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ORIGINAL REPORT

Phase III Postoperative Adjuvant Radiotherapy After Radical Prostatectomy Compared With Radical Prostatectomy Alone in pT3 Prostate Cancer With Postoperative Undetectable Prostate-Specific Antigen: ARO 96-02/AUO AP 09/95

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Local failure after radical prostatectomy (RP) is common in patients with cancer extending beyond the capsule. Two randomized trials demonstrated an advantage for adjuvant radiotherapy (RT) compared with a wait-and-see policy. We conducted a randomized, controlled clinical trial to compare RP followed by immediate RT with RP alone for patients with pT3 prostate cancer and an undetectable prostate-specific antigen (PSA) level after RP.

Methods
After RP, 192 men were randomly assigned to a wait-and-see policy, and 193 men were assigned to immediate postoperative RT. Eligible patients had pT3 pN0 tumors. Patients who did not achieve an undetectable PSA after RP were excluded from treatment according to random assignment (n = 78; 20%). Of the remaining 307 patients, 34 patients on the RT arm did not receive RT and five patients on the wait-and-see arm received RT. Therefore, 114 patients underwent RT and 154 patients were treated with a wait-and-see policy. The primary end point was biochemical progression-free survival.

Results
Biochemical progression-free survival after 5 years in patients with undetectable PSA after RP was significantly improved in the RT group (72%; 95% CI, 65% to 81%; *v* 54%, 95% CI, 45% to 63%; hazard ratio = 0.53; 95% CI, 0.37 to 0.79; $P = .0015$). On univariate analysis, Gleason score more than 6 and less than 7, PSA before RP, tumor stage, and positive surgical margins were predictors of outcome. The rate of grade 3 to 4 late adverse effects was 0.3%.

Conclusion
Adjuvant RT for pT3 prostate cancer with postoperatively undetectable PSA significantly reduces the risk of biochemical progression. Further follow-up is needed to assess the effect on metastases-free and overall survival.

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INTRODUCTION

Radiotherapy (RT) and radical prostatectomy (RP) provide excellent local control for organ-confined prostate cancer.[1-3] For pT3 cancer (extending beyond the capsule), the risk of local failure and biochemical progression varies at 20% to 70% after 5 years.[4] Gleason score, initial prostate-specific antigen (PSA) level, positive seminal vesicles, and positive margins are independent predictors of biochemical progression.[5,6]

Two randomized studies for patients with pT3 (R0 or R1) or pT2 (R1) disease have been reported, demonstrating that adjuvant RT reduces the risk of local relapse and biochemical progression by approximately 20% at 5 years.[7,8] Improved results have also been reported for the Southwest Oncology Group (SWOG) trial subgroup.[9] However, these reports do not show, prospectively tested as a primary objective, whether patients with undetectable PSA after RP would also benefit from adjuvant RT.

In 1996, the Arbeitsgemeinschaft Radiologische Onkologie und Urologische Onkologie of the German Cancer Society initiated a randomized, multicenter, phase III trial to test the hypothesis that immediate RT after RP improves biochemical no evidence of disease (bNED) in patients with pT3 tumors with undetectable PSA after RP and with high risk of tumor progression.

METHODS

Trial Design and Participants

Tumor stage was determined according to the 1992 International Union Against Cancer criteria.[10] Patients had histologically proven cT1-cT3 N0 prostate cancer preoperatively. Before entry, all patients underwent pre- and postoperative PSA test, 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 younger than 76 years, with a WHO performance status[11] of 0 or 1. RT began between 6 and 12 weeks after surgery. The protocol was approved by the local human use committee for each participating center. Written informed consent was obtained from all patients.

Procedures

Surgery was done before entry onto the study. Surgery consisted of open RP and pelvic lymphadenectomy (including the prostate gland and seminal vesicles). A uni- or bilateral nerve-sparing technique was allowed when it did not involve an increased risk of positive surgical margins.

After formalin fixation, the surgical specimen was marked with ink over the entire resection margin. Then the prostate was sectioned from the distal margins to the bladder neck. Positive margins were defined as direct contact of the margins with malignant cells. All specimens were assessed using the Gleason score. Central review was provided by two experienced uropathologists (R.G., S.S.). The sections were revisited, and new sections were performed if necessary.

Preparing RT, all patients underwent three-dimensional treatment planning with a simulation of treatment fields or virtual simulation. RT was given by linear accelerators of $\geq$ 10 MV, normally with a three- or four-field technique. The dose was specified according to International Commission on Radiation Units Report 50. A dose of 60 Gy was given in 30 fractions to a volume that included the surgical limits from the seminal vesicles, marked with clips intraoperatively, to the apex, with a 1-cm security margin to encompass subclinical disease in the periprostatic area. RT started between 6 and 12 weeks after surgery without major voiding problems.

Clinical examinations including digital rectal examinations, and PSA tests were done every 3 months for 2 years, then every 6 months until the end of the fifth year, then every year.

Within 2 weeks after surgery and directly after receiving the pathology report and confirmation of the tumor stage, patients were randomly assigned before achieving an undetectable PSA to receive a wait-and-see policy (arm A) or RT (arm B). The undetectable PSA is normally achieved within 2 to 6 weeks, depending on the primary PSA value. The randomization was performed centrally using computer-generated lists with permuted blocks of randomly varying size per stratum. If the undetectable PSA level after RP was not achieved, patients were excluded by protocol and were termed as having progressive disease. This early randomization immediately after surgery was chosen because in Germany surgeons are not involved in the further follow-up of patients after RP. Recommended treatment for these patients was immediate RT. Patients were stratified for Gleason score (< 7 *v* ≥ 7), margin status (positive *v* negative), neoadjuvant hormonal treatment before RP (3 months *v* none), and tumor stage (pT3a/b *v* pT3c).

PSA progression for patients with previously undetectable PSA was stated after two consecutive determinations with increasing PSA values (depending on the different local undetectable range). 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/European Organisation for Research and Treatment of Cancer (EORTC) was used to assess late toxicity.

Analysis Populations

Three analysis sets were defined prospectively before embarking on any evaluations of efficacy: intent-to-treat (ITT) approach on all eligible patients (ITT1, n = 388) was used on all randomly assigned patients except for those considered to be ineligible (n = 3). ITT approach on patients of primary interest (ITT2, n = 307) was as ITT1, but excluded patients not achieving an undetectable PSA value. These latter patients are defined as arm C. Per-protocol approach (PP) was as ITT2, but excluded patients (n = 5) who received RT although randomly assigned to wait-and-see approach (arm A) and patients who refused RT although randomly assigned to arm B (n = 34).

Statistical Aspects

Data were checked for plausibility, completeness, and validity by central monitoring and query procedures. Additional computer-based queries were generated and resolved before start of the analysis. Primary end point of the study was progression-free survival, with biochemical progression defined as two consecutive PSA increases above the detection limit of the respective PSA assay used, local or distant clinical recurrence, or death for whatever reason as an event, whichever occurred first. In the ITT1 analysis, all patients not achieving an undetectable PSA were counted as failures from the beginning (ie, at the time point of randomization). Secondary end points included metastases-free survival and overall survival (not yet analyzed) and acute and late toxicity.

A total of 266 assessable patients (ITT2 population) were recruited and observed for at least 5 years to achieve 80% power to identify an improvement from 50% to 65% in progression-free survival after 5 years at 5% significance (one-sided because a better progression-free survival in the observation arm would have the same practical consequences as a finding of no superiority of the RT approach). Some over-recruitment was planned to allow for a continuous drop-out process of up to 20% during the follow-up period. Event-related data were obtained from the time of randomization, estimated according to the method of Kaplan and Meier,[12] and compared between treatment and prognostic groups using the log-rank test. The same method was applied for the time to incidence of late complications, rather than the alternative cumulative incidence method, as the former better reflects the information relevant to the patient, and death events in the relevant period are rare anyway. For multivariate analysis, a Cox proportional hazards model was applied, implementing a stepwise backward procedure for variable

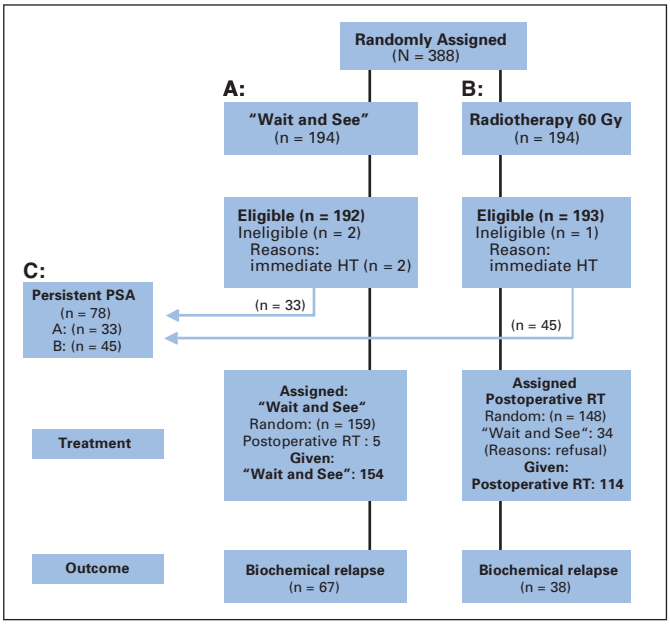

Fig 1. Trial profile. HT, hormonal treatment; PSA, prostate-specific antigen; RT, radiotherapy.

selection.[13] All tests except for the primary hypothesis are two-sided and of explorative nature.

RESULTS

From April 1997 to September 2004, 388 patients from 22 institutions entered the trial after RP before achieving an undetectable PSA: 194 patients were assigned to the wait-and-see policy (arm A), and 194 patients were assigned to adjuvant RT (arm B). Three patients were excluded because of immediate hormonal treatment (Fig 1). Seventy-eight patients (20%) did not achieve an undetectable PSA and were per protocol stated as having progressive disease (arm A, 33 patients; arm B, 45 patients). Of these 78 patients, 70 patients underwent RT; eight patients refused RT. The remaining 307 patients built the basis of the subsequent analyses. These had a PSA less than 0.1 ng/mL: 244 (80%) of 307 patients had PSA less than 0.05 ng/mL and 127 (41%) of 307 patients had PSA less than 0.03 ng/mL according to the detection limits of the various PSA assays. Thirty-four patients (19%) from the RT arm refused and did not receive RT. Therefore, 114 patients had adjuvant RT (arm B), and 159 patients had a wait-and-see policy (arm A). Of these, five patients underwent RT because of personal preferences (3.2%). Table 1 shows the baseline characteristics of the patients. Treatment information was available for all but three patients (0.75%) who had immediate hormonal treatment and were excluded from analysis.

RT was initiated a median of 81 days (range, 64 to 211 days) after surgery and lasted a median of 44 days (range, 42 to 47 days). The total dose was 60 Gy (range, 26 to 66 Gy); 82% received the planned dose.

The central pathology review was available for 262 (85%) of 307 patients who achieved an undetectable PSA. Therefore the steering committee decided to incorporate the 85% controlled pathology specimens into the original data set and to use the other 15% of specimens proven by the local pathologists.

A median of nine follow-up PSA measurements was available in both groups; all patients had at least one measurement (range, one to 16 measurements). The overall median follow-up period was 53.7 months (arm A, range, 1.3 to 102.5 months [interquartile range, 38.2 to 68.1 months]; arm B, range, 5.3 to 108.8 months [interquartile range, 38.3 to 65.1]). A total of 105 failures (67 in the wait-and-see group and 38 in the RT group) were recorded (Table 2). The planned

Table 1. Baseline Characteristics

Characteristic	Wait and See, PSA Undetectable (n = 159)		Irradiation, PSA Undetectable (n = 148)		Persistent PSA, Excluded (n = 78)		Total (N = 385)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median	64		65		64		64	
Range	51-75		50-77		53-72		50-77	
PSA before surgery, μg/L								
Median	9.4		9.7		16.5		10.4	
Range	0.6-76.5		0.1-57.9		2.8-99		0.1-99	
Neoadjuvant hormonal treatment before RP	19	12	16	11	8	10	43	11
Pathologic factors*								
Pathologic T category								
< 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								
pN0	156	98	146	100	78	100	380	100
cN0	3	2	2	1.6			5	1.2
Surgical margin								
Negative	62	39	48	32	15	19	125	32
Positive	97	61	100	68	63	81	260	68
Histopathologic grade, Gleason score								
≤ 6	57	36	56	38	10	13	123	32
7	86	54	74	50	45	60	205	54
8	11	7	11	7	8	18	30	8
9	5	3	7	5	12	27	24	6
7-9	102	64	92	62	65	97	259	68
8-9	16	10	18	12	20	27	54	14
Missing	—		—		3		3	
Median	7		7		7		7	

Abbreviations: PSA, prostate-specific antigen; RP, radical prostatectomy.
*Best information. Central pathology review, if available.

Table 2. Events in Long-Term Outcome

Event	Arm A: Wait and See (n = 159)		Arm B: RT (n = 148)		Persistent PSA (excluded; n = 78)	
	No.	%	No.	%	No.	%
Biochemical progression	67	42.1	38	25.7	78	100
Other treatment than randomized	5 (RT)	3.1	34 (wait and see)	23	—	
Clinical progression, distant failure	5	3.1	4	2	6	8
Death, all	8	5	5	3.4	10	12.8

Abbreviations: RT, radiotherapy; PSA, prostate-specific antigen.

primary end point, biochemical progression-free survival, was significantly higher in the irradiation group. Kaplan-Meier estimates of 5-year biochemical progression-free survival were 54% (95% CI, 45% to 63%) and 72% (95% CI, 65% to 81%), respectively (hazard ratio [HR] = 0.53; 95% CI, 0.37 to 0.79; $P = .0015$; ITT2). These results increased in the per protocol population to 54% (95% CI, 45% to 63%) versus 77% (95% CI, 69% to 86%, $P = .00017$; HR = 0.42, 95% CI, 0.26 to 0.67; Figs 2 and 3 and Appendix Fig A1, online only). For all randomly assigned eligible patients (n = 385), these figures were 44% (95% CI, 37% to 53%) and 55% (95% CI, 48% to 63%; $P = .05$; ITT1).

The possible end point of local relapse was not investigated because of the well-known problem that digital rectal palpation, even in case of a increasing PSA, is often false positive.

Fifteen patients (4.9%) had distant metastases: five patients (3.1%) from arm A, four patients (2%) from arm B, and six patients (8%) from arm C. Twenty-three (5.9%) of 385 patients died, eight (5%) in arm A, five (3.4%) in arm B, and 10 (12.8%) of 78 with persistently elevated PSA. Longer follow-up is needed for a statistically valid assessment of these end points (Table 2).

In an unplanned subgroup analysis, positive surgical margins ($P = .00018$), tumor stage pT3a/b ($P = .00039$), a preoperative PSA level more than 10 ng/mL ($P = .0018$), Gleason score ≤ 6 ($P = .019$), and Gleason score more than 6 ($P = .029$) defined populations with a nominally significant test result for RT efficacy (Fig 4).

In the stepwise multivariate analysis with the therapy arm included (Table 3), a preoperative PSA level more than 10 ng/mL ($P = .026$), RT ($P = .0042$), and tumor stage pT3a/b versus pT3c ($P = .000083$) were independent predictors of biochemical outcome.

There was only one event of grade 3 toxicity (bladder). No grade 4 events were recorded. There were three events (2%) for grade 2 genitourinary adverse effects in the RT arm compared with none in the other arms. In addition, two grade 2 GI adverse effects (1.4%) were seen in the RT arm compared with none in the other arms. Altogether, the cumulative rate of adverse effects for bladder and rectum (≥ grade 1) was 21.9% in the RT arm and 3.7% in the wait-and-see group ($P < .0001$; Appendix Fig A2, online only). 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.

DISCUSSION

Our results show, like two other randomized trials, a significant reduction of biochemical progression 5 years after adjuvant RT.[7,8] However, our study differs from both other studies in two major points, namely the inclusion criteria (achieving an undetectable PSA after RP) and the incorporation of the results of the central pathology review of 85% of all cases into the analysis. In contrast to the other studies, we were able to demonstrate that patients who achieved an undetectable PSA after RP do profit from adjuvant RT. In the primary ITT analysis of this target population (ITT2), the difference between both arms at 5 years was 18% in favor of adjuvant RT (HR = 0.53), whereas in terms of

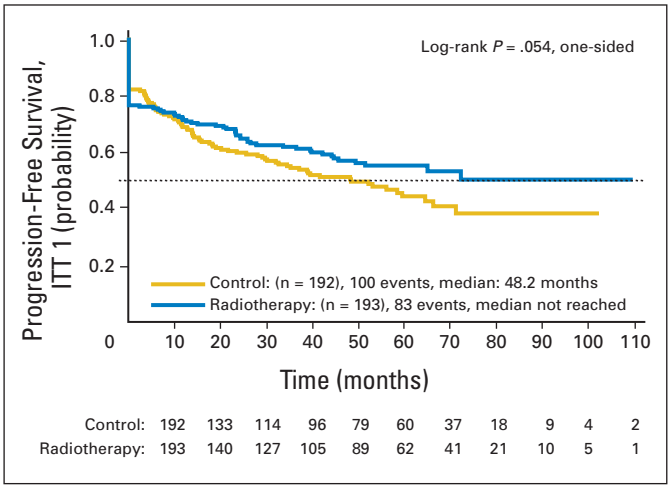

Fig 2. Biochemical progression-free survival of all randomly assigned patients (n = 385; intention-to-treat group 1 [ITT1]).

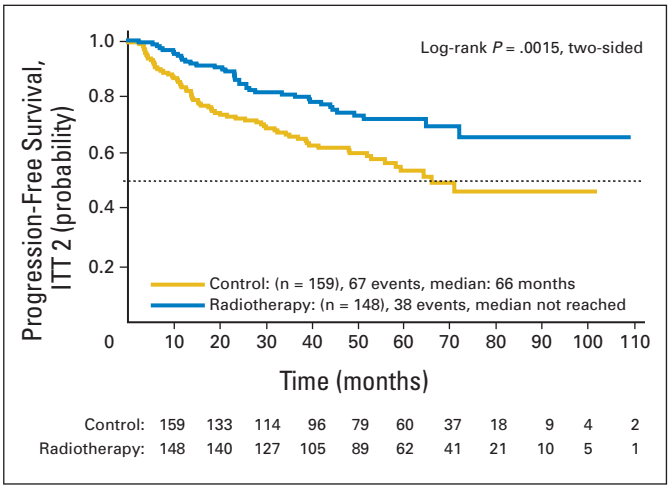

Fig 3. Biochemical progression-free survival of all patients with undetectable prostate-specific antigen after radical prostatectomy (intention-to-treat group 2 [ITT2]).

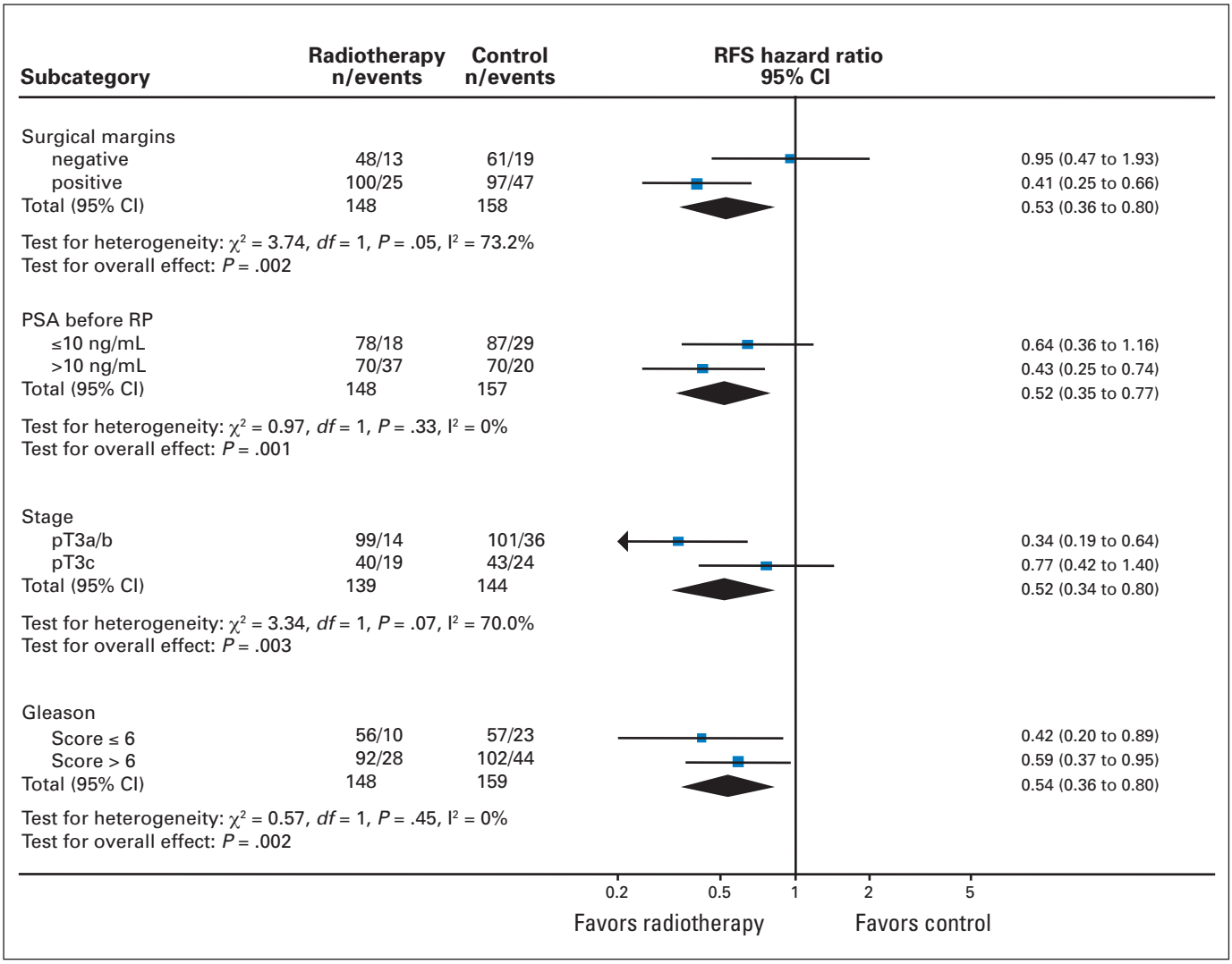

Fig 4. Treatment effects by prognostic factors (Forrest plot). RFS, recurrence-free survival; PSA, prostate-specific antigen; RP, radical prostatectomy.

treatment per protocol (ie, treated as randomly assigned), the difference was 23%. Although there was an imbalance of patients with persisting PSA by chance in favor of the control group and although these patient groups received an identical treatment, the ITT1 comparison based on all randomly assigned eligible patients is consistent with the primary result. Therefore, it should be clearly pointed out that adjuvant RT is a valid option in these patients. This new information helps to address the possible role of adjuvant RT in this patient population. However, our primary end point was not clinical progression or overall survival, which is known to be achievable at 10 or 15 years after treatment for prostate cancer. At present, there is no survival benefit in any of the three study sets. Clearly, all three sets should be underpowered to clarify this question. Moreover, after 5 years in EORTC 22911 and in our study, only 9% and 4% of patients had died, respectively. However, a significant improvement at 10 years was found for biochemical recurrence-free survival, but not for metastases-free survival.[8]

Our results support an analysis of the SWOG trial. In this randomized trial, part of the patients were treated before the PSA era. When the data of patients with a PSA level of less than 0.2 ng/mL were analyzed (the undetectable range at this time), there was a clearly significant benefit for bNED at 5 years (46% *v* 77%) and 10 years (28% *v* 58%). Our undetectable range was at least 0.1 ng/mL and defined progression at an earlier stage (0.4 ng/mL in the SWOG trial). Thus in the German trial, the 5-year results are better than in the SWOG trial.[9]

In both former trials, there was a significant reduction of the local relapse rate among patients who underwent RT. That is not surprising, because local treatment of the prostatic fossa must achieve at first a reduction of the local recurrence rate, thus reducing the late wave of metastases and leading to better clinical results.[14] In our study, the local recurrence rate was not assessed for two reasons: first, in the other trials, local recurrence was stated by digital rectal examination, which is known to give false results in approximately 25% of cases. Second, we recommended RT early on when the PSA level increased above the undetectable range. At this stage, a small tumor burden is unlikely to be palpable. However, our results can only be understood with a higher local control rate in the RT arm.

There is a major difference in the results of the subgroup analyses of all three studies. Although the EORTC 22911 study demonstrated a

Table 3. Multivariate Analysis of Progression-Free Survival (ITT2) With Therapy Arm

Factor and Parameter	Full Model, Model 1 (n = 304)	Final Model (n = 305)
Age ≥ 65 years		
RR	1.34	—
95% CI	0.91 to 2.01	
P	.13	
Gleason score > 6		
RR	1.39	—
95% CI	0.90 to 2.13	
P	.13	
pT stage, pT3a/b *v* pT3c		
RR	2.23	2.43
95% CI	1.49 to 3.33	1.65 to 3.59
P	.000086	.0000083
Positive surgical margins		
RR	1.43	—
95% CI	0.93 to 2.19	
P	.10	
Preoperative PSA level > 10 ng/mL		
RR	1.56	1.56
95% CI	1.05 to 2.31	1.05 to 2.30
P	.028	.026
Therapy arm, RT		
RR	0.52	0.56
95% CI	0.34 to 0.78	0.37 to 0.83
P	.0015	.0042

Abbreviations: ITT, intention to treat; RR, relative risk; PSA, prostate-specific antigen; RT, radiotherapy.

positive treatment effect for all subgroups (all types of surgical margins, all types of extracapsular extension, including infiltration of the seminal vesicles, and organ-confined disease with positive margins),[7,15] this was not seen in our patients. Our findings suggest positive margins, a PSA level more than 10 ng/mL before RP, or extracapsular extension without infiltration of the seminal vesicles to be predictors of an increased effect of RT. There are two possible explanations for these differences. First, our study consisted of only 385 patients compared with 1,000 patients in the EORTC study, and the differences could be explained with the smaller number of our patients. Second and more suggestive, our results were corrected after an extensive central pathology review in 85% of the cases. Recently, the results of the central pathology review of 50% of the specimens of the EORTC trial were published[16]: There was a relative low concordance between the local and central pathologists, with partly pronounced changes between stages and margin status. For example, the extracapsular extension versus organ-confined status changed in approximately 50% of the cases. These data could possibly lead to different results on reanalysis of the subgroups. Indeed, the reanalysis of the EORTC material led to the new conclusion that positive margins were the strongest predictor of better outcome with RT (not only in pT3 but also in pT2 cases).[16]

Compared with both other studies, the rate of adverse effects in our patients was low. The reason might be the three-dimensional treatment planning used for all patients in our trial, but not in the former trials. Three-dimensional planning is proven to reduce acute and late adverse effects for doses greater than 60 Gy.[17] Therefore, 60 Gy causes a small risk of severe late adverse effects. The EORTC Radiation Oncology Group recently published guidelines for target volume definition in postoperative RT.[18]

When the three trials started, between 1988 and 1996, 60 Gy was the recommended standard of adjuvant RT. However, due to the rate of local recurrences in the EORTC and the SWOG study, the total dose should be slightly higher, as prostate cancer is known to be relatively radioresistant. Therefore, the EORTC 22911 successor study recommended a total dose of 64 Gy to the prostatic bed. The combination with hormonal treatment is not standard at this time, and its role for treatment intensification needs to be explored in prospective studies, such as the ongoing phase III study of the EORTC, comparing 64 Gy and 64 Gy with concomitant hormonal treatment over 6 months.

It cannot be concluded that adjuvant RT is superior to RT after an early PSA increase above the lower detection limit.[19-21] In this case, a bNED of approximately 50% for 5 years was seen for PSA less than 0.5 ng/mL at start of RT. Retrospectively, the SWOG data showed a significant advantage for bNED of the early treatment compared with RT for a late PSA increase (5-year bNED, 77% *v* 38%; 122 patients *v* 34 patients).[9]

In conclusion, our study supports formerly reported results and gives evidence of an 18% benefit of bNED at 5 years after adjuvant RT for pT3 tumors with or without positive margins, even with an undetectable PSA after RP. Together with the results of the former trials, it additionally underscores the necessity of a central pathology review for phase III trials in prostate cancer. Longer follow-up is needed to clarify the impact of adjuvant RT on metastases-free survival and overall survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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