Radiation Therapy After Radical Prostatectomy: Impact on Metastasis and Survival

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Abbreviations and Acronyms

ADT = androgen deprivation therapy
ART = adjuvant radiation therapy
BCR = biochemical recurrence
PSA = prostate specific antigen
PSADT = PSA doubling time
RRP = radical retropubic prostatectomy
SRT = salvage radiation therapy
SWOG = Southwest Oncology Group

Submitted for publication March 4, 2009.
Study received institutional review board approval.

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Purpose: Although secondary radiation therapy decreases the risk of biochemical progression after radical prostatectomy, its impact on metastasis and survival is less well established. We evaluated the impact of adjuvant and salvage radiotherapy on clinical progression and mortality.

Materials and Methods: A total of 361 patients who received adjuvant radiation were matched based on clinicopathological features to patients who did not receive adjuvant radiation in a 2:1 case-control ratio. Postoperative survival was estimated using the Kaplan-Meier method and compared using the log rank test. A second cohort of 2,657 men who experienced biochemical recurrence after prostatectomy was separately evaluated. Cox proportional hazard regression models were used to analyze the impact of salvage radiotherapy on disease progression and survival.

Results: Adjuvant radiotherapy was associated with significantly improved 10-year biochemical recurrence-free survival (63% vs 45%, $p < 0.001$), local recurrence-free survival (97% vs 82%, $p < 0.001$) and a decreased need for late hormone therapy (17% vs 28%, $p = 0.002$) but did not impact systemic progression and overall survival ($p = 0.94$ and 0.27, respectively). Of the 2,657 patients who experienced biochemical recurrence after surgery 856 (32.3%) received salvage radiation. On multivariate analysis salvage radiotherapy decreased the risk of local recurrence (HR 0.13, 95% CI 0.06–0.28, $p < 0.0001$) and delayed hormonal therapy (HR 0.81, 95% CI 0.71–0.93, $p = 0.003$) and systemic progression (HR 0.24, 95% CI 0.13–0.45, $p < 0.0001$) but did not significantly impact mortality ($p = 0.48$).

Conclusions: Adjuvant and salvage radiation provide long-term local control and decrease the need for delayed hormonal therapy but neither improves survival. These results must be weighed against the potential morbidity of postoperative radiation when counseling patients.

Key Words: prostate, prostatic neoplasms, prostatectomy, radiotherapy, prostate-specific antigen

DESPITE the prostate cancer stage migration noted in the PSA era extraprostatic disease continues to be detected in 38% to 52% of patients who undergo RRP[1,2] and the 5-year BCR rate after surgery remains between 15% and 40%.[3,4] Therefore, considerable attention has focused on evaluating secondary local treatments to improve patient outcomes. In particular radiation therapy after RRP has been assessed in the adjuvant[5–11] and salvage[5,6,11–21] settings.

0022-5347/09/1826-2708/0
THE JOURNAL OF UROLOGY®
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Vol. 182, 2708-2715, December 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2009.08.027

However, the primary benefit of radiotherapy after surgery is a decreased incidence of biochemical failure. Indeed, the initial reports of 3 contemporary randomized trials of ART vs observation show that ART provides improved BCR-free and clinical recurrence-free survival but does not significantly impact metastasis-free or overall survival,[7–9] although a recent update of 1 of these trials with longer followup demonstrated decreased mortality for ART.[10] Likewise, with 1 exception[22] most SRT studies to date have shown an association with the end point of BCR only.[11–21]

Importantly using PSA progression as a clinical outcome measure remains questionable since the natural history of BCR varies. That is, while approximately 35% of patients experience PSA failure within 10 years after RRP,[1,23] BCR does not always translate into systemic progression and prostate cancer death.[1,24] Moreover, given the sensitivity of PSA to detect disease recurrence after RRP, the clinical course in patients with BCR is generally prolonged and in fact median survival was not attained 16 years after initial PSA failure in 1 study.[24] Thus, since men with prostate cancer are generally older than 60 years, competing causes of mortality may obscure the ability of BCR to predict death from prostate cancer.[25]

Therefore, since postoperative radiotherapy may be associated with toxicity, particularly in regard to rectal and urethral complications,[7–8,26] determining whether ART and SRT confer a benefit to the end points of metastasis and survival is important for patient counseling. We evaluated the impact of ADT and SRT on clinical progression and mortality after RRP.

MATERIALS AND METHODS

After receiving institutional review board approval we reviewed our prostatectomy registry to identify 13,308 consecutive patients who underwent RRP at Mayo Clinic between 1987 and 2003. A total of 106 men who refused to release records, 1,394 who received treatment before RRP and 559 foreign patients were excluded from analysis. Also, 646 patients with positive lymph nodes and 954 who received adjuvant ADT were excluded from study, leaving 9,244 patients for analysis.

Surgical procedures were performed by different surgeons using standardized techniques. Tumor stage was assigned using the 1997 UICC-American Joint Committee on Cancer TNM system.[27] Adjuvant therapy, defined as treatment received within 90 days of RRP, was administered at treating physician discretion. Salvage treatment was defined as therapy initiated greater than 90 days after RRP and was also administered by individual physicians. BCR was defined as PSA 0.4 ng/ml or greater. Local recurrence was defined as cancer on biopsy of the prostatic bed or clinically evident disease in the prostatic fossa. Systemic progression involved demonstrable metastasis on bone scan or on biopsies outside the prostatic bed. Vital status was identified from death certificates or physician correspondence. ADT included luteinizing hormone-releasing hormone agonists, oral antiandrogens and orchiectomy. Medical ADT was generally intended to be lifelong. However, given the retrospective nature of this study, it is uncertain whether some patients discontinued treatment.

Patients who received ART were matched based on clinicopathological features to patients who did not receive ART in a 2:1 case-control ratio using a weighted greedy algorithm. Features included age, surgery year, preoperative PSA, pathological Gleason score, tumor stage and surgical margin status. Comparison of clinicopathological features of patients between the groups was done using the chi-square and Wilcoxon rank sum tests as appropriate. Postoperative survival was estimated using the Kaplan-Meier method and compared with the log rank test. Patients were censored at last followup or death if the end point of interest was not attained.

A second cohort of men who experienced BCR after RRP was separately evaluated. Cox proportional hazard regression models were used to analyze the impact of SRT on disease progression and survival in this group. SRT and late ADT were analyzed as time dependent covariates with a 6-month lag used to minimize the potentially misleading effects of treatment administered immediately before an end point. Also, linearity of the variable log PSA at BCR was confirmed on a plot to assess functional form by graphing Martingale residuals from a null Cox model vs log PSA at BCR. Postoperative PSADT was calculated using slopes from individual logarithmic regression analysis[28] in men who had at least 2 PSA measurements available that were separated by at least 90 days. PSA values included for PSADT began 1 year before BCR and extended to 1 year after BCR or the initiation of late ADT, whichever was first. When the PSA slope was negative, PSADT was arbitrarily set at 10 years. Since SRT after BCR is a time dependent covariate, we used the Landmark method[29] to visually assess the impact of SRT on survival. Almost 70% of patients who received SRT did so within 2 years of BCR. Therefore, patients who were event-free at 2 years were stratified based on treatment received within 2 years after BCR and followed for the event of interest. All tests were 2-sided with $p \leq 0.05$ considered significant. Statistical analysis was done using SAS®, version 9.1.3.

RESULTS

We identified 361 patients who received ART after RRP. Table 1 lists clinical and pathological features in these men. Importantly no difference was noted in the percent of patients with vs without ART who did not achieve undetectable PSA postoperatively (38 or 10.5% vs 69 or 9.7%, $p = 0.66$).

At a median postoperative followup in each cohort of 11.0 years (range 1.8 to 19.7) 131 patients with ART and 386 controls experienced BCR, 9 and 126 had local recurrence, 34 and 68 had systemic relapse, and 76 and 174 died, including 17 and 42 of

Table 1. *Matched comparison of patients undergoing ART vs no ART*

Feature	ART		No ART Matched Cohort		p Value	Overall No ART	
No. pts	361		722			8,815	
No. RRP, yr (%):					0.73		
1987–1992	103	(28.5)	204	(28.3)		2,462	(27.9)
1993–1998	174	(48.2)	362	(50.1)		3,552	(40.3)
1999–2003	84	(23.3)	156	(21.6)		2,801	(31.8)
Median age at RRP (IQR)	65.0	(58.0, 68.0)	64.0	(58.0, 68.0)	0.96	64.0	(58, 68)
Median ng/ml preop PSA (IQR)	8.5	(5.5, 16.3)	8.1	(5.9, 13.2)	0.43	6.4	(4.4, 9.7)
No. pathological tumor stage (%):					0.97		
T2a	40	(11.1)	78	(10.8)		2,792	(31.7)
T2b	131	(36.3)	273	(37.8)		4,192	(47.6)
T3a	122	(33.8)	240	(33.2)		1,192	(13.5)
T3b/T4	68	(18.8)	131	(18.1)		616	(7.0)
No. pathological Gleason score (%):					0.71		
6 or Less	163	(45.2)	326	(45.2)		6,224	(70.6)
7	156	(43.2)	329	(45.6)		2,209	(25.1)
8–10	42	(11.6)	67	(9.3)		382	(4.3)
No. pos surgical margin (%):					1.00		
No	28	(7.8)	56	(7.8)		6,706	(76.1)
Yes	333	(92.2)	666	(92.2)		2,109	(23.9)

prostate cancer, respectively (fig. 1). Of note 191 controls (26.5%) subsequently received SRT. Patients who received ART had significantly improved 10-year BCR-free survival compared to patients who did not receive ART (63%, 95% CI 58–69 vs 45%, 95% CI 41–49, p <0.001, fig. 2). ART was also associated with better 10-year local recurrence-free survival (97%, 95% CI 95–99 vs 82%, 95% CI 79–85, p <0.001) and a decreased need for late ADT (17%, 95% CI 13–21 vs 28%, 95% CI 25–32, p = 0.002). Specifically patients who received ART were approximately 90% less likely to experience local recurrence and 45% less likely to experience BCR or require late ADT (table 2). However, patients who received ART did not have a significantly decreased rate of systemic progression at 10 years (7%, 95% CI 4–10 vs 9%, 95% CI 7–11, p = 0.94) or death from any cause (13%, 95% CI 9–16 vs 16%, 95% CI 13–19, p = 0.27, fig. 3). Also, ART did not decrease the risk of systemic progression or death on univariate or multivariate analysis (table 2). We repeated our evaluation of the impact of ART on outcome using

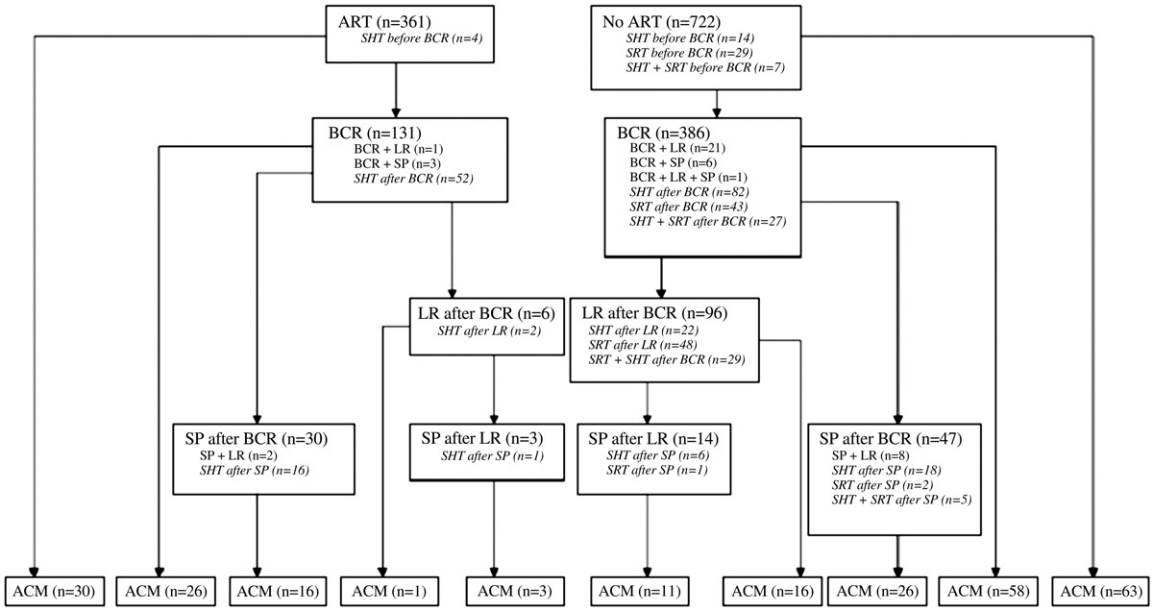

Figure 1. Outcome in matched cohorts of 361 patients who did vs 722 who did not receive ART after RRP. Boxes represent events within 30 days and treatments administered before next event. *LR*, local recurrence. *SP*, systemic progression. *ACM*, all cause mortality.

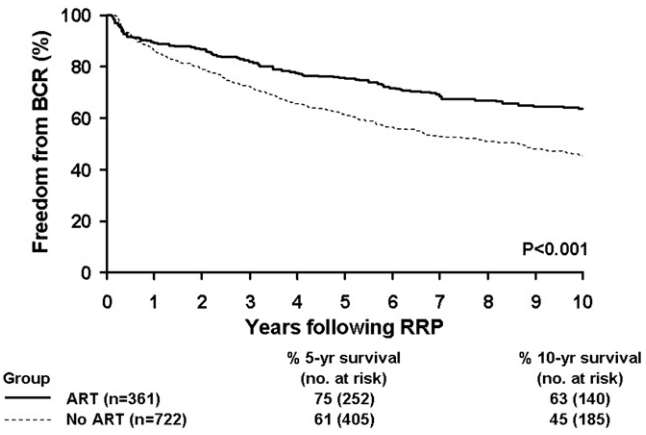

Figure 2. BCR-free survival in patients treated with ART vs controls.

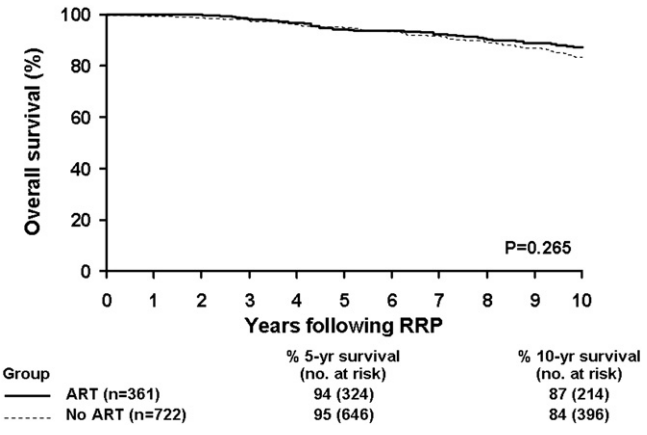

Figure 3. Overall survival in patients treated with ART vs controls.

competing risk analysis and obtained survival estimates that were almost identical (data not shown) to the Kaplan-Meier data.

We then separately evaluated the impact of SRT on survival after BCR after RRP. We identified 2,657 men who experienced BCR after RRP, of whom 856 (32.3%) received SRT (table 3). Median followup after RRP and BCR was 11.5 (IQR 8.1, 14.8) and 6.9 years (IQR 3.8, 10.5), respectively, in all patients with BCR. Patients who received SRT were followed a median of 5.9 years (IQR 3.2, 9.3) after radiotherapy. In men who received SRT the median time from BCR to SRT was 0.7 years (IQR 0.2, 2.0) and the median PSA at SRT was 0.8 ng/ml (IQR 0.50, 1.70).

Overall 534 men (63.6%) who received SRT achieved undetectable PSA after radiation. A total of 155 and 251 men in the SRT and nonSRT groups, respectively, experienced systemic relapse, 433 and 701 required salvage ADT, and 208 and 567 died, respectively (fig. 4). We evaluated the association of SRT with outcome on multivariate analysis, controlling for clinical and pathological factors likely to have been considered by physicians in recommending SRT. Patients who received SRT were at almost 90% decreased risk for local recurrence (HR 0.13, 95% CI 0.06–0.28, p <0.0001), at 20% decreased risk for late ADT (HR 0.81, 95% CI 0.71–0.93, p = 0.003) and at 75% decreased risk for systemic progression (HR 0.24, 95% CI 0.13–0.45, p <0.0001). However, no significant association of SRT with overall mortality was detected (table 4). Consistent with this finding, we noted that overall survival in patients who received SRT within 2 years of BCR was not significantly improved compared to that in patients who did not receive SRT within 2 years of BCR (fig. 5).

Lastly, since a recent study showed that SRT is particularly associated with survival in men with PSADT less than 6 months who received SRT within 2 years of BCR,[22] we repeated our analysis in this cohort and again found no significant association between SRT and survival (table 4).

DISCUSSION

We report a retrospective analysis of the impact of ADT and SRT on survival after RRP. At long-term followup ART and SRT improved the biochemical failure rate, provided local control and decreased the need for late ADT. Furthermore, SRT was associated with a decreased rate of systemic progression. However, regardless of the timing of delivery radia-

Table 2. *Proportional hazards models of ART impact on outcomes after RRP*

End Point	Univariate Analysis		Multivariate Analysis*	
	HR† (95% CI)	p Value	HR† (95% CI)	p Value
BCR	0.57 (0.45–0.71)	<0.0001	0.53 (0.42–0.67)	<0.0001
Local recurrence	0.11 (0.05–0.24)	<0.0001	0.11 (0.05–0.23)	<0.0001
Systemic progression	0.97 (0.62–1.51)	0.88	0.93 (0.58–1.49)	0.76
Late ADT	0.60 (0.45–0.81)	0.0008	0.57 (0.42–0.78)	0.0003
Death from any cause	0.85 (0.63–1.15)	0.85	0.81 (0.59–1.10)	0.18

* Controlling for matching variables and late ADT.
† Association of ART and end point with no ART as referent (HR 1).

Table 3. *Clinicopathological features in patients with BCR after RRP by SRT*

Feature	SRT	No SRT	p Value
No. pts	856	1,801	<0.0001
No. RRP yr (%):			
1987–1992	295 (34.5)	835 (46.4)	
1993–1998	352 (41.1)	706 (39.2)	
1999–2003	209 (24.4)	260 (14.4)	
Median age at RRP (IQR)	63.0 (58.0, 67.0)	66.0 (61.0, 70.0)	<0.0001
Median ng/ml preop PSA (IQR)	8.6 (5.6, 13.7)	8.1 (5.2, 13.6)	0.07
No. pathological tumor stage (%):			0.26
T2a	166 (19.4)	398 (22.1)	
T2b	334 (39.0)	682 (37.9)	
T3a	194 (22.7)	427 (23.7)	
T3b/T4	162 (18.9)	294 (16.4)	
No. pathological Gleason score (%):*			<0.0001
6 or Less	380 (44.4)	940 (52.2)	
7	368 (43.9)	625 (36.1)	
8–10	91 (10.6)	168 (9.3)	
No. pos surgical margin (%):			0.004
No	470 (54.9)	1,096 (60.9)	
Yes	386 (45.1)	705 (39.1)	
Median yrs postop PSADT (IQR)	1.3 (0.6, 10.0)	2.2 (0.8, 10.0)	<0.0001

* Missing in 17 patients with and 68 without SRT.

tion therapy after surgery was not significantly associated with overall mortality.

Numerous previous studies have described the role of ART[5–11] and SRT[5–6,11–22] after RRP. In particular the results of 2 randomized trials of ART vs observation were recently analyzed in detail.[7–10] European Organisation for Research and Treatment of Cancer 22911 randomized 1,005 patients to ART vs observation and showed significant improvement in BCR-free survival for ART (74% vs 53%) but no difference in overall survival (93% vs 92%).[7] Similarly SWOG 8794 enrolled 425 men and at a median followup of 10.6 years demonstrated improved PSA relapse and disease recurrence with ART but no significant difference in metastasis-free or overall survival.[8,9] At additional followup out to 12.6 years a significant improvement in overall survival was found (HR 0.72), although this difference reflects an excess of only 22 deaths in the observation arm.[10] Moreover, 32% to 35% of men in the SWOG trial had persistently detectable PSA postoperatively compared to only 10% in our series, which may in part account for the different outcomes reported.

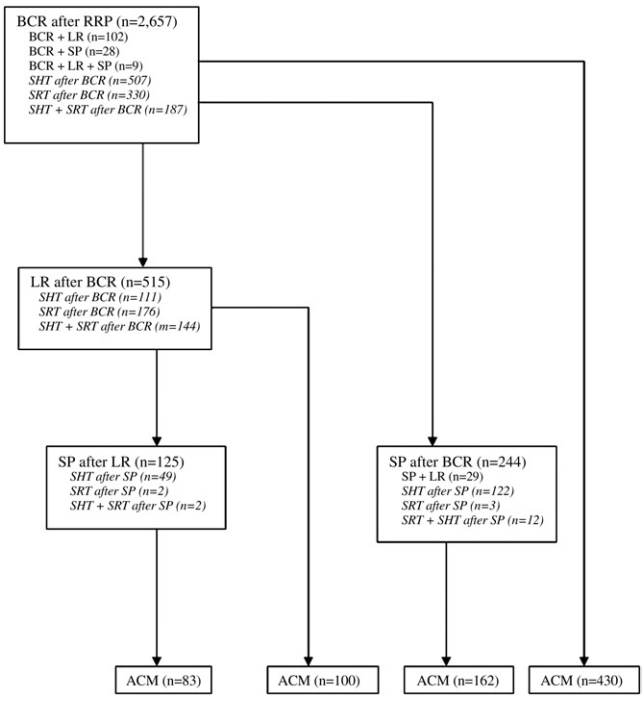

Figure 4. Outcome in 2,657 patients with BCR after RRP. Boxes represent events within 30 days and treatments administered before next event. *LR*, local recurrence. *SP*, systemic progression. *ACM*, all cause mortality.

Although SRT series to date indicate a long-term BCR-free rate of 30% to 50%,[16,18–19] only 1 recent series showed a significant impact on survival.[22] In that study Trock et al compared the outcome in 238 men treated with SRT to that in 397 with BCR after RRP who did not receive salvage treatment. SRT was associated with a 3-fold increase in prostate cancer specific survival but this benefit was limited to men with PSADT less than 6 months who received SRT within 2 years of BCR. We failed to find a similar association of SRT with survival, which may be a function of differences in patient selection. However, since we found that SRT impacted systemic progression, which has been almost invariably linked to prostate cancer death, we may detect an association of SRT with mortality after additional followup.

Table 4. *Proportional hazards models of risk of death from any cause after BCR*

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
RRP yr	0.95 (0.93–0.98)	<0.0001	0.99 (0.96–1.02)	0.47
Pathological tumor stage	1.19 (1.11–1.27)	<0.0001	1.15 (1.06–1.25)	0.001
Pathological Gleason	1.22 (1.14–1.30)	<0.0001	1.18 (1.10–1.28)	<0.0001
Pos surgical margin	1.06 (0.92–1.22)	0.46	1.06 (0.90–1.26)	0.48
RRP–BCR yrs	1.08 (1.05–1.10)	<0.0001	1.08 (1.05–1.12)	<0.0001
PSA at BCR (log)	1.40 (1.31–1.50)	<0.0001	1.34 (1.22–1.47)	<0.0001
PSADT	0.95 (0.94–0.97)	<0.0001	0.96 (0.94–0.98)	0.0001
Late ADT*	2.12 (1.82–2.45)	<0.0001	1.73 (1.44–2.08)	<0.0001
SRT*	0.69 (0.55–0.87)	0.0016	0.91 (0.69–1.18)	0.48
PSADT less than 6 mos:				
RRP yr	0.97 (0.92–1.03)	0.37	1.01 (0.97–1.06)	0.61
Pathological tumor stage	1.31 (1.08–1.58)	0.005	1.14 (0.99–1.31)	0.06
Pathological Gleason	1.30 (1.10–1.55)	0.003	1.15 (1.02–1.30)	0.03
Pos surgical margin	1.10 (0.73–1.65)	0.65	0.91 (0.68–1.21)	0.91
RRP–BCR yrs	1.09 (1.01–1.18)	0.04	1.08 (1.03–1.13)	0.002
PSA at BCR (log)	1.51 (1.27–1.78)	<0.0001	1.36 (1.23–1.51)	<0.0001
Late ADT*	2.34 (1.56–3.50)	<0.0001	1.46 (1.07–1.98)	0.02
SRT*	0.52 (0.24–1.12)	0.09	0.80 (0.47–1.37)	0.42

* Time dependent covariate.

Determining the impact of prostate cancer treatment on outcomes other than BCR remains clinically relevant since the natural history of PSA recurrence is variable and does not always translate into systemic progression and prostate cancer death.[1,24] Another important limitation to date of studies of the impact of postoperative radiotherapy on outcome is that often they did not include a control group of patients with BCR who did not receive radiation.[5–6,12,14–21] Without such a comparison group the impact of treatment on natural history in patients remains difficult to discern since the cohorts analyzed may represent patients whom clinicians believed would have benefitted from SRT and, thus, they are a biased selection of the BCR population.

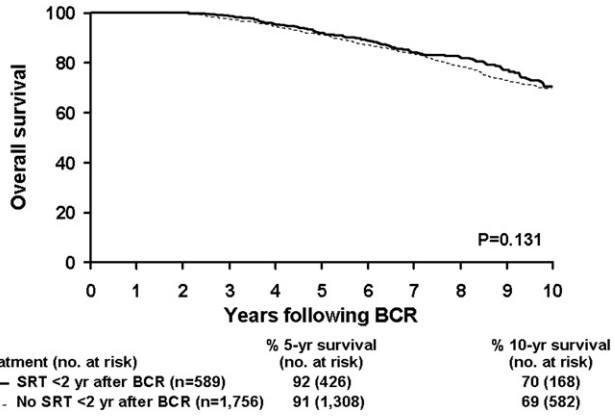

Figure 5. Overall survival by Landmark method in patients who did vs did not receive SRT within 2 years of BCR.

When deciding whether to administer ART/SRT, the potential benefits of treatment must be weighed against potential treatment toxicity.[30] Postoperative radiation is associated with late genitourinary and gastrointestinal toxicity in 10% to 20% of patients.[12,15,17] The SWOG ART trial described rectal proctitis and bleeding in 3.2% of patients, urethral stricture in 17%, urinary incontinence in 6.5% and a significantly higher overall rate of adverse events in men in the ART group than in the observation cohort (28.8% vs 11.9%).[8] Similarly SRT analysis revealed diarrhea in 31% of patients and proctitis in 41%.[26]

Our study is limited by its retrospective, nonrandomized design. As such, decisions to treat with ART and SRT, and the time to initiate therapy were based on patient preference and physician counseling. Thus, they were subject to inherent selection bias. The study period was long and institutional practice patterns have changed with time, such that 26% of patients with BCR who underwent RRP between 1987 and 1992 received SRT compared to 45% who underwent RRP between 1999 and 2003, and experienced BCR. Also, most of our patients received radiation elsewhere, which limited our ability to analyze the impact of radiation dose on outcome and assess the side effects of ART and SRT. Moreover, almost all patients in our ART analysis had positive surgical margins, which may have impacted our ability to discern an impact of ART on patients with other adverse pathological features. Furthermore, additional followup in our ART cohort may reveal a survival difference, as was recently found by SWOG investigators.[10]

Overall we believe that the data presented with large patient numbers and extended followup suggest that secondary radiotherapy may provide a limited overall survival benefit in patients after RRP. As we await continued reports of randomized ART trials as longer followup becomes available, of additional SRT series and of trials combining hormone therapy with postoperative radiotherapy, the current data should be considered in light of the potential toxicity from radiation therapy when counseling patients.

CONCLUSIONS

ART and SRT provide local control, improve long-term BCR-free survival and decrease the need for delayed ADT. SRT was further associated with a decreased rate of systemic progression but neither ART nor SRT improved overall survival during the followup reported. These results must be weighed against the potential morbidity of postoperative radiation when counseling patients.

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EDITORIAL COMMENT

From their analysis of patients who underwent radical prostatectomy at Mayo Clinic between 1987 and 2003 with or without immediate ART these authors conclude that immediate ART improves local control and decreases the need for delayed hormonal therapy but does not improve survival. Of the patients 92.2% in the matched patient subset analyzed had positive surgical margins compared to 76.1% in the whole cohort (table 1). This is because positive margins influences patient selection for ART. Likewise, pT3–4 and Gleason greater than 6 are over represented in the matched patient subset. However, since 92% of the patients in the analysis had positive margins and 90% had pT2b or higher, the conclusions apply only to this category of patients and the benefit of ART in patients with negative surgical margins is yet to be demonstrated.

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