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Concurrent androgen deprivation therapy during salvage prostate radiotherapy improves treatment outcomes in high risk patients

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Abstract

Purpose—To determine if concurrent androgen deprivation therapy (ADT) during salvage radiotherapy (RT) improves prostate cancer treatment outcomes.

Methods & Materials—A total of 630 post prostatectomy patients were retrospectively identified that were treated with 3-D conformal RT. Of these, 441 were found to be treated for salvage indications. Biochemical Failure (BF) was defined as PSA $\geq$ 0.2 ng/mL above nadir with another PSA increase or the initiation of salvage ADT. Progression-free survival (PFS) was defined as the absence of: BF, continued PSA rise despite salvage therapy, initiation of systemic therapy, clinical progression or distant failure. Multivariable-adjusted Cox proportional hazards modeling was performed to determine which factors predict PFS.

Results—Low, intermediate, and high risk patients made up 10%, 24%, and 66% of patients, respectively. Mean RT dose was 68Gy. Twenty-four percent of patients received concurrent ADT (HRT). Regional pelvic nodes were treated in 16% of patients. With a median follow-up of 3 years, the 3-yr PFS was 4.0 yrs for HRT vs. 3.4 yrs for non-HRT patients ($p=0.22$). Multivariable analysis demonstrated that concurrent ADT ($p=0.05$), Gleason score ($p<0.001$), and pre-RT PSA ($p=0.03$) were independent predictors of PFS. When stratified by risk group, the benefits of ADT ($HR = 0.65$, $p=0.046$) was significant only for high risk patients.

Conclusions—This retrospective study has demonstrated a PFS benefits of concurrent ADT during salvage prostate RT. This benefit was observed only in high risk patients.

Keywords

Prostatic neoplasms; prostate-specific antigen; radiotherapy; androgens, adjuvant radiotherapy; salvage therapy

Introduction

Approximately 20–40% of patients treated with prostatectomy for prostate cancer have evidence of PSA progression after long-term follow up^{1–3}. After PSA progression the median time to the development of metastatic disease is 8 years⁴. The subsequent risk of prostate cancer (PCA) death will be dependent on Gleason score, PSA doubling time, and

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failure-free interval⁵. In order to avoid PCA progression and PCA mortality after PSA failure, salvage RT is frequently employed. At this time there are no randomized controlled studies examining the impact of salvage RT, however a large multi-institutional retrospective analysis strongly supports its implementation early after PSA failure⁶. Unfortunately, successful salvage is not always achieved. Thus there is an interest in enhancing salvage therapeutic treatments with the use of systemic therapies.

Although there are several randomized trials demonstrating the benefit of adding ADT to RT for select patients with intact PCA, no such trials exists in the post prostatectomy setting. While several retrospective studies exist, they have demonstrated conflicting results⁷⁻⁹. Fortunately, there are two prospective randomized trials, RTOG 96-01 and the MRC RADICALS trial, which should shed light on this issue. However, these results may not be available for some time. Thus, we retrospectively examined the impact of ADT in a single institution cohort of patients treated with salvage RT.

Methods and Materials

Patient selection

Between 1987 and 2006, 630 patients with post prostatectomy cancer were treated with 3-D conformal RT at the University of Michigan Cancer Center Department of Radiation Oncology and its affiliates. With IRB approval, we retrospectively reviewed the medical records of the subset of patients treated with salvage RT that met our search criteria. Salvage patients were defined as those with a PSA > 0.2 ng/mL before the start of post prostatectomy RT. We excluded 109 patients treated with adjuvant RT as only 25 were treated with ADT. Required data for inclusion in this study included documentation of: pathologic T-stage, initial presurgical PSA (PSA), initial preradiation PSA (iPSA), Gleason Score (GS), and 3-D conformal field design. Exclusion criteria included the presence of a second primary pelvic malignancy, known lymphatic metastases, non-pelvic metastatic disease, treatment of para-aortic fields, the use of chemotherapy, as well as history of previous brachytherapy. This selection process eliminated 62 patients. We identified 441 patients that met our criteria. All patients had a pretreatment evaluation that included history, physical, and if clinically indicated bone scan/diagnostic CT. We risk stratified patients using a three-tier scheme using presurgery PSA combined with pathological T-stage and post-operative GS. Low risk patients are defined as having pT2a, GS ≤ 6 and PSA ≤ 10 ng/mL. High risk patients are defined as pT3 or higher, GS ≥ 8 or PSA ≥ 20 ng/mL. All others are considered intermediate risk.

Patient treatment

All patients were treated with CT-based, 3-D conformal RT. The mean prostate bed dose to the International Commission on Radiation Units and Measurements point was 68Gy (range 61–76 Gy). Currently patients are treated on a sliding RT dose scale: preradiation iPSA < 0.4 ng/mL, 0.4–1 ng/mL, and > 1 ng/mL were treated with 64.8Gy, 68.4Gy, and 70.2Gy respectively in 1.8Gy fractions. However, due to practice pattern variations this cohort was treated with mean doses (SD) of 66.0Gy (2.1), 67.2Gy (2.0), and 68.1Gy (2.6), respectively. Regional nodes were treated in 18% of patients. The typical pelvic field was treated to 45Gy. The use of mini vs. whole pelvis radiation was at the discretion of the treating physician. The use of ADT and nodal RT were at the discretion of the treating physician unless the patient was part of a treatment protocol. There were 21 (4.5%) patients who received both ADT and pelvic nodal RT.

Follow-up and end points

The median follow-up was 3 years. Patients were seen at regular intervals, every 3 to 6 months for physical examinations and serial PSA measurements. Radiologic evaluation was performed if clinically indicated. We utilized a BF definition of PSA ≥ 0.2 ng/mL with another increase or the initiation of salvage ADT. The censoring date for patients free of BF was the last date of PSA follow-up. PFS was based on the Stephenson et al. definition as the absence of BF, continued rise in PSA despite salvage therapy, initiation of systemic therapy, clinical progression, or distant failure⁶. PFS was defined starting from the end of RT.

Statistical analysis

Standard bivariate statistics including frequencies and means are reported for patient, tumor, and treatment factors. The association between concurrent ADT use during salvage RT and these factors was assessed using Fisher's exact test for categorical variables and the two-sample t-test assuming unequal variance for continuous variables. Kaplan-Meier methods were used to produce PFS estimates, as well as the median follow-up based on reverse censoring. The effect of ADT use during salvage RT on PFS was estimated using a Cox proportional hazards model that adjusted for the patient characteristics of interest. A backwards model selection procedure was employed, where the least significant variable was eliminated sequentially until only statistically significant variables remained in the model. Additionally, it was confirmed that none of the eliminated variables altered the estimate of the ADT effect by more than 10% upon removal. Hazard ratios (HR) and 95% confidence intervals based on the final model are reported, as are results by risk group. Because of a relatively small number of progression events that occurred among patients in the low risk group, the low and intermediate risk groups were combined for the analysis. All analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC). A two-sided p-value <0.05 was considered statistically significant.

Results

Patient characteristics

We identified 441 patients that meet our criteria. The median age at diagnosis was 61 years. Ninety percent of patients were Caucasian. ADT was utilized in 24% of patients. Low, intermediate, and high risk patients made up 10%, 24%, and 66% of patients, respectively. The median ADT duration for HRT patients was 11 months (range 0.9–34 months). The median time between surgery and salvage radiation was 2.3 years. The median year of surgery was 1997 and the median year of salvage RT was 2001.

Stratifying patients by ADT use during salvage RT revealed the groups to have similar distributions of GS, presurgery PSA, T-stage, risk group, surgical nodal dissection, extra capsular extension, seminal vesicle invasion, (+) margins, (+) biopsy before salvage RT, mean RT dose, regional nodal RT, race, age at diagnosis. However, HRT users tended to have more patients with iPSA before salvage RT ≥ 1 ng/mL, 56% vs. 37% ($p=0<0.0001$). In addition, HRT users were more likely to be treated during the late 1990's ($p<0.007$). The clinical and treatment characteristics for the each cohort are shown in Table 1.

Progression-free survival

We documented 196 total failures. Of these 35% were due to PSA ≥ 0.2 ng/mL above nadir followed by another increase while 59% were due to a continued PSA rise despite salvage therapy. In addition, 1% had distant failures and 5% were empirically started on ADT. There were no patients with local clinical or biopsy proven progression.

The median PFS of HRT users vs. non-HRT was 4.4 yrs and 3.4 yrs respectively ($p=0.22$). The estimated 3-year PFS rates were 63% vs. 55%, with 95% confidence intervals (52% – 72%) and (49% – 61%), respectively (Figure 1). When stratified by risk groups the results did not achieve significance (Table 2).

Multivariable analysis

Based on the Cox proportional hazards model, concurrent ADT use during salvage RT resulted in an estimated 30% lower hazard of progression relative to non-HRT, adjusted for Gleason score, seminal vesicle invasion, pelvic nodal RT, and RT dose ($HR = 0.70$, $p=0.05$). Increased Gleason score ($p<0.001$) and pre RT PSA ($p=0.03$) were associated with decreased PFS. These results did not significantly differ if the model included year of treatment or pre-RT PSA (results not shown). When patients were segregated by risk group, the advantages of concurrent ADT use ($HR = 0.65$, $p=0.04$) was limited to high risk patients. However, GS was predictive for all risk groups (Table 3).

Discussion

Approximately 70,000 patients undergo curative intent prostatectomies in the U.S.¹⁰. Of these, 20–40% have evidence of PSA progression after long term follow-up^{1–3}. While three randomized controlled trials support the use of adjuvant postoperative RT for unfavorable pathologic features,^{11–13} there has been a hesitancy to accept this data due to a concern of overtreating patients¹⁴. These hesitations can lead to patients not being referred for consultation until they have demonstrated PSA progression. Thus there is a need to optimize salvage therapeutic approaches.

At this time there are no randomized controlled trials examining the impact of salvage RT on PCA outcomes. However, a large multi-institutional retrospective analysis strongly supports its implementation early after PSA failure⁶. In addition, a recent nomogram has been developed to determine the efficacy of salvage RT in the post prostatectomy setting. Variables such as iPSA, Gleason score, margins, PSA-DT, ADT before or during salvage RT were found to be predictive of PFS.¹⁵

For select groups of patients with intact PCA treated with curative intent external beam RT, a number of trials have established a benefit of adding ADT to RT. These studies have demonstrated improvements in local control, metastatic-free interval, and overall survival^{16–21}. Unfortunately, little data exist examining the benefit of ADT in salvage post prostatectomy RT patients.

A number of small retrospective studies have demonstrated a benefit in biochemical control with the addition of ADT to adjuvant/salvage RT^{7–9,22,23}. In addition to enhanced biochemical control, the Stanford series also noted a trend towards improved survival²³. Two of the other studies demonstrated benefits in biochemical control however these studies were biased by the use of indefinite ADT^{8,24}. In contrast, two other studies found no benefit of ADT in the salvage setting^{9,25}. However, one of these used neoadjuvant ADT without concurrent administration during RT⁹. Fortunately, there are two prospective randomized trials which should shed light on this issue. However, these results may not be available for some time.

At this time RTOG 96-01 has completed accrual while the MRC RADICALS trial has yet to open. RTOG 96-01 randomized 840 patients with post prostatectomy BF to salvage RT alone or with 2 yrs ADT. The primary endpoint is overall survival. Results may become available in 2008 (RTOG web site). In Europe and Canada, the MRC is planning to implement a RADICALS trial that has 2 randomization steps examining the impact of both

post radical prostatectomy RT (adjuvant vs. salvage) as well as utility & duration of ADT (none vs. 6 vs. 24 months). With an accrual goal of approximately 4,000 the primary endpoint is cause-specific survival²⁶

The potential benefits of ADT use with salvage RT must be carefully weighed against any potential treatment related toxicities. Well established systemic complications from ADT include endocrine dysfunction, osteoporosis, metabolic syndrome, and cardiac morbidity^{29,30}. ADT may also increase the risk of local RT related side effects. In the intact prostate setting >6 months ADT during RT was associated with an increased 5 year risk of Grade 2 late rectal toxicity at 26% vs. 18% for shorter duration ADT or non users ($p=0.017$). In addition, ADT may contribute to increased late GU toxicity appears to^{31,32}.

Our own series supports a PFS benefit of ADT during salvage RT. Multivariable analysis demonstrated that concurrent ADT during RT ($p=0.05$) improved PFS. When patients were segregated by risk group, the advantages of concurrent ADT use ($p=0.046$) was limited to high risk patients only. In addition, we observed tumor features associated with inferior outcomes included: Gleason score ≥ 7 relative to <7 ($p<0.001$) and pre RT PSA ($p=0.03$).

Our study has many of the limitations associated with a retrospective study design. Although we attempted to control for many potential patient, tumor, and treatment variables that could impact PFS, the retrospective nature prevents us from accounting for unknown confounders. Secondly, due to limitations in our database we did not have enough adjuvant patients to analyze and thus cannot extrapolate our data to those patients. Thirdly the range of duration of ADT use during salvage RT varied. During this study the median duration of ADT was 11 months. However, the optimal duration in this setting is unknown. The adjuvant trials typically used 6 months. In contrast, the intact prostate trials for high risk patients have included ADT durations of up to 3 years. Whether such prolonged ADT use would be efficacious for postprostatectomy patients warrants further study. Finally, our short follow-up precludes conclusions about long term PFS differences. Thus, these limitations lead us to emphasize that these findings should be considered preliminary and in need of prospective validation and longer follow-up. The pending results of RTOG 96-01 and MRC RADICALS trial will hopefully give a definitive answer to this current treatment controversy.

Conclusions

This retrospective study has demonstrated that concurrent ADT during salvage RT is associated with a PFS benefits in high risk patients. In addition, increased Gleason score, and increased pre RT PSA during salvage prostate RT are associated with inferior PFS. As we await the results of two prospective randomized controlled trials, this data emphasizes the potential benefit of concurrent ADT use during salvage RT to improve treatment outcomes.

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No. at Risk:

ADT	115	85	54	38	22	9
No ADT	353	220	148	98	65	40

Figure 1. Kaplan-Meier estimates of progression-free survival (PFS) by ADT status ($p = 0.16$ from log-rank test)

Table 1

Patient characteristics by ADT status

Characteristic	No. of Patients (%)		<i>p</i> -value*
	ADT During RT (<i>n</i> = 107)	No ADT During RT (<i>n</i> = 334)	
Gleason score			0.18
<7	26 (25)	92 (28)	
7	52 (50)	174 (53)	
>7	27 (25)	61 (19)	
T-stage			0.08
<T2b	20 (19)	94 (28)	
T2b or T2c	18 (17)	52 (16)	
>T2c	67 (64)	188 (56)	
Pre-surgery PSA (ng/mL)			0.97
<10	43 (57)	115 (55)	
10 – 20	19 (25)	61 (29)	
>20	14 (18)	34 (16)	
Pre-RT PSA (ng/mL)			<0.0001
<1	47 (44)	210 (63)	
1 – 2	28 (26)	74 (22)	
>2	32 (30)	50 (15)	
Risk group			0.15
Low	7 (7)	36 (11)	
Intermediate	24 (22)	82 (24)	
High	76 (71)	216 (65)	
Pre-RT lymph node dissection			0.95
No	18 (17)	54 (17)	
Yes	87 (83)	266 (83)	
Extracapsular extension			0.55
No	40 (40)	139 (44)	
Yes	59 (60)	178 (56)	
Seminal vesicle invasion			0.25
No	81 (78)	271 (83)	
Yes	23 (22)	56 (17)	
Surgical margins			0.91
Negative	51 (52)	171 (53)	
Positive	48 (48)	154 (47)	
Post-surgery positive biopsy			0.64
No	105 (98)	330 (99)	
Yes	2 (2)	4 (1)	
Mean RT dose (Gy) (SD)	68 (2.4)	67 (2.3)	0.05
Pelvic nodal RT			0.99

Characteristic	No. of Patients (%)		<i>p</i> -value*
	ADT During RT (<i>n</i> = 107)	No ADT During RT (<i>n</i> = 334)	
No	90 (84)	279 (84)	
Yes	17 (16)	53 (16)	
Year of RT			0.007
1987 – 1991	0 (0)	15 (4)	
1992 – 1996	14 (13)	59 (18)	
1997 – 2001	55 (51)	120 (36)	
2002 – 2006	38 (36)	140 (42)	
Mean age at diagnosis (years) (SD)	60 (6.4)	61 (7.1)	0.77
Race			0.22
Caucasian	98 (92)	284 (88)	
African American/Other	8 (8)	38 (12)	

* *p*-values are from Fisher's exact test for categorical variables and two-sample t-test assuming unequal variances for continuous variables.

Table 2
Estimated median progression-free survival (PFS) in years by ADT status and Risk Group

	ADT During RT			No ADT During RT			Log-rank p-value
	No. with Progression	No. at Risk	Median PFS (years) (95% CI)	No. with Progression	No. at Risk	Median PFS (years) (95% CI)	
Overall	43	107	4.0 (3.3 – 5.9)	153	334	3.4 (2.5 – 4.1)	0.22
Risk Group [*]							
Low/Intermediate	12	31	5.7 (1.8 – 5.9)	43	118	4.2 (3.4 – 6.5)	0.91
High	31	76	3.8 (2.9 – ∞)	110	216	3.1 (2.3 – 3.8)	0.15

* Low risk patients are defined as having T-stage T2a, GS 6 and PSA 10 ng/mL. High risk patients are defined as T3 or higher, GS 8 or PSA 20 ng/mL. All others are considered intermediate risk.

Table 3

Multivariable Cox proportional hazards model for progression-free survival (PFS)

Variable	Overall			Risk Group [*]		
	HR (95% CI)	p-value		Low/Intermediate	High	
ADT During RT		0.05				0.046
No	1.00			1.00	1.00	
Yes	0.70 (0.49 – 1.00)			0.85 (0.43 – 1.68)	0.65 (0.43 – 0.99)	
Gleason score		<0.001				0.003
<7	1.00			1.00	1.00	
7	2.09 (1.42 – 3.07)			2.61 (1.42 – 4.82)	1.79 (1.08 – 2.98)	
>7	2.65 (1.69 – 4.13)			–	2.53 (1.48 – 4.33)	
Pre-RT PSA		0.03				0.16
<1	1.00			1.00	1.00	
1 – 2	1.36 (0.96 – 1.92)			1.36 (0.70 – 2.67)	1.38 (0.92 – 2.07)	
>2	1.62 (1.09 – 2.40)			2.03 (0.94 – 4.37)	1.44 (0.90 – 2.30)	

* Low risk patients are defined as having T-stage T2a, GS 6 and PSA 10 ng/mL. High risk patients are defined as T3 or higher, GS 8 or PSA 20 ng/mL. All others are considered intermediate risk.