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Clinical and biochemical outcomes of men undergoing radical prostatectomy or radiation therapy for localized prostate cancer

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Purpose: We analyzed outcomes of patients with prostate cancer undergoing either radical retropubic prostatectomy (RRP) +/– salvage radiation or definitive radiation therapy (RT) +/– androgen deprivation.

Materials and Methods: From 2003–2010 there were 251 patients who underwent RRP and 469 patients who received RT (≥7,560 cGy) for prostate cancer. Kaplan-Meier analysis was performed with the log-rank test to compare biochemical control (bCR), distant metastatic-free survival (DMPFS), and prostate cancer-specific survival (PCSS) between the two groups.

Results: The median follow-up was 70 months and 61.3% of the men were African American. For low risk disease the 6-year bCR were 90.3% for RT and 85.6% for RRP (p = 0.23) and the 6-year post-salvage bCR were 90.3% vs. 90.9%, respectively (p = 0.84). For intermediate risk disease the 6-year bCR were 82.6% for RT and 59.7% for RRP (p < 0.001) and 82.6% vs. 74.0%, respectively, after including those salvaged with RT (p = 0.06). For high risk disease, the 6-year bCR were 67.4% for RT and 41.3% for RRP (p < 0.001) and after including those salvaged with RT was 67.4% vs. 43.1%, respectively (p < 0.001). However, there were no significant differences between the two groups in regards to DMPFS or PCSS.

Conclusion: Treatment approaches utilizing RRP +/– salvage radiation or RT +/– androgen deprivation yielded equivalent DMPFS and PCSS outcomes. Biochemical control rates, using their respective definitions, appeared equivalent or better in those who received treatment with RT.

Keywords: Prostate cancer, Radiation therapy, Radical prostatectomy, Outcomes, Dose escalation, Comparative effectiveness

Introduction

The treatment for localized prostate cancer generally involves either radical prostatectomy (RRP), external beam radiation (RT) and/or brachytherapy. To date, there have been no modern randomized studies that have been able to compare the efficacy of these treatments, leaving only retrospective reviews.

There have been several such studies, and these have generally shown no difference in biochemical outcomes between the two modalities [1-6]. Based on these studies, some have suggested that RRP is the superior treatment of choice, particularly for younger patients, with the reasoning partially being that radiation can often be given after RRP but surgery after full dose radiation is fraught with difficulty [7]. However,

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the generalizability of these data to all patient populations is unclear. While in the radiation literature, race does not appear to be a significant predictor for biochemical recurrence [8,9], the surgical literature has suggested that African American (AA) patients have more aggressive disease than indicated by current National Comprehensive Cancer Network (NCCN) risk stratification criteria with associated poorer outcomes than expected [10].

In this study, we sought to analyze the outcomes of men who underwent treatment with RRP +/– salvage RT or high dose definitive RT (minimum dose of 7,560 cGy) +/– androgen deprivation at the New York Harbor Department of Veterans Affairs. At our institution, the patient population is more racially diverse with a higher representation of AA patients (60%) than in previously reported studies. In addition, we uniquely followed them through their salvage RT and sought to determine its impact on the biochemical control endpoints.

Materials and Methods

After approval by our Institutional Review Board, we retrospectively analyzed the charts of patients who underwent either RRP or RT for localized prostate cancer. From 2003–2010 there were 251 patients who underwent RRP and an additional 507 patients who underwent RT. Of those, 38 RT patients were excluded due to receiving a radiation dose of less than 7,560 cGy. This left 251 patients in the RRP group and 469 patients in the RT group as the subject of this analysis. Patients who received surgery followed by adjuvant RT were still included in this analysis as we sought to analyze their outcomes even with the presence of adjuvant or salvage radiation treatments.

The surgery patients underwent an open radical retropubic prostatectomy +/– bilateral pelvic lymph node dissection. The patients receiving definitive RT received radiation doses of 7,560–8,100 cGy using techniques previously described [11]. Briefly, the techniques evolved over time from a multifield three-dimensional conformal treatment (3D-CRT) (2003–2006) to intensity-modulated radiation therapy (IMRT) without image guidance (2007–2009), to finally IMRT with daily megavoltage cone-beam CT scan (2010). Generally speaking, the whole pelvis was treated for patients with high risk (HR) disease only, followed by a boost to the prostate. For 3D-CRT plans, a margin of 1.5 cm was placed around the clinical target volume to make the planning target volume, allowing additional room for penumbra. For IMRT plans, an 8-mm margin was placed all around the clinical target volume, with the exception of posteriorly where the margin was 5 mm.

Similarly, the patients who received adjuvant or salvage radiation therapy were treated using 3D-CRT earlier in this series, which were then switched over to IMRT, mirroring the definitive radiation therapy techniques using techniques previously described [12]. The clinical target volumes generally included the caudal vas deferens superiorly, penile bulb inferiorly, obturator internus muscles laterally, and the posterior aspect of the pubic symphysis and posterior 2 cm of bladder wall anteriorly. When 3D-CRT was used, a 1.5-cm margin was placed around the clinical target volume. When IMRT was used, an 8-mm margin was placed all around the clinical target volume. The radiation fields were generally limited to the prostate bed and the median radiation dose was 7,020 cGy (range, 6,380 to 7,020 cGy).

In regards to androgen deprivation (ADT), the radiation patients generally received at least two years of androgen deprivation for the HR patients and 6 months of ADT for the intermediate risk (IR) patients. The precise length of the hormone treatments were determined by the treating physician. When ADT was used, it was generally administered for two months neoadjuvantly prior to starting the radiation treatments. Surgical patients did not receive ADT as part of their definitive treatment course.

After completion of their treatments, patients generally had their prostate specific antigen (PSA) examined every 3–6 months for the first two years followed by yearly PSA checks. The definition for biochemical failure in the surgical patients was a PSA of ≥0.2 ng/mL followed by a repeat measurement higher than 0.2 ng/mL or the initiation of salvage treatment. Patients who were referred for adjuvant RT, defined as being referred for RT despite there being no evidence of biochemical failure, were not counted as biochemical failures unless their PSA subsequently rose above 0.2 ng/mL.

The definition of biochemical failure for the RT patients was nadir + 2 ng/mL or the initiation of androgen therapy. For patients who ultimately underwent salvage RT, we used the same definition for biochemical failure as was used in the surgical patients. PSA relapse was recorded based on the date of surgery or the date radiation treatments were completed. For those receiving adjuvant or salvage RT, PSA relapse was still recorded based on the date that their initial surgery completed.

Survival data and data regarding distant control were also gathered. If the cause of death was unknown and the patient was known to have uncontrolled or metastatic disease at the time of death, it was recorded in our database as a prostate cancer related death. PSA relapse, distant control (distant

metastatic-free survival [DMPFS]), PCSS, and overall survival (OS) were analyzed using the Kaplan-Meier method and compared using the log-rank test. Patients were divided into risk groups based on NCCN criteria [13]. The surgical patients were placed into their NCCN risk group based on their clinical presentation and their risk group was not impacted by the pathologic data. Univariate and multivariate Cox regression modeling was performed to determine the impact of covariates on biochemical and distant control. Statistical analysis was performed using SPSS ver. 21.0 (IBM Inc., Armonk, NY, USA) and statistical significance was achieved with a p-value ≤ 0.05.

Result

1. Patient characteristics
The median follow-up was 70 months (range, 11 to 127 months) for the RT patients and 69 months (range, 13 to 135 months) for the RRP patients. For the RT group, 96.3% of the patients were followed for at least 2 years and for the RRP group 96.8% of patients were followed for a minimum of two years. Details regarding the patient characteristics and comparisons between the two groups are available in Table 1. Men who received RRP tended to be younger, have a lower PSA value, lower Gleason score and were generally of lower risk disease compared to the RT patients. In addition, men who received RRP were more likely to have T1c disease than those who received RT.

None of the RRP patients received neoadjuvant ADT. In contrast, ADT was used for 194 patients (41.4%) in the RT group. Specifically, 4.1% of the low risk (LR) patients, 30.5% of the IR patients, and 88.9% of the HR patients received a course of ADT neoadjuvantly, concurrently and/or adjuvantly. The median length of androgen deprivation was 6 months for IR patients (interquartile range [IQR], 6 to 18 months) and 24 months for HR patients (IQR, 22 to 28 months). There were no significant differences in race between the two groups. The median RT dose was 7,560 cGy. Most patients (62%) underwent 3D-CRT, with the rest being treated with IMRT

Table 1. Summary of patient characteristics

	RRP group	RT group	p-value
Age (yr)	61 (57–64)	70 (62–75)	<0.001[a]
Race			
White	81 (32.2)	134 (28.6)	0.59
African American	149 (59.4)	293 (62.5)	
Hispanic	21 (8.4)	42 (9.0)	
Clinical T-stage			<0.001
T1c	239 (95.2)	345 (73.6)	
T2a-c	12 (4.8)	105 (22.4)	
T3a-b	0 (0)	19 (4.1)	
PSA (ng/mL)			<0.001
0–10	207 (82.5)	307 (65.5)	
10.1–20	31 (12.4)	108 (23.0)	
>20	13 (5.2)	54 (11.5)	
Gleason score			<0.001
≤6	117 (46.6)	164 (35.0)	
7	113 (45.0)	204 (43.5)	
≥8	21 (8.4)	101 (21.5)	
NCCN risk group			<0.001
Low	108 (43.0)	123 (26.2)	
Intermediate	115 (45.8)	203 (43.3)	
High	28 (11.1)	143 (30.5)	
Androgen deprivation			<0.001
No	251 (100)	275 (58.6)	
Yes	0 (0)	194 (41.4)	

Values are presented as median (interquartile range) or number (%).
RRP, radical retropubic prostatectomy; RT, external beam radiation therapy; PSA, prostate specific antigen; NCCN, National Comprehensive Cancer Network.
[a]Mann-Whitney test.

(38%).

A total of 17 patients who underwent RRP subsequently received adjuvant RT (6.8%). This was based on the discretion of the referring urologist but was generally due to the presence of pathologically aggressive features, such as extensive positive margins along with extracapsular or seminal vesicle invasion. An additional 36 patients ultimately received salvage RT (14.3%). Of the 36 patients who underwent salvage RT, 21 remained NED at last follow-up.

2. Biochemical control

1) Low risk: The 6-year biochemical control rates were 90.3% for the RT group and 85.6% for the RRP group (p = 0.23). There were 12 biochemical failures in the RT group and 17 failures in the RRP group. Nine of the RRP patients received salvage radiation therapy and 6 of these remained NED after their salvage treatments. Therefore, the 6-year post-salvage biochemical control rate in the RRP group was 90.9%. This was not significantly different from the 90.3% biochemical control in the RT group (p = 0.84).
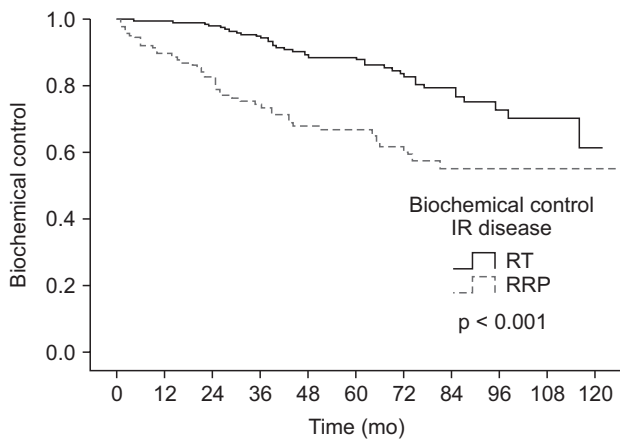
2) Intermediate risk: The 6-year biochemical control rates were 82.6% for the RT group and 59.7% for the RRP group (p < 0.001) (Fig. 1). There were 37 biochemical failures in the RT group and 42 biochemical failures in the RRP group. Twenty one of the 34 RRP patients underwent salvage RT and of these 14 remained biochemically NED. Therefore, their 6-year post-salvage biochemical control was 74.0%. When comparing this to the RT patients there was no longer a significant difference between the two groups (p = 0.06) (Fig. 2).

3) High risk: The 6-year biochemical control rates were 67.4% for the RT group and 41.3% for the RRP group (p < 0.001). There were 35 biochemical failures in the RT group and 15 biochemical failures in the RRP group. Six of the 15 RRP patients who had a biochemical failure underwent salvage RT and of these 1 remained biochemically NED. Therefore, their 6-year post-salvage biochemical control was 43.1% and remained statistically inferior to the biochemical control rates in the RT group (p < 0.001). A summary of the biochemical control rates are available in Table 2.
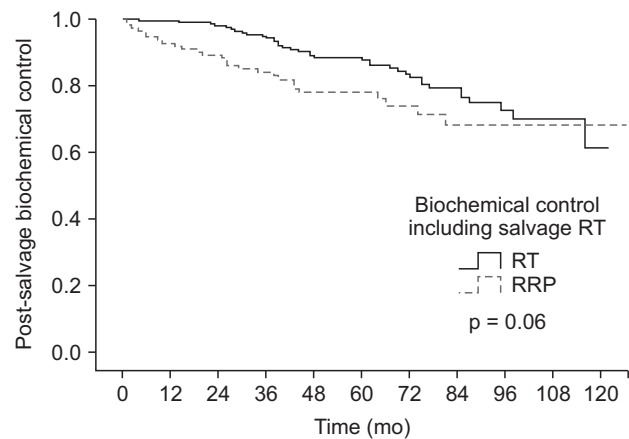

Fig. 1. This figure depicts the biochemical control rates between the RT and RRP patients with intermediate risk (IR) disease. RT, external beam radiation therapy; RRP, radical retropubic prostatectomy.

Fig. 2. This figure depicts the biochemical control rates between the RT and RRP patients (including post-salvage radiation) with intermediate risk disease. RT, external beam radiation therapy; RRP, radical retropubic prostatectomy.

Table 2. Summary of 6-year biochemical control rates with and without salvage radiation therapy

6-yr biochemical control rate	RT group (%)	RRP group (%)	p-value
Low risk	90.3	85.6	0.23
Low risk including salvage radiation	90.3	90.9	0.84
Intermediate risk	82.6	59.7	<0.001
Intermediate risk including salvage radiation	82.6	74.0	0.06
High risk	67.4	41.3	<0.001
High risk including salvage radiation	67.4	43.1	<0.001

RRP, radical retropubic prostatectomy; RT, external beam radiation therapy.

2. Distant control

There were a total of 27 distant failures, 17 in the RT group (3.6%) and 10 in the RRP group (4.0%). For the RT group, the actuarial rate of distant metastases was 0.8% for the LR patients, 2% for the IR patients, and 8.4% for the HR patients. For the RRP group, the actuarial rate of distant metastases was 0% for the LR patients, 5.2% for the IR patients, and 14.3% for the HR patients. For those with IR disease the 6-year DMPFS was 98.3% in the RT group and 95.3% in the RRP group (p = 0.24). For those with HR disease, the 6-year DMPFS was 91.8% in both groups (p = 0.62).

3. Comparison for intermediate risk excluding hormone usage

In order to account for the potential impact of hormone usage on delaying biochemical failures in the RT group, we separately compared the outcomes of patients receiving EBRT alone versus RRP for those with IR disease. For IR disease, there were 141 patients in the RT group and 115 patients in the RRP group. The 6-year biochemical control rates were 79.1% for RT compared to 59.7% for RRP (p = 0.003). After including salvage radiation treatments, the 6-year biochemical control in the RRP group improved to 75.9% and was no longer significantly different from the RT group (p = 0.79). The 6-year DMPFS was 97.6% for the RT group compared to 95.3% in the RRP group (p = 0.29).

4. OS and PCSS

Likely reflecting the age differences at time of treatment, fewer

RT patients were alive at last follow-up. Of the 469 RT patients, 358 were alive at last follow-up (76.3%). Prostate cancer was the cause of death in 10 patients (2.1%). Of the 251 RRP patients, 225 were alive at last follow-up (89.6%). Prostate cancer was the cause of death in 3 patients (1.2%). The 6-year OS was 80.3% in the RT group and 89.8% in the RRP group (p < 0.001). However, the 6-year PCSS was 98.3% in the RT group and 99.0% in the RRP group (p = 0.28). For patients with IR or HR disease, the 6 year PCSS was 97.7% for the RT group and 98.1% for the RRP group (p = 0.58).

5. Univariate and multivariate analyses

Univariate and multivariate analyses were performed analyzing both the initial biochemical response to treatment as well as the biochemical control including salvage radiation therapy. For both analyses, increasing NCCN risk group was associated with worse biochemical control on both univariate and multivariate analysis, while receipt of radiation was associated with improved biochemical control on multivariate analysis. The only other significant factor was increasing age on the post salvage control, which was associated with worse biochemical control. Tables 3 and 4 provide more detailed information.

Univariate and multivariate analysis was also performed to study the effect of covariates on distant control. On multivariate analysis both IR and HR disease were associated with an increased risk for distant metastases (hazard ratio [HR], 8.28; 95% confidence interval [CI], 1.05 to 65.5; p = 0.04 and HR, 26.4; 95% CI, 3.37 to 206.9; p = 0.002, respectively). There

Table 3. Univariate and multivariate analysis of biochemical control

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (continuous)	1.00 (0.98–1.02)	0.82	1.01 (0.99–1.04)	0.22
Year of treatment (continuous)	1.07 (0.99–1.16)	0.10	1.02 (0.94–1.11)	0.60
Race				
Caucasian	1		1	
Hispanic	1.14 (0.61–2.14)	0.67	1.23 (0.65–2.29)	0.53
African American	1.34 (0.93–1.92)	0.12	1.37 (0.95–1.98)	0.09
NCCN risk group				
Low	1		1	
Intermediate	2.28 (1.49–3.50)	<0.001	2.54 (1.64–3.92)	<0.001
High	3.01 (1.90–4.76)	<0.001	4.29 (2.63–6.99)	<0.001
Treatment				
RRP	1		1	
RT	0.54 (0.40–0.74)	<0.001	0.35 (0.24–0.51)	<0.001

HR, hazard ratio; CI, confidence interval; NCCN, National Comprehensive Cancer Network; RRP, radical retropubic prostatectomy; RT, external beam radiation therapy.

Table 4. Univariate and Multivariate analysis of biochemical control including post salvage radiation

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (continuous)	1.02 (1.00–1.04)	0.09	1.02 (0.99–1.05)	0.06
Year of treatment (continuous)	1.11 (1.01–1.22)	0.03	1.08 (0.98–1.18)	0.12
Race				
Caucasian	1		1	
Hispanic	1.21 (0.63–2.34)	0.56	1.22 (0.63–2.34)	0.56
African American	1.25 (0.85–1.85)	0.26	1.29 (0.87–1.92)	0.21
NCCN risk group				
Low	1		1	
Intermediate	4.15 (2.51–6.88)	<0.001	2.49 (1.52–4.08)	0.002
High	4.15 (2.51–6.88)	<0.001	4.75 (2.79–8.09)	<0.001
Treatment				
RRP	1		1	
RT	0.88 (0.62–1.25)	0.88	0.52 (0.34–0.80)	0.002

HR, hazard ratio; CI, confidence interval; NCCN, National Comprehensive Cancer Network; RRP, radical retropubic prostatectomy; RT, external beam radiation therapy.

were no differences based on the receipt of RRP or RT (HR, 0.44; 95% CI, 0.16 to 1.19; p = 0.10).

In order to account for the potential impact of androgen deprivation usage in the RT group biasing these results, we performed a separate multivariate analysis excluding any patients who received androgen deprivation. Treatment with RT remained strongly associated with improved biochemical control (HR, 0.51; 95% CI, 0.34 to 0.78; p = 0.002). Similarly, IR disease (HR, 2.74; 95% CI, 1.77 to 4.24; p < 0.001) and high risk disease (HR, 6.22; 95% CI, 3.54 to 10.94; p < 0.001) remained significant predictors for decreased biochemical control.

Discussion and Conclusion

In this retrospective study from a patient population that consists of approximately 60% AA men, we found that treatment with either RRP +/– salvage RT or RT +/– androgen deprivation yielded similar DMPFS and PCSS at 6 years. OS was significantly worse in those receiving RT, though this may be reflective of the 9-year age difference at the time of their treatment. There was a difference between the two treatment approaches regarding biochemical control, with treatment with RT being associated with improved biochemical control for those with IR and HR disease. However, for those with IR disease, treatment with salvage RT resulted in the biochemical control being no longer significantly different. We also separately compared IR risk patients between those receiving RT alone (without ADT) and RRP and found that the results

were unchanged.

The issue of which treatment is superior for prostate cancer is one which has been discussed at length in the medical literature. Some more modern retrospective studies have compared the biochemical outcomes between RRP and dose escalated RT and most have found no differences between the two for LR or IR disease. In a study by Aizer et al. [5] comparing 204 RRP patients with 352 RT patients, there were no significant differences in biochemical control between the two groups for both IR and LR disease. Only for HR disease did treatment with RT appear to be superior. In a recent study by Vassil et al. [6] with >5 years follow-up similarly found no differences between RT and RRP for IR disease. Several other studies have reported similar results [2,3]. However, all of these aforementioned studies either do not report their race distribution or have <20% of AA as their patient population, as compared to approximately 60% patient population of AA in our study. In addition, prior studies generally exclude patients who undergo adjuvant or salvage RT after RRP, whereas we have included them in order to retrospectively analyze what actually happens to these patients.

Though somewhat conflicting, most reports suggest that that AA race is a significant predictor of aggressive disease in patients undergoing surgery [10,14-19], though not for RT [8,9]. Therefore, the predominance of AA patients in our population may account for differences in outcome reporting between our findings and the other aforementioned reports. For example, our findings regarding the apparent biochemical superiority of definitive radiation for intermediate and HR prostate cancer

patients may be somewhat unique to our predominantly AA population.

There are a variety of limitations to our study, which are inherent to its retrospective nature as well as highlighting the difficulties when comparing these modalities. First, the surgical patients tended to be younger and have lower risk disease compared to the RT patients. In addition, 40% of the RT patients were treated with androgen deprivation compared to none in the RP group, which likely improved the biochemical control rates or at least delayed biochemical failure to the point where we have not yet detected it. However, on multivariate analysis excluding hormone usage, the use of RT remained strongly associated with improved biochemical control with a hazard ratio of 0.51 (95% CI, 0.34 to 0.78; p = 0.002). Third, the definitions of biochemical control differ significantly between the surgical and radiation literature. In terms of absolute PSA measurements, the surgical criteria for failure are clearly more stringent. However, we used the accepted surgical definition for failure recommended by the American Urological Association [20] as well as the accepted radiation definition for failure by the American Society for Radiation Oncology criteria [21]. Finally, although we have noted differences in biochemical control between the two modalities, we were unable to detect any significant differences in DMPFS or PCSS between the two groups.

In this study there were no differences between treatment with RRP +/– salvage RT or RT +/– androgen deprivation in regards to DMPFS or PCSS. While OS was lower in those receiving RT, this is likely a reflection of being a median of 70 years at the time of their treatment, compared to a median of 61 years for those receiving RRP. Biochemical control endpoints were equivalent or better in those being treated with RT compared to RRP when using their respective definitions. Longer follow-up is needed to determine whether any of the biochemical control differences noted will translate to differences in clinical outcomes.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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