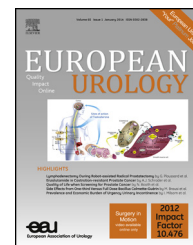




European Association of Urology



## Platinum Priority – Prostate Cancer

Editorial by Bruce J. Trock on pp. 251–252 of this issue

# Adjuvant Radiotherapy Versus Wait-and-See After Radical Prostatectomy: 10-year Follow-up of the ARO 96–02/AUO AP 09/95 Trial

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## Abstract

**Background:** Local failure after radical prostatectomy (RP) is common in patients with cancer extending beyond the capsule. Three prospectively randomized trials demonstrated an advantage for adjuvant radiotherapy (ART) compared with a wait-and-see (WS) policy.

**Objective:** To determine the efficiency of ART after a 10-yr follow-up in the ARO 96–02 study.

**Design, setting, and participants:** After RP, 388 patients with pT3 pN0 prostate cancer (PCa) were randomized to WS or three-dimensional conformal ART with 60 Gy. The present analysis focuses on intent-to-treat patients who achieved an undetectable prostate-specific antigen after RP (ITT2 population)—that is, 159 WS plus 148 ART men. **Outcome measurements and statistical analysis:** The primary end point of the study was progression-free survival (PFS) (events: biochemical recurrence, clinical recurrence, or death). Outcomes were compared by log-rank test. Cox regression analysis served to identify variables influencing the course of disease.

**Results and limitations:** The median follow-up was 111 mo for ART and 113 mo for WS. At 10 yr, PFS was 56% for ART and 35% for WS ( $p < 0.0001$ ). In pT3b and R1 patients, the rates for WS even dropped to 28% and 27%, respectively. Of all 307 ITT2 patients, 15 died from PCa, and 28 died for other or unknown reasons. Neither metastasis-free survival nor overall survival was significantly improved by ART. However, the study was

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underpowered for these end points. The worst late sequelae in the ART cohort were one grade 3 and three grade 2 cases of bladder toxicity and two grade 2 cases of rectum toxicity. No grade 4 events occurred.

**Conclusions:** Compared with WS, ART reduced the risk of (biochemical) progression with a hazard ratio of 0.51 in pT3 PCa. With only one grade 3 case of late toxicity, ART was safe.

**Patient summary:** Precautionary radiotherapy counteracts relapse after surgery for prostate cancer with specific risk factors.

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## 1. Introduction

For patients with localized prostate cancer (PCa), radical prostatectomy (RP) and external-beam radiotherapy (RT) enable an adjusted 10-yr overall survival (OS) of 83% and 89%, respectively [1]. After prostatectomy, 15–25% of the patients experience recurrence [2]. With adverse risk factors such as high serum levels of prostate-specific antigen (PSA), pT3, positive surgical margins (R1), and Gleason score  $\geq 8$ , the 10-yr biochemical recurrence rates may grow to 75% [3]. Although not all PSA-relapsing patients will develop clinical progression, surgery alone may be inadequate for specific subgroups [4].

Three randomized prospective trials—SWOG 8794, European Organization for Research and Treatment of Cancer (EORTC) 22911 (10-yr data), and ARO 96–02 (5-yr data)—reported improved (biochemical) progression-free survival (PFS) after adjuvant RT (ART) with hazard ratios (HRs) between 0.43 and 0.53 [5–7]. Only SWOG also found a profit in OS and metastasis-free survival (MFS). As PSA recurrence precedes clinical progression by a median of 8 yr, long-term results of these studies are of major interest [8]. In this paper, we report the 10-yr follow-up of the ARO/AUO trial. Exclusively including patients who achieved an undetectable PSA after RP, the ARO/AUO trial is the one truly adjuvant trial among the three. Different from the two older trials, ARO 96–02 consistently incorporated three-dimensional (3D) conformal treatment planning, improving comparability with recent techniques.

## 2. Methods

### 2.1. Trial design and participants

Tumor stages were determined according to the 1992 International Union Against Cancer criteria [9]. Patients had histologically proven cT1–cT3N0 PCa preoperatively. Before entry, all patients underwent preoperative and postoperative PSA testing, bone scan, and chest radiography. Eligible patients had histologically proven adenocarcinoma of the prostate with no known distant metastases and a pathologic stage pT3–4 pN0 with positive or negative surgical margins. Patients had to be  $< 76$  yr, with a World Health Organization performance status of 0 or 1 [10]. ART began between 6 and 12 wk after surgery. The protocol was approved by the local human use committee for each participating center. Written informed consent was obtained from all patients.

### 2.2. Clinical procedures

Patients were recruited after open RP that included the prostate gland and seminal vesicles, as well as pelvic lymphadenectomy. A unilateral or

bilateral nerve-sparing technique was allowed unless it raised the risk of positive surgical margins.

Surgical specimens were fixed with formalin and their entire margins marked with ink. The prostate was sectioned from the distal margins to the bladder neck. Positive margins were defined as direct contact of malignant cells with the stained margin. All specimens were assessed for Gleason score, R.G. and S.S. provided central pathology review.

Before achieving a post-RP undetectable PSA, patients were randomized to either wait-and-see (WS) (arm A) or ART (arm B). The undetectable PSA is usually achieved within 2–6 wk, depending on the initial PSA value. If the undetectable state was not achieved, patients were excluded by protocol (arm C, progressive disease). The recommended treatment for arm C patients was immediate RT. Patients were stratified for Gleason score ( $< 7$  vs  $\geq 7$ ), margin status (positive vs negative), neoadjuvant hormonal treatment (HT) before RP (3 mo vs none), and tumor stage (pT3a/b vs pT3c).

ART patients underwent 3D treatment planning with a simulation of treatment fields or virtual simulation. Treatment was scheduled 6–12 wk after RP. RT was given with linear accelerators, normally with a three- or four-field technique. The target volume received 60 Gy in 30 fractions, as described previously [7].

Follow-up examinations including digital rectal examinations and PSA tests were done every 3 mo for 2 yr, then biannually until the end of the fifth year, and then every year. PSA progression for patients with previously undetectable PSA was stated after two consecutive determinations with increasing PSA values above the respective local detection limit. Acute adverse effects of RT were scored according to the Radiation Therapy Oncology Group (RTOG) scale. The Late Radiation Morbidity Scoring scheme of the RTOG/EORTC was used to assess late toxicity.

### 2.3. Analysis population and statistics

The current report focuses on 307 patients who achieved a post-RP undetectable PSA (ITT2 population), 159 of whom were assigned to WS and 148 to ART (Fig. 1). Details on statistical design and procedures have been published previously [7]. The primary end point was PFS, defined as the nonoccurrence of any of the following events: biochemical progression (two consecutive PSA increases above detection limits), local or distant clinical recurrence, or death from any cause. All time-to-event periods were calculated from the date of randomization.

## 3. Results

From 1997 to 2004, 388 patients entered the trial after RP but before achieving an undetectable PSA: 194 patients were assigned to the WS policy (arm A), and 194 patients were assigned to ART (arm B). Three patients were excluded because of immediate HT (Fig. 1). Seventy-eight patients (20%) who did not achieve an undetectable PSA were stated to have progressive disease (arm A, 33 patients; arm B, 45 patients). Of these 78 patients, 74 underwent RT; 4 patients

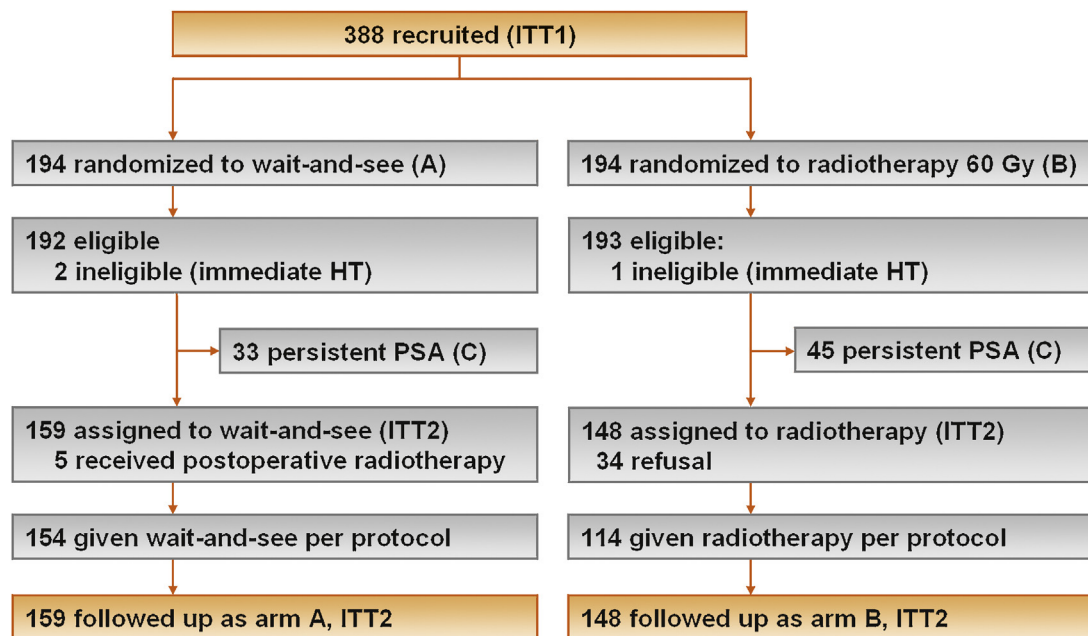


Fig. 1 – Consolidated Standards of Reporting Trials (CONSORT) diagram.  
HT = hormonal treatment; ITT = intent-to-treat; PSA = prostate-specific antigen.

refused RT. In this paper, we focus on the remaining 307 patients. These patients all had a PSA <0.1 ng/ml, 80% had a PSA <0.05 ng/ml, and 41% had a PSA of even <0.03 ng/ml, depending on the detection limits of the different assays. Thirty-four patients (19%) from arm B eventually refused RT. Thus, 114 men received ART, and 159 had a WS policy. Five of the latter patients (3.2%) underwent RT by personal request. Table 1 summarizes patient characteristics. Treatment information was available for all but three patients (0.75%), who were excluded from analysis because of immediate HT.

As the median, RT began 81 d (range: 34–211) after surgery and lasted 44 d (range: 42–47). The total dose was 60 Gy (range: 26–66); 82% had the prescribed dose. A central pathology review was available for 262 of the 307 patients (85%) [11]. The current analysis is based on Gleason score, surgical margins, and pT stage, according to reference pathology where available or else local pathology.

The median follow-up period was 112.2 mo: arm A, 113.2 mo (range: 1.3–161.4; quartiles: 86.6–129.6), and arm B, 111.3 mo (range: 2.3–167.8; quartiles: 88.1–127.9). A total of 161 failures (100 in the WS group and 61 in the RT group) were recorded for the ITT2 cohort. Throughout the trial, the first statement of progression referred to biochemical recurrence. PFS was significantly better in the irradiation group. The 10-yr Kaplan-Meier estimates were 35% versus 56% (HR: 0.51; 95% confidence interval [CI], 0.37–0.70;  $p < 0.0001$ , two-tailed log-rank test) (Fig. 2). The advantage was still more pronounced in the per-protocol group (excluding patients who did not receive the randomized treatment or strategy): 97 of 154 WS patients and 43 of 114 RT patients had recurrences (HR: 0.45; 95% CI, 0.31–0.64;  $p < 0.0001$ ). For the entire eligible cohort

(ITT1,  $n = 385$ ), the HR was 0.71 (95% CI, 0.55–0.92;  $p = 0.0050$ ), favoring RT.

In ITT2, 49 WS and 41 ART patients received salvage HT ( $p = 0.42$ ). Twenty-two WS versus 25 ART men developed distant metastases ( $p = 0.53$ ). Twenty WS and 23 ART patients died during 14 yr of follow-up ( $p = 0.59$ ). For the latter end points, events are too rare to achieve sufficient statistical power (Supplemental Fig. 1–3).

Subgroup analysis shows a significant advantage from ART for men with positive surgical margins and tumor stage pT3a/b (Fig. 3). For pT3b alone, the 10-yr PFS was 28% (WS) versus 47% (RT). However, only 50 men had that stage. In contrast, positive surgical margins may give a solid indication for ART ( $n = 197$ ;  $p < 0.0001$ ), especially when confirmed by reference pathology: The 10-yr PFS was 27% (WS) versus 57% (RT).

In the stepwise multivariate analysis with the randomization arm included, surgical margins (positive), pT stage ( $\geq 3c$ ), and Gleason Score ( $> 6$ ; statistically borderline significant) were independent unfavorable prognostic parameters (Table 2).

There was only one event of grade 3 toxicity (bladder). No grade 4 events were recorded.

There were three events of grade 2 genitourinary adverse effects (2%) in the RT arm compared with none in the WS arm. Similarly, two grade 2 gastrointestinal tract adverse effects (1.4%) were seen after RT, compared with none after WS. In total, 21.9% of RT patients and 3.7% of WS patients developed grade  $\geq 1$  adverse effects of the bladder and/or rectum ( $p < 0.0001$ ). One urethral stricture occurred in arm A, and two occurred in arm B. Incontinence was not assessed, because it is not mentioned in the RTOG/EORTC scoring scheme (see Table 3).

**Table 1 – Baseline characteristics**

	Wait-and-see (n = 159), PSA undetectable	Irradiation (n = 148), PSA undetectable	Persistent PSA (n = 78), excluded	Total (n = 385)
Age, yr (range)	64 (51–75)	65 (50–77)	64 (53–72)	64 (50–77)
PSA before surgery, µg/l (range)	9.4 (0.6–76.5)	9.7 (0.1–57.9)	16.5 (2.8–99)	10.4 (0.1–99)
Neoadjuvant hormonal treatment before RP, no. (%)	19 (12)	16 (11)	8 (10)	43 (11)
Pathologic factors				
Pathologic T category, no. (%)				
<pT3a	2 (1)	4 (3)	–	6 (2)
pT3a	74 (47)	76 (51)	24 (31)	174 (45)
pT3b	27 (17)	23 (16)	14 (18)	64 (17)
pT3c	43 (27)	40 (27)	26 (33)	109 (28)
pT4a	13 (8)	5 (3)	13 (17)	31 (8)
N category, no. (%)				
pN0	156 (98)	146 (99)	78 (100)	380 (99)
cN0	3 (2)	2 (1)	–	5 (1)
Lymph nodes removed, no., median	8	8	7	8
Surgical margins, no. (%)				
Negative	62 (39)	48 (32)	15 (19)	125 (32)
Positive	97 (61)	100 (68)	63 (81)	260 (68)
Histopathologic grade				
Gleason score, no. (%)				
≤6	57 (36)	56 (38)	10 (13)	123 (32)
7	86 (54)	74 (50)	45 (60)	205 (54)
8	11 (7)	11 (7)	8 (11)	30 (8)
9	5 (3)	7 (5)	12 (16)	24 (6)
7–9	102 (64)	92 (62)	65 (97)	259 (68)
8–9	16 (10)	18 (12)	20 (27)	54 (14)
Missing, no.	–	–	3	3
Median, no.	7	7	7	7

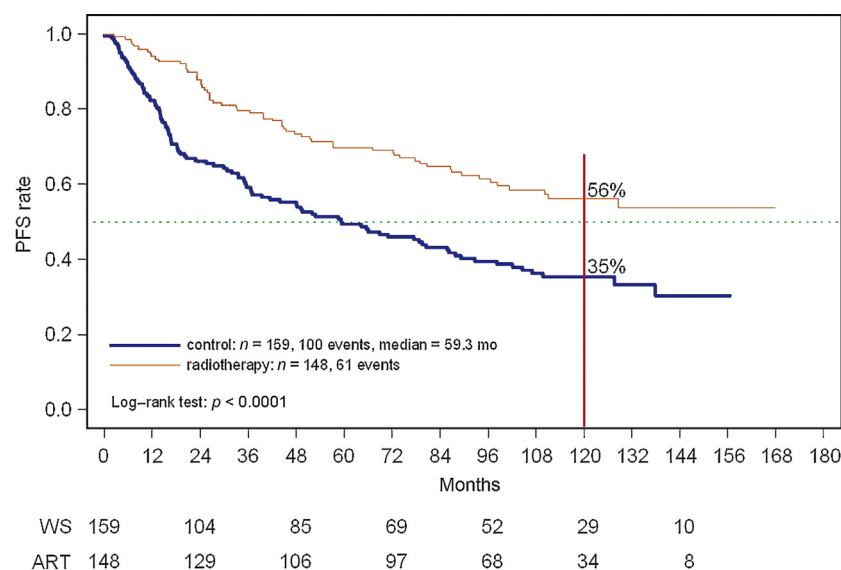
PSA = prostate-specific antigen; RP = radical prostatectomy.

Best available information is given (ie, reference pathology data are used wherever available).

#### 4. Discussion

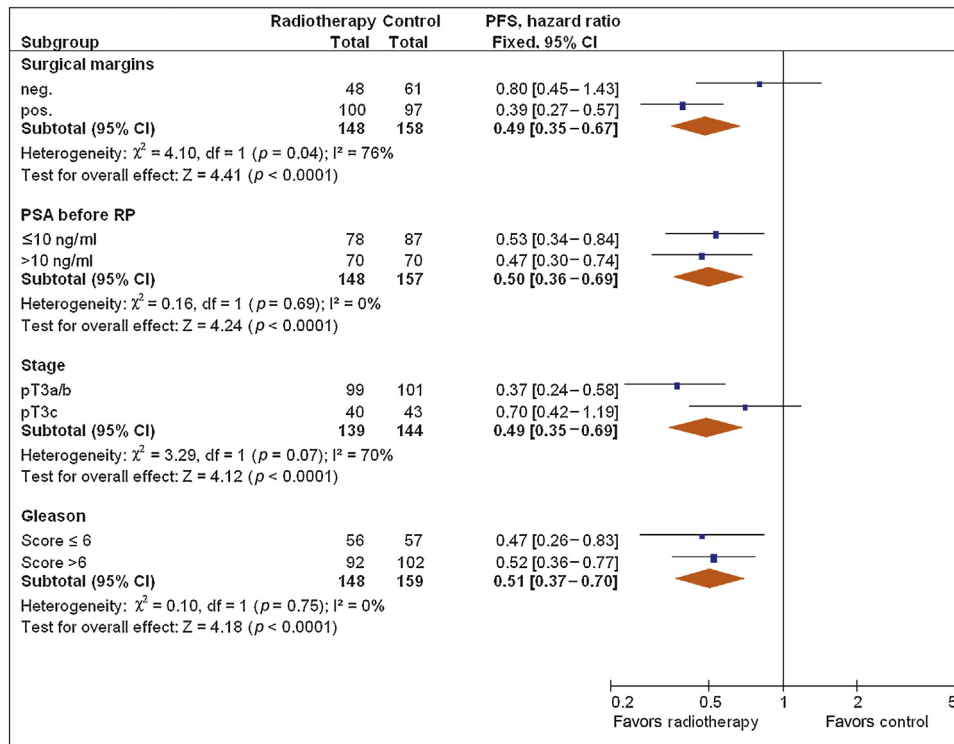
Concordant with earlier results and other prospectively randomized clinical trials, our data show an improved PFS after ART that reduced the relative risk of long-term

biochemical relapse by 51% [5–7]. Our study differs from the SWOG and the EORTC trials in that achieving an undetectable PSA after RP (<0.5 ng/ml) was mandatory for inclusion. Thus, the ITT2 cohort demonstrates directly that PSA-negative patients do profit from ART after RP.



**Fig. 2 – Kaplan-Meier plot of progression-free survival after radical prostatectomy (RP) with and without adjuvant radiotherapy in intent-to-treat patients who achieved an undetectable prostate-specific antigen after RP (ITT2). Bottom: Patients at risk in the wait-and-see or adjuvant radiotherapy trial arm.**

ART = adjuvant radiotherapy; PFS = progression-free survival; WS = wait-and-see.



**Fig. 3 – Forest plot for risk factors influencing the hazard ratio of progression-free survival in intent-to-treat patients who achieved an undetectable prostate-specific antigen after radical prostatectomy (ITT2) cohort with and without adjuvant radiotherapy.**

CI = confidence interval; neg. = negative; PFS = progression-free survival; pos. = positive; PSA = prostate-specific antigen; RP = radical prostatectomy.

Indirectly, this finding had also been deduced from study group crossovers in the SWOG trial, which focused on MFS and OS. [5]. Along the same lines, our per-protocol cohort had a still lower HR for recurrence in the RT arm (0.45) than

the ITT2 patients had. For men with an initial WS strategy, retrospective analyses have shown that in the case of PSA relapse, an early onset of salvage RT (SRT) is crucial, suggesting a PSA threshold of  $\leq 0.5$  or even  $\leq 0.3$  ng/ml [12–16]. A matched-control analysis suggested that early SRT and ART yield similar results regarding biochemical recurrence [13]. With modern application forms such as arc RT or intensity-modulated RT (IMRT), doses well above 70 Gy can be given to optimize the second chance for cure [17].

The ongoing RADICALS trial aims to compare SRT and ART directly, both with and without HT (6 mo vs 24 mo) [18]. GETUG-17/0702 applies ART and SRT, each with 66 Gy and with concomitant HT for 6 mo [19]. In RAVES, patients with pT3 or with positive margins and post-RP PSA  $\leq 0.1$  ng/ml are randomized to ART or early (PSA  $\geq 0.2$  ng/ml)

**Table 2 – Multivariate analysis of factors influencing progression-free survival after radical prostatectomy with and without adjuvant external-beam radiotherapy**

Factor	Statistical parameter	Model 1 (n = 304)	Model 2 (n = 306)
Age	Relative risk	1.26	–
≥65 yr	95% CI	0.92–1.74	
	p	0.15	
Gleason score	Relative risk	1.44	1.39
>6	95% CI	1.02–2.03	0.99–1.95
	p	0.038	0.057
pT stage	Relative risk	1.8	1.87
≥pT3c	95% CI	1.30–2.49	1.36–2.57
	p	0.00037	0.00012
Surgical margins	Relative risk	1.59	1.58
positive	95% CI	1.12–2.24	1.12–2.23
	p	0.0092	0.009
PSA preoperatively	Relative risk	1.27	–
>10 ng/ml	95% CI	0.92–1.75	
	p	0.14	
Treatment arm,	Relative risk	0.46	0.49
adjuvant RT	95% CI	0.33–0.65	0.35–0.67
	p	<0.0001	<0.0001

CI = confidence interval; PSA = prostate-specific antigen; RT = radiotherapy. A Cox proportional hazards model was applied: Model 1: Cox regression including all factors; Model 2: Cox regression with stepwise exclusion of nonsignificant factors.

**Table 3 – Toxicity to the urinary and the gastrointestinal tracts**

	ART	WS	ART	WS
All	148	159	148	159
RTOG	Bladder (late)		GI tract (late)	
Grade 0, no. (%)	124 (84)	155 (97)	132 (89)	154 (97)
Grade 1, no. (%)	20 (14)	4 (3)	14 (9)	5 (3)
Grade 2, no. (%)	3 (2)	–	2 (1)	–
Grade 3, no. (%)	1 (3)	–	–	–
Grade 4, no. (%)	–	–	–	–
Stricture, %	3	1	–	–

ART = adjuvant radiotherapy; GI = gastrointestinal; RTOG = Radiation Therapy Oncology Group; WS = wait-and-see.



SRT. The RT dose is 64 Gy in both arms, and biochemical failure is the primary end point [20].

In the present study, the effect of RT on biochemical recurrence in R1 patients could in part be confirmed only after central pathology review (available for 85% of the cases) [11]. Cross-checks are thus highly recommended for phase 3 clinical trials. The result itself is in agreement with other studies showing the detrimental influence of positive margins on PFS, even including pT2, and much more so when combined with other high-risk factors [6,21–23]. An impact on PCa-specific survival has been doubted [21,23]. Given the prevalence of competing-cause deaths in the largely senior PCa patients, subgroup analyses may require bigger cohorts and longer follow-up to find significant effects on the hard end points [24].

Unlike ARO 96–02, EORTC [6] and SWOG [5] report less frequent salvage HT after ART. SWOG also found a significant effect on MFS and OS. However, it was argued that the benefit in the RT arm (HRs were 0.71 for MFS and 0.72 for OS) was largely because of a lower rate of competing-cause deaths without evidence of distant metastasis [2]. With 307 patients in ITT2 and approximately 112 mo of follow-up, our study was not powered for these end points. Even in the EORTC trial that recruited 1005 patients and covered 10.6 yr of median follow-up, the OS did not differ significantly between therapy arms ( $p > 0.2$ ), and PCa-specific mortality was 3.9% versus 5.4% (RT vs WS, respectively), with a wide overlap of CIs [6].

In the ARO/AUO study, radiation-induced toxicity was low (worst events: one grade 3 and five grade 2). This result was certainly because of the combination of 3D planning and limiting the dose to 60 Gy. No new adverse events were reported for the second half of the observation period. Similarly, in the EORTC trial, an excess of grade 1 or 2 events was confined to the first 3 yr after treatment. Compared with our results, there were more adverse effects of all types and grades, affecting 70.8% of the patients with RT (60 Gy) and 59.7% with WS. This finding may have been expected for treatment in the era before 3D planning. The cumulative incidence of late grade 3 adverse effects was 5.3% with RT versus 2.5% with WS ( $p = 0.052$ ) [6]. In the SWOG trial, 60–64 Gy was applied without 3D planning (enrollment started in 1988). Proctitis or rectal bleeding, urethral stricture, and total bladder incontinence were all more common with RT than with WS; the rate of complications was 23.8% versus 11.9%, respectively ( $p = 0.02$ ) [25]. The trial was accompanied by a quality-of-life analysis that collected data, over 5 yr, on the emotional, physical, social, and role function of 217 patients (107 WS plus 110 RT) [26]. Six weeks after therapy, RT and WS patients were affected by bowel impairment at 60% and 5%, frequent urination at 35% and 20%, and erectile dysfunction at 90% and 95%, respectively. In the following year, bladder and erectile function showed slight improvements while retaining the offset between therapy arms. In contrast, RT-related bowel impairment recovered, and at the end of the reporting period it was only slightly more frequent than in WS (15% vs 10%).

All three randomized trials concerning ART after RP started before IMRT with inverse treatment planning and

image-guided patient positioning/irradiation were available for clinical routine, not to mention arc techniques. Such recent approaches may reduce adverse effects even with significantly higher doses that should allow still better local control. In a retrospective analysis, the shift from 3D conformal SRT with 66 Gy to salvage IMRT with 72 Gy reduced the incidence of late grade  $\geq 2$  gastrointestinal effects from 13.2% to 7.6%. Grade  $\geq 2$  genitourinary toxicity regressed from 20.8% to 13.4%. However, follow-up was 70 mo for 3D but only 36 mo for IMRT [27]. In patients who received salvage IMRT with 76 Gy, meticulous preparation, including bladder-filling checks and cone-beam computed tomography versus portal vision-assisted positioning, reduced acute grade 2 effects to 16% versus 30%. Grade 3 events occurred in 1 of 80 patients versus 3 of 116 patients, respectively [28].

The adjuvant setting has been calculated to require approximately 6-Gy smaller doses, which can tangibly reduce toxicity [29,30]. This should be a strong argument for the decision between immediate post-RP RT and WS, with an expected biochemical recurrence rate of 60–80%, depending on risk factors.

Limitations of our analysis concern its small patient number, which prevents hard end point analysis. The RT technique does not reflect recent standards. Reliable toxicity documentation is difficult over long-term follow-up.

## 5. Conclusions

We demonstrated that ART can improve biochemical PFS after RP for pT3 PCa. RT-related toxicity was rare and largely mild to moderate. Men with positive surgical margins are the most likely candidates to profit from adjuvant treatment. However, proving an effect on hard end points may require larger patient cohorts and longer follow-up.

**Author contributions:** Thomas Wiegel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Wiegel, Steiner, Hinkelbein, Miller.

**Acquisition of data:** Wiegel, Bartkowiak, Bottke, Bronner, Steiner, Siegmann, Golz, Störkel, Willich, Semjonow, Stöckle, Rube, Rebmann, Kälble, Feldmann, Wirth, Hofmann, Engenhart-Cabillic, Hinke, Hinkelbein, Miller.

**Analysis and interpretation of data:** Wiegel, Bartkowiak, Bottke, Hinke, Miller.

**Drafting of the manuscript:** Wiegel, Bartkowiak, Hinke.

**Critical revision of the manuscript for important intellectual content:** Wiegel, Bartkowiak, Bottke, Bronner, Steiner, Siegmann, Golz, Störkel, Willich, Semjonow, Stöckle, Rube, Rebmann, Kälble, Feldmann, Wirth, Hofmann, Engenhart-Cabillic, Hinke, Hinkelbein, Miller.

**Statistical analysis:** Hinke.

**Obtaining funding:** Wiegel, Hinkelbein, Miller.

**Administrative, technical, or material support:** Wiegel, Bottke, Bronner, Siegmann, Hinkelbein.

**Supervision:** None.

**Other (specify):** None.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2014.03.011>.

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