Articles

Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial

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Summary

Background We did a randomised phase III trial comparing external irradiation alone and external irradiation combined with an analogue of luteinising-hormone releasing hormone (LHRH) to investigate the added value of long-term androgen suppression in locally advanced prostate cancer.

Methods Between 1987 and 1995, 415 patients were randomly assigned radiotherapy alone or radiotherapy plus immediate androgen suppression. Eligible patients had T1–2 tumours of WHO grade 3 or T3–4 N0–1 M0 tumours; the median age of participants was 71 years (range 51–80). In both treatment groups, 50 Gy radiation was delivered to the pelvis over 5 weeks, and 20 Gy over 2 weeks as a prostatic boost. Goserelin (3·6 mg subcutaneously every 4 weeks) was started on the first day of irradiation and continued for 3 years; cyproterone acetate (150 mg orally) was given for 1 month starting 1 week before the first goserelin injection. The primary endpoint was clinical disease-free survival. Analyses were by intention to treat.

Findings 412 patients had evaluable data, with median follow-up of 66 months (range 1–126). 5-year clinical disease-free survival was 40% (95% CI 32–48) in the radiotherapy-alone group and 74% (67–81) in the combined-treatment group (p=0·0001). 5-year overall survival was 62% (52–72) and 78% (72–84), respectively (p=0·0002) and 5-year specific survival 79% (72–86) and 94% (90–98).

Interpretation Immediate androgen suppression with an LHRH analogue given during and for 3 years after external irradiation improves disease-free and overall survival of patients with locally advanced prostate cancer.

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Introduction

The long-term outcome after external irradiation alone in locally advanced prostate cancer, staged T3–4N0M0 according to the classification of the International Union against Cancer[1] is poor,[2] especially for biochemically defined disease-free survival.[3] From the mid-1980s, two approaches to improve these results were investigated: first, the combination of androgen suppression and external irradiation in an attempt to decrease the local failure rate and to destroy hormone-dependent micrometastases outside the planning target volume; and second, three-dimensional conformal radiotherapy to improve local control,[4] by increasing the dose delivered to the prostate. Three phase III randomised trials have shown an improvement of overall survival with the combination of radiotherapy and androgen suppression. For two of these trials,[5,6] this improvement was greatest for a subset of patients with Gleason 8–10 T2c–T4 tumours, whereas an EORTC trial[7] found a significant difference in 5-year overall survival, irrespective of the histological grade. Here, we present the long-term results of this trial, with a multivariate prognostic-factor analysis, and assessment of the serum testosterone profile after the end of the long-term androgen suppression.

Methods

Patients

Eligible patients were younger than 80 years, with histologically proven T1–2 prostatic adenocarcinoma of WHO histological grade 3, or T3–4 prostatic adenocarcinoma of any histological grade. The clinical investigation was based on bone scan, chest radiograph, and ultrasonography or CT of the abdomen. Lymph nodes were assessed by CT scan, bipedal lymphangiography, or extraperitoneal lymphadenectomy. The laboratory studies included complete blood count and measurements of creatinine, serum testosterone, and prostate specific antigen (PSA) assessed by radioimmunoassaay or enzyme immunoassay. Patients had to have newly diagnosed prostate cancer and to have given informed consent in writing. Approval by local ethics committees was obtained in all centres. We excluded patients with a history of previous malignant disease, except for adequately treated basal-cell carcinoma of the skin, or evidence of distant metastases, including involvement of common iliac or para-aortic lymph nodes. Pathological samples were centrally reviewed.

Design and procedures

Randomisation was centralised at the EORTC Data Centre. Patients were stratified by institution, clinical stage of disease (T1–2 grade 3 *vs* T3–4 grade 1–3), results of pelvic-lymph-node dissection (N0 *vs* N1), and irradiation technique (extended fields *vs* limited fields). Randomisation was done by two independent secretaries

with the minimisation technique.[7] Patients were assigned external irradiation alone or external irradiation combined with an analogue of luteinising-hormone releasing hormone (LHRH) by a computer-generated system. The methods of treatment have been described previously.[8] Briefly, irradiation with photons of 10 MV and above was recommended. The first planning target volume was the whole pelvis and the second encompassed the prostate and the seminal vesicles. A four-field technique was used to irradiate the whole pelvis; at some centres limited fields were preferred. The second planning target volume was irradiated with the same technique or with three fields. The specification of the dose was given at the intersection of the beam axes according to report 29 of the International Commission on Radiation Units and Measurements.[9] Patients were treated once a day, 5 days a week, for 7 weeks: the first planning target volume was irradiated up to 50 Gy and the second received an additional 20 Gy. Goserelin acetate, the LHRH analogue, was administered subcutaneously every 4 weeks, starting on the first day of pelvic irradiation, and continued for 3 years; this method of administration is now obsolete, owing to the availability of a 3-monthly depot preparation.

A steroidal antiandrogen (cyproterone acetate) was given orally for 1 month, 50 mg three times daily, starting a week before the start of goserelin, to prevent the flare resulting from the surge in testosterone that arises after LHRH.

We measured PSA 2 months after the end of external irradiation, then every 3 months for 3 years, and every 6 months thereafter; in practice, the mean number of PSA measurements available per patient during follow-up in addition to the baseline assessment was seven (range none to 23). Follow-up PSA measurements were available for 388 patients (94%), 197 in the radiotherapy-alone group and 191 in the combined-treatment group. Measurement of testosterone concentration was asked for as a check of the validity of adjuvant hormonal treatment by LHRH analogues; these measurements had to be done with the same frequency as PSA measurements. However, owing to poor compliance, follow-up testosterone data were available for only 110 patients.

Acute side-effects of radiotherapy were scored according to the WHO scale.[1] Late toxic effects were scored according to the Radiotherapy Oncology Group. Local failure was defined as an increase of more than 50% in the product of the two maximum perpendicular diameters of the primary lesion as measured digitally, by CT or transabdominal ultrasonography; in case of doubt, biopsy was strongly recommended. Local progression was defined as recurrence of a palpable tumour after initial regression. Regional failure, in the area of the pelvis or the para-aortic lymph nodes, was detected by ultrasonography or CT and confirmed by biopsy. Distant metastases in bones, parenchymal organs, or soft tissues were identified radiologically and then by biopsy if deemed necessary. Quality assurance in calibration of linear accelerators and treatment technique have been described elsewhere.[10] Quality-of-life data were not gathered in this study.

Statistical analysis

The primary endpoint was disease-free survival at 5 years. With the assumption of 5-year disease-free survival of 40% in the group assigned radiotherapy alone, we estimated that 75 patients had to be followed up until relapse or death in each treatment group for us to detect a 15% difference in the 5-year disease-free survival with power of 80% and a type-I error probability of 0·05.[11] This difference corresponds to an increase from 3·8 to 5·8 years in the median disease-free survival (on the assumption of exponentiality). Clinical disease-free interval (time to first clinical evidence of progression), clinical disease-free survival (time to first clinical progression or death from any cause), and overall survival were calculated from the date of randomisation to the date of event and have already been defined.[8] Survival curves were estimated by the Kaplan-Meier technique. We compared duration of overall and disease-free survival and the disease-free interval by a two-sided log-rank test. Cumulative incidence curves were used to assess the rates of locoregional failure and distant failure. The time until the first treatment failure after a biological response was measured from the date of randomisation to the date of clinically determined progression, PSA-defined progression, or the latest follow-up. PSA-defined progression was a concentration higher than 1·5 μg/L and increasing on two consecutive measurements.[3] The multivariate prognostic-factor analysis used Cox's proportional-hazards regression model. The prognostic index was obtained as the sum of the log (hazard ratio) associated with each patient's profile; the value was 0 plus 0·36 (if WHO performance status was above 0), plus 0·56 (if grade G3), plus 0·55 (if PSA concentration was above 10 μg/L). The prognostic index could therefore be between 0 and 1·52. Three risk groups were formed by classing together patients with similar values of the prognostic index to obtain the maximum separation between survival of the groups. All analyses were by intention to treat.

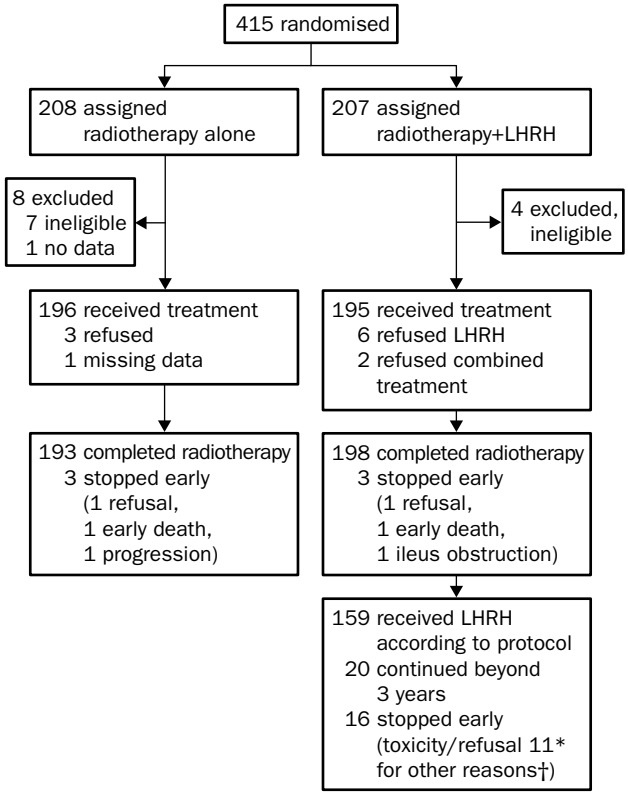


Figure 1: **Trial profile**

All randomised patients were included in the intention-to-treat analyses. *Five refused further treatment owing to hot flushes and three refused further treatment at the end of radiotherapy; two stopped because of depression and one because of mastodynia and galactorrhoea. †Two underwent orchiectomy because of poor compliance with goserelin; one needed urethrotomy and reconstruction owing to recurrent strictures; one was lost to follow-up after 15 months; and one had poor compliance owing to the cost of treatment so underwent orchiectomy.

	Radiotherapy alone (n=198)	Combined treatment (n=203)
Median (range) age, years	70 (51–80)	71 (54–80)
Performance status		
0	157 (79%)	158 (78%)
1	37 (19%)	38 (19%)
2	4 (2%)	7 (4%)
WHO grade		
G1	37 (19%)	44 (22%)
G2	90 (45%)	96 (47%)
G3	67 (34%)	62 (30%)
Unknown	4 (2%)	1 (1%)
Gleason grade		
2–4	16 (8%)	10 (5%)
5–6	38 (19%)	49 (24%)
7–10	71 (36%)	66 (33%)
Unknown	73 (37%)	78 (38%)
Classification		
T1	0	2 (1%)
T2	17 (7%)	15 (7%)
T3	163 (82%)	167 (82%)
T4	18 (9%)	19 (9%)
T according to grade		
T1–T2 G3	17 (9%)	17 (8%)
T3–T4 all grades	181 (91%)	186 (92%)
N classification		
N0	176 (89%)	181 (89%)
N1	5 (3%)	4 (2%)
N2	1 (1%)	4 (2%)
Unknown	16 (8%)	14 (7%)
PSA concentration (mg/L)		
⩽4·0	10 (5%)	15 (7%)
4·1–10·0	21 (11%)	24 (12%)
10·1–20·0	36 (18%)	28 (14%)
20·1–40·0	48 (24%)	47 (23%)
>40·0	62 (31%)	72 (35%)
Unknown	21 (11%)	17 (8%)

Data are number of patients unless otherwise stated.

Table 1: **Baseline characteristics of treatment groups**

Role of the funding source
Astra Zeneca provided the goserelin, but had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

Results

Between May, 1987, and September, 1995, 415 patients entered the study: 208 were randomly assigned to the radiotherapy-alone group and 207 to the combined-treatment group (figure 1). At the time of the analysis reported here, median duration of follow-up was 66 months (range 1–126). 412 patients could be centrally evaluated and 11 were ineligible (four assigned combined treatment and seven assigned radiotherapy alone). The reasons for ineligibility were incomplete examination before randomisation (one), inadequate disease staging or histopathology (nine), or poor physical condition (one). The characteristics of eligible patients showed good balance between the treatment groups in age, WHO performance status, clinical stage, pelvic-lymph-node status, WHO histological grade, Gleason grade, and baseline PSA (table 1). Baseline PSA concentration was defined in relation to the normal value of each PSA measurement. Cardiovascular disease was present in 58 (29%) patients in the radiotherapy group and 49 (24%) in the combined-treatment group; no chronic disease was mentioned for 95 (48%) patients in the radiotherapy group compared with 108 (53%) in the combined-treatment group.

Type of progression	Radiotherapy (n=208)	Combined treatment (n=207)
Any clinical progression	90	27
Local	15	3
Local and regional	3	0
Distant	56	22
Local and distant	13	2
Local, regional, and distant	3	0

Table 2: **Sites of disease progression**

Treatment information was available for 403 patients (figure 1; 200 in the radiotherapy group and 203 in the combined-treatment group). 196 patients in the radiotherapy-alone group received external irradiation; three refused treatment. In the combined-treatment group, 195 of the 203 patients received the treatment; two patients refused all treatment, and six refused hormonal therapy. 21 (11%) patients received the hormone injections with irregular intervals. 159 (87%) patients received the hormonal treatment planned by the protocol; 127 (65%) received the full 3 years of treatment, 23 (12%) stopped earlier than 3 years owing to progression or death, and 20 (10%) received the 3 years of treatment but did not stop at that point. For another nine patients, total follow-up is presently less than 3 years and they remain on treatment. 11 (6%) stopped earlier than 3 years because of toxic effects or the patient's wish, and five stopped earlier than 3 years for other reasons.

After a median of 65·7 months, progression has occurred in 90 patients in the radiotherapy group and 27 in the combined-treatment group (table 2). In the radiotherapy group, the treatment given at the time of progression was goserelin in 65 cases (72%), surgical castration in seven, another LHRH analogue in five, delayed treatment in five, unspecified treatment in two, no treatment because the patient refused in one case, no treatment because of death from another cause in one case, or no documented treatment (four). In terms of locoregional control, the outcome was better in the combined-treatment group than in the radiotherapy group (5-year cumulative incidence of locoregional failure 16·4% [95% CI 10·8–22·1] *vs* 1·7% [0–3·7]; p<0·0001). There was also a significant difference in favour of combined treatment in the cumulative incidence of distant metastases (5-year cumulative incidence 29·2% [22·7–35·6] in the radiotherapy group *vs* 9·8% [5·4–14·2]; p<0·0001). There was no difference in the rate of second primary tumours between groups (6% *vs* 5%).

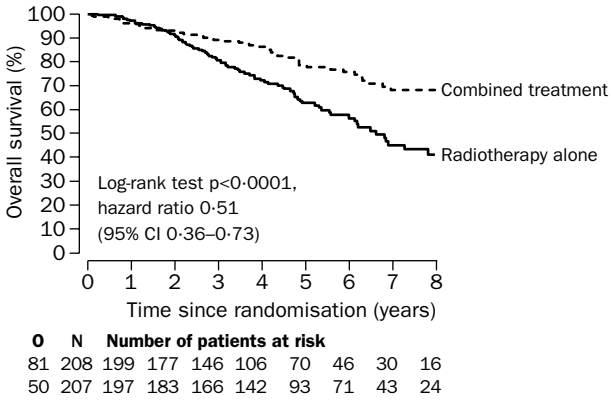


Figure 2: **Kaplan-Meier estimates of overall survival by treatment group**
O=number of deaths; N=number of patients.

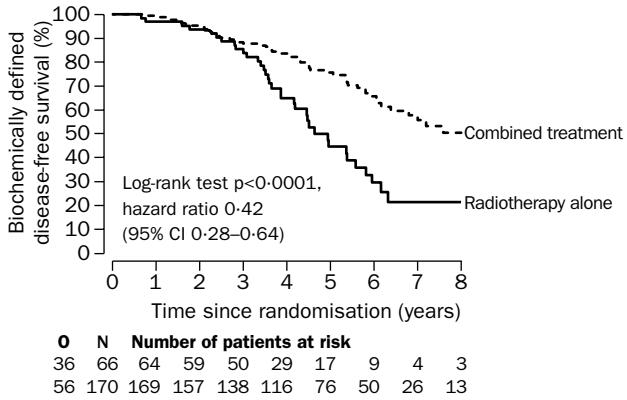


Figure 3: **Kaplan-Meier estimates of the biochemically defined disease-free survival**
O=number of failures; N=number of patients.

There was a significant difference between the groups in clinical disease-free survival (time to clinical failure or death from any cause; the hazard ratio was 0·34 (0·26–0·46; p<0·0001) with 74% (67–81) of patients in the combined-treatment group clinically disease free at 5 years compared with 40% (32–48) in the radiotherapy-alone group.

Overall survival also differed significantly between groups, with a hazard ratio of 0·51 (95% CI 0·36–0·73); the 5-year survival was 78% (72–84) in the combined-treatment group and 62% (52–72) in the radiotherapy group (p=0·0002; figure 2). 78 deaths were registered in the radiotherapy group and 50 in the combined-treatment group, with 42 and 12 deaths, respectively, due to prostate cancer. 5-year specific survival was 94% (90–98) in the combined-treatment group and 79% (72–86) in the radiotherapy group (p=0·0001; hazard ratio 0·26 [0·15–0·44]).

In terms of the biochemical disease-free survival, combined treatment was also better than radiotherapy alone (hazard ratio 0·42 [0·28–0·64]; p<0·0001; 5-year values 76% [69–83] *vs* 45% [30–60]; figure 3).

The results were similar in the cohort of patients with T3–4 disease (89% of the whole sample); 5-year overall survival was better in the combined-treatment group than in the radiotherapy group (78% *vs* 60%; hazard ratio 0·46 [0·32–0·65]; p=0·0001) as was specific survival (94% *vs* 78%; hazard ratio 0·23 [0·14–0·41]; p=0·0001).

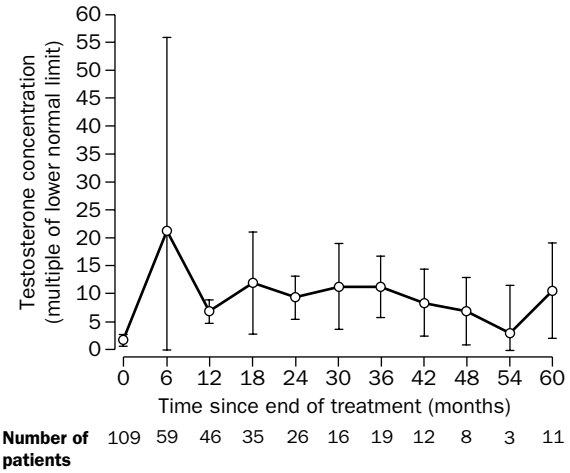


Figure 4: **Testosterone concentrations after the end of the combined treatment**
Values are arithmetic means; bars are 95% CIs. The dashed horizontal bar represents the castration value or lower limit of the normal range.

Variable	Relative-risk estimate (95% CI)	p
WHO performance status		
0*	100	
>0	1·43 (1·01–2·03)	0·0459
WHO grade		
G1–2*	1·00	
G3	1·84 (1·33–2·54)	0·0002
PSA concentration (mg/L)		
<10*	1·00	
>10	1·83 (1·17–2·88)	0·0085

*Reference category.

Table 3: **Multivariate prognostic-factors model**

Figure 4 shows the testosterone concentration (expressed as multiples of the lower normal limit) after withdrawal of goserelin treatment. In 82 of 109 patients assessed for testosterone concentration after the end of the adjuvant hormonal treatment, the testosterone concentration rose above the lower limit of normal (castration value).

According to the univariate analysis, the prognostic factors for clinical disease-free survival were WHO performance status (0 *vs* >0; p=0·001), associated chronic disease (none or disease other than cardiovascular *vs* cardiovascular disease; p=0·02), G grade (G1–2 *vs* G3; p=0·0003), and initial PSA concentration (≤10 μg/L *vs* >10 μg/L; p=0·016). The effect of N category could not be analysed because only 16 patients were N1. The variables associated cardiovascular disease, WHO performance status, grade G3, and baseline PSA concentration were entered in the multivariate model selection procedure. Associated cardiovascular disease dropped out of the model, leading to the final multivariate model described in table 3. Risk categories can be formed by calculating the prognostic index and classifying patients according to their prognostic indices as shown in table 4. Owing to missing values, only 365 patients could be classified in the risk groups: 43 (12%) low risk, 195 (53%) intermediate risk, and 127 (35%) high risk. The 5-year clinical disease-free survival was 83·8% (95% CI 71·7–96·0), 60·0% (52·4–67·7), and 43·4% (33·6–53·1), respectively, for these categories. Figure 5 shows disease-free survival by risk category for both treatment groups. The hazard ratio for combined treatment versus radiotherapy alone was 0·12 (0·01–1·01; p=0·0508) in the low-risk category, 0·28 (0·18–0·46; p=0·0001) in the intermediate-risk category, and 0·39 (0·24–0·63; p=0·0001) in the high-risk category. However, the overall test for a differing treatment effect according to risk category (interaction) was not significant (p=0·20), indicating homogeneous treatment effect in the three risk categories.

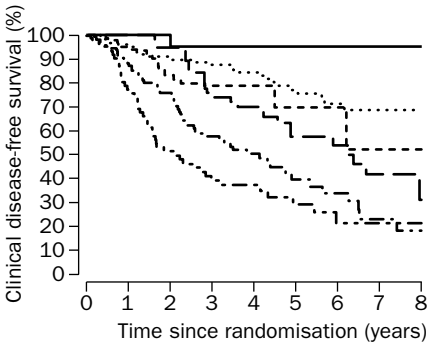
Discussion

The combination of 3 years of androgen suppression with external irradiation was associated with better 5-year overall survival of locally advanced prostate

Risk category	Prognostic index	Interpretation
Low	<0·4	No risk factors or WHO >0 as the only risk factor
Intermediate	>0·4–0·6	Grade G3 or PSA >2·5 times lower normal limit as only risk factor
High	>0·6	Two or more risk factors

Prognostic index=0+0·36 (if WHO PS >0)+0·56 (if grade G3)+0·55 (if PSA >10 mg/L).

Table 4: **Risk categories**



O	N	Number of patients at risk								Radiotherapy alone
6	20	20	18	14	11	8	4	3	3	Low risk
55	96	84	68	47	30	16	12	5	3	Intermediate risk
44	63	48	30	22	15	10	5	4	1	High risk
										Combined treatment
1	23	23	21	18	17	12	9	8	2	Low risk
26	99	94	89	84	71	46	33	17	10	Intermediate risk
27	64	59	47	40	34	20	15	8	3	High risk

Figure 5: **Clinical disease-free survival by risk category and treatment group**

O=number of failures; N=number of patients.

cancer than radiotherapy alone. These updated results, with median follow-up of 65·7 months, accord with those reported in 1996, when the median follow-up was 33 months,[12] and in 1997 with median follow-up of 45 months.[8] Androgen suppression provides a method to improve the outcome of external irradiation alone, possibly by elimination of occult systemic disease. Moreover, androgen suppression and external irradiation seem to have an additive effect on local control by induction of apoptosis.[13–15]

Adjuvant androgen deprivation is also effective with surgery, and in one prospective randomised study,[16] overall survival was better with long-term adjuvant hormonal treatment after radical prostatectomy than after surgery alone. In that study, 98 men who underwent radical prostatectomy and who had pelvic nodal metastases were randomly assigned goserelin or bilateral orchiectomy or to be followed up until disease progression without further treatment. After a median period of 7·1 years, there were significant benefits in overall survival (p=0·02), specific survival (p=0·001), and progression-free survival (p<0·001) in favour of the combined-treatment group. Conversely, short-term neoadjuvant androgen suppression followed by radical prostatectomy was associated with a lower rate of positive margins and lower tumour pathological stage, but there was no difference in overall survival.[17–19] Finally, there is a parallel between breast and prostate cancers: in both disorders the long-term outcome is improved by combination of radiotherapy and hormonal treatment,[20,21] and long-term adjuvant hormonal treatment significantly improves overall survival.[22]

Other clinical studies have addressed the role of androgen suppression with external irradiation. The Radiation Therapy Oncology Group has reported three randomised studies. Protocol 86-10[23,24] compared androgen deprivation plus radiotherapy with radiotherapy alone and included 456 patients with large T2 or T3–4 tumours. Flutamide was given daily and goserelin every 4 weeks, both started 2 months before radiotherapy began and were withdrawn at the completion of radiotherapy. Hormonal therapy increased the 5-year rates of local control (p<0·002) and freedom from distant metastases (p<0·03), and significantly increased 8-year progression-free survival (including PSA >4 μg/L as failure; p<0·0001). Protocol 85-31[5] investigated adjuvant androgen suppression with goserelin in patients classified as T1–2 with regional-lymph-node involvement, T3 whatever the regional-lymph-node status, or pT3 after prostatectomy. Goserelin was started at the end of the radiotherapy and continued indefinitely. With median follow-up of 4·5 years, there was an increase in the rates of local control (p<0·0001) and freedom from distant metastases (p<0·001) as well as disease-free survival (p<0·001). In patients with centrally reviewed tumours with a Gleason score of 8–10, there was a difference in actuarial 5-year survival in favour of the adjuvant-goserelin group (p=0·03). In protocol 92-02,[6] patients with T2c–T4 tumours and PSA concentrations below 150 μg/L received goserelin and flutamide for 2 months before and 2 months during radiation and were randomly assigned no further therapy or 24 additional months of goserelin alone. With median follow-up of 4·8 years, the group assigned long-term androgen suppression had significantly better disease-free survival (p=0·0001), local control (p=0·0001), time to distant metastasis (p=0·001), and time to biochemical failure (p=0·0001); disease-specific survival was slightly but not significantly higher (p=0·07). These studies of radiation, in combination with androgen deprivation in patients with locally advanced prostate cancer, have been criticised, because there was no group receiving hormone treatment only. A current National Cancer Institute of Canada trial is addressing the role of hormone treatment alone, comparing maximum androgen blockade with maximum androgen blockade plus pelvic irradiation in stages T3–4 N0 M0.

In our trial, the radiotherapy technique was conventional, far from being optimum. The contribution of radiotherapy to local control can be further improved by three-dimensional conformal radiotherapy. That approach enables physicians to delineate the planning target volume more accurately and to increase the dose to the tumour without increasing acute and late toxic effects. Preliminary results of a study[4] comparing conventional irradiation (70 Gy) and three-dimensional conformal radiotherapy (78 Gy) show that for patients with stage T1–2 disease and PSA concentrations above 10 μg/L, 4-year disease-free-survival is 55% with 70 Gy and 93% with 78 Gy (p=0·003). Zelefsky and colleagues[25] have shown that 5-year actuarial PSA-defined relapse-free survival is significantly better in patients with intermediate and unfavourable prognosis receiving more than 75·6 Gy (p<0·05).

What is an adequate duration of androgen deprivation therapy? It is not yet known. The period of 3 years of adjuvant hormonal treatment was chosen empirically; shortening of this period would reduce costs and side-effects of androgen deprivation (eg, hot flushes, fatigue, sexual dysfunction) and may be possible, since patients with locally advanced prostate cancer in the late 1990s had less tumour burden and were younger than those of the mid 1980s. This is the rationale for the EORTC equivalence trial 22961 started in 1997, which is comparing surveillance with hormone therapy (triptoreline) for 2·5 years after external irradiation and 6 months of combined androgen blockade. A period of 6 months of maximum androgen blockade followed by reinstitution of hormone therapy in case of relapse could achieve equivalent survival to the 3-year androgen-suppression regimen; after 6 months of maximum androgen blockade, any subsequent tumour growth would still allow hormonal treatment of the proliferating

androgen-dependent stem cells,[26] before tumour progression due to overgrowth by androgen-independent cells.

In the future, management of locally advanced prostate cancer will certainly be tailored according to prognostic factors, with a possible escalation of the dose and the addition of chemotherapy[27] to hormonal treatment for high-risk categories.

Contributors

M Bolla developed the protocol and coordinated the study. L Colette did the statistical analysis. M Pierart was responsible for data collection. All investigators, including L Blank who took over from D Gonzalez, enrolled patients and were involved in the writing of the report.

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Conflict of interest statement

None declared.

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