, was optimum. In EORTC 22961, 970 patients who had received radiotherapy plus 6 months of androgen suppression were randomly assigned to two groups—one to receive no further treatment (short-term androgen suppression) and the other to receive 2·5 years of further treatment (long-term androgen suppression). We found that at 5 years, overall mortality was higher with short-term than with long-term suppression, as was prostate-cancer-specific mortality and all other efficacy endpoints, whereas overall quality of life did not differ significantly between the two groups. We concluded that non-inferiority could not be shown and hence short-term androgen suppression was inferior to long-term suppression.[5]

We assessed cardiovascular mortality retrospectively by taking into account all deaths linked to cardiovascular disease. Long-term androgen suppression did not significantly increase cardiovascular mortality in patients who declared cardiovascular problems at study entry or in those who had no such problems. This finding is in line with those of the RTOG 92-02 and 85-31 trials.[25,26] We have not evaluated the effect of prevalent diabetes on mortality since this information was not recorded on our case report forms. Additionally, we did not centrally review cause of death, and some attribution bias cannot be excluded. In RTOG 92-02 trial, weight but not diabetes was associated with prostate-cancer mortality.[27] However, we should remain cautious about long-term androgen suppression in patients with a cardiovascular condition and diabetes.

When the trial was launched we were not aware that LHRH agonists might decrease bone mineral density. Participating centres were therefore only retrospectively asked to report on peripheral and vertebral fractures. Only two patients suffered bone fractures. With this finding we could not confirm the epidemiological data of Shahinian and colleagues,[7] who noticed an increased risk of fractures in patients treated with androgen suppression. We should be cautious in the interpretation of our data on this point because of their retrospective nature.

The combination of radiotherapy and 3 years of androgen suppression improved long-term overall survival, without increasing late cardiovascular mortality, and should be regarded as standard of care for treatment of men with prostate cancer who are at high metastatic

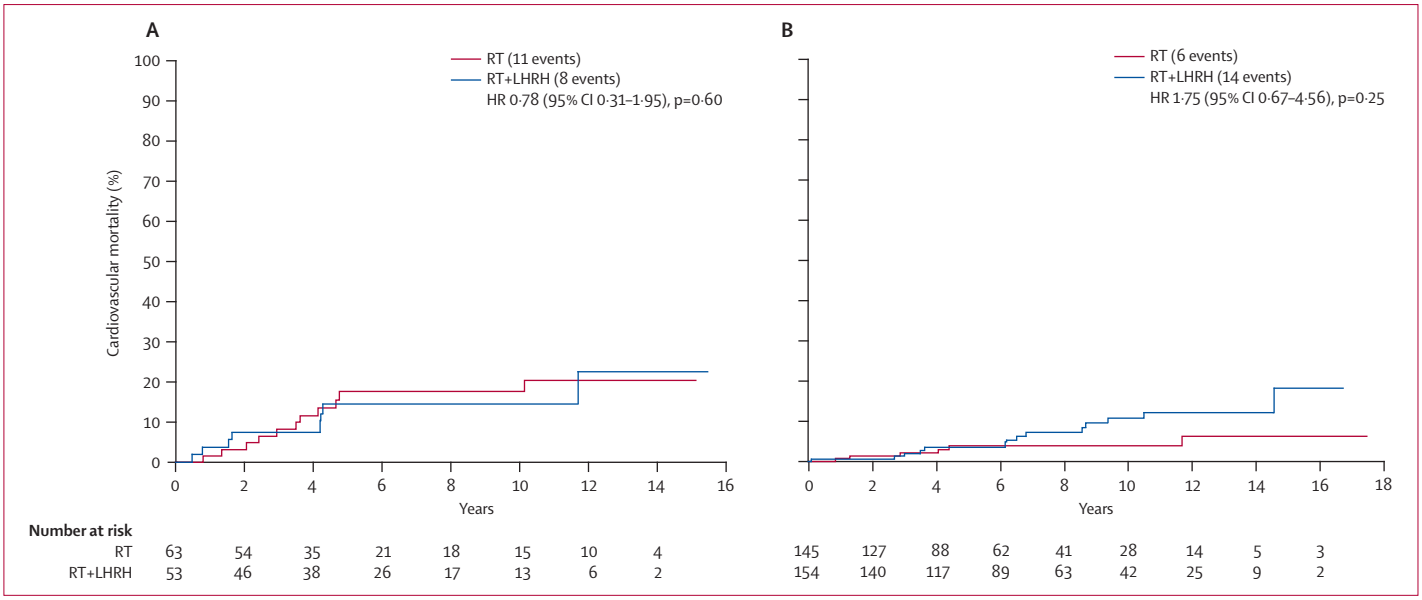

Figure 5: **Cardiovascular mortality**
Patients who (A) did and (B) did not report cardiovascular disease at entry to the study. RT=radiotherapy. LHRH=luteinising-hormone-releasing hormone.

	Year of publication	TNM classification (2002)	Number of patients	Androgen suppression therapy	External irradiation	Effect on overall survival
Adjuvant (+/-concomitant) androgen suppression plus RT *vs* RT alone						
EORTC 22863[1]	2002	T1–2 poorly differentiated and M0, or T3–4 N0–1 M0	415	LHRH agonist for 3 years	70 Gy RT	Significant benefit for combined treatment (HR 0·51, 95% CI 0·36–0·73, p=0·0002)
RTOG 85-31[4]	2005	T3 or N1 M0	977	Orchiectomy or LHRH agonist	65–70 Gy RT	Significant benefit for combined treatment (p=0·002) seems to be mostly caused by patients with Gleason score 7–10
Granfors[18]	2006	T3 N0–1 M0	91	Orchiectomy	65 Gy RT	Significant benefit (p=0·02), mainly caused by lymph-node-positive tumours
D'Amico[19]	2008	T2 N0 M0 (localised unfavourable risk)	206	LHRH agonist plus flutamide for 6 months	70 Gy 3D-CRT	Significant benefit (HR 0·55, 95% CI 0·34–0·90, p=0·01) that may pertain only to men with no or minimal comorbidity
Neoadjuvant and concomitant androgen suppression plus RT *vs* RT alone						
TROG 96-01[20]	2005	T2b–4 N0 M0	802	Goserelin plus flutamide 3 or 6 months before, plus concomitant suppression	66 Gy 3D-CRT	No significant difference in overall survival reported; benefit in prostate-cancer-specific survival (HR 0·56, 95% CI 0·32–0·98, p=0·04)
RTOG 94-13[21]	2007	T1c–4 N0–1 M0	1292	2 months neoadjuvant plus concomitant versus 4 months adjuvant suppression	Whole pelvic RT versus prostate only; 70·2 Gy	No significant difference between neoadjuvant plus concomitant versus adjuvant androgen suppression therapy groups (interaction suspected)
RTOG 86-10[22]	2008	T2–4 N0–1	456	Goserelin plus flutamide 2 months before, plus concomitant therapy	65–70 Gy RT	No significant difference at 10 years
Short-term *vs* long-term androgen suppression adjuvant (+/- concomitant) to RT						
RTOG 92-02[3]	2008	T2c–4 N0–1 M0	1554	LHRH agonist given for 2 years as adjuvant after 4 months as neoadjuvant	65–70 Gy RT	p=0·73 overall; significant benefit (p=0·044) in subset with Gleason score 8–10
EORTC 22961[5]	2009	T1c–2ab N1 M0, T2c–4 N0–1 M0	970	LHRH agonist for 6 months versus 3 years	70 Gy 3D-CRT	Better result with 3-year treatment than with 6 months (3·8% improvement in survival at 5 years)
Androgen suppression plus RT *vs* suppression alone						
SPCGF-7/SFUO-3[17]	2009	T1b–2 Grade 2–3, T3 N0 M0	880	LHRH agonist for 3 months plus continuous flutamide	70 Gy 3D-CRT versus no RT	Significantly better survival with combined treatment (HR 0·68, 95% CI 0·52–0·89, p=0·004)
NCIC CTG PR.3/ MRC PR07/SWOG[23]	2010	T3–4 N0 M0	1205	Continuous LHRH agonist	65–70 Gy 3D-CRT versus no RT	Significant benefit in favour of combined treatment (HR 0·77, 95% CI 0·61–0·98, p=0·033)
Mottet[24]	2010	T3–4 N0 M0	273	LHRH agonist for 3 years	70 Gy 3D-CRT versus no RT	Significant reduction of clinical progression; effect on overall survival not reported

LHRH=luteinising-hormone-releasing hormone. RT=radiotherapy. HR=hazard ratio. 3D-CRT=three-dimensional conformal radiotherapy.

Table 3: **Phase 3 studies addressing use and duration of androgen suppression and irradiation dose as combined modality adjuvant treatments for prostate cancer**

Panel: Research in context

Systematic review

All results of randomised studies of androgen deprivation therapy adjuvant to or concomittant with external beam radiation in prostate cancer (Medline) published since 2000 and reporting disease-free survival or overall survival, or both, were selected for this systematic review. Additionally, abstracts from American Society of Clinical Oncology and American and European Society for Radiation Oncology congresses of 2009 and 2010 were searched for updated results. This review obviously cannot avoid the publication bias and problems resulting from differences in patient characteristics, treatment schemes, and others.

Interpretation

For men with prostate cancer at high metastatic risk, with a WHO performance status of 0–2 and no contraindicating coexisting conditions, EORTC 22863 showed that 3 years of androgen deprivation starting with external irradiation improved long-term overall survival. The benefit observed at 5 years of median follow-up was sustained at 10 years' median follow-up. The results of this trial are in line with those of other studies. The optimum duration of treatment should be adapted to risk factors and comorbid conditions of individual patients.

risk, with a WHO performance status of 0–2, and who have no contraindicating coexisting conditions (panel). Three-dimensional conformal radiotherapy plus or minus intensified modulated radiotherapy has now replaced conventional irradiation, allowing dose escalation with improvement of locoregional control without increasing severe toxicity;[28] this finding also seems to be true for patients treated with radiation and long-term androgen suppression, for whom in Zapatero and colleagues' study[29] 5-year biochemical disease-free survival was increased. Metastatic risk outside the irradiated volume is still substantial in high-risk patients, and systemic chemotherapy such as docetaxel deserves to be assessed in phase 3 trials in view of the improvement of overall survival that this drug could offer to castration-resistant patients.[30,31]

Contributors

MB developed the protocol and coordinated the study. LC did the statistical analysis. MB and LC wrote the report. All the investigators enrolled patients and were involved in the writing of the report, and reviewed and approved the final version. A list of participating centres and principal investigators can be found in the webappendix.

See Online for webappendix

Conflicts of interest

MB has received payment for development of educational presentations from Astellas and Ipsen. JLT has received honoraria from AstraZeneca Spain. All other authors declared no conflicts of interest.

Acknowledgments

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