Adjuvant Radiotherapy for Pathologically Advanced Prostate Cancer

A Randomized Clinical Trial

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Context Despite a stage-shift to earlier cancer stages and lower tumor volumes for prostate cancer, pathologically advanced disease is detected at radical prostatectomy in 38% to 52% of patients. However, the optimal management of these patients after radical prostatectomy is unknown.

Objective To determine whether adjuvant radiotherapy improves metastasis-free survival in patients with stage pT3 N0 M0 prostate cancer.

Design, Setting, and Patients Randomized, prospective, multi-institutional, US clinical trial with enrollment between August 15, 1988, and January 1, 1997 (with database frozen for statistical analysis on September 21, 2005). Patients were 425 men with pathologically advanced prostate cancer who had undergone radical prostatectomy.

Intervention Men were randomly assigned to receive 60 to 64 Gy of external beam radiotherapy delivered to the prostatic fossa (n=214) or usual care plus observation (n=211).

Main Outcome Measures Primary outcome was metastasis-free survival, defined as time to first occurrence of metastatic disease or death due to any cause. Secondary outcomes included prostate-specific antigen (PSA) relapse, recurrence-free survival, overall survival, freedom from hormonal therapy, and postoperative complications.

Results Among the 425 men, median follow-up was 10.6 years (interquartile range, 9.2-12.7 years). For metastasis-free survival, 76 (35.5%) of 214 men in the adjuvant radiotherapy group were diagnosed with metastatic disease or died (median metastasis-free estimate, 14.7 years), compared with 91 (43.1%) of 211 (median metastasis-free estimate, 13.2 years) of those in the observation group (hazard ratio [HR], 0.75; 95% CI, 0.55-1.02; $P=.06$). There were no significant between-group differences for overall survival (71 deaths, median survival of 14.7 years for radiotherapy vs 83 deaths, median survival of 13.8 years for observation; HR, 0.80; 95% CI, 0.58-1.09; $P=.16$). PSA relapse (median PSA relapse–free survival, 10.3 years for radiotherapy vs 3.1 years for observation; HR, 0.43; 95% CI, 0.31-0.58; $P<.001$) and disease recurrence (median recurrence-free survival, 13.8 years for radiotherapy vs 9.9 years for observation; HR, 0.62; 95% CI, 0.46-0.82; $P=.001$) were both significantly reduced with radiotherapy. Adverse effects were more common with radiotherapy vs observation (23.8% vs 11.9%), including rectal complications (3.3% vs 0%), urethral strictures (17.8% vs 9.5%), and total urinary incontinence (6.5% vs 2.8%).

Conclusions In men who had undergone radical prostatectomy for pathologically advanced prostate cancer, adjuvant radiotherapy resulted in significantly reduced risk of PSA relapse and disease recurrence, although the improvements in metastasis-free survival and overall survival were not statistically significant.

Trial Registration clinicaltrials.gov Identifier: NCT00394511

JAMA. 2006;296:2329-2335 www.jama.com

RADICAL PROSTATECTOMY IS selected for treatment of localized prostate cancer by approximately one third of the 230 000 patients newly diagnosed each year in the United States.[1] It is commonly accepted that this treatment has optimal results in patients with cancer confined to the prostate. Despite a stage-shift to earlier stages and lower tumor volumes, extraprostatic disease is detected at radical prostatectomy in 38% to 52% of patients.[2,3] Each stratum of extraprostatic disease—ie, pathologic extension beyond the prostate, positive surgical margins, or invasion of the seminal vesicle—is associated with a risk of disease recurrence, progression, and death.[4-6]

The optimal treatment for patients with extraprostatic disease noted after radical prostatectomy is unknown. Adjuvant radiotherapy has been used for more than 4 decades to reduce the risk of disease recurrence.[7] A randomized controlled clinical trial of adjuvant radiotherapy has demonstrated a reduction in prostate-specific antigen (PSA) relapse and local progression, but due to short follow-up, it is unknown if radiation reduces risk of metastases or im-

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proves survival.[8] Here, we report the results of a randomized, prospective clinical trial comparing ajuvant radiation therapy with usual care and observation alone for patients with extraprostatic disease after radical prostatectomy and examining metastasis-free survival and overall survival as end points.

METHODS

Patient Selection

The study was a randomized multiinstitutional clinical trial of adjuvant radiation therapy for locally advanced prostate cancer following radical prostatectomy. At the time of study activation on August 15, 1988, to be eligible, patients must have undergone a radical prostatectomy within 16 weeks prior to randomization, had a negative bone scan result, and met 1 or more of 3 criteria for extraprostatic disease: extracapsular tumor extension, positive surgical margins, or seminal vesicle invasion, confirmed by the institutional pathology report. A pelvic lymphadenectomy was required; patients with involved pelvic lymph nodes were ineligible for enrollment. Beginning in June 1995, 4 groups of patients at very low risk for involved pelvic lymph nodes were not required to undergo lymphadenectomy: (1) clinical stage T1a or T2a, Gleason score 2 through 6, and PSA level less than 10 ng/mL; (2) stage T1b-c, Gleason 2 through 5, and PSA level less than 10 ng/mL; (3) stage T2b, Gleason 2 through 6, and PSA level less than 6 ng/mL; and (4) stage T2c, Gleason 2 through 6, and PSA level less than 4 ng/mL.

An undetectable PSA level at enrollment was not required. Radiation therapy at a dose of 60 to 64 Gy delivered to the pelvic fossa in 30 to 32 fractions was initiated within 10 working days after randomization. Ports included the prostatic fossa and paraprostatic tissues. Patients must have had evidence of adequate bone marrow and liver function and a performance status of 0 through 2. Patients must not have had total urinary incontinence, intraoperative rectal injury, persistent urinary extravasation, or pelvic infection. Previous radiotherapy or chemotherapy for prostate cancer was not allowed. Toxicity was monitored weekly during radiotherapy.

Patients were stratified by extent of tumor (ie, tumor at inked surgical margins or beyond the anatomical capsule vs tumor within the seminal vesicle vs tumor at both the inked surgical margins or beyond the anatomical capsule and within the seminal vesicle) and by preprostatectomy hormonal use. Central randomization occurred at the Southwest Oncology Group Statistical Center. A dynamically balanced method was used to minimize imbalance in treatment assignment within the levels of the stratification factors.[9] Patients and investigators were not blinded to treatment assignment. Follow-up visits at participating institutions were scheduled every 3 months for 1 year, every 6 months for 2 years, and annually thereafter.

Complications potentially related to treatment were recorded on study flow sheets at clinic visits. Rectal complications and urethral strictures were not graded but were recorded if annotated on study flow sheets. Total urinary incontinence, while not predefined, was interpreted as no ability to control urinary leakage. At each visit, a PSA level was obtained, as were additional staging studies (eg, bone scans) as clinically indicated. Quality of life was assessed in a subgroup of participants in a companion clinical trial, which will be reported separately. Treatment at disease progression, including androgen deprivation therapy, was not prescribed by the study protocol.

Central pathologic review of radical prostatectomy histological slides was specified in the protocol to confirm eligibility. Nonetheless, there was a significant number of individuals for whom no slides were available or the sample was inadequate to assess eligibility. We chose to include all patients whose institutional pathology report found stage pT3 N0 M0 prostate cancer,[10] regardless of central pathology review status. Although including all patients precludes absolute certainty with the pathologic diagnosis, the study groups more closely reflect those patients to whom the results may be generalizable. Radiotherapy review was conducted in 2 parts. The completed radiotherapy dosimetry was reviewed by the Radiologic Physics Center, and the overall adherence to the protocol was reviewed by the radiotherapy study coordinator (J.P.).

All patients provided written informed consent, and the study was approved by the institutional review boards of the participating institutions.

Study End Points and Statistical Analyses

The primary study end point was metastasis-free survival, defined as the time from randomization to first evidence of metastatic disease or death due to any cause. Metastatic disease included bony or visceral metastases or extrapelvic nodal metastases. This end point was selected because the development of metastatic disease generally leads to morbid therapies (eg, hormonal therapy), is associated with morbid complications and events (eg, pathologic fracture, ureteral obstruction, neurologic complications), and has a median survival of between 30 and 33 months.[11]

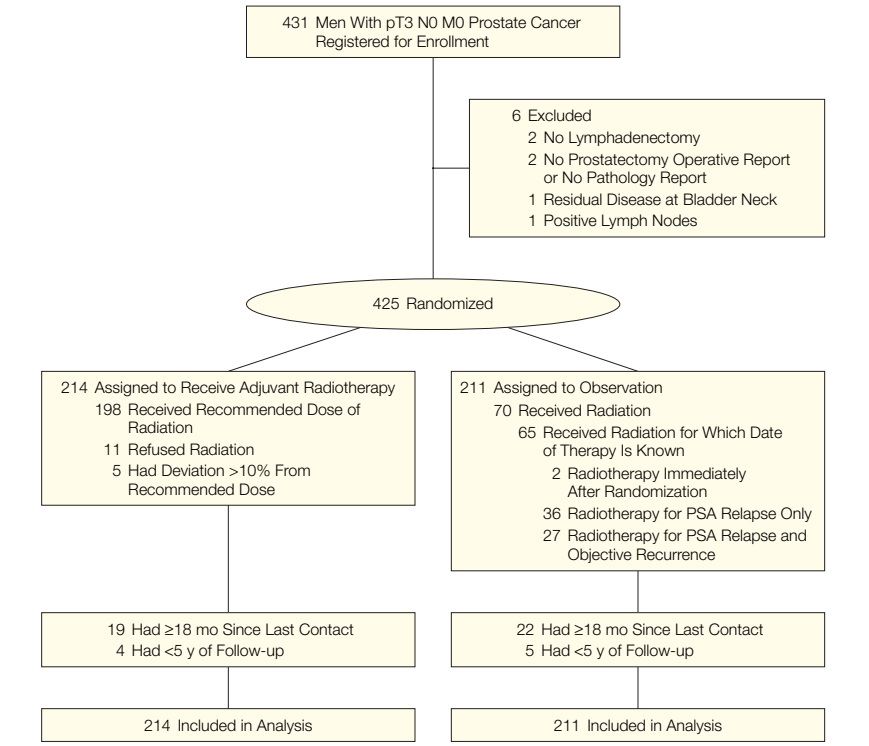
This study was planned using a 1-sided type I error probability of .05; power of 0.8; and an assumption that the primary end point, median metastasis-free survival, would be 6 years and that adjuvant radiation therapy would decrease the metastasis-free survival hazard rate by one third. A total sample size of 558 patients accrued over 5 years with 1 year of follow-up was specified. Based on recommendations by the study's independent data and safety monitoring committee because of a lower than expected event rate, the study was revised in April 1996 to assume a 50% prolongation of the median metastasis-free survival for a median of 12 years (twice the original estimate) in the observation group. The sample-size goal was changed to 408,

and 6 years of follow-up would be required after completing accrual to attain 80% power for the primary end point of metastasis-free survival.

Secondary outcomes included PSA relapse-free interval, defined for the subset of men with a postsurgical PSA level of 0.4 ng/mL or lower as the time to first occurrence of a PSA level greater than 0.4 ng/mL, and recurrence-free survival, defined as the first evidence of any objective recurrence (not including PSA relapse—for example, biopsy-proven local recurrence) or death due to any cause. Patients without the event of interest were censored at their last contact date (last PSA assessment date for PSA relapse). Time to hormonal treatment was calculated as the time from randomization to initiation of hormonal treatment. Patients who died without receiving hormonal treatment were censored at the date of death. Except for the PSA relapse–free interval end point, which was assessed in a subset of 347 men, all 425 eligible patients were used for each end-point analysis.

The methods of Kaplan and Meier[12] were used to generate the time-to-event curves. Proportional hazards regression models were used to estimate hazard ratios (HRs), corresponding 95% confidence intervals (CIs), and *P* values with only an indicator for treatment in the model. Analyses were performed using SAS version 9.0 (SAS Institute Inc, Cary, NC). All analyses were conducted with an intent-to-treat approach, and all reported *P* values are 2-sided.

Figure 1. Flow of Patients in the Study



PSA indicates prostate-specific antigen.

RESULTS

Of 431 men registered for this trial, 425 were eligible for analysis (FIGURE 1). Patients were enrolled between August 15, 1988, and January 1, 1997. The database was frozen for the statistical analysis based on follow-up through September 21, 2005. Six patients were excluded because lymphadenectomy was not performed (2), a prostatectomy operative report or pathology report was not submitted (2), there was residual disease at the bladder neck (1), or they had lymph nodes positive for cancer (1). Mean follow-up for eligible patients was 10.9 years (median, 10.6 years; interquartile range, 9.2-12.7 years). Nine patients had less than 5 years of follow-up: 4 in the radiotherapy group and 5 in the observation group. Characteristics of eligible study participants are displayed in the TABLE.

Metastasis-Free Survival

The primary study end point was metastasis-free survival. At the time of the original study design, based on previously published studies, it was anticipated that the median metastasis-free survival in the observation group would be 6 years. The actual median metastasis-free survival for the observation group in this study was 13.2 years, with 5- and 10-year metastasis-free survival of 84% and 63%, respectively.

A total of 91 (43.1%) of 211 patients in the observation group were diagnosed with metastatic disease or died (median metastasis-free estimate, 13.2 years) vs 76 (35.5%) of 214 (median metastasis-free estimate, 14.7 years) in the adjuvant radiotherapy group. The Kaplan-Meier metastasis-free survival curves are shown in FIGURE 2. The HR for metastasis-free survival with adjuvant radiotherapy was 0.75 but was not statistically significant (95% CI, 0.55-1.02; $P=.06$). Among the 167 men in both groups who were diagnosed with metastatic disease or who died, 115 (68.9%) died without documented metastatic disease. There were 35 cases of metastatic disease noted in the observation group and 17 in the radiation therapy group, a much lower event rate than expected.

Biochemical Relapse

An undetectable PSA level was not required for study eligibility. Nevertheless, postoperative (randomization) PSA levels were available for a subset of 376 patients enrolled. Of these, 249 (66.2%) had undetectable

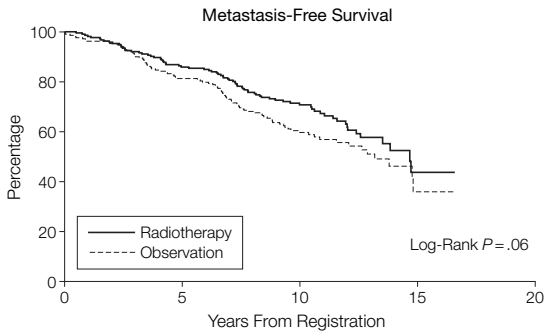
levels (≤0.2 ng/mL). With a definition of biochemical relapse as a PSA level exceeding 0.4 ng/mL after enrollment for those with a postsurgical PSA level of 0.4 ng/mL or lower (n = 347), 112 (64.0%) of 175 patients in the observation group had PSA relapse, compared with 60 (34.9%) of 172 in the adjuvant radiotherapy group. The Kaplan-Meier PSA relapse–free interval curves are shown in FIGURE 3. Adjuvant radiotherapy was associated with a significant reduction of PSA relapse (median PSA relapse–free survival, 10.3 years for radiotherapy vs 3.1 years for observation; HR, 0.43; 95% CI, 0.31-0.58; $P<.001$).

Table. Characteristics of Eligible Patients

Characteristic	No. (%)	
	Adjuvant Radiotherapy (n = 214)	Observation (n = 211)
Age, median (range), y	64.1 (43.8-78.0)	65.8 (47.4-79.2)
Race*		
White	154 (72)	140 (67)
African American	41 (19)	42 (20)
Other	19 (9)	29 (13)
Preoperative hormonal therapy use		
Yes	19 (9)	17 (8)
No	195 (91)	193 (92)
Extent of disease		
Beyond capsule or positive margins	143 (67)	142 (68)
Seminal vesicle invasion	22 (10)	23 (11)
Beyond capsule, positive margins, and seminal vesicle invasion	49 (23)	45 (21)
Gleason score (n = 325 with data)	n = 166	n = 159
≤6	94 (57)	73 (46)
7	57 (34)	60 (38)
8-10	15 (9)	26 (16)
PSA prior to radical prostatectomy (n = 302 with data)	n = 148	n = 154
<10 ng/mL	70 (51)	80 (53)
≥10 ng/mL	78 (59)	74 (47)
PSA after radical prostatectomy (n = 376 with data)	n = 190	n = 186
<0.2 ng/mL	123 (65)	126 (68)
≥0.2 ng/mL	67 (35)	60 (32)

Abbreviation: PSA, prostate-specific antigen.
*Self-reported by patient; ≥1 race could be selected by a patient during the latter portion of the trial's accrual.

Figure 2. Metastasis-Free Survival in Patients Randomized to Adjuvant Radiotherapy or Observation



Recurrence-Free Survival

Disease recurrence after study randomization was defined as any evidence of measurable or evaluable disease (eg, bone lesions), not including PSA relapse. A total of 111 (52.6%) of 211 patients in the observation group experienced a recurrence of disease or death (median recurrence-free estimate, 9.9 years), compared with 84 (39.3%) of 214 (median recurrence-free estimate, 13.8 years) in the adjuvant radiotherapy group. The Kaplan-Meier recurrence-free survival curves are shown in Figure 3. Adjuvant radiotherapy was associated with a significant reduction of disease recurrence (HR, 0.62; 95% CI, 0.46-0.82; $P=.001$).

Overall Survival

Figure 3 shows the overall survival rates of the 2 study groups. A total of 83 (39.3%) of 211 patients in the observation group died during follow-up (median survival, 13.8 years), compared with 71 (33.2%) of 214 in the radiotherapy group (median survival, 14.7 years). The HR for overall survival with adjuvant radiotherapy was 0.80 but was not statistically significant (95% CI, 0.58-1.09; $P=.16$).

Time to Initiation of Hormonal Therapy

Acknowledging the adverse effects associated with hormonal therapy, we analyzed the impact of adjuvant radiotherapy on the time to initiation of hormonal therapy. Figure 3 shows the Kaplan-Meier curves for time to hormonal therapy. Among patients in the observation group, 21% had received hormonal therapy by 5 years, compared with 10% among those in the radiotherapy group (HR, 0.45; 95% CI, 0.29-0.68; $P<.001$).

Adherence and Crossover

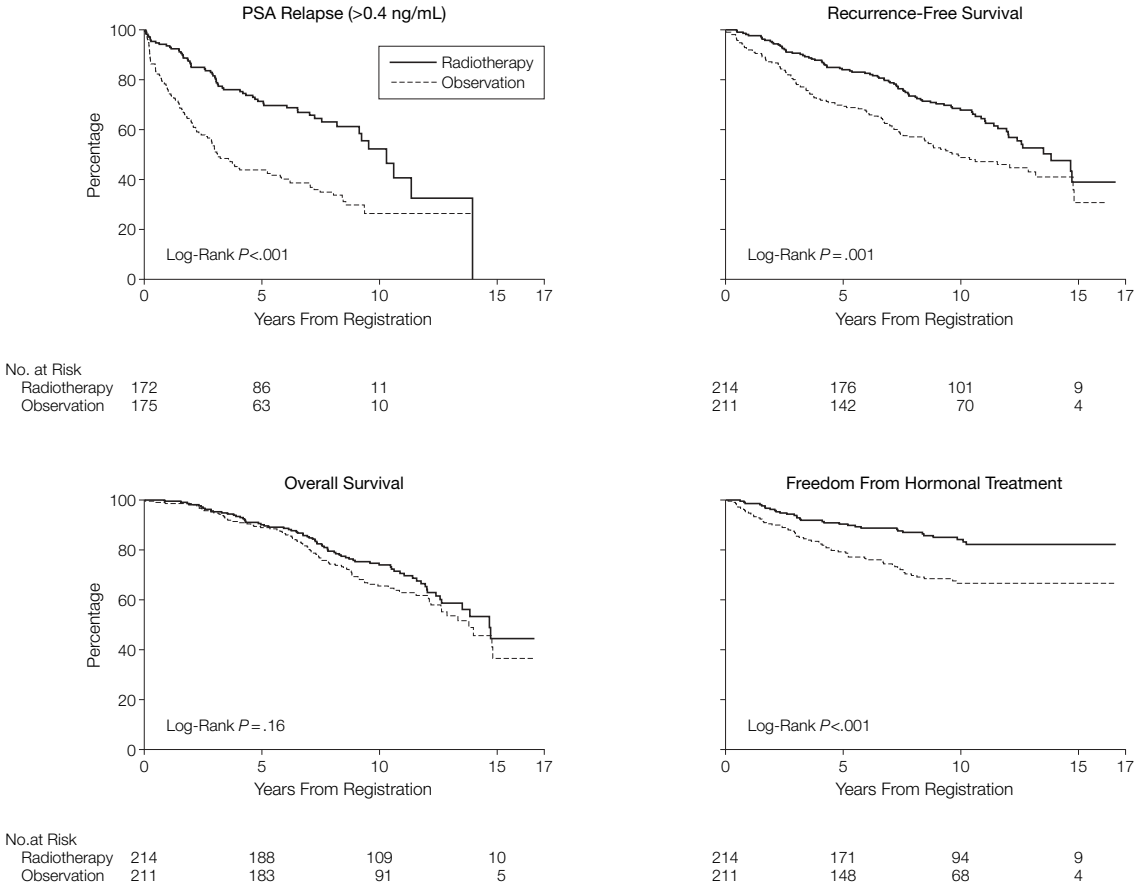
Of the 214 men in the radiation group, 16 were coded as having major devia-

tions in the study protocol. Eleven refused all treatment, and 5 had a deviation of more than 10% of the recommended radiation dose. Twenty patients had no central radiation therapy review, but dates and doses submitted on the clinical report forms would suggest that all protocol treatment was received. Of the 211 men in the observation group, 70 reported ultimately receiving pelvic radiotherapy, but only 65 specified a date on which treatment had begun. Among these 65 patients, radiotherapy was initiated after PSA relapse in 36 (55.4%), after PSA relapse and objective recurrence in 27 (41.5%), and after refusal of the randomized assignment and crossover to radiotherapy in 2 (3.1%). Crossover occurred between 3 days and 9.7 years after randomization, with a median of 2.0 years (interquartile range, 11 months-4.5 years). Of the 63 men with evidence of disease relapse prior to radiotherapy (median follow-up after initiation of radiotherapy, 5.9 years), metastatic disease developed in 8 (12.7%), and another 14 (22.2%) died without metastases.

Extent of Disease and Biochemical Relapse

In exploratory analyses, we evaluated the association of extent of disease with both PSA relapse and objective recurrence, and the effect of radiotherapy on each of these pathologic subgroups. Although the numbers of patients in the 3 general pathologic strata were small and not equal, adjuvant radiotherapy reduced risk of PSA relapse and objective recurrence in all strata. The test of interaction of pathologic finding × adjuvant radiation therapy was nonsignificant for both the PSA relapse and the objective recurrence end points ($P = .82$ and $P = .41$, respectively, by χ^2_2 test). For PSA relapse–free interval, the hazard rate was significantly reduced in each group (HR, 0.44; 95% CI, 0.30-0.65 for positive margins; HR, 0.23; 95% CI, 0.06-0.84 for seminal vesicle involvement; and HR, 0.40; 95% CI, 0.20-0.77 for both). For recurrence-free survival, the treatment HRs and corresponding 95% CIs were 0.64 (0.45-0.93) for positive margins, 0.76

Figure 3. PSA Relapse–Free, Recurrence-Free, and Overall Survival and Freedom From Hormonal Treatment in Patients Randomized to Adjuvant Radiotherapy or Observation



Prostate-specific antigen (PSA) relapse–free survival indicates survival with a PSA level ≤0.4 ng/mL; recurrence-free survival indicates survival with no objective recurrence (ie, not including PSA relapse).

(0.33-1.74) for seminal vesicle involvement, and 0.47 (0.27-0.81) for both. The extent of disease at randomization was related to the risk of both PSA relapse and objective recurrence. Because there was no evidence of an interaction of pathologic extent with treatment, we combined treatment groups. Patients with disease beyond the prostatic capsule or with positive margins (n=283) had a 6.1-year median time to PSA relapse, compared with a 2.1-year median time to relapse in those with seminal vesicle invasion (n=43) and a 3.1-year median time to relapse for patients with both pathologic findings (n=93). For recurrence-free survival, the medians were 13.8, 11.0, and 8.5 years, respectively.

Complications

Complications during follow-up were more commonly seen among patients in the radiotherapy group (51/214 [23.8%] than in the observation group (25/211 [11.9%]) (relative risk, 2.0; 95% CI, 1.3-3.1; *P*=.002). Rectal complications such as proctitis or rectal bleeding occurred in 7 (3.3%) of 214 men in the radiotherapy group and in no men in the observation group (*P*=.02, relative risk cannot be calculated). Urethral stricture was more common with radiotherapy (38/213 [17.8%]) than with observation (20/210 [9.5%]) (relative risk, 1.9; 95% CI, 1.1-3.1; *P*=.02). Total urinary incontinence was more common with radiotherapy (14/214 [6.5%]) than with observation (6/211 [2.8%]) (relative risk, 2.3; 95% CI, 0.9-5.9; *P*=.11).

COMMENT

The treatment of men with pathologically advanced prostate cancer after radical prostatectomy has remained a subject of intense interest for decades. The Southwest Oncology Group 8794 trial was developed at the outset of the "PSA era," as PSA testing swept across the United States. While it was hoped that through early detection, pathologically advanced prostate cancer (ie, tumors that had extended beyond the prostate, had extended to the surgical margins, or had invaded the seminal vesicles) would diminish substantially, contemporary series continue to report high rates of extraprostatic disease.[2,3]

The results of this study provide guidance for clinicians and patients in weighing options for adjuvant radiotherapy for pathologically advanced disease. Arguments in favor of radiotherapy include the approximately 50% reduction in risk of PSA relapse or disease recurrence, and perhaps the nonsignificant reduction (*P*=.06) in risk of metastasis-free survival, the primary study end point. PSA relapse and disease recurrence are associated with several adverse consequences, including patient anxiety and use of adjuvant therapies with potential adverse effects. Such treatments can include radiotherapy and hormonal therapy, which is associated with risks of osteoporosis, sexual dysfunction, hot flashes, sarcopenia, and reduced quality of life.[13,14] In our study, adjuvant radiotherapy significantly reduced the risk of receiving adjuvant hormonal therapy. The ability of this study to detect a significant improvement in metastasis-free and overall survival may have been attenuated by the one third of patients who were initially randomized to observation but who ultimately received pelvic radiotherapy.

Arguments against adjuvant radiotherapy must include that the study had negative findings, ie, a significant reduction in metastatic disease was not demonstrated. Despite prolonged follow-up of these patients, the rate of metastatic disease was significantly less than anticipated. Based on the data in this series, censoring death without metastatic disease, we estimate that at 13.2 years, the metastasis-free survival estimate would be 78%. To detect an HR of 1.25 and assuming 10 years of accrual (approximately 290 patients per year), 10 years of follow-up, a 2-sided α of .05, and 80% power, the study sample size would require 2900 patients. With 6 years of accrual, 10 years of follow-up, and a very large HR of 1.50, the sample size would be 1100. These estimates demonstrate the need for improved accrual of men with prostate cancer to clinical trials or inclusion of higher-risk patients, such as those with Gleason scores of 7 or greater. However, such a severe limitation in eligibility would limit the generalizability of results.

Currently, there is debate as to whether a PSA response to treatment can serve as a surrogate for disease-related outcomes; thus, the implications of a reduced risk of PSA relapse after radiotherapy are unknown.[7,15,16] This study demonstrates the potential inconsistency of PSA relapse and the primary end point, with a significant reduction in the former but no significant relation in the risk of metastatic disease. In addition to the lack of significant improvements in metastasis-free and overall survival, patients receiving radiotherapy more commonly had urinary or bowel complications.

In lieu of immediate adjuvant radiotherapy for patients with pathologically advanced prostate cancer, it has been advocated that patients receive surveillance of PSA levels during follow-up, with delayed radiotherapy if a detectable value is noted.[17] Ultimately, this was the approach in the observation group of this study, because approximately one third of this group eventually received radiation. With a lack of a statistically significant improvement in metastasis-free and overall survival in the 2 study groups, this approach may be a reasonable alternative. Arguing against this approach was the fact that 8 (12.7%) of 63 of these patients ultimately developed metastatic disease.

Other studies of adjuvant therapies are currently under way, including a National Cancer Institute study comparing androgen deprivation for 2 years with androgen deprivation plus adjuvant mitoxantrone.[18] With the recognition that 35 (16.6%) of 211 men in the observation group of our study ultimately developed metastatic disease within 10 to 15 years of follow-up, the need for completion of long-term studies with appropriately selected disease end points is clear.

CONCLUSIONS

Adjuvant radiotherapy in men with pathologically advanced prostate cancer resulted in significantly reduced risk of PSA relapse and disease recurrence, although the improvements in metastasis-free survival and overall survival were not statistically significant, and the risk of complications was increased. The results of this study may provide guidance for clinicians and patients considering options for adjuvant therapy for pathologically advanced disease.

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Author Contributions: Dr Tangen had full access to all of 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: Thompson, Paradelo, Crawford.
Acquisition of data: Thompson, Tangen, Lucia, Troyer, Forman, Chin, Canby-Hagino.
Analysis and interpretation of data: Thompson, Tangen, Messing, Forman, Chin, Swanson.
Drafting of the manuscript: Thompson, Tangen, Paradelo, Messing, Swanson, Crawford.
Critical revision of the manuscript for important intellectual content: Thompson, Tangen, Lucia, Troyer, Forman, Chin, Swanson, Canby-Hagino.
Statistical analysis: Tangen.
Administrative, technical, or material support: Thompson, Paradelo, Lucia, Troyer, Messing, Chin.
Study supervision: Thompson, Crawford.
Financial Disclosures: None reported.
Funding/Support: This study was supported in part by the following Public Health Service Cooperative Agreement grants awarded by the National Cancer Institute, Department of Health and Human Services: CA38926, CA32102, CA14028, CA58416, CA58658, CA42777, CA27057, CA46136, CA35431, CA58882, CA12644, CA58861, CA35090, CA37981, CA76429, CA04919, CA76132, CA35119, CA35178, CA35176, CA46282, CA67575, CA45377, CA46113, CA74647, CA35261, CA04920, CA20319, CA76447, CA58723, CA12213, CA22433, and CA46441, and by National Cancer Institute of Canada grant PR-2.
Role of the Sponsor: The National Cancer Institute and the National Cancer Institute of Canada reviewed the design and conduct of the study but had no role in the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

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