

# Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991

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Terms in blue are defined in the glossary, found at the end of this article and online at [www.jco.org](http://www.jco.org).

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## ABSTRACT

### Purpose

Up to 30% of patients who undergo radiation for intermediate- or high-risk localized prostate cancer relapse biochemically within 5 years. We assessed if biochemical disease-free survival (DFS) is improved by adding 6 months of androgen suppression (AS; two injections of every-3-months depot of luteinizing hormone-releasing hormone agonist) to primary radiotherapy (RT) for intermediate- or high-risk localized prostate cancer.

### Patients and Methods

A total of 819 patients staged: (1) cT1b-c, with prostate-specific antigen (PSA)  $\geq$  10 ng/mL or Gleason  $\geq$  7, or (2) cT2a (International Union Against Cancer TNM 1997), with no involvement of pelvic lymph nodes and no clinical evidence of metastatic spread, with PSA  $\leq$  50 ng/mL, were centrally randomized 1:1 to either RT or RT plus AS started on day 1 of RT. Centers opted for one dose (70, 74, or 78 Gy). Biochemical DFS, the primary end point, was defined from entry until PSA relapse (Phoenix criteria) and clinical relapse by imaging or death of any cause. The trial had 80% power to detect hazard ratio (HR), 0.714 by intent-to-treat analysis stratified by dose of RT at the two-sided  $\alpha = 5\%$ .

### Results

The median patient age was 70 years. Among patients, 74.8% were intermediate risk and 24.8% were high risk. In the RT arm, 407 of 409 patients received RT; in the RT plus AS arm, 403 patients received RT plus AS and three patients received RT only. At 7.2 years median follow-up, RT plus AS significantly improved biochemical DFS (HR, 0.52; 95% CI, 0.41 to 0.66;  $P < .001$ , with 319 events), as well as clinical progression-free survival (205 events, HR, 0.63; 95% CI, 0.48 to 0.84;  $P = .001$ ). In exploratory analysis, no statistically significant interaction between treatment effect and dose of RT could be evidenced (heterogeneity  $P = .79$  and  $P = .66$ , for biochemical DFS and progression-free survival, respectively). Overall survival data are not mature yet.

### Conclusion

Six months of concomitant and adjuvant AS improves biochemical and clinical DFS of intermediate- and high-risk cT1b-c to cT2a (with no involvement of pelvic lymph nodes and no clinical evidence of metastatic spread) prostatic carcinoma, treated by radiation.

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## INTRODUCTION

Screening<sup>1</sup> increases the incidence of localized prostate cancer, for which prognosis is predicted by the D'Amico classification.<sup>2</sup> Prostate cancer treatment is based on radical prostatectomy, external radiation, and brachytherapy for a selected group of

patients. Whereas the combination of radiotherapy (RT) with androgen suppression (AS) is well established for locally advanced prostate cancer,<sup>3-7</sup> it is not as clear for intermediate- and high-risk (by D'Amico<sup>2</sup>) localized prostate cancer.<sup>8</sup> Several trials were launched<sup>9-11</sup> to determine whether short-term AS combined with RT would improve biochemical disease-free survival (DFS) with respect to RT alone.

The European Organisation for Research and Treatment of Cancer (EORTC) opened protocol 22991 in 2001 to randomize patients between RT alone and the same regimen combined with a 6-month AS; the duration was considered an acceptable compromise between effectiveness and maintenance of quality of life.<sup>12</sup> Centers were asked to select one of three radiation doses (70, 74, or 78 Gy).

## PATIENTS AND METHODS

Eligible patients had histologically confirmed prostate adenocarcinoma T1b to T2a (International Union Against Cancer 1997 staging criteria)<sup>13</sup> with prostate-specific antigen (PSA) > 10 ng/mL or Gleason  $\geq$  7; no involvement of pelvic lymph nodes as assessed by computed tomography scan, magnetic resonance imaging, or laparoscopic surgery; no clinical evidence of metastatic spread; or clinical tumor stages T2b to T4 and a PSA level of up to 12.5 times the upper limit of the normal range (UNL); a WHO performance status  $\leq$  2; no previous pelvic irradiation or radical prostatectomy; no previous hormonal therapy; no other malignancy except adequately treated basal cell carcinoma of the skin or another malignancy cured for at least 5 years. The pathologic specimens were not centrally reviewed. The protocol was reviewed and approved by the ethics committee at each participating institution. All patients gave written informed consent according to the Good Clinical Practice guidelines of the International Conference on Harmonization and national regulations.

### Randomization

Patients were randomly assigned at the EORTC headquarters in a 1:1 ratio between primary RT and RT plus AS according to a minimization algorithm (variance method)<sup>14</sup> with factors institution, clinical tumor stage (T1b-c v T2a), Gleason sum (2 to 6 v 7 to 10), PSA ( $2.5 \times$  UNL,  $2.5$  to  $4.0 \times$  UNL, and  $> 4.0 \times$  UNL). There was no blinding in the study. Because the radiation dose was a center-chosen characteristic, the minimization was stratified by the dose level.

### Procedures and End Points

In both groups, three-dimensional (3D) conformal RT or **intensity-modulated radiation therapy** (IMRT) was performed with an isocentric beam arrangement, based on a computed tomographic definition of 3D planned target volumes (PTV). PTV I included the prostate, the whole seminal vesicles, and, according to the discretion of each institution, the pelvic lymph node for patients who were at 15% risk or higher of involvement. PTV II encompassed the prostate and the proximal part of seminal vesicles. PTV III encompassed the prostate. The PTV margins were specified by the protocol; no image-guided policy was given. Photons of 6 MV or higher were mandatory.

The dose was specified at the intersection of the beam axes, according to the guidelines of the International Commission on Radiation Units for 3D treatment. The absorbed dose should be within a given percentage value of the prescribed dose, ie,  $-5\%$  to  $+7\%$  for 3D or IMRT.<sup>15</sup> The same dose homogeneity constraints for the PTV applied for IMRT as for 3D treatments. RT was delivered once per day, five fractions per day of 2 Gy per week at a dose of 46 Gy for PTV I; 24 Gy for PTV II; and 0, 4, or 8 Gy for PTV III, depending on center policy, resulting in total doses of 70, 74, or 78 Gy, respectively. Treatment accuracy for each PTV had to be checked by electronic portal images at least once per week during treatment.

Dose-volume histograms were generated and were required to fulfill the following constraints: (1) the maximum dose delivered to the rectum had to be  $\leq$  74 Gy; (2) at most 25% of the rectum received  $>$  72 Gy and at most 50% of the rectum received  $>$  60 Gy; and (3) at most 50% of the bladder received greater than 60 Gy and at most 20% of the bladder received  $>$  65 Gy. Methods used for calibration of the beams, dummy run, and individual case review were reported elsewhere.<sup>16,17</sup> AS consisted of

two subcutaneous injections of every-3-months depot of luteinizing hormone-releasing hormone (LHRH) analog (goserelin; AstraZeneca, Macclesfield, United Kingdom) given the first day of RT, then 3 months later. Flare protection consisted of 1 month of antiandrogen (bicalutamide; 50 mg/d) started 1 week before the first LHRH injection.

The initial staging included complete blood count, ALT and AST, total bilirubin, serum creatinine, serum testosterone, and PSA measurements (bone scanning if PSA was  $>$  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 according to the Common Toxicity Criteria version 2.0<sup>18</sup> during RT, at 1 month after RT, and at the end of the hormonal therapy, and according to the modified EORTC/Radiation Therapy Oncology Group (RTOG) scale during follow up.<sup>19</sup> Health-related quality of life (HRQOL) was assessed at randomization; 6 months; and 1, 2, and 3 years after the start of RT using the EORTC Quality of Life questionnaires (QLQ-C30, version 3.0)<sup>20</sup> supplemented with an early version of the QLQ-PR25 prostate cancer module.<sup>21</sup>

Biochemical DFS, the primary end point, was defined from entry until PSA relapse (defined after an amendment dated July 2009 according to the RTOG–American Society for Therapeutic Radiology and Oncology Phoenix criteria)<sup>22</sup> and clinical relapse by imaging or death of any cause to the first event of biochemical relapse. In the analysis, patients who started second-line treatment in the absence of per-protocol progression were counted as biochemical failure when starting that treatment. Clinical relapse was: (1) a palpable enlargement of an existing abnormality or regrowth by 25% or more (of the product of the two largest diameters) of a previously regressed prostate gland, (2) urethral obstruction, or (3) regional and distant metastases documented by imaging. Secondary efficacy end points included clinical DFS and overall survival defined from randomization to, respectively, clinical relapse or death from any cause, and death from any cause. For the cumulative incidence of local relapse, the time equaled clinical DFS time, but first events other than local relapse were analyzed as competing risks. Confirmation of local or regional relapse by biopsy was not mandated in the analysis. Censoring was applied at the last follow-up visit.

### Statistical Methods

A 5-year biochemical DFS of 70% was assumed for the RT arm, based on the experience of Zelefsky et al.<sup>23</sup> The study was sized to detect hazard ratio (HR), 0.714, with a two-sided 5% significance level log-rank test and 80% power (278 events needed),<sup>24</sup> estimated to require 800 patients. Unless otherwise specified, statistical tests were conducted at the two-sided 5% significance level, by intent-to-treat (in all patients for efficacy; in all treated patients for safety); 95% CIs are reported. Overall survival and DFS rates were estimated by Kaplan-Meier curves<sup>25</sup> and compared by log-rank test stratified by radiation dose.<sup>26</sup> Local relapse rates were estimated by cumulative incidence and compared by Gray test stratified by radiation dose.<sup>27</sup> Exploratory analyses were conducted to assess homogeneity of the results across RT dose levels.

HRQOL outcomes were scored using EORTC guidelines<sup>28</sup> into values ranging from zero to 100 (representing maximum function or maximum adverse effects). Changes in score from baseline were compared using linear mixed-effects models. The primary scales of interest were global health status/quality of life, hormonal treatment-related symptoms, sexual activity, and sexual functioning; for the latter, a value of zero was assigned when no activity was reported. Only data from valid HRQOL forms up to year 3 were analyzed. Because of multiplicity, an adjusted significance level of 1% was used for HRQOL. A difference of ten points or more was considered to be clinically relevant.<sup>29</sup> Two safety interim analyses were conducted per protocol, with clinical cutoff dates on September 5, 2003 and May 4, 2004, respectively, and concluded to safety in both instances.

RESULTS

Between September 21, 2001 and April 24, 2008, a total of 819 patients were recruited by 37 centers from 14 countries (13 countries in Europe and Israel) and underwent randomization (Fig 1): 409 patients to RT (including 20 patients with deviations to protocol eligibility criteria) and 410 patients to RT plus AS (including 19 patients with deviations to protocol eligibility criteria). Table 1 details baseline characteristics, which were well balanced between the two groups. In the RT arm, 407 of 409 patients (99.5%) were treated; one patient was deemed to have

metastatic cancer and did not receive RT, and one refused RT. In the combination arm, 403 of 410 patients (98.3%) received the combined treatment; one patient with metastatic cancer was not treated in the protocol, three refused all treatment, and three received RT only (Fig 1).

IMRT was used in 68 of 407 patients (16.7%) in the RT arm and in 75 of 406 patients (18.5%) in the combination arm. The RT durations and doses are displayed in Table 2. RT was stopped prematurely in seven patients because of death (of two patients in the RT arm, one death was unexpected and the other was due to lung edema); other causes of death were toxicity (three patients),

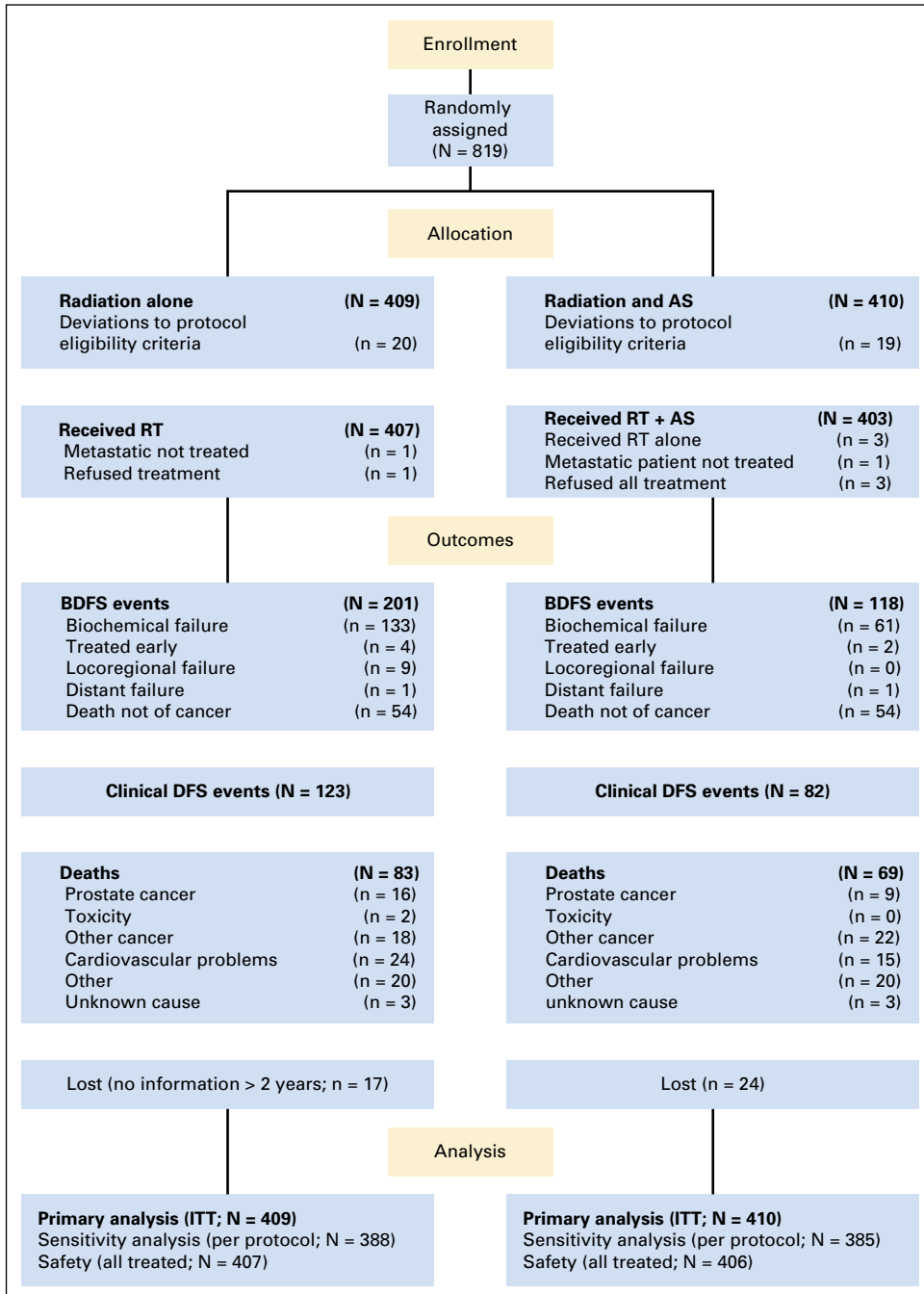


Fig 1. CONSORT diagram. AS, androgen suppression; BDFS, biochemical progression-free survival; DFS, disease-free survival; ITT, intent to treat; RT, radiotherapy.

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**Table 1.** Patient Demographics and Clinical Characteristics

Variable	RT Only (N = 409)	RT + AS (N = 410)	Total (N = 819)
Age, years			
Median	70	71	70
Range	43-80	47-80	43-80
IQR	66-74	66-74	66-74
WHO performance status			
0	349 (85.3)	372 (90.7)	721 (88.0)
1	59 (14.4)	37 (9.0)	96 (11.7)
2	1 (0.2)	1 (0.2)	2 (0.2)
Testosterone level			
≤ Institution's lower limit of normal	18 (4.4)	22 (5.4)	40 (4.9)
> Institution's lower limit of normal	290 (70.9)	318 (77.6)	608 (74.2)
Unknown	101 (24.7)	70 (17.1)	171 (20.9)
Other chronic disease present at baseline			
No	164 (40.1)	157 (38.3)	321 (39.2)
Yes	245 (59.9)	253 (61.7)	498 (60.8)
Cardiovascular	107 (43.7)	107 (42.3)	214 (43.0)
Respiratory	11 (4.5)	27 (10.7)	38 (7.6)
Diabetes	12 (4.9)	18 (7.1)	30 (6.0)
Genitourinary	3 (1.2)	3 (1.2)	6 (1.2)
GI	7 (2.9)	7 (2.8)	14 (2.8)
Multiple	77 (31.4)	61 (24.1)	138 (27.7)
Other	28 (11.4)	30 (11.9)	58 (11.6)
Time from first histologic diagnosis to randomization, months			
Median	2.7	2.5	2.5
Range	0.6-129.7	0.2-69.6	0.2-129.7
IQR	1.8-3.8	1.7-4.0	1.7-3.9
Clinical T category (UICC 1997)			
T1a (ineligible)	1 (0.2)	0 (0.0)	1 (0.1)
T1b	16 (3.9)	11 (2.7)	27 (3.3)
T1c	180 (44.0)	187 (45.6)	367 (44.8)
T2a	207 (50.6)	210 (51.2)	417 (50.9)
T2b (ineligible)	5 (1.2)	2 (0.4)	7 (0.9)
Clinical N category			
N0	407 (99.5)	409 (99.8)	816 (99.6)
Unknown	2 (0.5)	1 (0.2)	3 (0.4)
Pathologic N category			
pN0	55 (13.4)	46 (11.2)	101 (12.3)
Clinical M category			
M0	408 (99.8)	409 (99.8)	817 (99.8)
M1 (ineligible)	1 (0.2)	1 (0.2)	2 (0.2)
Gleason sum			
< 6	46 (11.2)	46 (11.2)	92 (11.2)
6	155 (37.9)	155 (37.8)	310 (37.9)
7	171 (41.8)	164 (40.0)	335 (40.9)
8-10	37 (9.0)	45 (11.0)	82 (10.0)
Baseline PSA, ng/mL (institution's normal limit [UNL] = 4 ng/mL)			
Median	10.3	10.4	10.4
Range	0.4-97.9	0.3-50.7	0.3-97.9
IQR	7.0-15.9	6.8-15.7	6.9-15.8
≤ 2.5 × UNL	198 (48.4)	199 (48.5)	397 (48.5)
> 2.5 × UNL to ≤ 4 × UNL	143 (35.0)	152 (37.1)	295 (36.0)
> 4 × UNL	68 (16.6)	59 (14.4)	127 (15.5)
NCCN risk group*			
Low (ineligible)	2 (0.5)	1 (0.2)	3 (0.4)
Intermediate	174 (42.5)	187 (45.6)	361 (44.1)
T2a (1997) with one other intermediate risk factor	80 (19.6)	84 (20.5)	164 (20.0)
High	153 (37.4)	138 (33.7)	291 (35.5)
D'Amico risk group <sup>2</sup>			
Low (ineligible)	2 (0.5)	1 (0.2)	3 (0.4)
Intermediate	301 (73.6)	312 (76.1)	613 (74.8)
High	106 (25.9)	97 (23.7)	203 (24.8)

NOTE. All values are expressed as No. of patients (%), unless otherwise stated. Abbreviations: AS, androgen suppression; IQR, interquartile range; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; RT, radiotherapy; UICC, International Union Against Cancer; UNL, upper normal limit; WHO, World Health Organization.

\*The NCCN risk groups are defined as: low risk if TNM 2002 stage T1c or T2a with PSA < 10 ng/mL and Gleason ≤ 6; intermediate risk if TNM 2002 stage T2b to T2c, or Gleason = 7, or PSA ≥ 10 and < 20 ng/mL; and high risk if TNM 2002 stage T3a or PSA ≥ 20 ng/mL or Gleason > 7 or two high-risk features.

**Table 2.** Radiotherapy Technique and Dose Delivered

Variable	RT Alone, Gy Dose			RT + AS, Gy Dose		
	70 (N = 100)	74 (N = 207)	78 (N = 100)	70 (N = 100)	74 (N = 209)	78 (N = 97)
RT duration, days						
Median	51	54	57	51	55	57
Range	38-64	51-72	36-66	45-57	29-108	50-68
IQR	49-52	52-57	54-58	48-52	52-57	55-58
No. of patients who stopped RT early, %	1 (1.0)	2 (1.0)	2 (2.0)	0 (0.0)	2 (1.0)	0 (0.0)
Total dose, Gy						
Median	70.0	74.0	78.0	70.0	74.0	78.0
Range	48.0-72.0	70.0-84.0	52.0-78.2	66.0-70.0	40.0-76.0	70.0-78.0
IQR	70.0-70.0	74.0-74.0	78.0-78.0	70.0-70.0	74.0-74.0	78.0-78.0
No. of fractions						
Median	35	37	39	35	37	39
Range	24-36	32-42	26-39	33-35	20-38	35-39
IQR	35-35	37-37	39-39	35-35	37-37	39-39
PTVI includes obturator and iliac nodes, No. (%)	0 (0.0)	19 (9.2)	5 (5.0)	0 (0.0)	28 (13.4)	9 (9.3)
IMRT use, No. (%)	—	11 (5.3)	57 (57.0)	—	17 (8.0)	58 (59.8)

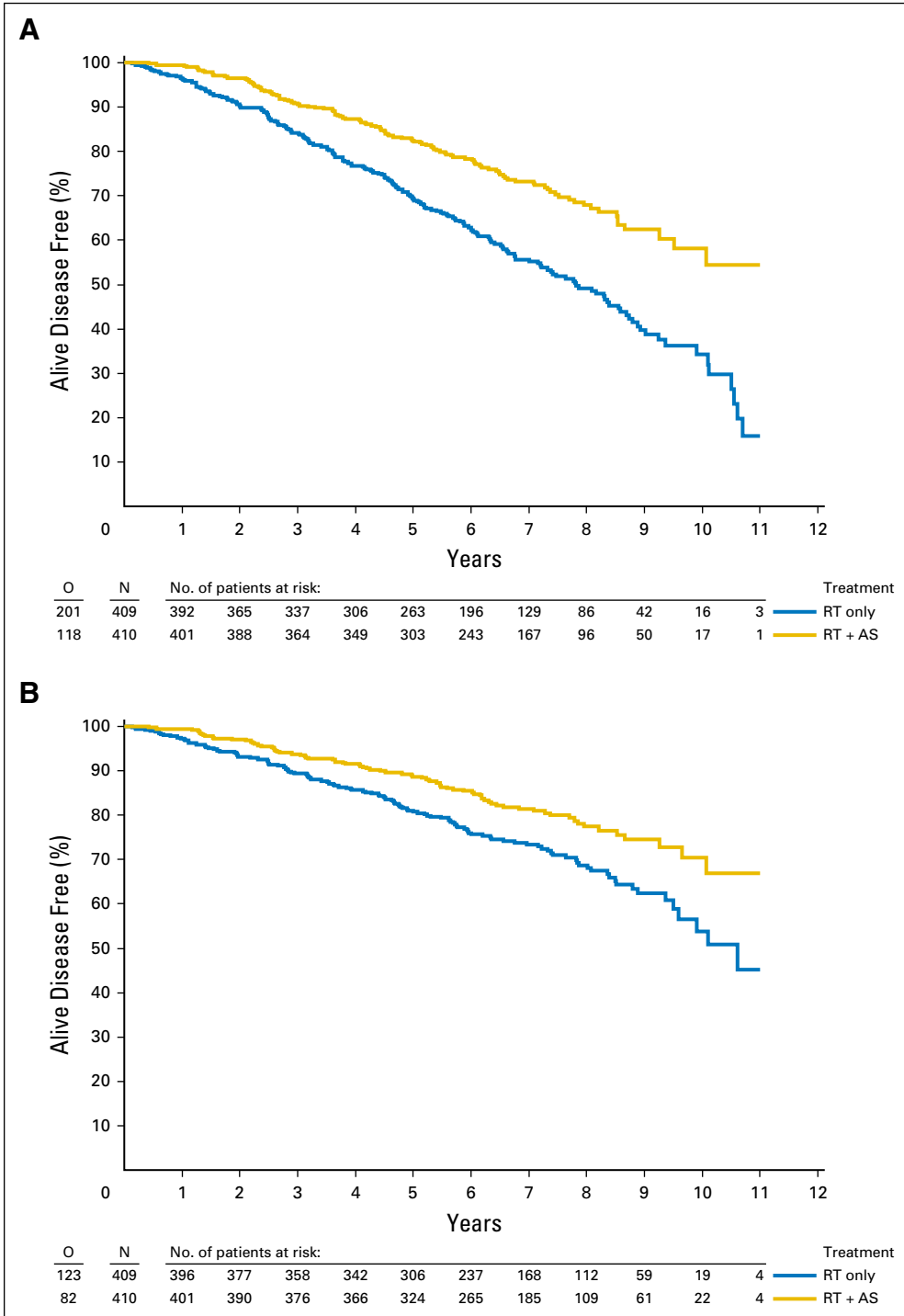
Abbreviations: AS, androgen suppression; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; PTVI, planning target volume I; RT, radiotherapy.

intestinal occlusion (one patient), and lymphocele sepsis (one patient). Bicalutamide was started in 403 patients and given for a median duration of 29 days (range, 20 to 91 days; interquartile range, 28 to 31 days). Goserelin was administered to 401 patients (99.5%), and another LHRH agonist was given to two patients (0.5%). Eleven patients (2.7%) received one injection of LHRH either because of toxicity (six patients), the patient's decision to decline treatment (four patients), or other reasons (one patient). The adverse effects of the 6-month AS were hot flushes more than once per day in 127 of 403 treated patients (31.5%), gynecomastia in 27 patients (6.7%), diarrhea of grade 3 or higher in two patients (0.5%), and elevation of ALT/AST in 20 patients (5.0%). Respectively, 5.9% and 3.6% of patients, on RT plus AS and on RT, reported late grade 3 to 4 genitourinary toxicity ( $P = .14$ ), whereas 27.0% and 19.4% of patients reported severe impairment of sexual function ( $P = .010$ ).

As of the data cutoff date of October 20, 2013, the median follow-up period was 7.2 years, similar in the two treatment arms ( $P = .475$ ). Events for the primary end point biochemical DFS were reported in 201 of 409 patients (49.1%) and 118 of 410 patients (28.8%) in the RT and the combination arm, respectively. Fifty-four patients in each arm died in absence of disease progression. The 5-year biochemical DFS was 82.6% for the combination arm (95% CI, 78.4 to 86.1) and 69.8% for the RT arm (95% CI, 64.9 to 74.2), corresponding to an observed HR of 0.52 (95% CI, 0.41 to 0.66;  $P < .001$ ; Fig 2A). Exploratory heterogeneity tests indicated no statistically significant impact of the radiation dose or the risk group on the unadjusted treatment effect ( $P > .1$ ; Fig 3A). Exploratory analyses using Cox models adjusted for risk group (National Comprehensive Cancer Network or D'Amico, with low risk lumped with intermediate risk due to small numbers), RT dose, AS, and the interaction between radiation dose and treatment, revealed no statistically significant interaction ( $P > .5$ ) between the radiation dose and the effect of AS and confirmed statistically significant effects overall and within all dose levels. The appendices (online only) include details of the analysis by radiation dose level, including patient characteristics (Appendix Table A1, online only), adjusted effects by dose level (Table A2, online only), and Kaplan-Meier estimates of biochemical DFS by randomized treatment and RT dose (Fig A1, online only).

In the RT arm, the treatment given upon relapse in 147 patients who had biochemical or clinical relapse was wait and see in 66 cases (44.9%), LHRH agonist in 50 cases (34%), complete androgen blockade in 15 patients (10.2%), and another treatment in 16 patients (10.9%). In the combination arm, LHRH was given to 21 of 64 patients (31.8%) who relapsed, complete androgen blockade to five (7.6%), surgery to two (3.0%), wait and see to 26 (39.4%), and another treatment to 10 (15.2%). The 5-year clinical DFS was 88.7% for the combination arm (95% CI, 85.2% to 82.11%) and 80.8% for the RT arm (95% CI, 76.5 to 84.3), corresponding to an observed HR of 0.63 (95% CI, 0.48 to 0.84;  $P = .001$ ; Fig 2B). Exploratory heterogeneity tests indicated no statistically significant impact of the radiation dose or the risk group on the unadjusted treatment effect (Fig 3B). Exploratory analyses using Cox models adjusted for risk group (National Comprehensive Cancer Network or D'Amico, with low risk lumped with intermediate risk due to small numbers) RT dose, AS, and the interaction between RT dose and treatment with AS revealed no statistically significant interaction ( $P > .1$ ) between the radiation dose and the effect of AS and confirmed statistically significant overall treatment effect (Appendix Table A2, online only) and showed effects within dose levels similar to those shown in Figure 3B.

At 5 years, the cumulative local relapse rate was 6.6% (95% CI, 4.1 to 9.1) in the RT arm and 2.1% (95% CI, 0.7 to 3.6) in the combination arm (competing risk adjusted HR, 0.37; 95% CI, 0.21 to 0.68;  $P = .001$ ; Appendix Fig A2, online only). Distant metastases were diagnosed in 31 of 409 patients (7.6%) and 18 of 410 patients (4.4%) in the RT and combination groups, respectively ( $P = .05$ ; Appendix Fig A3, online only). There was no difference in the breakdown of second cancers between groups: 46 of 409 patients (11.2%) had a second cancer after RT alone and 57 of 410 patients (13.9%) after the combination treatment. A total of 83 patients receiving radiation alone and 69 patients receiving short-term AS have died. The deaths were due to prostate cancer in 16 and nine patients, respectively, and to cardiac problems in 24 and 15 patients, respectively. Two patients in the RT arm died of radiation-induced grade 4 proctitis at months 13 and 14, respectively. The 5-year overall survival was 88.4% (95% CI, 84.7 to 91.3) for the RT arm and 91.3% (95% CI, 88.0 to 93.7) for the combination arm (Appendix Fig A4, online only). Additional follow up is required for this end point.



**Fig 2.** (A) Biochemical disease-free survival by treatment arm in the intent-to-treat population. Hazard ratio (RT + AS v RT alone) = 0.52 (95% CI, 0.41 to 0.66);  $P < .001$ . (B) Clinical disease-free survival by treatment arm in the intent-to-treat population. Hazard ratio (RT + AS v RT alone) = 0.63 (95% CI, 0.48 to 0.84);  $P = .001$ . AS, androgen suppression; O, number of events; N, number of patients; RT, radiotherapy.

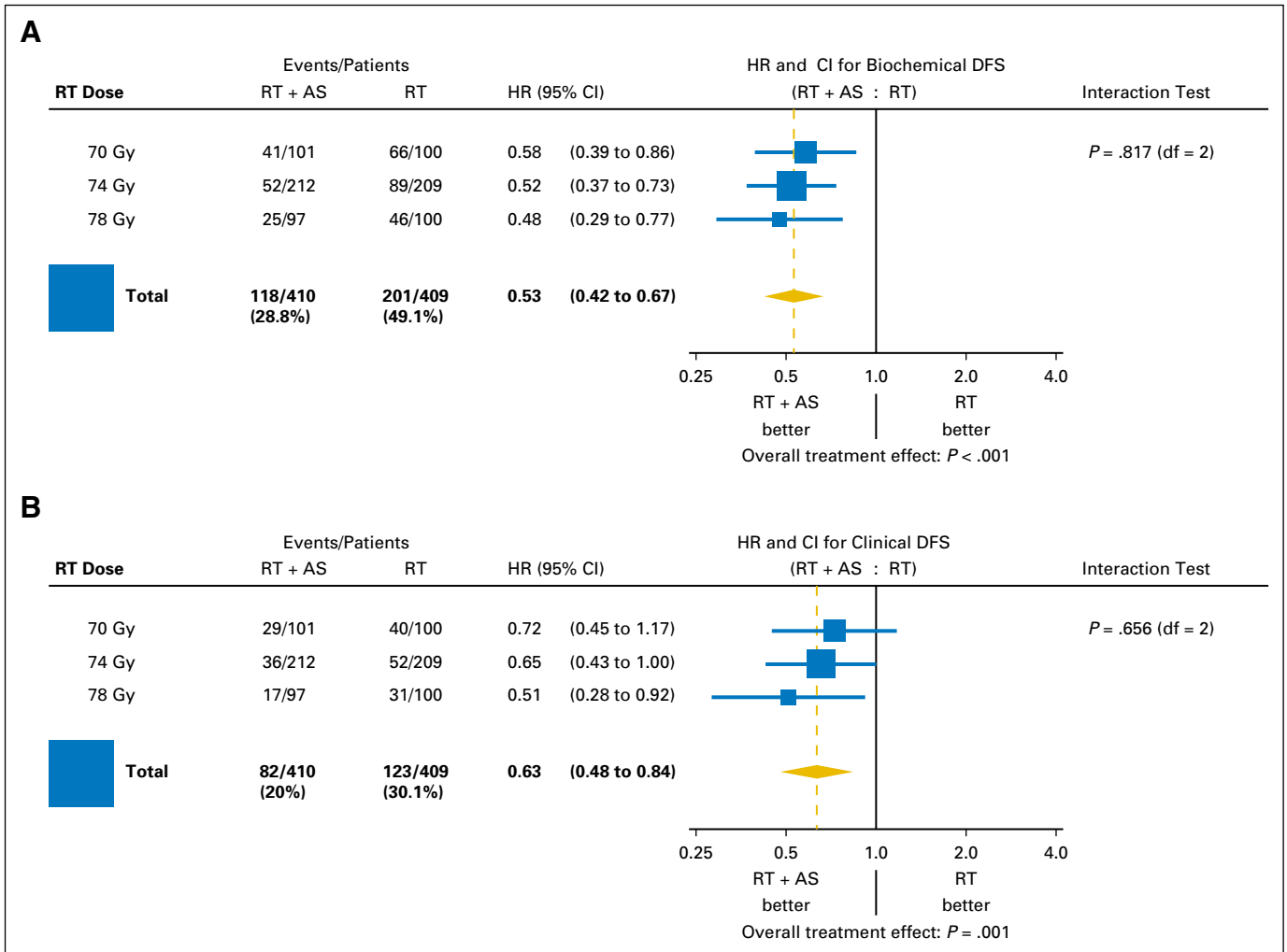
Completion rates for the HRQOL questionnaires were similar in the two groups, ranging from 87.3% at randomization to 79.3% 3 years after the treatment (see Appendix Tables A4, A5, A6, online only). Mean change scores from baseline for the four primary HRQOL scales are shown in Appendix Figure A5 and Table A7. No clinically relevant difference in HRQOL was found between the groups. Hormonal treatment symptoms, as well as sexual activity and functioning scales, were clinically significantly impaired by AS at month 6 and at year 1. However, no

marked difference was seen between the arms from year 2 onward (Fig A5, Table A7).

## DISCUSSION

Our aim was to assess the value of concomitant and adjuvant AS with goserelin combined with RT at three dose levels selected by the centers: 70 Gy (24.6%), 74 Gy (51.1%), and 78 Gy (24.2%). Stage





**Fig 3.** Forest plot. (A) Biochemical disease-free survival (DFS) and (B) clinical DFS by treatment and RT dose. AS, androgen suppression; HR, hazard ratio; RT, radiotherapy.

T2b (T2c by International Union Against Cancer TNM 2002) disease defined as an involvement of both lobes was excluded, because the larger tumor burden would have required longer AS.<sup>5,6</sup> With median follow up of 7.2 years, the combined approach improved local control, biochemical DFS, and clinical DFS compared with RT alone. Exploratory analysis and heterogeneity analysis among subgroups by dose levels showed the results for biochemical DFS are maintained irrespective of RT dose, which has not been disclosed yet. Although no statistically significant interaction between the effect of AS on clinical PFS and dose could be demonstrated, longer follow up is needed to confirm the benefit at the lower dose level of 70 Gy for this end point. Longer follow up is also needed to assess the effect on metastases and survival.

Several trials have examined the effect of AS on biochemical DFS and/or overall survival in intermediate- and high-risk localized prostate cancer. The D’Amico trial (with 220 patients) compared conventional RT (70 Gy) combined with 6-month complete AS for patients with intermediate- and high-risk prostate cancer and showed an increased 8-year overall survival (*P* = .01).<sup>9</sup> Protocol 94-08 from the RTOG (with 1,979 patients) showed that low radiation dose (66 Gy) with complete AS 2 months before and during RT improved the 10-year overall survival of intermediate-risk patients only (*P* = .03).<sup>10</sup> Protocol 94-06 from RTOG (with 583

patients) showed that the addition of AS from 2 to 3 months before RT but no longer than 6 months to escalated dose (from 73.8 to 84.3 Gy) did not significantly improve biochemical DFS or clinical DFS.<sup>11</sup> The MRC RT01 trial randomly assigned 843 patients between escalated-dose (74 Gy) and low-dose (66 Gy) conformal RT, combined with neoadjuvant AS given from 3 to 6 months before the onset of RT to its end. The dose-escalated regimen significantly improved the 10-year biochemical DFS (*P* = .001).<sup>31</sup> Exclusive RT with higher dose (78 Gy) also increases biochemical DFS.<sup>32-34</sup> Such treatment can now be delivered through IMRT<sup>8,34a</sup> without severe late toxicity.

Our results suggest that adding 6-month AS as a concomitant and adjuvant modality improves biochemical DFS even at a dose of 78 Gy, with acceptable adverse effects. Furthermore, for patients with low-volume high-risk localized prostate cancer, our results pave the way to using a combination approach with 78-Gy RT plus a short AS duration. Such an approach should be formally compared with long-term<sup>5,6</sup> or intermediate<sup>35</sup> duration of AS.

Since we designed the trial in 1999, RT techniques have improved worldwide through the use of daily image-guided IMRT. With improved reproducibility and conformity, IMRT enables the safe delivery of 78 to 80 Gy to the prostate and to irradiate pelvic

lymph nodes at an adequate dose for patients with high-risk disease. Other RT modalities may also be introduced, such as IMRT combined with brachytherapy or hypofractionation.

In conclusion, this study showed that 6 months of AS combined with RT significantly improved biochemical DFS and clinical DFS of patients with intermediate- or high-risk (by D'Amico) localized prostate cancer, as compared with RT alone, irrespective of the radiation dose level.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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### GLOSSARY TERMS

**disease-free survival:** the survival period spanning the time from surgery to a recurrence of cancer.

**intensity-modulated radiation therapy:** radiation treatment using beams with nonuniform fluence profiles that shape the dose distribution in the target volume and adjacent normal structures. Beam modulation is typically achieved via multileaf collimators or custom-milled compensators to achieve the appropriate fluence profiles calculated by inverse optimization algorithms. The radiation beam is divided into beamlets of varying

intensity such that the sum from multiple beams via inverse planning results in improved tumor targeting and normal tissue sparing. A technique of radiation therapy delivery in which the intensity of each beamlet of radiation coming from a specific angle can be adjusted to provide a desired dose distribution when the doses delivered from all beamlets are added from a single angle and from all dose delivery angles. An advanced type of high-precision radiation therapy, which aims to improve the coverage of the radiation therapy target and/or minimize radiation dose to surrounding normal tissue.

**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991**

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### Appendix

#### Analysis by Treatment Arm and Radiotherapy Dose Level

<b>Table A1.</b> Baseline Patient Demographics and Clinical Characteristics by Treatment Arm and Radiotherapy Dose						
Characteristic and Demographic	Treatment Arm					
	RT Alone, 70 Gyr Dose (N = 100)	RT + AS, 70 Gyr Dose (N = 101)	RT Alone, 74 Gyr Dose (N = 209)	RT + AS, 74 Gyr Dose (N = 212)	RT Alone, 78 Gyr Dose (N = 100)	RT + AS, 78 Gyr Dose (N = 97)
Age, years						
Median	69	71	70	71	70	70
Range	56-79	55-80	54-80	47-79	43-78	49-78
IQR	65-74	66-73	67-74	66-74	64.5-74	66-73
WHO performance status						
0	88 (88.0)	91 (90.1)	180 (86.1)	196 (92.5)	81 (81.0)	85 (87.6)
1	12 (12.0)	10 (9.9)	28 (13.4)	15 (7.1)	19 (19.0)	12 (12.4)
2	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Testosterone level						
≤ Castrate level	3 (3.0)	5 (5.0)	14 (6.7)	16 (7.5)	1 (1.0)	1 (1.0)
> Castrate level	75 (75.0)	81 (80.2)	146 (69.9)	159 (75.0)	69 (69.0)	78 (80.4)
Unknown	22 (22.0)	15 (14.9)	49 (23.4)	37 (17.5)	30 (30.0)	18 (18.6)
Associated chronic disease present						
Cardiovascular	58 (58.0)	57 (56.4)	124 (59.3)	134 (63.2)	63 (63.0)	62 (63.9)
Respiratory	22 (37.9)	17 (29.8)	54 (43.5)	55 (41.0)	31 (49.2)	35 (56.5)
Diabetes	3 (5.2)	4 (7.0)	4 (3.2)	18 (13.4)	4 (6.3)	5 (8.1)
Genitourinary	1 (1.7)	7 (12.3)	10 (8.1)	9 (6.7)	1 (1.6)	2 (3.2)
GI	1 (1.7)	2 (3.5)	2 (1.6)	1 (0.7)	0 (0.0)	0 (0.0)
Multiple	3 (5.2)	3 (5.3)	3 (2.4)	4 (3.0)	1 (1.6)	0 (0.0)
Other	18 (31.0)	16 (28.1)	38 (30.6)	34 (25.4)	21 (33.3)	11 (17.7)
	10 (17.2)	8 (14.0)	13 (10.5)	13 (9.7)	5 (7.9)	9 (14.5)

(continued on following page)

EORTC Trial 22991 for Intermediate- and High-Risk Prostate Cancer

**Table A1.** Baseline Patient Demographics and Clinical Characteristics by Treatment Arm and Radiotherapy Dose (continued)

Characteristic and Demographic	Treatment Arm					
	RT Alone, 70 Gyr Dose (N = 100)	RT + AS, 70 Gyr Dose (N = 101)	RT Alone, 74 Gyr Dose (N = 209)	RT + AS, 74 Gyr Dose (N = 212)	RT Alone, 78 Gyr Dose (N = 100)	RT + AS, 78 Gyr Dose (N = 97)
Time since first histologic diagnosis, months						
Median	2.1	2.1	2.8	2.6	2.7	2.6
Range	0.6-13.5	0.7-54.9	0.6-56.0	0.2-55.6	0.8-129.7	0.8-69.6
IQR	1.5-3.1	1.5-3.4	2.1-4.0	1.9-4.2	1.8-4.0	2.0-4.1
T category (UICC TNM 1997)						
T1a (ineligible)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
T1b	7 (7.0)	7 (6.9)	6 (2.9)	1 (0.5)	3 (3.0)	3 (3.1)
T1c	47 (47.0)	51 (50.5)	92 (44.0)	89 (42.0)	41 (41.0)	47 (48.5)
T2a	46 (46.0)	43 (42.6)	107 (51.2)	120 (56.6)	54 (54.0)	47 (48.5)
T2b-c (ineligible)	0 (0.0)	0 (0.0)	3 (1.4)	2 (1.0)	2 (2.0)	0 (0.0)
Clinical N category						
cN0	100 (100.0)	100 (99.0)	209 (100.0)	212 (100.0)	98 (98.0)	97 (100.0)
Unspecified	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)
Pathologic N category						
pN0	10 (10.0)	14 (13.9)	21 (10.0)	16 (7.5)	24 (24.0)	16 (16.5)
Not done	90 (90.0)	87 (86.1)	188 (90.0)	196 (92.5)	76 (76.0)	81 (83.5)
Clinical M category						
M0	100 (100.0)	101 (100.0)	208 (99.5)	211 (99.5)	100 (100.0)	97 (100.0)
M1 (ineligible)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Gleason sum						
< 6	16 (16.0)	14 (13.9)	24 (11.5)	22 (10.4)	6 (6.0)	10 (10.3)
6	36 (36.0)	39 (38.6)	80 (38.3)	77 (36.3)	39 (39.0)	39 (40.2)
7	35 (35.0)	33 (32.7)	94 (45.0)	93 (43.9)	42 (42.0)	38 (39.2)
8-10	13 (13.0)	15 (14.9)	11 (5.3)	20 (9.4)	13 (13.0)	10 (10.3)
Baseline PSA (UNL = 4 ng/ml)						
Median	11.7	13.0	9.3	9.3	12.0	11.9
Range	0.5-45.0	0.3-40.0	0.4-54.9	1.7-50.7	2.6-97.9	1.0-50.3
IQR	7.4-19.8	8.0-17.6	6.5-13.9	6.2-13.5	7.2-18.8	7.2-17.2
≤ 2.5 × UNL	39 (39.0)	38 (37.6)	117 (56.0)	120 (56.6)	42 (42.0)	41 (42.3)
> 2.5 × UNL to ≤ 4 × UNL	37 (37.0)	40 (39.6)	69 (33.0)	72 (34.0)	37 (37.0)	40 (41.2)
> 4 × UNL	24 (24.0)	23 (22.8)	23 (11.0)	20 (9.4)	21 (21.0)	16 (16.5)
NCCN risk						
Low (ineligible)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)
Intermediate	34 (34.0)	45 (44.6)	103 (49.3)	102 (48.1)	37 (37.0)	40 (41.2)
T2a (1997) with one other intermediate-risk factor	20 (20.0)	13 (12.9)	40 (19.1)	47 (22.2)	20 (20.0)	24 (24.7)
High	46 (46.0)	43 (42.6)	64 (30.6)	63 (29.7)	43 (43.0)	32 (33.0)
D'Amico <sup>2</sup> risk						
Low	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)
Intermediate	65 (65.0)	67 (66.3)	169 (80.9)	173 (81.6)	67 (67.0)	72 (74.2)
High	35 (35.0)	34 (33.7)	38 (18.2)	39 (18.4)	33 (33.0)	24 (24.7)

NOTE: All values are expressed as No. of patients (%), unless otherwise stated.

Abbreviations: AS, androgen suppression; IQR, interquartile range; N, normal; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; RT, radiotherapy; UICC, International Union Against Cancer; WHO, World Health Organization.

**Table A2.** Treatment Effects Within Dose Level, Adjusted by Risk Group and Dose Level

Treatment Effect	Dose Level (Gy)	Hazard Ratio	95% CI		Treatment <i>P</i>	Interaction <i>P</i>
Biochemical DFS adjusted for NCCN risk group	70	0.60	0.41	0.89	.0108	.77
	74	0.50	0.36	0.71	< .001	
	78	0.51	0.31	0.82	.0063	
Biochemical DFS adjusted for D'Amico <sup>2</sup> risk group	70	0.59	0.40	0.87	.0074	.84
	74	0.51	0.36	0.72	.001	
	78	0.50	0.31	0.82	.0060	
Clinical DFS adjusted for NCCN risk group	70	0.76	0.47	1.22	.2520	.68
	74	0.65	0.42	0.99	.0443	
	78	0.54	0.30	0.97	.0394	
Clinical DFS adjusted for D'Amico <sup>2</sup> risk group	70	0.73	0.45	1.18	.2001	.70
	74	0.65	0.42	1.00	.0478	
	78	0.53	0.29	0.95	.0341	

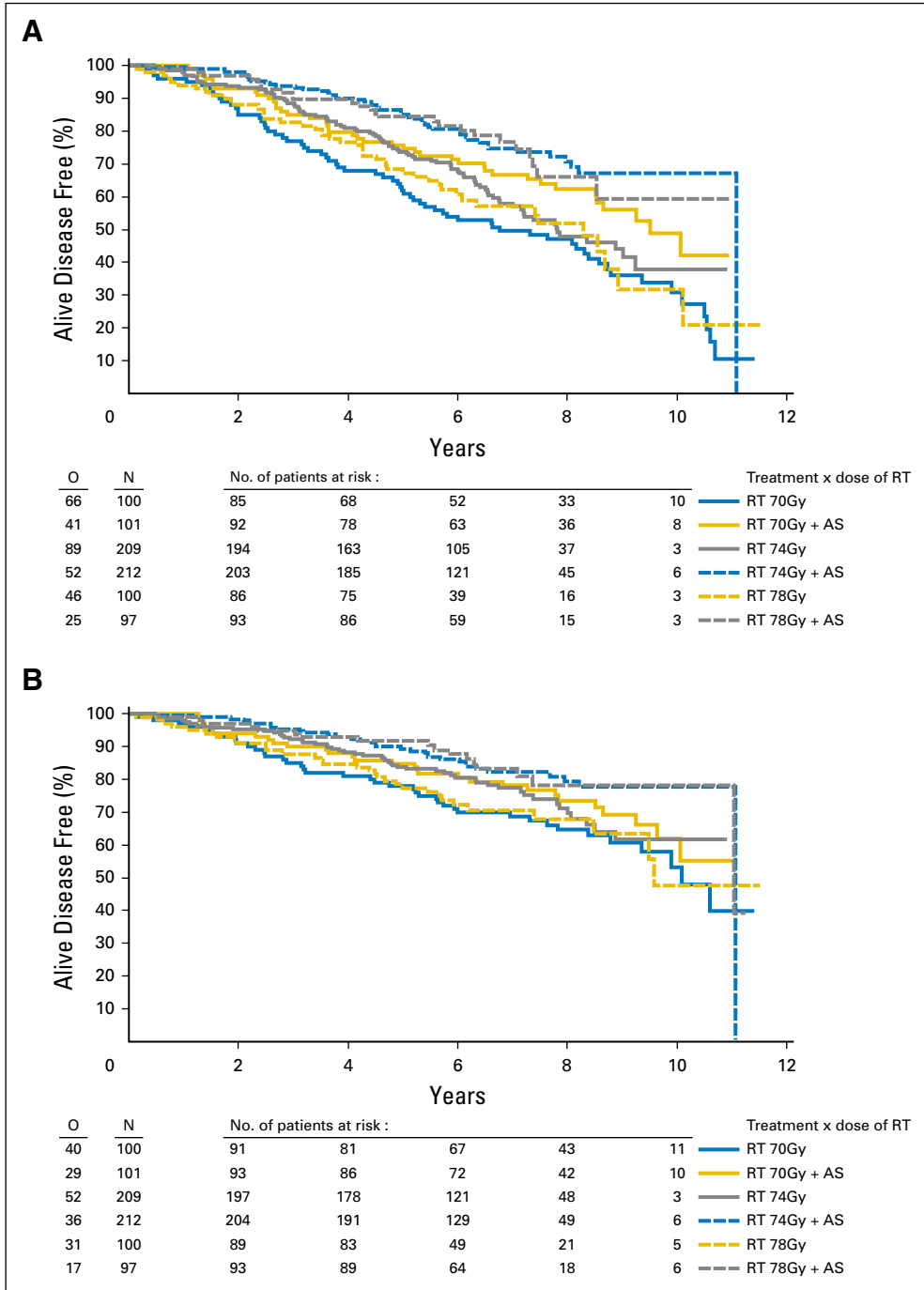
Abbreviations: NCCN, National Comprehensive Cancer Network; DFS, disease-free survival.

**Table A3.** Protocol Time Windows Schedule

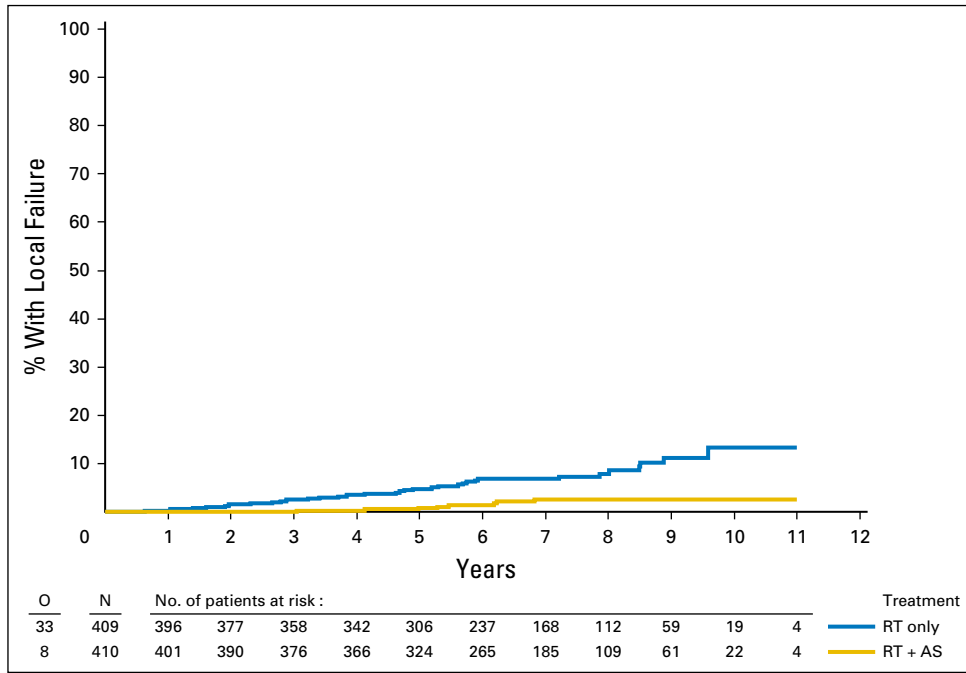
Time Point	Ti	Li	Ui	Window Length
Baseline	D0	D0-3 weeks	Not later than first day of protocol treatment or 3 weeks after randomization	6 weeks maximum
6 Months	D0 + 6 months	D0 + 3 months	D0 + 10 months	7 months
1 Year	D0 + 1 year	D0 + 10 months	D0 + 1.5 years	8 months
2 Years	D0 + 2 years	D0 + 1.5 years	D0 + 2.5 years	12 months
3 Years	D0 + 3 years	D0 + 2.5 years	D0 + 3.5 years	12 months
4 Years	D0 + 4 years	D0 + 3.5 years	D0 + 4.5 years	12 months
5 Years	D0 + 5 years	D0 + 4.5 years	D0 + 5.5 years	12 months
> 5 Years	D0 + 6 years	D0 + 5.5 years	D0 + 8 years	30 months

Abbreviation: D0, day of randomization.

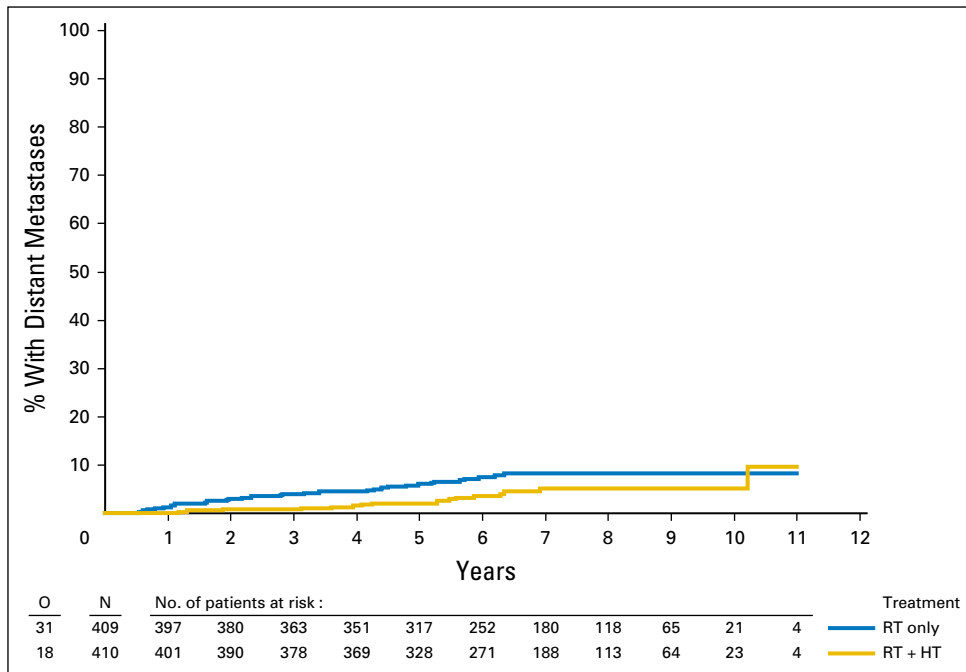




**Fig A1.** (A) Kaplan-Meier curves of biochemical disease-free survival by randomized treatment and RT dose. (B) Kaplan-Meier curves of clinical disease-free survival by randomized treatment and RT dose. AS, androgen suppression; N, number of patients; O, number of events; RT, radiotherapy.

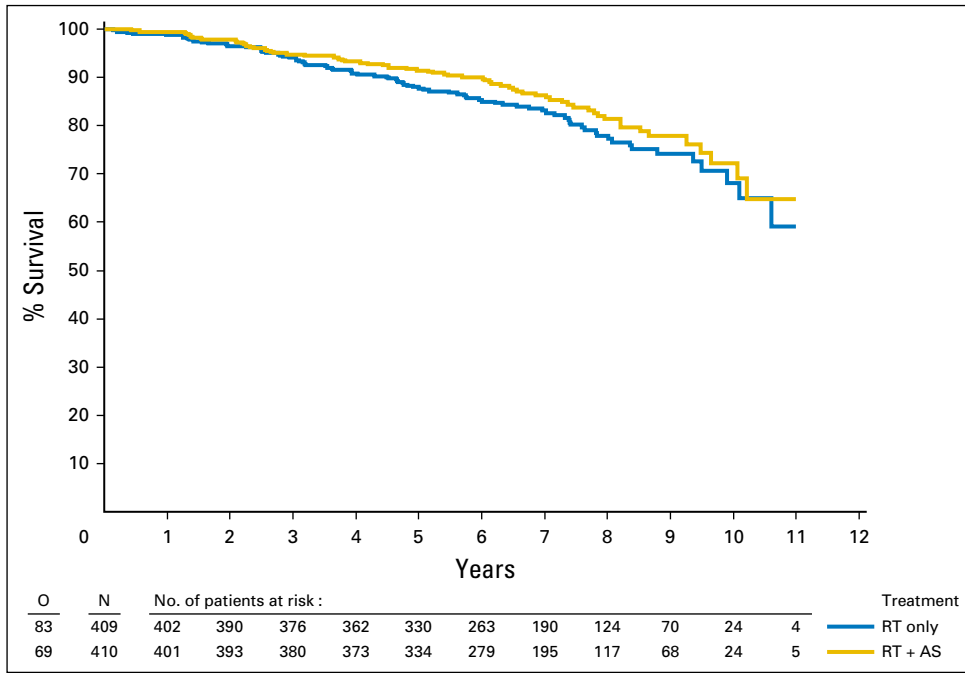


**Fig A2.** Secondary endpoint: Local relapse. Competing risk adjusted hazard ratio, 0.37; 95% CI, 0.21 to 0.68;  $P = .001$ . AS, androgen suppression; N, number of patients; O, number of events; RT, radiotherapy.



**Fig A3.** Cumulative incidence of distant metastases. Competing risk adjusted hazard ratio, 0.37; 95% CI, 0.32 to 1.01,  $P = .053$ . AS, androgen suppression; N, number of patients; O, number of events; RT, radiotherapy.

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**Fig A4.** The 5-year overall survival was 88.4% (95% CI, 84.7 to 91.3) for the radiotherapy arm and 91.3% (95% CI, 88.0 to 93.7) for the combined treatment arm. Additional follow up is required for this end point. AS, androgen suppression; N, number of patients; O, number of events; RT, radiotherapy.

**Health-Related Quality of Life Results by EORTC QLQ-C30 and QLQ-PR25****Compliance to Health-Related Quality of Life (HRQOL) Assessments**

Compliance for a group of patients at a certain time point  $T_i$  is defined as:

$$\text{Compliance}(T_i) = \frac{\text{Valid HRQOL form within } [L_i, U_i]}{\text{HRQOL form expected at } T_i}$$

Where  $L_i$  and  $U_i$  are the lower and upper bound of the time windows associated with  $T_i$ .

HRQOL forms are considered invalid if either:

- All questions on the form are blank.
- The completion date is unknown or it cannot be assigned to a single assessment time point.
- The completion date falls outside the time windows.
- Multiple forms are received during the same time window. In this case, the form closest to the intended assessment time will be kept. In case of equidistance, the earlier form will be kept.

Forms are expected at  $T_i$  for each patient who was within the assessment window. A patient is considered to be within the assessment time window if at least one of the following conditions is met:

- A valid HRQOL form is received within  $L_i$  and  $U_i$ .
- The patient was still under study follow-up at  $T_i$ .

For the baseline assessment, all randomly assigned patients are expected to have a completed baseline HRQOL form.

**Time Windows**

The time windows schedule as defined above can be applied to this study. Because no time windows were explicitly stated in the protocol, the upper and lower limits were set to maximize the resulting compliance. The resulting values for  $T_i$ ,  $L_i$ , and  $U_i$  are summarized in [Table A4](#).

An evaluation of the compliance according to the time windows schedule listed in [Table A3](#) was done on the trial database. The window around assessment time at approximately the 6-month time point is unequal because there was indication of undue loss of forms falling after the 6-month time point.

A total of 5,178 forms were recorded in the database. Of these, 1,192 (23.0%) forms were excluded because duplicate forms fell within one window or because the form was received either before the baseline window or after the last (year 5) window. The exclusion reasons are similarly distributed over the two treatment arms.

**Compliance Rates by Assessment Point**

The remaining 3,986 forms could be uniquely assigned to existing time windows. The resulting compliance rates for this trial are summarized in [Tables A4-A6](#).

Noticeably, the compliance rates drop dramatically after year 3 ([Table A4](#)). This corresponds to the protocol-defined follow-up schedule, which stopped at year 3 assessment.

This resulting compliance rates per treatment arm are summarized in [Tables A5 and A6](#).

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**Table A4.** Health-Related Quality of Life Compliance Rates, Overall

Assessment Time	No. of Forms Received	No. of Forms Expected	Compliance (%)
Baseline	715	819	87.3
6 Months	584	814	71.7
1 Year	617	812	76.0
2 Years	655	797	82.2
3 Years	614	774	79.3
4 Years	330	755	43.7
5 Years	270	736	36.7
> 5 Years	201	660	30.5

**Table A5.** Compliance, Radiotherapy Only

HRQOL Compliance	Assessment Time								Total
	Baseline	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years	> 5 Years	
Missing	45 (11.0)	130 (32.1)	109 (27.0)	71 (17.9)	79 (20.5)	219 (58.9)	226 (62.8)	224 (69.1)	1,103
Received	364 (89.0)	275 (67.9)	295 (73.0)	325 (82.1)	306 (79.5)	153 (41.1)	134 (37.2)	100 (30.9)	1,952
Total	409	405	404	396	385	372	360	324	3,055

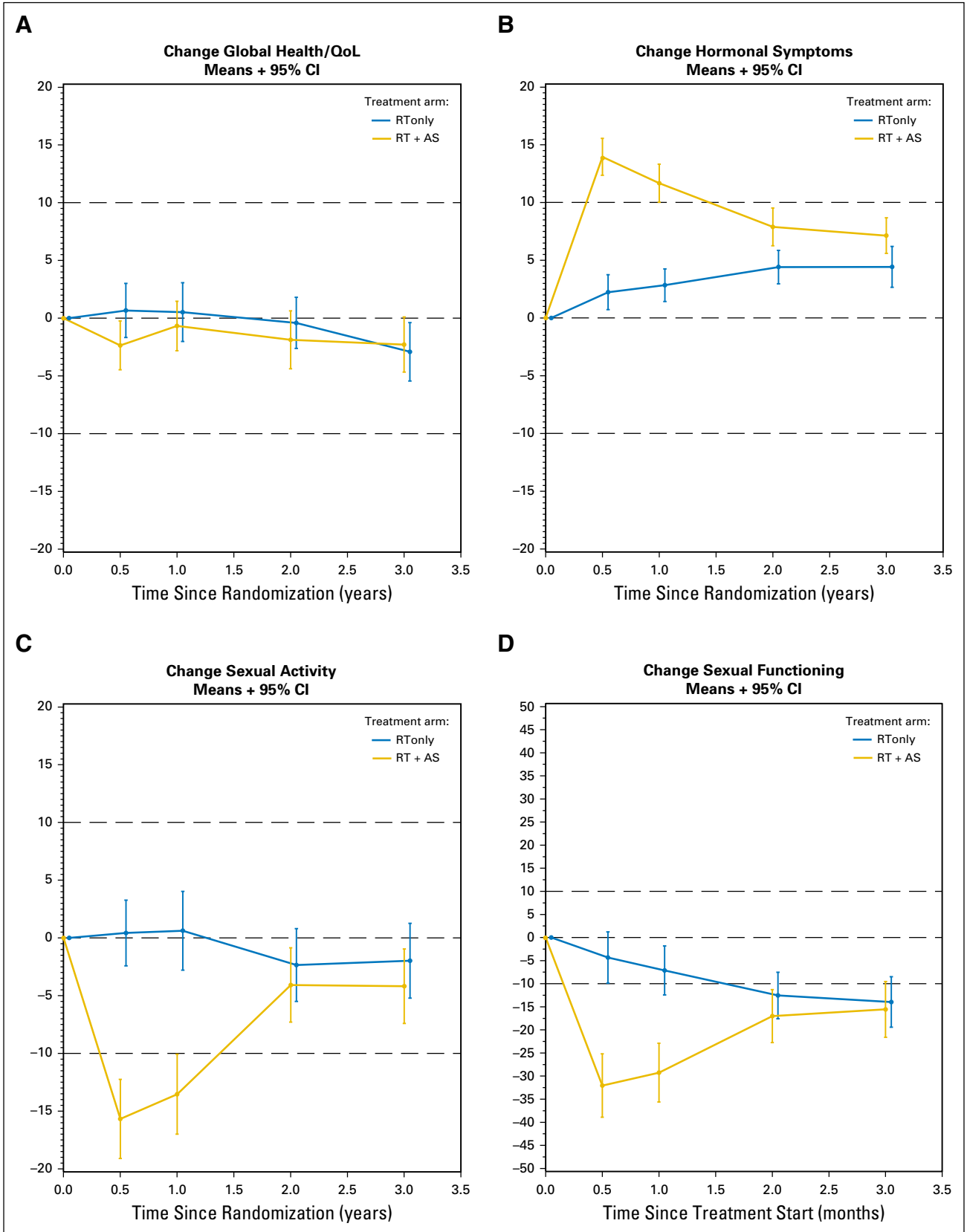
NOTE: Values are expressed as No. (%). The frequency missing = 217.  
Abbreviation: HRQOL, health-related quality of life.

**Table A6.** Compliance, Radiotherapy Plus Androgen Suppression

HRQOL Compliance	Assessment Time								Total
	Baseline	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years	> 5 Years	
Missing	59 (14.4)	100 (24.4)	86 (21.1)	71 (17.7)	81 (20.8)	206 (53.8)	240 (63.8)	235 (70.0)	1,078
Received	351 (85.6)	309 (75.6)	322 (78.9)	330 (82.3)	308 (79.2)	177 (46.2)	136 (36.2)	101 (30.0)	2,034
Total	410	409	408	401	389	383	376	336	3,112

NOTE: Values are expressed as n (%). The frequency missing = 168.  
Abbreviation: HRQOL, health-related quality of life.





**Fig A5.** Health-related quality of life results. Mean change scores from baseline for the primary scales. (A) Overall quality of life/health status, (B) symptoms related to hormonal treatment, (C) sexual activity, and (D) sexual functioning (assigned a score of zero in absence of activity). AS, androgen suppression; QoL, quality of life; RT, radiotherapy.

Overall, compliance for the protocol scheduled time points was acceptable with 87% at baseline and remaining above 70% for the first 3 years. Compliance tended to be higher in the in the RT+AS arm, especially during the first year. There is a clear treatment effect noticeable on the hormonal treatment symptom scale and the sexual activity and functioning scales. The effect is largest at month 6 with clinical relevant differences in each of these three scales. By year 1, these treatment differences are still present but less so and only clinically relevant for the sexuality related scales. By year 2, no relevant treatment difference remained.

**Table A7.** Mean Scores and Mean Score Change from Baseline for the Primary Health-Related Quality of Life Scales

Characteristic	Score		Score Change From Baseline	
	RT Only (N = 364)	RT+AS (N = 351)	RT Only (N = 364)	RT+AS (N = 351)
<b>Global health status / QoL</b>				
Baseline				
Median	83.3	83.3	—	—
Range	0.0-100.0	0.0-100.0	—	—
IQR	66.7-91.7	66.7-91.7	—	—
Mean (SD)	77.04 (18.72)	78.15 (17.71)	—	—
No.	359	347	—	—
Month 6				
Median	83.3	83.3	0.0	0.0
Range	0.0-100.0	0.0-100.0	-83.3-75.0	-66.7-58.3
IQR	66.7-91.7	66.7-91.7	-8.3-8.3	-8.3-8.3
Mean (SD)	78.54 (18.17)	76.97 (18.32)	0.66 (18.39)	-2.36 (17.33)
No.	271	305	239	261
Year 1				
Median	83.3	83.3	0.0	0.0
Range	0.0-100.0	16.7-100.0	-83.3-83.3	-50.0-83.3
IQR	66.7-91.7	66.7-91.7	-8.3-8.3	-8.3-8.3
Mean (SD)	77.65 (18.65)	78.52 (16.43)	0.52 (20.61)	-0.68 (17.91)
No.	289	315	255	270
Year 2				
Median	83.3	83.3	0.0	0.0
Range	0.0-100.0	8.3-100.0	-66.7-100.0	-75.0-83.3
IQR	66.7-91.7	66.7-91.7	-8.3-8.3	-16.7-8.3
Mean (SD)	78.09 (18.76)	77.10 (18.75)	-0.41 (19.04)	-1.88 (21.10)
No.	321	322	286	275
Year 3				
Median	83.3	83.3	0.0	0.0
Range	0.0-100.0	0.0-100.0	-66.7-100.0	-66.7-83.3
IQR	66.7-83.3	66.7-91.7	-16.7-8.3	-16.7-8.3
Mean (SD)	75.58 (19.47)	77.20 (18.85)	-2.91 (21.08)	-2.29 (19.60)
No.	301	307	269	262
<b>Hormonal symptoms</b>				
Baseline				
Median	5.6	0.0	—	—
Range	0.0-50.0	0.0-53.3	—	—
IQR	0.0-11.1	0.0-11.1	—	—
Mean (SD)	7.58 (10.32)	6.67 (9.59)	—	—
No.	308	306	—	—
Month 6				
Median	5.6	16.7	0.0	11.1
Range	0.0-55.6	0.0-83.3	-38.9-55.6	-11.1-66.7
IQR	0.0-11.1	11.1-27.8	0.0-5.6	5.6-22.2
Mean (SD)	9.47 (11.66)	19.32 (13.65)	2.23 (10.62)	13.95 (12.01)
No.	235	264	193	219
Year 1				
Median	8.3	16.7	0.0	11.1
Range	0.0-53.3	0.0-61.1	-33.3-42.2	-27.8-46.7
IQR	0.0-16.7	5.6-27.8	0.0-6.7	0.0-22.2
Mean (SD)	10.85 (11.99)	18.07 (14.11)	2.83 (10.54)	11.66 (12.68)
No.	257	274	216	230
Year 2				
Median	6.7	11.1	0.0	5.6
Range	0.0-58.3	0.0-60.0	-44.4-44.4	-33.3-54.4

(continued on following page)

**Table A7.** Mean Scores and Mean Score Change from Baseline for the Primary Health-Related Quality of Life Scales (continued)

Characteristic	Score		Score Change From Baseline	
	RT Only (N = 364)	RT+AS (N = 351)	RT Only (N = 364)	RT+AS (N = 351)
IQR	0.0-16.7	5.6-22.2	0.0-11.1	0.0-11.1
Mean (SD)	11.21 (11.99)	13.67 (12.89)	4.40 (11.33)	7.89 (12.58)
No.	281	279	237	231
Year 3				
Median	8.3	11.1	0.0	5.6
Range	0.0-66.7	0.0-66.7	-44.4-55.6	-22.2-46.7
IQR	0.0-16.7	0.0-22.2	0.0-11.1	0.0-11.1
Mean (SD)	11.68 (12.87)	12.79 (12.83)	4.42 (13.38)	7.13 (11.53)
No.	263	262	221	218
Sexual activity				
Baseline				
Median	33.3	33.3	—	—
Range	0.0-100.0	0.0-100.0	—	—
IQR	0.0-33.3	0.0-33.3	—	—
Mean (SD)	27.99 (24.71)	27.43 (22.63)	—	—
No.	309	302	—	—
Month 6				
Median	33.3	0.0	0.0	-16.7
Range	0.0-100.0	0.0-100.0	-50.0-66.7	-100.0-100.0
IQR	0.0-33.3	0.0-16.7	0.0-16.7	-33.3-0.0
Mean (SD)	27.09 (22.41)	10.84 (19.22)	0.43 (20.22)	-15.67 (25.66)
No.	235	266	196	218
Year 1				
Median	33.3	0.0	0.0	-16.7
Range	0.0-100.0	0.0-100.0	-66.7-100.0	-100.0-100.0
IQR	0.0-41.7	0.0-33.3	-16.7-16.7	-33.3-0.0
Mean (SD)	27.60 (24.87)	14.96 (21.93)	0.62 (25.41)	-13.54 (26.60)
No.	256	273	216	229
Year 2				
Median	33.3	16.7	0.0	0.0
Range	0.0-100.0	0.0-100.0	-66.7-100.0	-100.0-100.0
IQR	0.0-33.3	0.0-33.3	-16.7-16.7	-16.7-0.0
Mean (SD)	25.73 (22.42)	24.29 (23.30)	-2.35 (24.52)	-4.08 (24.88)
No.	274	280	234	233
Year 3				
Median	33.3	16.7	0.0	0.0
Range	0.0-100.0	0.0-100.0	-83.3-100.0	-83.3-100.0
IQR	0.0-33.3	0.0-33.3	-16.7-16.7	-16.7-0.0
Mean (SD)	26.88 (24.11)	24.08 (23.32)	-1.98 (24.34)	-4.19 (23.96)
No.	261	263	219	215
Sexual functioning (assigned a score of 0 in absence of activity)				
Baseline				
Median	50.0	56.9	—	—
Range	0.0-100.0	0.0-100.0	—	—
IQR	0.0-75.0	0.0-83.3	—	—
Mean (SD)	40.49 (37.50)	43.91 (38.96)	—	—
No.	253	230	—	—
Month 6				
Median	33.3	0.0	0.0	-8.3
Range	0.0-100.0	0.0-100.0	-91.7-83.3	-100.0-75.0
IQR	0.0-66.7	0.0-0.0	-16.7-0.0	-75.0-0.0
Mean (SD)	35.33 (34.67)	5.85 (17.76)	-4.34 (33.44)	-32.05 (39.79)
No.	181	211	142	132
Year 1				
Median	25.0	0.0	0.0	-16.7
Range	0.0-100.0	0.0-100.0	-100.0-75.0	-100.0-75.0
IQR	0.0-66.7	0.0-0.0	-22.2-0.0	-61.1-0.0
Mean (SD)	33.11 (34.76)	12.65 (25.14)	-7.14 (31.98)	-29.25 (38.45)
No.	189	208	142	143
Year 2				
Median	20.8	13.9	-8.3	-8.3
Range	0.0-100.0	0.0-100.0	-91.7-83.3	-100.0-83.3
IQR	0.0-58.3	0.0-58.3	-33.3-0.0	-33.3-0.0
Mean (SD)	30.63 (32.55)	28.18 (31.90)	-12.55 (33.30)	-17.03 (35.02)
No.	210	202	170	146

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**Table A7.** Mean Scores and Mean Score Change from Baseline for the Primary Health-Related Quality of Life Scales (continued)

Characteristic	Score		Score Change From Baseline	
	RT Only (N = 364)	RT+AS (N = 351)	RT Only (N = 364)	RT+AS (N = 351)
Year 3				
Median	25.0	8.3	0.0	-8.3
Range	0.0-100.0	0.0-100.0	-91.7-91.7	-100.0-100.0
IQR	0.0-58.3	0.0-58.3	-33.3-0.0	-33.3-0.0
Mean (SD)	31.25 (32.96)	27.95 (31.64)	-13.96 (34.64)	-15.56 (34.95)
No.	197	195	157	131

Abbreviations: AS, androgen suppression; IQR, interquartile range; RT, radiotherapy; SD, standard deviation.