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Short Androgen Suppression and Radiation Dose Escalation in Prostate Cancer: 12-Year Results of EORTC Trial 22991 in Patients With Localized Intermediate-Risk Disease

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abstract

PURPOSE The European Organisation for Research and Treatment of Cancer (EORTC) trial 22991 (NCT00021450) showed that 6 months of concomitant and adjuvant androgen suppression (AS) improves event- (EFS, Phoenix) and clinical disease-free survival (DFS) of intermediate- and high-risk localized prostatic carcinoma, treated by external-beam radiotherapy (EBRT) at 70-78 Gy. We report the long-term results in intermediate-risk patients treated with 74 or 78 Gy EBRT, as per current guidelines.

PATIENT AND METHODS Of 819 patients randomly assigned between EBRT or EBRT plus AS started on day 1 of EBRT, 481 entered with intermediate risk (International Union Against Cancer TNM 1997 cT1b-c or T2a with prostate-specific antigen (PSA) ≥ 10 ng/mL or Gleason ≤ 7 and PSA ≤ 20 ng/mL, N0M0) and had EBRT planned at 74 (342 patients, 71.1%) or 78 Gy (139 patients, 28.9%). We report the trial primary end point EFS, DFS, distant metastasis–free survival (DMFS), and overall survival (OS) by intention-to-treat stratified by EBRT dose at two-sided $\alpha = 5\%$.

RESULTS At a median follow-up of 12.2 years, 92 of 245 patients and 132 of 236 had EFS events in the EBRT plus AS and EBRT arm, respectively, mostly PSA relapse (48.7%) or death (45.1%). EBRT plus AS improved EFS and DFS (hazard ratio [HR] = 0.53; CI, 0.41 to 0.70; $P < .001$ and HR = 0.67; CI, 0.49 to 0.90; $P = .008$). At 10 years, DMFS was 79.3% (CI, 73.4 to 84.0) with EBRT plus AS and 72.7% (CI, 66.2 to 78.2) with EBRT (HR = 0.74; CI, 0.53 to 1.02; $P = .065$). With 140 deaths (EBRT plus AS: 64; EBRT: 76), 10-year OS was 80.0% (CI, 74.1 to 84.7) with EBRT plus AS and 74.3% (CI, 67.8 to 79.7) with EBRT, but not statistically significantly different (HR = 0.74; CI, 0.53 to 1.04; $P = .082$).

CONCLUSION Six months of concomitant and adjuvant AS statistically significantly improves EFS and DFS in intermediate-risk prostatic carcinoma, treated by irradiation at 74 or 78 Gy. The effects on OS and DMFS did not reach statistical significance.

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ASSOCIATED CONTENT

Appendix

Data Sharing Statement

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Current guidelines[1-3] distinguish several risk categories of localized prostate cancer (PCa) defined by D'Amico classification[4] according to risk of biochemical relapse after radical prostatectomy or external-beam radiotherapy (EBRT). Patients with disease stage cT1b-T2b (International Union Against Cancer [UICC] 2002[5]) are classed intermediate risk if prostate-specific antigen (PSA) is in 10-20 ng/mL and/or Gleason sum equals 7; as well as patients with PSA < 10 ng/mL, Gleason sum < 7, and cT2b disease. Either a PSA > 20 ng/mL, a Gleason sum > 7, or a disease stage > cT2c is classified high-risk disease.

Radical prostatectomy and EBRT are recommended treatment options for intermediate- and high-risk PCa,[1-3] with similar long-term outcomes between the two approaches.[6] For both risk groups, a minimum radiation dose of 74 Gy is recommended based on several randomized controlled trials[7-12] and a well-conducted propensity-matched retrospective analysis.[13]

Numerous studies demonstrated the benefit of combining androgen suppression (AS) with EBRT[14-18] as

CONTEXT

Key Objective

Does short-term androgen suppression (AS) and radiation dose escalation to 74-78 Gy improve the long-term outcome of patients with localized intermediate-risk prostate cancer compared with radiation alone?

Knowledge Generated

With 12-year median follow-up of 481 intermediate-risk patients randomly assigned in EORTC trial 22991, we showed that six months of concomitant and adjuvant AS statistically significantly improves event-free survival (biochemical relapse by Phoenix, clinical relapse, or death) and clinical disease-free survival. The effect on overall survival and distant metastasis–free survival did not reach statistical significance, with limited statistical power.

Relevance

These are the most robust data from a randomized trial with long-term follow-up addressing this question. They shed light on the important clinical question of the value of AS in men treated with radiation if dose escalation is used.

initial treatment of localized PCa. Although the optimal treatment duration remains unclear, around 2-3 years of AS for localized high-risk disease is recommended, whereas a duration of 4-6 months of (neo)-adjuvant AS is considered sufficient for intermediate-risk patients.[1]

The European Organisation for Research and Treatment of Cancer (EORTC) trial 22991 was launched in 2001 to assess the benefit of 6 months of AS concomitant and adjuvant to EBRT in men with intermediate- and limited high-risk localized PCa. The treating centers selected the EBRT dose (70, 74, or 78 Gy) and the technique (three-dimensional conformal radiation therapy and intensity-modulated radiotherapy) that was their standard practice. The first results[19] published in 2016 with 7.2 years of median follow-up showed that 6-month concomitant and adjuvant AS combined with EBRT improved 5-year event-free survival (EFS) and clinical disease-free survival (DFS) of intermediate- and limited high-risk PCa compared with those treated with EBRT alone. Recognizing that today, patients with high-risk disease would receive long-term AS and that irradiation at the dose of 70 Gy is suboptimal, we report updated results with a median follow-up of 12.2 years in the subset of intermediate-risk patients treated with minimum 74 Gy of radiation.

PATIENTS AND METHODS

Eligibility criteria were defined based on the UICC 1997 staging criteria[20]: patients with bilateral involvement were classed T2b, whereas they would fall into the T2c category according to the UICC 2002 (and later) TNM staging system.

The subgroup of interest comprises all intermediate-risk patients eligible to the trial: patients with histologically confirmed prostate adenocarcinoma T1b-T2a (UICC 1997, ie, T1b-T2b UICC 2002) with PSA $\leq$ 20 ng/mL and either PSA $\geq$ 10 ng/mL or Gleason sum equal to 7; no involvement of pelvic lymph nodes (N0) assessed by computer tomography scan, magnetic resonance imaging, or laparoscopic surgery; no clinical evidence of metastatic spread (M0); a WHO performance status $\leq$ 2; no previous pelvic irradiation or radical prostatectomy; no previous hormonal therapy; and no other malignancy except adequately treated basal cell skin carcinoma or malignancies cured for a minimum of 5 years.

Limited high-risk patients and all patients treated with 70 Gy were excluded from the present analysis.

The Protocol (online only) was reviewed and approved by all participating institutions' ethics committees. Patients provided written informed consent according to the Good Clinical Practice guidelines of the International Conference on Harmonization and national regulations (ClinicalTrials.gov NCT00021450).

Random Assignment

A total of 819 patients were centrally randomly assigned at the EORTC headquarters in 1:1 ratio between EBRT and EBRT plus AS by minimization (variance method)[21] with factors institution, clinical tumor stage (T1b-c *v* T2a), Gleason sum (2-6 *v* 7-10), and PSA (2.5 $\times$ upper normal limit [UNL], 2.5-4.0 $\times$ UNL, and $>$ 4 $\times$ UNL). There was no blinding in the study.

Procedures

The details of the EBRT and procedures were described earlier.[19] Per protocol, EBRT was delivered once a day, five daily fractions of 2 Gy a week at a dose of 46 Gy for planning target volume (PTV) I (prostate and seminal vesicles), 24 Gy for PTV II (prostate and proximal part of seminal vesicles), and 0, 4, or 8 Gy for the PTV III (prostate) depending on center policy. Pelvic lymph nodes were irradiated to 46 Gy when indicated. Quality control and assurance was reported elsewhere.[22,23] AS consisted of two subcutaneous injections of 3-monthly depot of luteinizing hormone–releasing hormone (LHRH) analog (goserelin; AstraZeneca, Macclesfield, United Kingdom) given the first day of irradiation, then 3 months later. Flare protection consisted of 1 month of antiandrogen (bicalutamide; 50 mg daily) started 1 week before the first LHRH injection.

The initial staging included complete blood count, transaminases, total bilirubin, serum creatinine, serum testosterone, and PSA measurements, bone scanning if PSA was above 10 ng/mL, chest X-ray, and computed tomography or magnetic resonance imaging of the abdomen and pelvis. Clinical assessments, laboratory testing, and PSA measurements were repeated every 6 months for 5 years and yearly thereafter. Imaging was repeated upon suspicion of biochemical disease progression. Acute and late toxicity were scored by Common Toxicity Criteria version 2.0[24] during EBRT, at 1 month after EBRT, and at the end of the hormonal therapy and by modified EORTC and Radiation Therapy Oncology Group (RTOG) scale during follow-up.[25]

End Points

The primary end point EFS is defined from entry until the first of PSA relapse (RTOG-ASTRO Phoenix criteria[26]), clinical relapse, start of second-line treatment in absence of per protocol progression, or death. Local clinical relapse was diagnosed by palpation or imaging.[19] Regional and distant metastases were documented by imaging. Confirmation of local or regional relapse by biopsy was not mandated in the analysis. Secondary end points were clinical DFS (defined from entry until any clinical relapse or death), overall survival (OS, defined from entry to death), and distant metastasis–free survival (DMFS, defined from entry until distant metastasis or death). For the cumulative incidence of locoregional relapse (LR), the time equaled DFS time, but first events other than local relapse were analyzed as competing risks. For PCa-specific mortality, deaths from other causes than PCa were analyzed as competing risk. Censoring was applied at the last follow-up visit.

Statistical Methods

All statistical tests were conducted at the two-sided .05 significance level, by intention-to-treat (in all patients for efficacy; in all treated patients for safety), and 95% CIs are reported. OS, EFS, DFS, and DMFS rates were estimated by Kaplan-Meier curves[27] and compared by log-rank test stratified by radiation dose.[28] LR was estimated by cumulative incidence and compared by Gray[29] test stratified by radiation dose. The proportional hazard assumption was checked.[30] Sensitivity analyses using multivariate models adjusted for known prognostic variables (age—continuous, PSA level—continuous, comorbidities, clinical tumor stage, and Gleason sum) and stratified by radiation dose were performed. Exploratory heterogeneity analyses were conducted by EBRT dose levels and by age (< 70 $v \geq 70$ years) using forest plots and a test for interaction between each variable and treatment in Cox models.

RESULTS

From September 21, 2001, until April 24, 2008, a total of 819 patients were recruited by 37 centers from 14 countries and underwent random assignment (Fig 1): 409 to EBRT and 410 to EBRT plus AS. Of those patients, 481 (58.7%) presented with intermediate-risk disease and were entered with EBRT dose level 74 or 78 Gy; 245 were randomly assigned to EBRT plus AS and 236 to EBRT only.

Table 1 details the baseline characteristics, well balanced between the two groups. In the radiotherapy arm, 235 of 236 patients (99.6%) were treated (one refused). In the combination arm, 243 of 245 received the combined treatment (99.2%, two refused) (Fig 1). The EBRT durations and doses are displayed in the Data Supplement (online only). EBRT was stopped prematurely in five patients because of toxicity (three patients), intestinal occlusion (one patient), and lymphocele sepsis (one patient). Goserelin was administered to 242 patients (99.6%) and another LHRH was given to one patient (0.4%). Six patients (2.5%) received one injection of LHRH, either because of toxicity (three patients), patient's decision to decline treatment (two patients), or other reason (one patient).

As of the data cutoff of November 16, 2019, the median follow-up period was 12.4 years for the whole study and 12.2 years in the intermediate-risk subgroup, similar in both arms.

Regarding the toxicity profile, 7.4% and 4.3% of patients on EBRT plus AS and on EBRT, respectively, reported late grade ≥ 3 genitourinary toxicities ($P = .174$), whereas 30.9% and 22.1% of patients reported late severe impairment of sexual function ($P = .038$). In total, six patients (1.3%, three in each arm) reported late grade ≥ 3 gastrointestinal toxicities. We did not find evidence against the proportional hazard assumption for any of the end points.

In the EBRT arm, 132 of 236 patients (55.9%) reported events for the primary end point EFS against 92 of 245 patients (37.6%) in the EBRT plus AS arm (Table 2). Forty-nine patients in the EBRT arm and 52 in the EBRT plus AS arm died without progression. The 10-year EFS was 68.1% for the EBRT plus AS arm (95% CI, 61.6 to 73.7) and 49.3% for the radiation only arm (95% CI, 42.4 to 55.8), corresponding to an observed hazard ratio (HR) of 0.53 (95% CI, 0.41 to 0.70; $P < .001$; Fig 2A), showing that the between-group difference in EFS was sustained in the longer term. Of the 83 patients with biochemical or clinical progression in the EBRT arm, 34 (41.0%) received no active treatment until last follow-up (27 on wait-and-see and seven incomplete information) and 49 (59.0%) went on to receive at least one line of active treatment. Of the 40 patients who relapsed in the EBRT plus AS arm, 11 (27.5%) received no active treatment until last follow-up (seven on wait-and-see and four incomplete information) and 29 (72.5%) received at least one line of active treatment. The documented salvage treatments are detailed in the Data Supplement. The first active treatment was initiated at a median of 5.7 years (interquartile range: 2.9-7.9 years) after study entry for the 49 patients in the EBRT arm and 5.7 years (interquartile range: 3.3-8.2 years) after entry for the 29 patients in the EBRT plus AS arm.

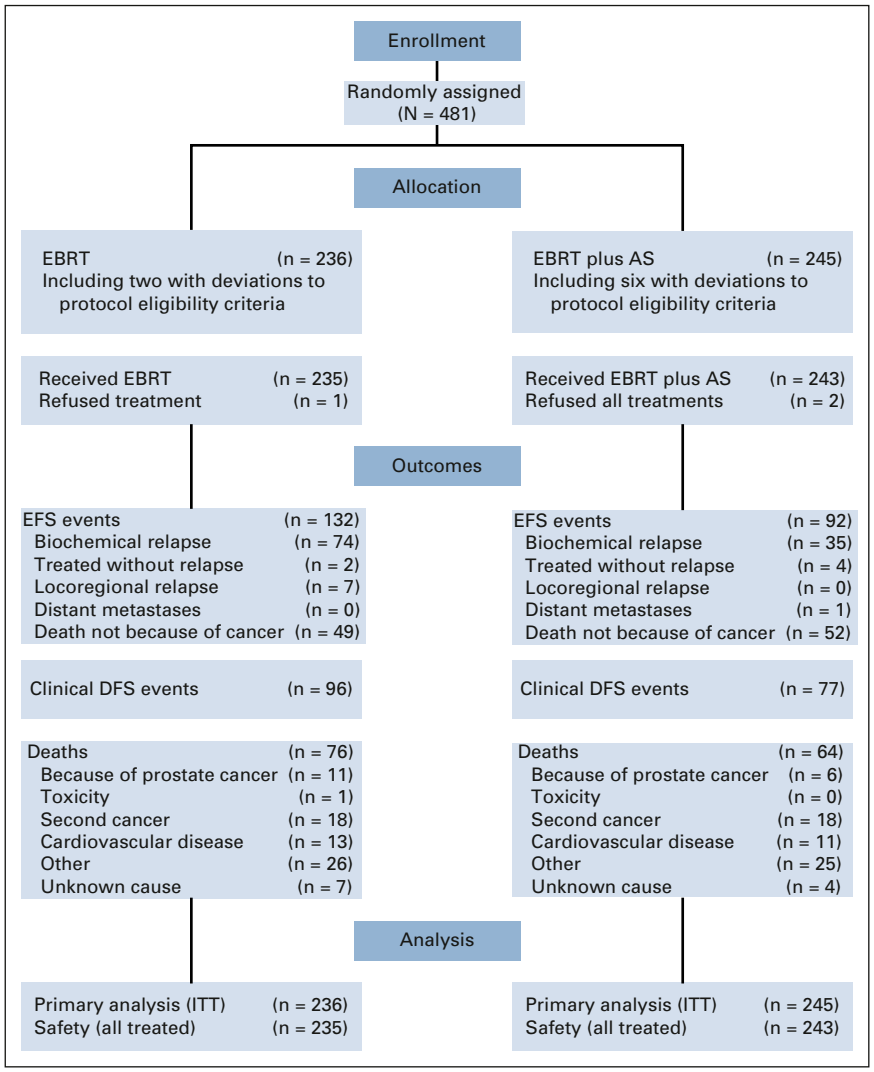

FIG 1. CONSORT diagram in intermediate-risk patients treated with 74-78 Gy of EBRT. AS, androgen suppression; EBRT, external-beam radiotherapy; EFS, event-free survival; DFS, disease-free survival; ITT, intent-to-treat.

For clinical DFS, 173 events (96 in the EBRT arm and 77 in the EBRT plus AS arm) were reported. In the EBRT arm, 58 patients died in the absence of clinical progression versus 54 in the EBRT plus AS arm. The 10-year DFS was 76.2% for the EBRT plus AS arm (95% CI, 70.1 to 81.3) and 66.0% for the EBRT arm (95% CI, 59.2 to 71.9), corresponding to an observed HR of 0.67 (95% CI, 0.49 to 0.90; $P = .008$; Fig 2B). The difference in DFS was mainly driven by the differences in locoregional relapses (27 in the EBRT arm and 13 in the EBRT plus AS arm). At 10 years, the cumulative LR was 9.6% (95% CI, 6.1 to 13.9) in the EBRT arm and 4.4% (95% CI, 2.3 to 7.7) in the EBRT plus AS arm (competing risk-adjusted HR = 0.44; 95% CI, 0.23 to 0.84; $P = .013$; Fig 2C).

A total of 76 patients receiving radiation alone and 64 patients receiving short-term AS died. The death was because of PCa in 11 and six patients, cardiac problems in 13 and 11, and second primary in 18 and 18, respectively. One patient in the EBRT arm died of radiation-induced grade 4 proctitis at month 14. The 10-year OS was 80.0% (95% CI, 74.1 to 84.7) in the EBRT plus AS arm and 74.3% (95% CI, 67.8 to 79.7) in the EBRT arm. The effect on OS was not statistically significant (HR = 0.74; 95% CI, 0.53 to 1.04; $P = .082$; Fig 3A). Because of the low number of events, PCa-specific mortality could not be tested statistically (Data Supplement).

In the EBRT arm, 20 (8.5%) patients developed distant metastases compared with 14 (5.7%) in the EBRT plus AS arm. At 10 years, DMFS was 79.3% (95% CI, 73.4 to 84.0) in the EBRT plus AS arm and 72.7% (95% CI, 66.2 to 78.2) in the EBRT arm with an observed HR of 0.74 (95% CI, 0.53 to 1.02; $P = .065$; Fig 3B). The breakdown of second cancers

TABLE 1. Patient Demographics and Clinical Characteristics

Characteristic	EBRT (n = 236) No. (%)	EBRT Plus AS (n = 245) No. (%)	Total (N = 481) No. (%)
Age, years			
Median	70	71	71
Range	43-80	49-79	43-80
IQR	66-74	66-73	66-74
WHO performance status			
0	194 (82.2)	222 (90.6)	416 (86.5)
1	41 (17.4)	22 (9.0)	63 (13.1)
2	1 (0.4)	1 (0.4)	2 (0.4)
Testosterone level			
≤ Institution's lower limit of normal	13 (5.5)	12 (4.9)	25 (5.2)
> Institution's lower limit of normal	169 (71.6)	191 (78.0)	360 (74.8)
Unknown	54 (22.9)	42 (17.1)	96 (20.0)
Other chronic disease present at baseline			
No	93 (39.4)	89 (36.3)	182 (37.8)
Yes	143 (60.6)	156 (63.7)	299 (62.2)
If yes, specify			
Cardiovascular	64 (44.8)	73 (46.8)	137 (45.8)
Respiratory	5 (3.5)	17 (10.9)	22 (7.4)
Diabetes	8 (5.6)	9 (5.8)	17 (5.7)
Genitourinary	2 (1.4)	0 (0.0)	2 (0.7)
Gastrointestinal	4 (2.8)	3 (1.9)	7 (2.3)
Multiple	45 (31.5)	35 (22.4)	80 (26.8)
Other	15 (10.5)	19 (12.2)	34 (11.4)
Time from first histologic diagnosis to random assignment, months			
Median	2.8	2.6	2.8
Range	0.6-129.7	0.2-69.6	0.2-129.7
IQR	2.0-4.2	1.9-4.2	2.0-4.2
Clinical T category (UICC 1997)			
T1b	9 (3.8)	2 (0.8)	11 (2.3)
T1c	97 (41.1)	103 (42.0)	200 (41.6)
T2a	130 (55.1)	140 (57.1)	270 (56.1)
Clinical N category			
N0	236 (100.0)	245 (100.0)	481 (100.0)
Pathologic N category			
pN0	22 (9.3)	17 (6.9)	39 (8.1)
Gleason sum			
< 6	24 (10.2)	29 (11.8)	53 (11.0)
6	95 (40.3)	99 (40.4)	194 (40.3)
7	117 (49.6)	117 (47.8)	234 (48.6)

(continued on following page)

TABLE 1. Patient Demographics and Clinical Characteristics (continued)

Characteristic	EBRT (n = 236) No. (%)	EBRT Plus AS (n = 245) No. (%)	Total (N = 481) No. (%)
Baseline PSA (institution's normal limit [UNL] = 4 ng/mL)			
Median	9.0	8.8	9.0
Range	0.4-20.0	1.0-19.7	0.4-20.0
IQR	6.4-12.9	5.9-12.8	6.2-12.8
≤ 2.5 × UNL	138 (58.5)	145 (59.2)	283 (58.8)
> 2.5 × UNL to ≤ 4 × UNL	98 (41.5)	100 (40.8)	198 (41.2)

NOTE. All values are expressed as number of patients (%), unless otherwise stated.

Abbreviations: AS, androgen suppression; EBRT, external-beam radiotherapy; IQR, interquartile range; PSA, prostate-specific antigen; UICC, International Union Against Cancer; UNL, upper normal limit.

was not significantly different between the groups: 45 of 236 patients (19.1%) had a second cancer in the EBRT arm against 37 of 245 (15.1%) in the EBRT plus AS arm.

The results were unchanged in sensitivity analyses adjusting for known prognostic variables and stratified by EBRT (Data Supplement). For the end points EFS, DFS,

TABLE 2. Events at Long-Term Follow-Up in Intermediate-Risk Patients

Events for Efficacy End Points	EBRT (n = 236) No. (%)	EBRT Plus AS (n = 245) No. (%)	Total (N = 481) No. (%)
First event for EFS	132 (55.9)	92 (37.6)	224 (46.6)
Treated without relapse	2 (0.8)	4 (1.6)	6 (1.2)
Biochemical relapse	74 (31.4)	35 (14.3)	109 (22.7)
Locoregional relapse	7 (3.0)	0 (0.0)	7 (1.5)
Distant metastases	0 (0.0)	1 (0.4)	1 (0.2)
Death	49 (20.8)	52 (21.2)	101 (21.0)
First event for clinical DFS	96 (40.7)	77 (31.4)	173 (36.0)
Locoregional relapse	27 (11.4)	13 (5.3)	40 (8.3)
Distant metastases	11 (4.7)	10 (4.1)	21 (4.4)
Death	58 (24.6)	54 (22.0)	112 (23.3)
First event for DMFS	81 (34.3)	69 (28.2)	150 (31.2)
Distant metastases	20 (8.5)	14 (5.7)	34 (7.1)
Death	61 (25.8)	55 (22.4)	116 (24.1)
Death	76 (32.2)	64 (26.1)	140 (29.1)
Progression	11 (4.7)	6 (2.4)	17 (3.5)
Toxicity	1 (0.4)	0 (0.0)	1 (0.2)
Infection	8 (3.4)	4 (1.6)	12 (2.5)
Second cancer	18 (7.6)	18 (7.3)	36 (7.5)
Cardiovascular disease	13 (5.5)	11 (4.5)	24 (5.0)
Associated chronic disease	5 (2.1)	4 (1.6)	9 (1.9)
Cerebrovascular cause	3 (1.3)	1 (0.4)	4 (0.8)
Other—not PCa	10 (4.2)	16 (6.5)	26 (5.4)
Unknown	7 (3.0)	4 (1.6)	11 (2.3)
Second cancer	45 (19.1)	37 (15.1)	82 (17.0)

NOTE. All values are expressed as number of patients (%), unless otherwise stated.

Abbreviations: AS, androgen suppression; DFS, disease-free survival; DMFS, distant metastasis–free survival; EBRT, external-beam radiotherapy; EFS, event-free survival; PCa, prostate cancer.

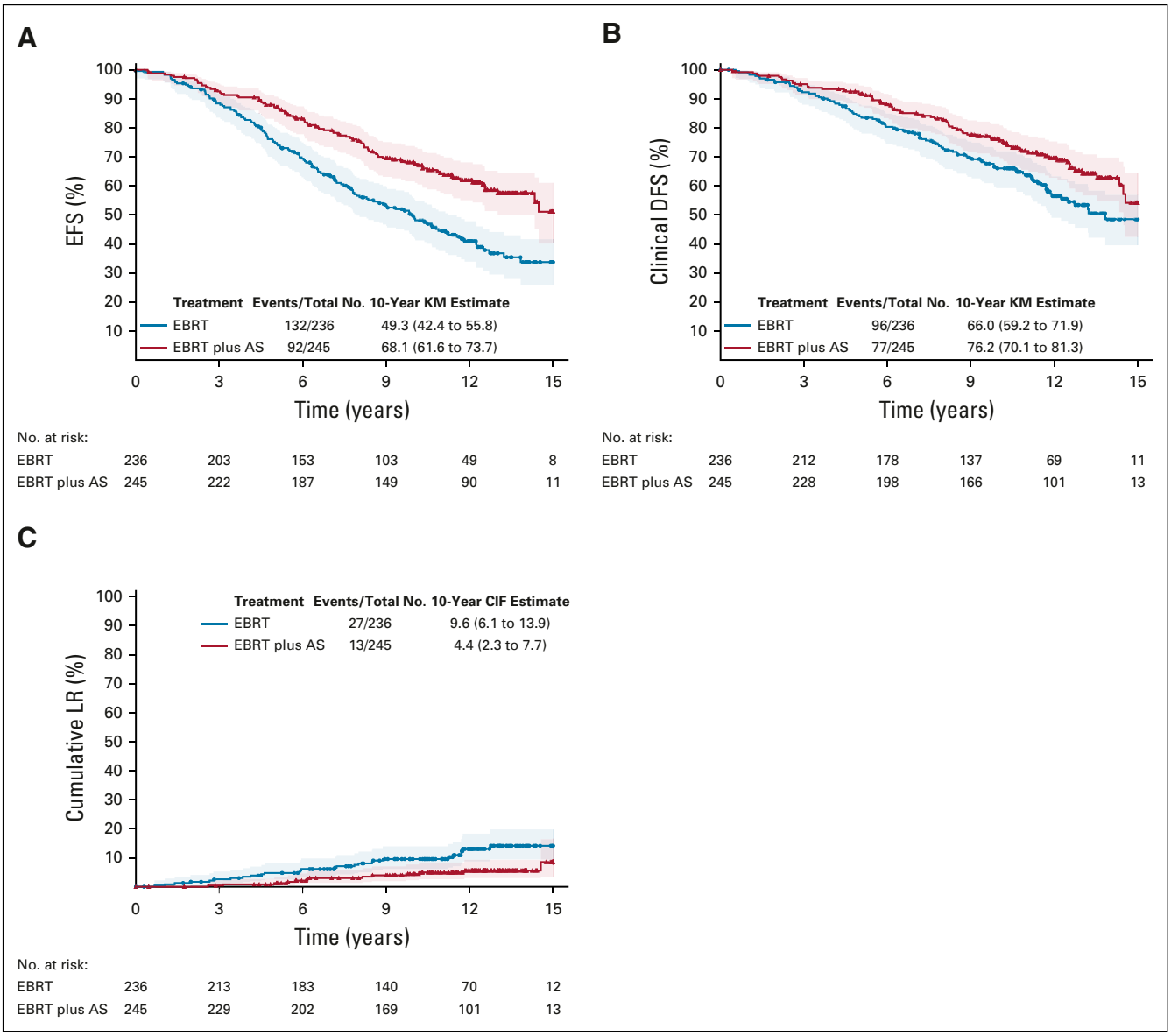

FIG 2. (A) EFS by treatment arm in the intent-to-treat population. HR (EBRT plus AS *v* EBRT) = 0.53 (95% CI, 0.41 to 0.70); $P < .001$. (B) Clinical DFS by treatment arm in the intent-to-treat population. HR (EBRT plus AS *v* EBRT) = 0.67 (95% CI, 0.49 to 0.90); $P = .008$. (C) Locoregional control by treatment arm in the intent-to-treat population. Competing risk-adjusted HR (EBRT plus AS *v* EBRT) = 0.44 (95% CI, 0.23 to 0.84); $P = .013$. AS, androgen suppression; CIF, cumulative incidence function; DFS, disease-free survival; EBRT, external-beam radiotherapy; EFS, Event-free survival; HR, hazard ratio; KM, Kaplan Meier; LR, loco-regional relapse.

and OS, exploratory heterogeneity tests indicated no statistically significant interaction between the radiation dose or age and addition of short-term AS (Fig 4).

Section B of the Data Supplement reports efficacy results for the whole study. Section C reports the PCa-specific mortality in patients with limited high-risk disease.

DISCUSSION

The EORTC trial 22991 was developed more than 2 decades ago. By design, the study allowed entry of patients with limited high-risk localized PCa and allowed centers to opt for a radiation dose as low as 70 Gy. To reflect current practice, high-risk patients and all patients treated with 70 Gy were excluded from the present report that focuses on intermediate-risk patients who were irradiated at a minimum target dose of 74 Gy.

With a median follow-up of 12.2 years in this group of interest, the results confirm that the addition of 6-month AS concomitant and adjuvant significantly improves EFS ($P < .001$; HR = 0.53; 95% CI, 0.41 to 0.70), clinical DFS ($P = .008$; HR = 0.67; 95% CI, 0.49 to 0.90), and locoregional control ($P = .013$; HR = 0.44; 95% CI, 0.23 to

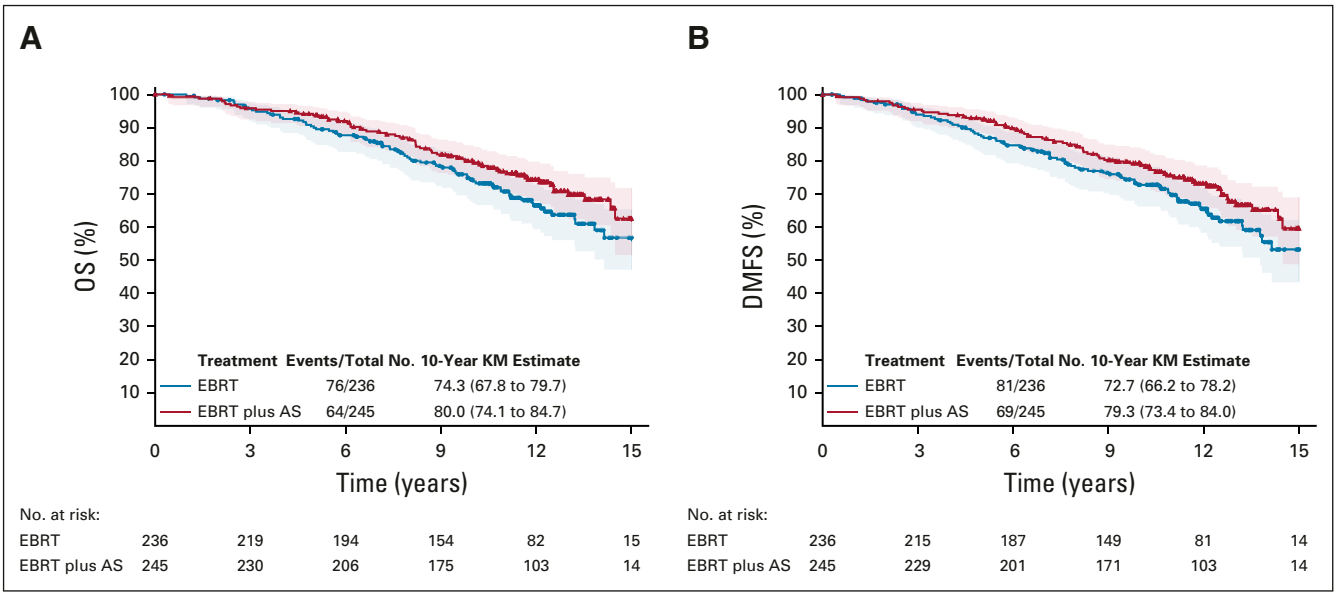

FIG 3. (A) OS by treatment arm in the intent-to-treat population. HR (EBRT plus AS *v* EBRT) = 0.74 (95% CI, 0.53 to 1.04); $P = .082$. (B) DMFS by treatment arm in the intent-to-treat population. HR (EBRT plus AS *v* EBRT) = 0.74 (95% CI, 0.53 to 1.02); $P = .065$. AS, androgen suppression; DMFS, distant metastasis–free survival; EBRT, external-beam radiotherapy; HR, hazard ratio; KM, Kaplan Meier; OS, overall survival.

0.84). These effects were seen across age groups (< 70 *v* ≥ 70 years) and were independent of radiation dose (74 *v* 78 Gy). The observed improvements in DMFS ($P = .065$; HR = 0.74; 95% CI, 0.53 to 1.02) and OS ($P = .082$; HR = 0.74; 95% CI, 0.53 to 1.04) did not reach statistical significance. This is not unexpected with only 150 events for DMFS and 140 events for OS. Neither OS nor DMFS was the primary end point and thus the study was not powered for these end points. Although one notes a significant reduction of PCa-specific mortality in the whole study, this effect mostly results from the patients with limited high-risk disease being undertreated in the EBRT group (Data Supplement, Section C) and should not be overinterpreted.

Our findings in the intermediate-risk disease subgroup are in line with recent studies showing that DMFS is a strong surrogate for OS but that EFS is not.[31,32] In the past decade, the number of effective salvage therapies has dramatically increased; consequently, patients experiencing a biochemical progression may subsequently receive several lines of secondary therapies that prolong survival. However, reducing the use of salvage therapies and avoiding their associated adverse events have important implications on the quality of life of the patients. Both study treatments had a comparable toxicity profile except that in health-related quality of life analysis, patients receiving AS reported impaired sexual activity and functioning at 6 months and at 1 year[19]: the benefit of avoiding salvage therapies has to be weighed against the increased sexual disorders in the individual patient.

The literature so far provides little evidence of survival benefit with short-term AS in intermediate-risk disease, apart from the D'Amico trial[16] and an initial post hoc subgroup analysis of RTOG 94-18.[33] This subgroup analysis (of 1,068 patients) initially showed that low radiation dose (66.6 Gy) with complete AS 2 months before and during EBRT improved the 10-year OS of intermediate-risk patients only, but updated 18-year follow-up results[34] could not confirm the OS benefit. These trials are criticized for delivering suboptimal radiation doses. The PCS III trial[35] randomly assigned 600 intermediate-risk patients between 6 months of complete AS followed by irradiation at either 70 or 76 Gy or only irradiation to 76 Gy. At a median follow-up of 11.3 years, there was no significant difference in OS between the three groups. The GETUG14[36] trial that assesses high-dose EBRT (80 Gy) with or without 4-month AS has not reported OS results yet. In our study, the risk of distant metastasis or death and the risk of death in intermediate-risk patients were 26% lower in the EBRT plus AS arm than in the EBRT arm. Effects were not statistically significant, but the power was limited.

There is also no evidence that prolonging the AS duration before radiation improves OS or prevents distant metastases compared with short-term AS. The RTOG 9910[37] trial, which randomly assigned 1,489 intermediate-risk patients between 8 or 28 weeks' neoadjuvant complete AS before irradiation at 70.2 Gy and 8 additional weeks of AS, showed no difference in 10-year OS rates or in the 10-year distant metastasis cumulative incidence. Thus, for intermediate-risk patients, 4-6 months of AS seems to be sufficient.

Dose-escalated EBRT is considered an option by current guidelines in patients not willing to undergo AS. However, the RTOG 0126[7] trial, which randomly assigned 1,532

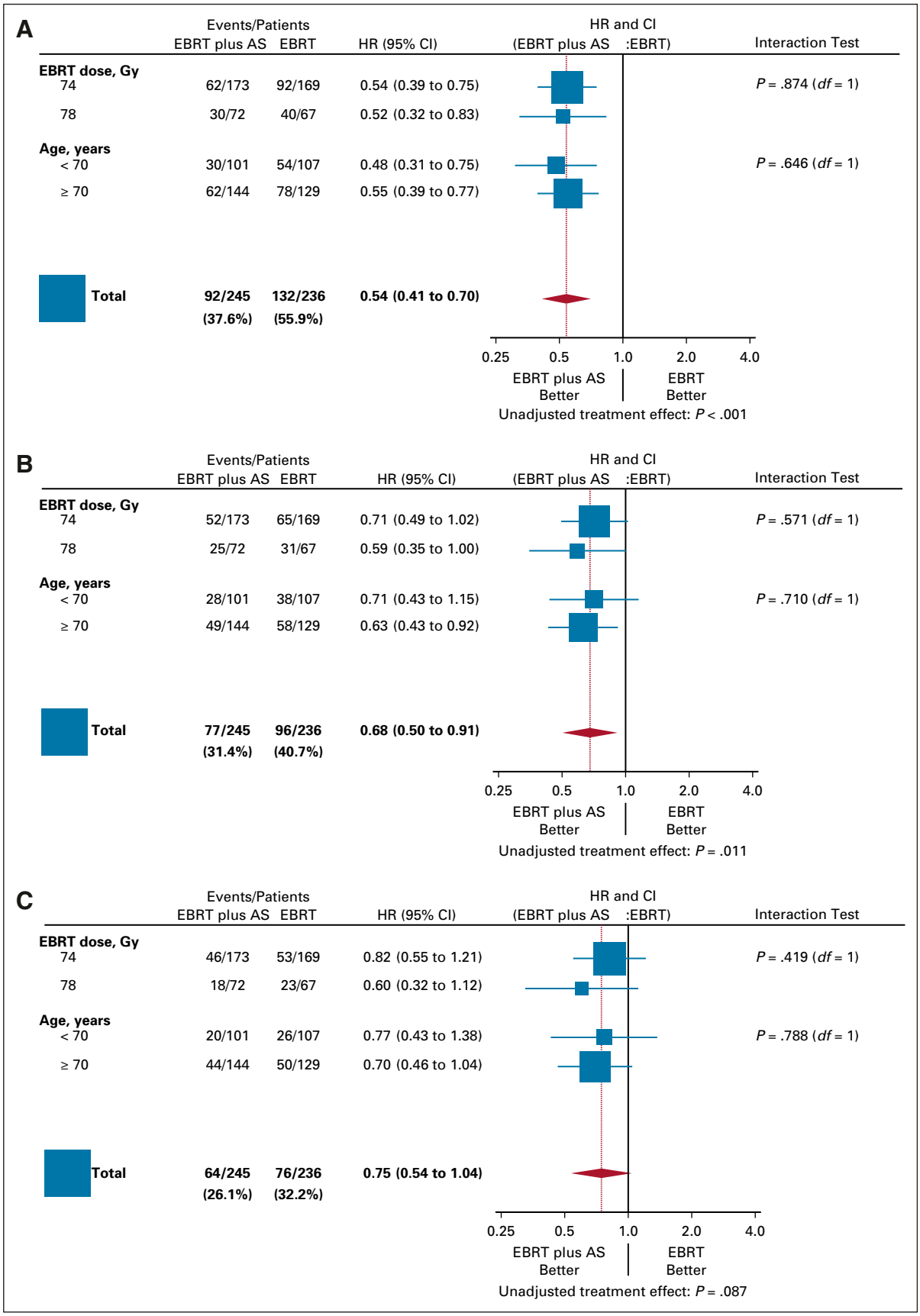

FIG 4. Forest plots. (A) Event-free survival. (B) Clinical disease-free survival. (C) Overall survival. An unstratified univariate Cox model was used to estimate the HRs in the EBRT plus AS arm compared with the EBRT only arm among all the patients. (continued on following page)

FIG 4. (Continued). An unstratified Cox model including the trial group, a covariate of interest (eg, age < 70 $v \geq 70$ years), and the interaction term (eg, age $\times$ treatment) was used to perform the interaction test and estimate the HRs for the subgroups. *P* values were yielded by the test of the treatment difference in the overall intention-to-treat population or by the test of interaction; for each, the Wald test was used. The sizes of the blue boxes are nonlinearly proportional to the numbers of events. The red diamond is centered on the overall HR (dashed line) and covers its 95% CI. In the subgroup analyses, 95% CIs (blue lines) are presented. AS, androgen suppression; EBRT, external-beam radiotherapy; HR, hazard ratio.

intermediate-risk patients between 79.2 Gy and 70.2 Gy, failed to demonstrate an OS benefit. By contrast, recent retrospective analyses[38,39] in intermediate-risk patients suggested that the addition of short-term AS did not improve survival outcomes over dose-escalated EBRT.

Given the inherent shortcomings of retrospective analyses and the conflicting results between studies, the benefit of AS in intermediate-risk PCa remains a topic of debate.[40] The results of the recently completed RTOG 0815 (NCT00936390) that tests addition of AS to dose-escalated EBRT are awaited.

The EORTC 22991 results cannot directly be compared with results obtained with modern radiation alone. Indeed, nowadays, only intensity-modulated radiotherapy or volumetric modulated arc radiotherapy is recommended for the treatment of patients with PCa, and daily image guidance of soft tissues or fiducial markers is mandatory. Meanwhile, centers may also have opted for a hypofractionated scheme 60 Gy in 20 fractions over 4 weeks[41] or 70 Gy in 28 fractions in 6 weeks,[42] as recommended in the current guidelines. EORTC 22991 allowed three-dimensional conformal radiation therapy, and no strict image-guided policy was given since the equipment was not standard at the time, but portal film or electronic portal images had to be obtained once a week.

Furthermore, it is nowadays recognized that intermediate-risk PCa is a heterogeneous group with highly variable prognoses, which present challenges to provide uniform treatment recommendations.[43-45] A retrospective analysis of the RTOG 9408 trial[46] suggests to restrict the use of AS to patients they define as unfavorable intermediate-risk PCa (primary Gleason pattern 4, percentage of positive biopsy cores $\geq 50\%$, or multiple intermediate-risk factors). Further exploration of the trial 22991 within subgroups of intermediate-risk patients is not possible because the study did not include stage T2b UICC TNM 1997, Gleason patterns 1 and 2 were not prospectively collected, and could only be retrieved for 198 intermediate-risk patients with Gleason sum 7. The study RTOG 0815 may allow such investigations.

In conclusion, the long-term analysis of EORTC 22991 confirms that in intermediate-risk PCa treated with conventional EBRT at 74-78 Gy, 6 months of concomitant and adjuvant AS statistically significantly improves EFS and clinical DFS. Effects on OS and DMFS did not reach statistical significance.

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DISCLAIMER

The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The sponsor of the trial was the EORTC. The corresponding author had full access to all study data and the final responsibility for the decision to submit for publication. Trial design, conduct, and analysis were done at the EORTC independent of all funding bodies.

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DATA SHARING STATEMENT

EORTC is committed to ensuring that the data generated from its studies be put to good use by the cancer research community and, whenever possible, are translated to deliver patient benefit. It is therefore EORTC's policy (EORTC Policy 009) to consider for sharing upon request from qualified scientific and medical researchers all data generated from its research while safeguarding intellectual property, the privacy of patients and confidentiality. Requests for accessing the data of published trials should be filed through the data sharing tab on the EORTC website (www.eortc.org).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Short Androgen Suppression and Radiation Dose Escalation in Prostate Cancer: 12-Year Results of EORTC Trial 22991 in Patients With Localized Intermediate-Risk Disease

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