Does neoadjuvant hormone therapy improve outcome in prostate cancer patients receiving radiotherapy after radical prostatectomy?

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Purpose: *To assess outcome and predictive factors in men with prostate cancer who receive post radical prostatectomy (RP) radiotherapy (RT) either in the adjuvant or salvage setting, with or without neoadjuvant androgen deprivation therapy (NADT).*

Methods: *A retrospective analysis was performed on 175 patients with clinically localized prostate cancer treated with RP who subsequently received RT (dose range 50 Gy-68 Gy). Twenty-two patients received adjuvant RT (ART), 57 received NADT + ART, 15 received salvage RT (SRT), and 81 received NADT + SRT. Outcome was assessed by biochemical disease free survival (BDFS), prostate cancer specific survival and overall survival (OS).*

Results: *Although BDFS favored patients who received NADT with 5 year rates of 67%, 80%, 27% and 62% for the ART, NADT + ART, SRT, and NADT + SRT groups respectively; this was not a significant predictor on multivariable analysis. Significant independent predictive factors of improved BDFS were pre-RT PSA ≤ 0.2 ng/ml, low Gleason score and positive surgical margins. Age and Gleason score were independent predictors of OS.*

Conclusions: *Pre-RT PSA is an important predictor of outcome. NADT appears to benefit patients who presented with a pre-RT PSA > 0.2 ng/ml, particularly for patients receiving SRT. NADT can be considered for patients receiving RT after RP who present with a high pre-RT PSA but may not be necessary for patients without. Results of ongoing randomized studies such as RADICALS will also help clarify the role of hormone therapy in conjunction with RT.*

Key Words: prostate cancer, prostatectomy, hormone therapy, radiotherapy, prostate-specific antigen

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Introduction

Although radical prostatectomy (RP) has long been considered an excellent treatment option for men with clinically localized prostate cancer, a non-trivial proportion of men will be faced with unfavorable pathological features following RP such as the presence of extracapsular or seminal vesicle extension, positive surgical margins, or the presence of a high grade cancer. Adjuvant radiotherapy (ART) can be offered to men who have unfavorable risk features following RP. Several randomized studies have demonstrated

an improvement in biochemical control and clinical relapse rates with ART.[1-3] However up to 60% of patients with adverse pathological features will not develop recurrence if untreated.[4-6] There is also a modest increased risk of urinary, bowel and sexual toxicity with postoperative radiotherapy noted from randomized studies. Salvage radiotherapy (SRT) is typically administered to patients who are observed after RP but subsequently present with a rising PSA or local recurrence. Most studies demonstrate a much worse outcome using SRT compared to ART, and particularly when there is a high PSA level (e.g. PSA > 1 ng/ml) at time of radiotherapy.[7] The combination of neoadjuvant androgen suppression therapy (NADT) and RT is a treatment strategy worth considering in the adjuvant or salvage setting particularly for patients with a high PSA. However, the role of ADT has not been established.

The purpose of this retrospective review is to evaluate the role of neoadjuvant ADT (NADT) in combination with ART or SRT and to examine the predictive factors such as PSA that can help select patients more appropriately for use of ADT in combination with RT.

Material and methods

Patient population

One hundred eighty seven men with the diagnosis of localized prostate adenocarcinoma were referred to our institution and received ART or SRT following RP between January 1990 and September 2003. RP consisted of a standard open Walsh retropubic technique. Patients considered for this analysis did not receive hormone therapy initially in conjunction with RP. Sampling of pelvic lymph nodes was at the discretion of the urologist. Patient, disease and treatment characteristics are shown in Table 1. Patients with involved regional lymph nodes at the time of surgery or insufficient follow up (i.e. less than 1.5 years post RT) were excluded from this study, leaving a total of 175 patients for further analysis.

Treatment

Postoperative treatment was at the discretion of the treating oncologist and comprised of ART for unfavorable pathology (e.g. positive margins, seminal vesicle invasion) or non-zero PSA after RP, or SRT for subsequent biochemical or clinical failure. Of the 175 patients reviewed in this study, four treatment groups were identified: 22 ART, 57 NADT + ART, 15 SRT and 81 NADT + SRT.

RT consisted of multifield arrangement, fractionated radiation treatment techniques. A 4 field box technique was used for the majority of patients. Beam energy consisted of high energy photons between 10 to 23 MV for all patients except six who received treatment using Cobalt-60 and one with 4 MV photon beam energy. The beam energy was not available for four patients. Beginning in 1995, all patients were planned using CT simulation and conformal planning techniques. The final target volume included the prostate bed and adjacent periprostatic tissue and a margin for set up variation. The pelvic lymph nodes were not part of the intended target volumes. Treatment was given on a daily basis for 5 days per week. Total dose ranged from 50 Gy to 68 Gy with fraction size ranging from 2.75 Gy to 1.8 Gy. Patients receiving the lower total doses of RT were treated with the larger fraction sizes and vice versa. Dose and fractionation schedule was at the discretion of the radiation oncologist.

Seventy nine percent (138/175) of patients received NADT which included 72 and 84 percent of ART and SRT patients respectively. The use of NADT was at the discretion of the treating radiation oncologist and was generally given to contend with long wait times for RT machines during that era. ADT consisted of various hormone agents including luteinizing hormone releasing hormone (LHRH) agonists, nonsteroidal and steroidal anti-androgens (e.g. Cyproterone) and diethylstilbestrol (DES). The majority received DES or Cyproterone prior to 1995 and after 1995 LHRH agonists with or without anti-androgens were used. The median duration of NADT was 5.7 months (range: 0.7 to 20.7). One hundred one of 138 patients also received concurrent ADT during RT and 65 of these patients received adjuvant ADT after RT was completed. The median duration of adjuvant ADT was 1.9 months. The median total duration of ADT was 8.5 months (range: 0.7 to 22.1).

PSA measurements

PSA values were recorded prior to RP (pre-RP PSA), NADT (pre-NADT PSA) and RT (pre-RT PSA). In patients that received salvage therapy, the pre-salvage PSA was also determined. In patients receiving NADT + SRT, the PSA prior to start of NADT (pre-NADT PSA) was used to define the pre-salvage PSA whereas in patients who received SRT alone, the pre-RT PSA was used to define the pre-salvage PSA. The PSA doubling time (DT) after RP was calculated in patients receiving salvage therapy. DT was calculated using the Memorial Sloan-Kettering Prostate Nomogram (accessed at http://www.mskcc.org/mskcc/html/10088.cfm).

TABLE 1. **Patient, cancer and treatment characteristics**

Treatment group	Sample size	Homogeneity test** p-value	ART (n = 22)	NADT + ART (n = 57)	SRT (n = 15)	NADT + SRT (n = 81)
			% of patients (number)			
Age at diagnosis (years)	175	0.395				
<= 64			50 (11)	42 (24)	47 (7)	57 (46)
> 64			50 (11)	58 (33)	53 (8)	43 (35)
Clinical risk group	151	0.304 (FE)				
Low			23 (5)	15 (8)	31 (4)	26 (16)
Intermediate			63 (14)	50 (27)	38 (5)	53 (33)
High			14 (3)	35 (19)	31 (4)	21 (13)
Pathological risk group*	166	< 0.001 (FE)				
Low			5 (1)	0	7 (1)	0
Intermediate			28 (6)	4 (2) -	7 (1)	43 (32) +
High			67 (14)	96 (53)	86 (13)	57 (43)
Pathological GS*	175	0.095 (FE)				
2-6			36 (8)	23 (13)	53 (8)	32 (26)
7			50 (11)	49 (28)	27 (4)	56 (45)
8-10			14 (3)	28 (16)	20 (3)	12 (10)
Pathological T-stage*	175	< 0.001 (FE)				
T1a-T2a			5 (1)	0 -	7 (1)	12 (10)
T2b			14 (3)	7 (4) -	7 (1)	42 (34)
T3a-T4			82 (18)	93 (53) +	87 (13)	46 (37)
Surgical margins	175	< 0.001 (FE)				
Positive			77 (17)	93 (53) +	60 (9)	49 (40) -
Negative			23 (5)	7 (4) -	40 (6)	51 (41) +
Pre-surgical PSA (ng/ml)	160	0.158 (FE)				
< 10			55 (12)	50 (28)	69 (9)	52 (36)
10-20			36 (8)	34 (19)	0	33 (23)
> 20			9 (2)	16 (9)	31 (4)	15 (10)
Pre-salvage PSA	96	0.986				
<= 1			NA	NA	53 (8)	53 (43)
> 1			NA	NA	47 (7)	47 (38)
Pre-RT PSA	165	< 0.001 (FE)				
<= 0.2			80 (16)	98 (53)	13 (2) -	83 (63)
> 0.2			20 (4)	2 (1) -	87 (13)	17(13) +
PSA DT (months)	72	1.00 (FE)				
<= 10			NA	NA	67 (8)	65 (39)
> 10			NA	NA	33 (4)	35 (21)
NADT duration (months)	138	0.689				
< 4			NA	30 (17)	NA	24 (19)
4-8			NA	44 (25)	NA	49 (40)
> 8			NA	26 (15)	NA	27 (22)
Total ADT duration (months)	138	0.498				
<4			NA	18 (10)	NA	15 (12)
4-8			NA	28 (16)	NA	21 (17)
>8			NA	54 (31)	NA	64 (52)

TABLE 1 (cont'd)

BED (Gray)	175	0.018 (FE)				
< 100 §			95 (21)	91 (52)	67 (10)	78 (63)
>= 100			5 (1)	9 (5)	33 (5)	22 (18)

ART = adjuvant radiation therapy; NADT = neoadjuvant androgen deprivation therapy; SRT = salvage radiation therapy; GS = Gleason score; PSA = prostate-specific antigen; DT = doubling time; BED = biological equivalent dose; NA = not applicable; +,- = large positive, negative contributions to Pearson chi-square test statistic

*Based on radical prostatectomy specimen

§100 Gray BED is equivalent to 60 Gray in 2 Gray fractions using α/β ratio = 3

**Fisher's exact (FE) test for tables with expected cell frequencies < 5; otherwise Pearson's chi-square test

The median pre-RP PSA was 9.2 ng/ml (range: 0.6 to 142) for the entire group. The median pre-RT PSA was 0.1 ng/ml (range: 0.01 to 18.8). For patients receiving SRT or NADT + SRT, the median pre-salvage PSA was 0.91 ng/ml (range: 0.07 to 24) and the median pre-RT PSA was 0.02 ng/ml (range: 0.01 to 3.6). There were five patients in the NADT + SRT group who did not have pre-RT PSA values available. In the NADT + SRT group, 83% (63/76) achieved pre-RT PSA levels 0.2 ng/ml or less with the use of NADT including five men who had pre-NADT PSA levels of greater than 5 ng/ml. The median PSA DT for salvage patients was 8.2 months (0.9 to 43.3).

Statistical considerations

Outcomes measured were biochemical disease free survival (BDFS), prostate cancer disease specific survival (DSS) and overall survival (OS). Time to events was measured from end of RT. Biochemical failure was defined as a rising serum PSA level ≥ 0.4 ng/ml[8] in the absence of clinically detectable persistent disease or recurrence (e.g. negative imaging and with negative digital rectal examination or no biopsy proven recurrence) or the initiation of palliative hormone therapy for clinical recurrence in the absence of PSA follow up data in two patients. The date of the first serum PSA ≥ 0.4 ng/ml after RT was defined as the date of biochemical failure. DSS was defined as death due to prostate cancer. Patients were advised to have PSA tests every 3 months for the first 2 years and then semi-annually post treatment.

The following candidate factors were analyzed for their possible influence on BDFS, DSS and OS for all patients: age, clinical T stage (using American Joint Committee on Cancer 1997 staging system), biopsy Gleason score (GS), pathological T stage, pathological GS, seminal vesicle involvement, surgical margin status, clinical risk group,[9] pathological risk group, pre-RP PSA, pre-RT PSA, PSA DT, treatment type (NADT + SRT, SRT, NADT + ART, ART), RT biological equivalent dose (BED), NADT duration and total ADT duration. RT dose was converted to BED using the equation BED = total dose (1 + (fraction size / α/β ratio)) using an α/β ratio of 3 before making statistical comparisons between different dose fractionation schedules used.[10,11] The analysis was repeated for patients receiving salvage therapy and for patients receiving NADT + SRT. Pre-salvage PSA was included in the set of variables for these latter two analyses.

Pearson's chi-square test of homogeneity and Fisher's exact test were used to evaluate the distribution of predictive factors between treatment groups in Table 1. Kaplan-Meier survival curves and log-rank tests of homogeneity were used to evaluate the effect of candidate factors on outcomes. Associations between candidate factors and outcomes were modeled using Cox proportional hazards regression.[12] Hazard ratios for effects in univariable and multivariable models were computed wherever possible, that is, for predictive variable levels that contributed at least one failure. For variables comprised of levels with no failures, only log-rank test p-values are provided since these hazard ratios are either zero or infinite.[12] A p value ≤ 0.05 was considered statistically significant.

Results

The median biochemical and clinical follow up duration after RT for all patients was 3.2 and 5.1 years respectively. Median biochemical follow up times were 1.2, 2.8, 7.1 and 3.7 years for SRT, NADT + SRT, ART and NADT + ART and treatment groups respectively. Median biochemical follow up time was considerably shorter for the SRT group compared to other groups because most of these patients (11 of 15) experienced a biochemical failure at a median of 0.7 years from RT. The respective median clinical follow up durations were 8.3, 4.2, 11.2 and 4.8 years.

Distribution of factors across treatment groups,Table 1

Based on Pearson's chi-square test, there were a smaller percentage of patients in the NADT + SRT with locally advanced pathological T stage compared to the other three treatment groups. Patients in the adjuvant radiotherapy treatment groups had a higher positive surgical margin status compared to the salvage groups and tended to receive lower doses of RT. There were more patients with a high pre-RT PSA in the SRT group. However, there was no statistical difference in distribution of pre-salvage PSA levels between the SRT and NADT + SRT groups.

Outcomes

Regarding the entire group (n = 175), treatment type was a significant predictor of BDFS on univariable analysis as shown in Table 2. The 5 year BDFS for the SRT, NADT + SRT, ART and NADT + ART treatment groups were 23%, 63%, 67% and 80% respectively, Figure 1. Mean time to biochemical failure calculated by Kaplan-Meier method was 2.8, 5.8, 8.2 and 10.1 years for SRT, NADT + SRT, ART and NADT + ART treatment groups. As shown in Figure 1, using pairwise comparisons, patients treated with SRT had the worst BDFS compared with all other treatment groups. Men receiving NADT + ART did not appear to do better than ART alone. However, those that received NADT + ART did better than NADT + SRT. There was no statistical difference in outcome between those that received NADT + SRT versus ART alone. Other factors significant on univariable analysis were pathological GS, surgical margin status and pre-RT PSA. Five year BDFS was 74% for pathological GS 2-6 versus 55% for GS 8-10, 64% for GS 7 versus 55% for GS 8-10, 72% for positive surgical margins versus 50% for

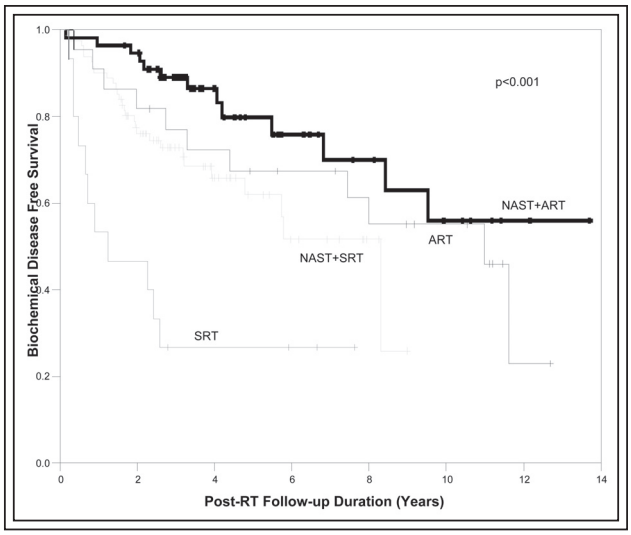

Figure 1. Biochemical disease free survival curves for patients receiving adjuvant radiotherapy (ART), salvage radiotherapy (SRT), with or without neoadjuvant androgen suppression therapy (NADT). Log rank test was used to compare outcomes.

TABLE 2. **Factors associated with outcome on univariate analysis**

	All patients (n = 175)		
Outcome variable (reference group)	**BDFS**	**DSS**	**OS**
	p values (hazard ratios; CI)		
Treatment group (ART for all patients; SRT for all salvage patients)	< 0.001 (SRT vs ART: 4.4; 1.8-10.6)	ns	ns
Age (> 64 years)	ns	ns	0.033 (0.4; 0.1-0.9)
Pathological GS (GS ≥ 8)	0.008 (GS ≤ 6 vs ≥ 8: 0.4: 0.2-0.7) (GS 7 vs ≥ 8: 0.5: 0.3-0.8)	0.001*	0.031 (GS ≤ 6 vs ≥ 8: 0.3: 0.1-0.7) (GS 7 vs ≥ 8: 0.4: 0.1-0.7)
Surgical margins (positive)	0.004 (2; 1.2-3.6)	ns	ns
Pre-RT PSA (> 0.2 ng/ml)	< 0.001 (0.2; 0.1-0.4)	0.02 (0.1; 0.02-0.6)	ns
Pre-salvage PSA (> 1 ng/ml)	NA	NA	NA

TABLE 2 (cont'd)

Outcome variable (reference group)	BDFS	DSS	OS
	All salvage patients (n = 96)		
	p values (hazard ratios; CI)		
Treatment group (ART for all patients; SRT for all salvage patients)	0.002 (0.3; 0.2-0.7)	ns	ns
Age (> 64 years)	0.048 (0.5; 0.3-1)	ns	0.026 (0.2; 0.04-0.8)
Pathological GS (GS ≥ 8)	0.004 (GS < 6 vs ≥ 8: 0.3; 0.1-0.6) (GS 7 vs ≥ 8: 0.3; 0.1-0.6)	0.021*	ns
Surgical margins (positive)	ns	ns	ns
Pre-RT PSA (> 0.2 ng/ml)	< 0.001 (0.2; 0.1-0.5)	0.019*	ns
Pre-salvage PSA (> 1 ng/ml)	0.037 (0.5; 0.3-1.0)	ns	ns
	NAST + SRT patients (n = 81)		
Outcome variable (reference group)	**BDFS**	**DSS**	**OS**
	p values (hazard ratios; CI)		
Treatment group (ART for all patients; SRT for all salvage patients)	NA	NA	NA
Age (> 64 years)	ns	ns	ns (p = 0.085)
Pathological GS (GS ≥ 8)	0.012 (0.2: GS ≤ 6 vs ≥ 8) (0.4: GS 7 vs ≥ 8)	0.047*	ns
Surgical margins (positive)	ns (p = 0.053)	ns	ns
Pre-RT PSA (> 0.2 ng/ml)	0.028 (0.3; 0.1-0.7)	0.018*	ns
Pre-salvage PSA (> 1 ng/ml)	ns	ns	ns

Factors not significant were excluded from table.
CI = Confidence interval; NAST = neoadjuvant androgen suppression therapy; SRT = salvage radiation therapy; ART = adjuvant radiation therapy; BDFS = biochemical disease free survival; DSS = prostate cancer disease specific survival; OS = overall survival; GS = Gleason score; PSA = prostate specific antigen; RT = radiation therapy; ns = not significant; NA = not applicable
*hazard ratios not provided for factors with no failures as software does not converge with hazard ratios of zero or infinity

negative margins. As shown in Figure 2a, BDFS was 76% for pre-RT PSA ≤ 0.2 ng/ml versus 28% for PSA > 0.2 ng/ml. None of the patients who had a pre-RT PSA near zero (i.e. pre-RT PSA ≤ 0.02 ng/ml) failed. On multivariable analysis (MVA) pathological GS, surgical margin status and pre-RT PSA were statistically significant predictors of BDFS, Table 3.

In the group that received salvage therapy (n = 96), use of NADT with SRT and pre-salvage PSA were predictors of BDFS on univariable, but not MVA. As shown in Figure 2b, pre-RT PSA was a strong predictor of BDFS in salvage RT treatment groups with 5 year BDFS 62% for PSA ≤ 0.2 ng/ml versus 22% for PSA > 0.2 ng/ml (p < 0.001). For patients that received

TABLE 3. **Factors associated with outcome on Cox multivariable regression analysis**

	All patients (n = 175)	
Outcome variable (reference group)	**BDFS**	**OS**
	p values (hazard ratios; CI)	
Treatment group (ART for all patients; SRT for all salvage patients)	ns	ns
Age (> 64 years)	ns	0.048 (0.4; 0.144-0.993)
Pathological GS (GS ≥ 8)	< 0.001 (GS ≤ 6 vs ≥ 8: 0.2; 0.07-0.3) (GS 7 vs ≥ 8: 0.3; 0.2-0.6)	0.048 (GS < 6 vs =>8: 0.3; 0.095-0.913) (GS 7 vs =>8: 0.4; 0.136-0.967)
Surgical margins (positive)	0.001 (2.7; 1.5-5.0)	ns
Pre-RT PSA (> 0.2 ng/ml)	0.001 (0.2; 0.1-0.5)	ns
Pre-salvage PSA (> 1 ng/ml)	NA	NA
	All salvage patients (n = 96)	
Outcome variable (reference group)	**BDFS**	**OS**
	p values (hazard ratios; CI)	
Treatment group (ART for all patients; SRT for all salvage patients)	ns	ns
Age (> 64 years)	ns	0.017 (0.1; 0.028-0.702)
Pathological GS (GS ≥ 8)	< 0.001 (GS ≤ 6 vs ≥ 8: 0.1; 0.03-0.3) (GS 7 vs ≥ 8: 0.3; 0.1-0.7)	ns
Surgical margins (positive)	0.001 (4; 1.7-9.0)	ns
Pre-RT PSA (> 0.2 ng/ml)	0.003 (0.2; 0.09-0.5)	ns
Pre-salvage PSA (> 1 ng/ml)	ns	ns
	NAST + SRT patients (n = 81)	
Outcome variable (reference group)	**BDFS**	**OS**
	p values (hazard ratios; CI)	
Treatment group (ART for all patients; SRT for all salvage patients)	NA	NA
Age (> 64 years)	ns	0.038 (0.2; 0.038-0.168)
Pathological GS (GS ≥ 8)	< 0.001 (GS ≤ 6 vs ≥ 8: 0.04; 0.009-0.2) (GS 7 vs ≥ 8: 0.2; 0.06-0.5)	ns
Surgical margins (positive)	0.001 (5; 2.0-14.0)	ns
Pre-RT PSA (> 0.2 ng/ml)	0.034 (GS ≤ 6 vs ≥ 8: 0.08; 0.008-0.8) (GS 7 vs ≥ 8: 0.1; 0.05-0.5)	ns
Pre-salvage PSA (> 1 ng/ml)	ns	ns

CI = Confidence interval; NAST = neoadjuvant androgen suppression therapy; SRT = salvage radiation therapy; ART = adjuvant radiation therapy; BDFS = biochemical disease free survival; PCaSS = prostate cancer specific survival; OS = overall survival; GS = Gleason score; PSA = prostate-specific antigen; RT = radiation therapy; ns = not significant; NA = not applicable

adjuvant RT (n = 77), pre-RT PSA was not a predictor of BDFS (data not shown). The analysis was repeated for patients receiving NADT + SRT (n = 81). Again, pre-RT PSA, Figure 2c but not pre-salvage PSA was a predictor of BDFS on MVA. Pathological GS and pre-RT PSA were significant predictors of outcome for DSS in all salvage patients and NADT + SRT patients. There were too few events to permit calculation of effect of factors on DSS on MVA, however the trends paralleled those of BDFS using pre-RT PSA as a factor. For OS, age was the only consistent factor significantly affecting outcome with the addition of pathological GS significant for the entire group.

Discussion

Several series have reported a high PSA level at time of RT after surgery as an negative predictor of outcome, particularly in the salvage setting.[7] A high PSA (e.g. PSA > 1 ng/ml) may signify missed therapeutic window for effective salvage therapy and likely indicates the presence of large tumor burden where moderate doses of radiation cannot effectively eradicate or the presence of occult metastatic disease. There is a need for more effectively selecting post-RP patients who are suitable for surveillance as opposed to ART, for determining the appropriate timing of administering salvage therapy at time of recurrence and administering more effective salvage therapy, particularly for those patients with a high PSA at time of recurrence.

Androgen deprivation therapy (ADT) is an effective and important treatment for both metastatic and nonmetastatic prostate cancer. ADT can be given in a neoadjuvant fashion prior to RT with the benefits of causing tumor and prostate gland shrinkage and inducing apoptosis and triggering an immune response against cancer cells.[13] In vivo studies have shown that by sequencing of ADT in a neoadjuvant fashion, a lower effective dose of radiation is required for comparable cell kill compared to the use of radiation therapy alone or combined with ADT following RT.[14,15] The combination of neoadjuvant hormone therapy and RT is thus an attractive treatment strategy in the postoperative setting. Although the addition of ADT to RT in the post RP setting is appealing, its role is yet to be determined. Some but not all nonrandomized series have demonstrated improved biochemical control by adding ADT to postoperative RT, Table 4.[16-24] Our study did not confirm the use of ADT as a predictive factor on MVA. Unfortunately, there are no reported randomized studies addressing the role of ADT. RTOG P-0011 which was a three arm study comparing ART versus

TABLE 4. **Nonrandomized studies of androgen suppression therapy and postoperative radiotherapy**

Reference	Patient population	n	Treatment	FFBF (yrs)
Cheung[16]	PSA failure	46	SRT	~60% (5)
		55	SRT + ADT	~85%
Corn[17]	High risk pathology features	68	ART	42% (5)
[sub analysis of RTOG 8531]		71	ART + AADT	65%
de la Taille[18]	PSA failure	18	SRT	32%
		34	SRT + ADT	61%
Eulau[19]	High risk pathology features,	74	ART or SRT	27% (5)
	PSA and local failures	31	NADT + (ART or SRT)	56%
Katz[20]	PSA failure with > 1 risk factor	81	SRT	
			SRT+ADT	better (p = 0.03)
King[21]	Not described	53	ART or SRT	31% (5)
		69	NADT+ (ART or SRT)	57%
Pacholke[22]	High risk pathology features,	62	ART or SRT	HR 0.5
	PSA failure and local failures	38	NADT + (ART or SRT)	
Stephenson[23]	PSA failure	418	SRT	ns
		83	NADT + SRT	
Taylor[24]	PSA failure	36	SRT	~50% (5)
		35	SRT+AADT	~80%

FFBF = freedom from biochemical failure; ART = adjuvant radiotherapy; SRT = salvage radiotherapy; ADT = androgen deprivation therapy; AADT = adjuvant ADT; NADT = neoadjuvant ADT; ns = not significant; HR = hazard ratio

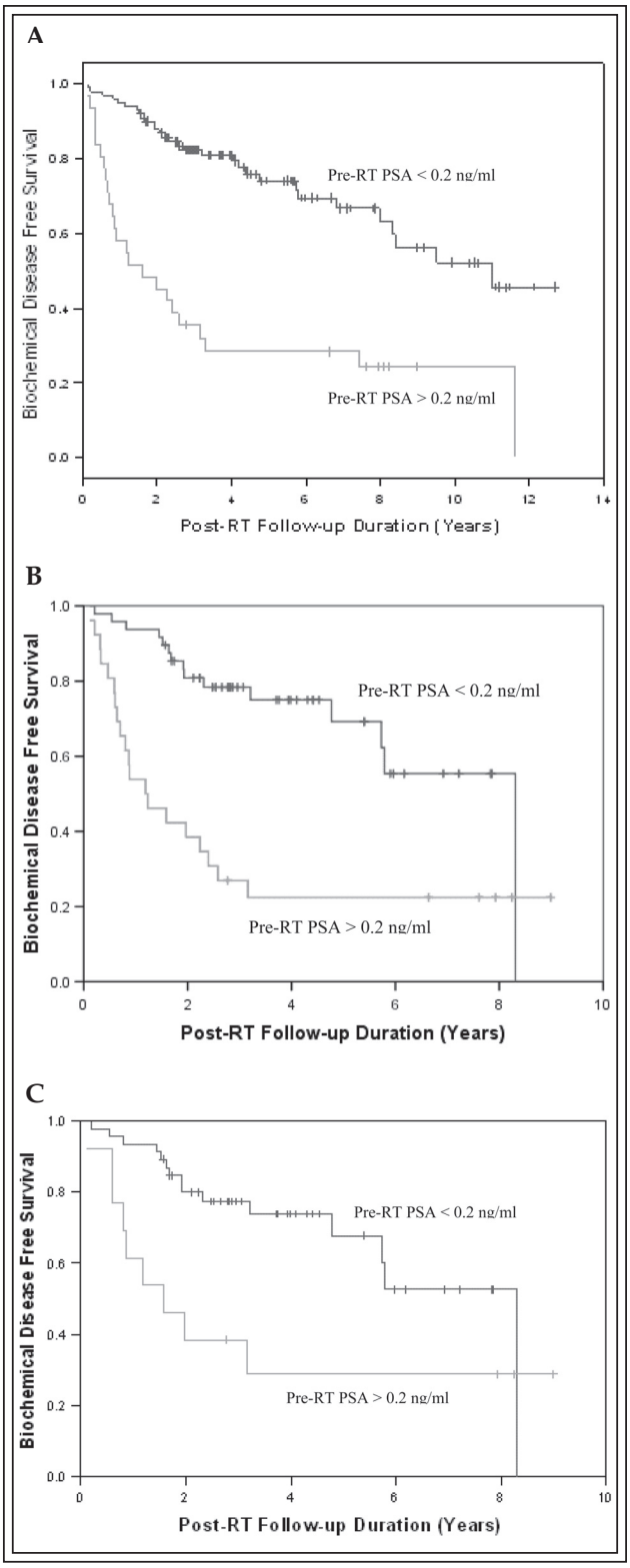

Figure 2. Biochemical disease free survival curves for (a) all patients (n = 175), (b) all salvage patients (n = 96) and (c) NADT + SRT (n = 81) patients grouped according to pre-RT PSA levels.

ADT versus ART + ADT failed to accrue sufficient patients. The results from RTOG 96-01 comparing ART versus ART + 2 years adjuvant bicalutamide have not yet been reported. The UK Medical Research Council's Radiotherapy and Androgen Deprivation in Combination after Local Surgery (RADICALS) Trial Management Group have opened a multicentered study that will randomize RP patients to adjuvant versus salvage RT for PSA failure.[25] A second level of randomization will occur for all patients receiving RT to RT alone, RT + 6 months of hormone therapy or RT + 2 years of hormone therapy. This study is open in Canada under the auspices of National Cancer Institute of Canada - Clinical Trials Group as PR.13.

Our analysis, however, confirms the predictive value of PSA, particularly in patients receiving salvage therapy. In regards to PSA, (i) the timing of a non-zero or rising PSA after RP, (ii) PSA kinetics and (iii) PSA level have all been associated with outcome after SRT. As reviewed by Hayes et al, some controversy exists as to the predictive value of timing of PSA rise or the presence of a non-zero PSA after RP.[26] In some series but not others, patients who have a non-zero PSA after RP have worse biochemical control after SRT compared to those who have a delayed rise in PSA after RP. More recent attention has been given to PSA kinetics after RP, in particular PSA doubling time (PSA DT) which is associated with biochemical and clinical outcomes. When PSA DT is short (e.g. < 3-12 months) there is a higher risk of distant metastases, poorer biochemical control and prostate cancer specific mortality following SRT.[23,27-34] Some clinicians recommend avoiding RT in these clinical scenarios. However, the predictive value of PSA DT when post RP PSA is in the very low range (e.g. < 1 ng/ml) may be more difficult to interpret.[26] As discussed by Hayes et al, the appropriate time to assess PSA DT is not known, especially when PSA is in the very low range. Our study did not show an effect of PSA DT on outcome in salvage patients. Our results are consistent with Pollack et al's large multi-institutional analysis of 1200 men which showed that pre-RT PSA rather than PSA DT was predictive of outcome.[35]

The most convincing PSA parameter that has been shown to consistently predict outcome is the PSA level at time of salvage treatment. A well-defined pre-RT PSA cut off point has not been established, but the majority of studies show that a pre-SRT PSA > 1 to 4 ng/ml predicts worse biochemical control as reviewed by Hayes, Parker and Slawin.[7,26,36] A high PSA at time of salvage is representative of larger local tumor burden that would be more difficult to eradicate with standard postoperative doses of RT between 60-68 Gy or the presence of occult metastatic disease. Fewer studies,

however, have examined the prognostic significance of pre-SRT PSA levels in the much lower range that is measurable using ultrasensitive PSA assays.[16,35] In this series, Figure 2 illustrates the importance of very low pre-RT PSA which was a significant predictor of BDFS in the entire group, Figure 2a and in salvage RT groups, Figures 2b, 2c. Particularly noteworthy were salvage patients who had a high PSA prior to commencement of NADT (i.e. high pre-salvage PSA level). If these patients were able to achieve a low PSA (e.g. $\leq$ 0.2 ng/ml) through the use of NADT, they had more favorable outcomes. However, salvage patients with a low pre-salvage PSA did not seem to benefit from NADT in this series. Thus, NADT can be selectively used for those patients presenting with a high pre-salvage PSA in the absence of level one evidence. To our knowledge, this is the first study examining the role of NADT and the predictive value of pre-RT PSA in post-RP patients.

Our results are consistent with others that have examined the significance of very low pre-RT PSA cut off points. An analysis in abstract form from Pollack et al of 1168 men who received either ART or SRT, with or without ADT examined the significance of pre-RT PSA and other factors.[35] Seventy-eight percent of men received SRT and 16% received adjuvant ADT. Pre-RT PSA was grouped into < 0.2, 0.2-0.99 and $\geq$ 1 ng/ml. Patients receiving SRT with a high pre-RT PSA, seminal vesicle involvement and high Gleason score had an increased risk of biochemical relapse on MVA. Use of ADT was not a significant predictor of outcomes. Cheung et al analyzed 101 men who received SRT with or without ADT.[16] Fifty-nine patients received ADT, which was given in a neoadjuvant fashion in 7 patients. Patients were divided into favorable and unfavorable risk groups based on their pre-RT PSA and margin status. The use of ADT had a significant impact on BDFS in the unfavorable group consisting of patients with a pre-RT PSA $\geq$ 0.5 ng/ml or negative surgical margins. The use of ADT with SRT did not however improve outcome for patients who had a pre-RT PSA < 0.5 ng/ml. These results and our study indicate that the pre-RT PSA level is an important determinant of outcome and that the benefit of ADT seems to be limited to those with a high PSA.

We have previously published on over 400 patients with high risk localized prostate cancer treated with NADT and radical RT at our institution.[37] Pre-RT PSA was a significant predictor of BDFS and DSS. Patients who had a pre-RT PSA of $\leq$ 0.1 ng/ml had improved outcomes. BDFS and DSS were not dependent of NADT and duration of hormone therapy as in this study.

The improved outcomes observed by achieving an ultra low pre-RT PSA prior to definitive or postoperative RT through the use of NADT may be explained by significant cytoreduction of tumor volume with the irradiated field and eradication of androgen sensitive prostate cancer cells in those patients harboring occult metastatic disease. Cytoreduction may sufficiently decrease the residual cancer cell load in the postoperative bed to a sufficiently low number that can be more effectively eradicated with moderate doses of radiation typically used in the postoperative setting. The advantages of using NADT are supported by animal studies such as those by Zietman et al[38] and Kamanski et al.[14] Other effects such as decreasing hypoxic regions around cancer cells through androgen deprivation cell kill [39,40] and triggering an immune response against cancer cells [13] are speculative but may also explain the added benefit of NADT for those with larger tumor burdens.

With regards to patients who receive NADT and fail to achieve a pre-RT PSA of < 0.2 ng/ml, these may represent hormone refractory and biologically aggressive disease that would less likely be successfully eradicated with further RT. Thus, it is possible that the use of pre-RT PSA in patients receiving NADT is simply a means to select out those with hormone insensitive and inherently aggressive disease.

This study is limited by the retrospective nature and small sample sizes, particularly in the SRT group. However, the 5 year BDFS of 23% is comparable to other published series. From table 1, the patient and cancer characteristics were heterogeneous and some imbalances were noted as described in the results section that may have contributed to difference in outcomes. Regarding PSA levels, despite more patients having had high pre-RT PSA in the SRT compared to the NADT + SRT group, the pre-salvage PSA levels in these groups were not unequally distributed. We also acknowledge that various hormonal agents were used including nowadays outdated ones such as DES which may have influenced results. To our knowledge, however, there is no clear relationship between the use of various hormonal agents and biochemical outcome, with the exception of some reports showing worse tumor control with the use of anti-androgens alone.[41] None of these patients received anti androgens alone. We acknowledge that randomized studies are required to determine the role of ADT in the postoperative setting. Pre-RT PSA should be incorporated as a predictive factor.

The use of ADT also creates some challenges in defining biochemical relapse after RT. Patients who receive NADT will have a drop in their PSA prior RT

compared to those that do not and may be subject to delay in relapse because of additional time to recovery from androgen deprivation. This study was limited due to lack of sufficient testosterone measurements. Some patients may have had incomplete recovery of testosterone levels which could have impacted the PSA levels and biochemical recurrence rates. However, most patients should have had full recovery or stabilization of testosterone levels prior to last PSA measurement in this study, which in previous studies have been shown levels to occur at a median of 10 months after ADT.[42] However, identifying patients who relapse within the first 10 months or so after completion of ADT may not be valid with the use of 0.4 ng/ml PSA threshold. The authors also make note that toxicity from ADT and RT was not available. Future randomized studies will hopefully address the question of whether overall toxicity is increased through the use of ADT with RT. □

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