

External beam radiation therapy after radical prostatectomy: efficacy and impact on urinary continence

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Introduction and Objectives: The efficacy of adjuvant and salvage external beam radiation (AXRT + SXRT) for prostate cancer after radical prostatectomy (RP) has been debated because of the inability to rule out systemic occult metastasis, uncertainty that radiation eradicates residual local disease and the potential of exacerbating impotency and incontinence. To characterize the effectiveness and treatment morbidity a retrospective review was performed.

Methods: In all, 38 patients received AXRT and 91 received SXRT. The SXRT group was stratified by PSA level, age, race, pathologic stage, margin status, worst Gleason sum, radiation dose and pelvic field. Complications evaluated were impotence and incontinence. Median follow-up was 60.2 months.

Results: The 5-y disease-free survival (DFS) rate was 61.3% for AXRT and 36.3% for SXRT. Multivariate analysis of the SXRT cohort showed Gleason score, pathologic stage and pre-XRT PSA to be predictors of disease recurrence. After XRT 26% had worsened continence.

Conclusions: Patients who recur after RP whose pathologic stage is pT2 or pT3c, Gleason score of 8 or higher or pre-XRT PSA is >2.0 ng/dl may have microscopic metastatic disease and a decreased chance of cure with SXRT alone. Continence was further impaired after XRT.

Prostate Cancer and Prostatic Diseases (2004) 7, 170–177. doi:10.1038/sj.pcan.4500718
Published online 11 May 2004

Keywords: prostate carcinoma; radical prostatectomy; external beam radiation; outcomes

Introduction

Radical prostatectomy (RP) is one of the most common forms of treatment for clinically localized prostate cancer;

however, it may be associated with considerable morbidity, notably urinary incontinence and impotence. In addition, a study of Medicare patients who had undergone RP showed that <60% had organ-confined disease on surgical pathology and 35% required additional treatment of their prostate cancer within 5 y of surgery.¹ These men may be offered external beam radiation treatment (XRT) postoperatively in an effort to provide further definitive local treatment. The timing of such treatment and who may benefit is addressed by multiple articles.^{2–8} Unfortunately, these retrospective reviews frequently include few patients, include preprostate-specific antigen (PSA)-era patients, have short follow-up or do not adequately comment on the long-term

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the US Army or the Department of Defense.

Received 24 November 2003; revised 23 February 2004; accepted 27 February 2004; published online 11 May 2004

complications, specifically urinary incontinence and erectile dysfunction. In an effort to better quantify the effectiveness and complications of definitive post-RP radiotherapy in the PSA-era, we reviewed our combined experiences at Walter Reed Army Medical Center and National Naval Medical Center.

Materials and methods

The Center for Prostate Disease Research longitudinal database was searched in a retrospective manner for all data points. There were 943 radical prostatectomies done at WRAMC and NNMC between January 1989 and December 1996. This time frame was chosen because pretreatment PSA was available and allowed a 5-y follow-up. The PSA test used during this timeframe was the Hybritech PSA Assay. In total, 129 (14%) received definitive post-RP radiotherapy including 38 AXRT and 91 SXRT. Surgery was performed by multiple staff urologists with resident assistants. We divided the group into adjuvant external beam radiation therapy (AXRT) and salvage external beam radiation therapy (SXRT) treatment arms. AXRT was defined as XRT given prior to a PSA recurrence. SXRT was defined as XRT given after a PSA recurrence. Post-RP and post-XRT PSA recurrence was defined as two consecutive serum PSA values ≥ 0.2 ng/ml or any PSA value ≥ 0.5 ng/ml. Follow-up schedule was a digital rectal exam and PSA every 3 months after RP or XRT for the first year, every 6 months for the next 2 years and yearly thereafter provided there was no evidence of recurrence. Mean follow-up for the AXRT and SXRT groups were 70.7 and 60.2 months, respectively. If there was evidence of recurrence pre-XRT biopsy was at the physician's discretion and most did not undergo repeat biopsy. Overall, 20 patients had palpable recurrence and 14 of these were biopsied. Of these, 10 showed recurrent prostate cancer, three showed fibrosis and one showed benign prostatic glands. Six patients had no palpable recurrence but underwent biopsy of the urethral anastomosis and five of these showed fibrosis and one was recurrent prostate cancer. Eight of the 91 SXRT patients (8.8%) were noncompliant with the follow-up schedule and presented years after their RP with markedly elevated PSA and were excluded from the time to recurrence after RP calculations. Because of the uncertainty of residual disease in the AXRT patients they were only further evaluated for their urinary continence and potency statuses. Comparison between AXRT and SXRT pretreatment factors and XRT factors are given in Table 1. SXRT factors were further evaluated for predictors of treatment efficacy. Staging was done according to the 1992 American Joint Committee on Cancer staging system.⁹ Margins were defined as positive if there was cancer in the inked margins. Most (123 of 129) underwent conventional processing and did not have whole mounting of the prostatectomy specimen. SXRT was stratified by pathologic stage, margin status, worst RP specimen Gleason score, race, age, XRT dose, highest post-RP PSA, pelvic field, palpable local recurrence, adjuvant hormonal therapy (HT) with XRT, time from prostatectomy to PSA recurrence and pre-RP PSA (Table 2).

Follow-up was defined as time from start of XRT to last clinical contact or death. The efficacy of A + SXRT was evaluated by lack of PSA recurrence and duration of response. Complications evaluated were erectile dysfunction and urinary incontinence. Erectile function and urinary continence status were compared between pre-RP, post-RP and post-XRT time frames. Pre-RP potency and urinary continence are reported as documented on the pretreatment Center for Prostate Disease Research (CPDR) Registration standardized clinical report form. Pre-XRT potency and urinary continence are given as reported in the last standardized CPDR follow-up form or progress note prior to starting XRT. Validated questionnaires were not used. Post-XRT potency and urinary continence status are reported as of most recent standardized CPDR follow-up form. Potency was described as impotent, partial potency and fully potent. Impotent was defined as no erectile function, partial potency was a partial erection inadequate for intercourse and fully potent was an erection adequate for intercourse. Potency results are reported as unassisted erections only, that is, without sildenafil or other treatments. Partial potency was felt to be important because these patients may be more likely to have useful erections with sildenafil.¹⁰

Urinary continence was described as complete continence if the patient did not leak urine and wore no pads, partial continence was described as minimal leaking of urine requiring ≤ 1 pad/day and incontinent was > 1 pad/day. Totally, 110 patients had complete urinary continence and potency data reporting at all time frames. The change from pre-XRT to post-XRT continence was categorized as worsened (complete to partial or incontinent) continence or improved (partial to complete or incontinent to partial or complete) continence. Changes in continence status after XRT were then compared by XRT dose, PSA recurrence after XRT, pelvic field and nerve sparing done at time of RP (Table 3).

All patients received staging work-up prior to XRT: chest X-ray, complete blood count, liver function tests, computed tomography scan of the abdomen and pelvis and bone scan. All were felt to have no evidence of persistent nodal disease and no evidence of metastatic disease prior to starting XRT. Indium-111 Capromab Pentdide (Prostascint^R) was not used during this time period of treatment.

Of the 91 SXRT patients, 60 (67%) had unilateral or bilateral nerve sparing radical prostatectomy. Pretreatment PSA ranged from 2.4 to 137 ng/dl with a mean of 17.1 and a median of 11.1 ng/ml, excluding a single patient with a pretreatment PSA of 1060. In all, 18 patients had Gleason score 5–6, 38 had Gleason 7, 27 had Gleason 8–9 and eight did not have Gleason scoring performed. In total, 21 (23%) were African-American and 70 (77%) were Caucasian or other race. Eight (9%) received pre-RP hormonal therapy only, with a range of 3–5 months and a mean of 3.3 months. Of these, 16 (18%) received neoadjuvant XRT hormonal therapy for 1–17 months with a mean of 5.0 months. Included into the neoadjuvant hormonal therapy group were all patients who received any type of hormonal therapy while being given XRT. LH–RH agonist alone *vs* LH–RH agonist + antiandrogen and duration of hormonal therapy was at the discretion of the attending physician.

Table 1 Distribution of 129 XRT patients by demographic, clinical, pathological and treatment variables

Variable	Total N	%	Type of XRT		SXT vs AXRT	
			SXRT N	AXRT N	Fisher's exact P-value	M-H trend P-value
Total	129	100.0	91	38		
Age					0.633	0.841
< 60	38	29.5	26	12		
60-64	49	38.0	37	12		
> 64	42	32.6	28	14		
Race					0.821	0.696
Caucasian+Other	98	76.0	70	28		
African American	31	24.0	21	10		
Totals						
Pre-RP PSA				0.737	0.304	
0-4	5	4.0	3	2		
4-10	51	40.8	34	17		
10-20			37	26	11	
20-40	22	17.6	18	4		
> 40	10	8.0	7	3		
Unknown	4		3	1		
Gleason score				0.670	0.409	
4	2	1.7	2	0		
5-6	27	22.6	16	11		
7			55	38	17	
8-10	35	29.4	27	8		
Unknown	10		9	2		
Surgical margins					0.453	0.332
Positive	103	81.7	70	33		
Negative	23	18.3	18	5		
Unknown	3		3	0		
Pathologic stage					0.282	0.337
T1	1	0.8	1	0		
T2	14	10.9	13	1		
T3a, b	77	59.7	53	24		
T3c	27	20.9	16	11		
T4	5	3.9	4	1		
Node positive	5	3.9	4	1		
Unknown						
XRT dose (cGy)					0.131	0.075
5040-6120	63	52.5	40	23		
6300-6480	38	31.7	31	7		
6600-7100	19	15.8	15	4		
Unknown	9		5	4		
Pelvis in XRT field					0.007	0.006
Yes	46	40.0	39	7		
No	69	60.0	42	27		
Unknown	14		10	4		

Radiation dose ranged from 5040 to 7100 centiGray (cGy) with a mean dose of 6273 cGy and median dose of 6300 cGy. In all, 42 (52%) received radiation to the prostatic bed only and 39 (48%) received radiation to the prostatic bed and prophylactic radiation to the pelvis. Radiation was delivered as hi-energy photons from a linear accelerator (15 mx-18 mx) in 180-200 cGy fractions. CT findings or surgical clips were used to help delineate the surgical bed. If pelvic lymph nodes were targeted, the fields were extended to the L5/SI interspace. The majority were treated with 3-D conformal techniques but a portion of the earlier patients were treated with

conventional simulation based on 2-D treatment planning. There were no standard inclusion or exclusion criteria for administration of XRT and the decision to treat was up to the attending radiation oncologist.

Data analysis for predictors of DFS was by Kaplan-Meier methodology and the log-rank test. Variables that had a P-value ≤ 0.1 were included in a multivariate analysis using Cox regression with backward elimination of insignificant variables, a P-value ≤ 0.05 was considered significant. Data analysis of categorical variables used Fisher's Exact test and the Mantel-Haenszel trend

Table 2 PSA recurrence after salvage XRT in 91 patients

Variable	Total number	Recurred		P-value*
		Number	%	
All SXRT	91	54	59.3	0.722
Pre-RP PSA				
<10	37	20	54.1	
10–20	26	14	53.9	
>20	25	19	76.0	
Unknown	3	1	33.3	
Age				0.013
<60	26	10	38.5	
>60	65	44	67.7	
Race				0.855
Caucasian+Other	70	40	57.1	
African American	21	14	66.7	
Pathologic stage				0.012
T2	14	9	64.3	
T3a+b	55	28	50.9	
T3c	17	14	82.4	
T1,T4 or any N+	5	3	60.0	
Margins				0.085
Positive	70	38	54.3	
Negative	18	13	72.2	
Unknown	3	3	100	
Gleason score:				<0.001
4–6	18	7	38.9	
7	38	19	50.0	
8–9	27	22	81.5	
Not reported	8	6	75.0	
Time to recurrence ^a				0.760
<24 months	69	42	60.9	
>24 months	14	7	50.0	
Non-compliant	8	5	62.5	
Palpable recurrence				0.886
Yes	20	10	50.0	
No	61	38	62.3	
Unknown	10	6		
Post-RP PSA				0.042
≤2.0	64	35	54.7	
>2.0	27	19	70.4	
SXRT+HT				0.461
Yes	16	6	37.5	
No	74	47	63.5	
Unknown	1	1		
XRT dose (cGy)				0.331
5040–6120	40	29	72.5	
6300–6480	31	13	41.9	
6600–7100	15	7	46.7	
Unknown	5	5		
Pelvic field				0.720
Yes	39	18	46.2	
No	42	28	66.7	
Unknown	10	6		

*P-value for the log-rank test of no difference between variable levels in DFS based on Kaplan–Meier analysis.

^aTime to recurrence is measured from date of RP to date of PSA recurrence prior to SXRT.

test. Comparison of variables affecting post-XRT continence used McNemar’s test. Comparison of observed vs expected continence after XRT used Fisher’s exact test.

Results

Pre-RP PSA, margin status, XRT dose, Gleason score and pathologic stage were similar between the AXRT and SXRT groups with the exception that most T2 patients were in the SXRT group (Table 1). All T2 patients had negative margins.

The AXRT group had a 5-y DFS rate of 61.3 and 36.3% for the SXRT group. In the SXRT group, 34 (37%) are alive with no evidence of disease, 50 (55%), are alive with disease, four (4%), have died of prostate cancer, two (2%), have died of other causes and one (1%), has died from an unknown cause. After SXRT 60 of 91 (66%) achieved a PSA nadir of 0.2 ng/ml or less, the remainder have recurred, however two patients had nadir PSAs of 0.5 ng/ml and have not had a PSA elevation in 2 y.

The influences of various factors on DFS after SXRT is shown in Table 2. Lower RP Gleason scores correlated with decreased recurrence (Figure 1). Stage pT3a + b had decreased recurrence rates compared to pT2 and pT3c (+ seminal vesicle invasion) (Figure 2). Pre-XRT PSA level was examined and initially three ranges were reviewed: ≤1 vs >1, ≤1.5 vs >1.5 and ≤2.0 vs >2.0; only the 2.0 cutoff was significant (Figure 3). Age <60 vs ≥60 was significant with the younger men doing better. Pretreatment PSA was examined with PSA >20 showing an increased number of recurrences but this did not reach statistical significance. Negative surgical margins were associated with increased recurrences but this did not reach statistical significance. There was no significant difference in recurrence based on race, time to recurrence, palpable local recurrence, adjuvant HT with XRT or pelvic field. Multivariate analysis that simultaneously compared age, pathologic stage, margin status, Gleason score and highest post-RP PSA showed that only stage, Gleason score and the highest post-RP PSA were independent predictors of PSA recurrence after SXRT.

Both the AXRT and SXRT groups were combined to evaluate long-term potency and urinary continence status. Overall, 110 patients had complete potency and continence data. All patients were continent prior to RP. Totally, 68 were fully continent before XRT, 22 were partially continent and 20 were incontinent. The time from RP to start of XRT varied between groups with medians of 5.1, 13.5 and 8.6 months for the incontinent, partially continent and continent groups. After XRT, at last follow-up in the post-RP incontinent patients: 62% continued to be incontinent, 17% became partially continent and 21% were continent. In the post-RP partially continent patients: 42% became incontinent, 37% remained partially continent and 21% became continent. In the post-RP continent patients: 10% became incontinent, 14% became partially continent and 76% remained continent. The median follow-up times of the post-XRT incontinent, partial continent and continent groups were 71.4, 56.9 and 57.5 months, respectively. To statistically evaluate the effect of A + SXRT on continence, the group comprising full and partial continent after RP and before XRT were compared to their own continence status after XRT. Worsened continence was considered going from the continent to the partial continent or incontinent group or going from partially continent to the incontinent group after XRT. There were 90 men who were continent or partially continent post-RP, 68 of them had stable or improved continence after

XRT and 22 had worsened continence. The rate of worsened continence (25.6%) in this group was compared to an expected rate of 0% worsened incontinence and a 'worst case' rate of 10% worsened continence using Fisher's exact test with *P*-values of <0.001 and 0.010, respectively. Post-XRT continence was also compared to radiation dose, pelvic field, nerve sparing and PSA recurrence. Radiation dose was divided into a high-dose

(6480–7100 cGy) vs a low-dose group (5200–6400 cGy). Nerve sparing was associated with preservation of continence after XRT. Lack of pelvic field was associated with worsened incontinence. PSA recurrence after XRT and XRT dose had no statistical effect on long-term continence (Table 3).

Pre-RP, 74 (73%) reported full potency, nine (9%) had partial potency and 18 (18%) were impotent. No pre-RP impotent patient regained partial or full potency after RP or XRT. All nine pre-RP partial potency patients became impotent after RP, however, one (11%) again became partially potent post-XRT in long-term follow-up. Seven (9%) patients that were fully potent pre-RP remained fully potent after RP and 14 (19%) became partially potent. In this post-RP potent and partial potent group, at last follow-up, after XRT 9 (43%) became impotent, 10 (48%) had partial potency and two (10%) were fully potent. In this select group, 20 of 21 had post-XRT PSA recurrence and had been started on HT.

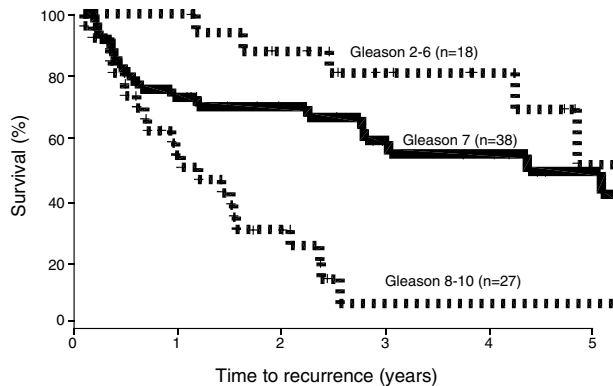


Figure 1 Recurrence-free survival by Gleason Score.

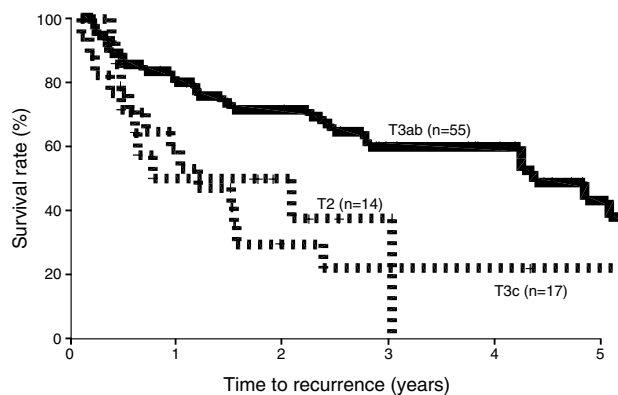


Figure 2 Recurrence-free survival by Pathological Stage.

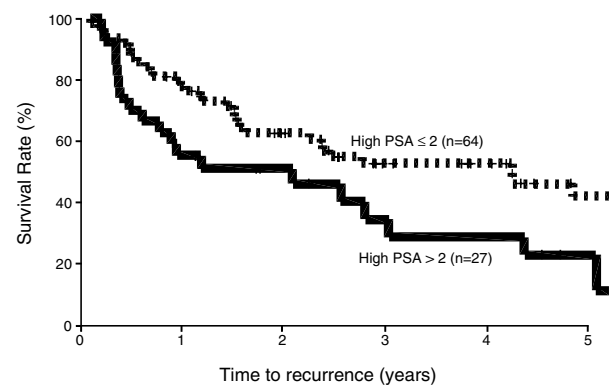


Figure 3 Recurrence-free survival by High Pre-XRT PSA group.

Discussion

The most important findings of our long-term follow-up of the combined A+SXT group was the statistically

Table 3 Influence of selected variables on the change in continence after salvage or adjuvant XRT in 110 men

Variable	Number patients	Improved continence	Worsened continence	<i>P</i> -value
Radiation dose (cGy)				
< 6480	69	10	18	0.185
≥ 6480	35	3	4	1
Unknown	6			
Pelvic field				
Yes	38	6	2	0.289
No	62	7	20	0.019
Unknown	10			
Nerve sparing				
Yes	75	10	12	0.832
No	17	1	8	0.039
Unknown	18			
Post-XRT PSA recurrence at 1 y follow-up				
Yes	23	1	2	1
No	86	12	21	0.163
Unknown	1			

significant worsening incontinence after XRT and in the SXRT group the poorer DFS in patients with Gleason's sum 8–10, seminal vesicle invasion and pre-XRT PSA > 2. Overall, our SXRT cohort had a lower DFS (36%) than reported in the literature, however, our follow-up (median 60.2 months) starts after XRT compared to many studies that start follow-up after RP and our criteria for PSA recurrence after XRT is stringent.

The AXRT group had better DFS compared to the SXRT group, but this is not unexpected because the AXRT patients have no documentation of recurrent disease. They can be expected to have at least a DFS rate equivalent to those with positive margins or seminal vesicle involvement after RP alone. This is reported as 32–74% DFS rate at 5y follow-up as defined by lack of PSA recurrence in RP only with positive margins or positive seminal vesicles.^{11,12} To prove treatment benefit of AXRT a prospective randomized trial comparing observation to postoperative radiotherapy, such as, SWOG 8794, is required. This study is currently in the follow-up phase.

On multivariate analysis our SXRT group revealed some of the same factors (Gleason \geq 8, seminal vesicle invasion, pre-XRT PSA >2) that others have found to be predictive for recurrence. In our study, pathologic T2 patients had increased PSA recurrence after SXRT (64%), with response rates to SXRT similar to those reported by Caddeau *et al.*² Pre-RP PSA >20 and surprisingly negative margins were also associated with increased recurrence rates (76 and 72%). However, these did not reach statistical significance possibly because of small patient numbers and considerable late recurrences in all groups. An argument could be made that negative margins and local disease (pT2) that was completely removed at time of surgery should not have local recurrence and therefore any PSA recurrence is representative of metastatic disease. A similar argument could

be made for patients who recur who had a pre-RP PSA >20.

Pelvic field did not have a statistically significant beneficial effect on disease recurrence. Increased radiation dose did not seem to be of any statistical benefit in this group, but patients who received higher doses of radiation also tended to be more likely to have a pre-XRT PSA >2.0 ng/dl (Table 4).

Owing to the small number of patients who received hormonal therapy in conjunction with XRT, the inconsistent type of hormonal therapy and the variable duration of treatment no conclusions could be drawn in this group. However, there is a prospective randomized trial that does support the use of luteinizing hormone-releasing hormone agonist in the AXRT setting.¹³

Potentially confounding factors are lack of whole-mount prostatectomy specimens, a single post-RP needle biopsy that showed residual benign prostatic glands, use of hormonal therapy and lower doses of radiation than are currently recommended by the American Society for Therapeutic Radiology and Oncology (ASTRO).¹⁴

In contrast to other papers that report on XRT after RP, our patients had considerably worsened potency and decreased urinary continence after XRT compared to after RP only (Table 5).^{15–19}

Many of the patients who received radiation while incontinent remained incontinent (60%) and 22% of patients who received radiation while continent became incontinent or partially incontinent. Many of the patients who were incontinent or partially incontinent pre-XRT were <6 months from the time of RP. The worsened continence that was associated when no pelvic field was used may be due to the lowered dose of radiation, the external sphincter itself receives or may be a statistical phenomenon caused by the small numbers of patients that received pelvic radiation. The worsened continence

Table 4 Salvage XRT dose compared to predictors of recurrence

XRT dose	N=	Recurred	Median follow-up (months)	Gleason score \geq 7	Stage T3a+b	Pre-XRT PSA >2.0 ng/ml
<6120	40	29(73%)	60.4	80% ^a	24 (60%)	8 (20%)
6300–6480	31	13(42%)	47.1	73% ^a	17 (55%)	8 (26%)
6600–7100	15	7(47%)	35.4	87% ^a	11 (73%)	10 (67%)
Unknown	5					

^aShown as percentage because not all specimens received Gleason scoring.

Table 5 Comparison of incontinence and erectile function after prostatectomy and XRT

Author	#	Follow-up (months)	XRT dose (cGy)	Worsened erectile dysfunction	Worsened incontinence
Petroski <i>et al</i> (2004)	110	60	63	52%	26%
Formenti <i>et al</i> (2000)	94	36	45–54	Similar to a group of men who received RP alone	
Schild <i>et al</i> (1996)	60	32	62	Not eval'ed	7%
Morris <i>et al</i> (1997)	88	31	60–64	66%	6.4%
Van Cangh <i>et al</i> (1998)	48	24	60	Not eval'ed	No difference between RP and RP+XRT groups (23 vs 17%)
Forman <i>et al</i> (1998)	67	30	66	Not eval'ed	'<10%'
Pisansky <i>et al</i> (2000)	166	52	64	Not eval'ed	<1%
Vallicenti <i>et al</i> (1998)	69	39	64.8	Not eval'ed	1.5%

in those that did not undergo nerve sparing RP may infer that nerve sparing is associated with better surgical dissection and less direct injury to the external sphincter or that preservation of the nerves improve sphincter function. However, it also may be influenced by small numbers of patients in the non-nerve sparing group. A larger study would be required to definitively determine if nerve sparing RP and pelvic field affect post-RP + XRT continence. After RP alone patients regain urinary continence at varying times with 22% reporting no problem with urinary incontinence at 6 months, 37% at 12 months and 38% at 24 months.²⁰ A prospective randomized study comparing 48 patients who were treated with AXRT within 16 weeks after RP and 52 who had RP alone showed similar incontinence rates (23 vs 17%) at a mean 24 months follow-up post-RP.¹⁹ Our increased incidence of urinary incontinence and erectile dysfunction may be explained by our long follow-up. It has been noted that there is a latency in developing complications of the urinary tract compared to other sites and that the median interval between radiation therapy and development of complications is 28 months.²¹ Questions on potency and continence are included on all standardized follow-up forms thereby prompting the provider to inquire and document the status of each.

Potency status declines with age at a rate of 1% per year in this age group.²² With 5y follow-up, we could expect potency in the post-RP potent group to decrease only 5%, however, after XRT 52% have worsened potency. A confounding factor is that most of this patient group develops recurrent disease and is started on hormonal therapy. Of the 21 patients in the post-RP partial and fully potent group, 20 have recurred after XRT and started hormonal therapy, 50% of these are impotent. Unfortunately the use of hormonal therapy in this group precludes any definite conclusions on the effects of A + SXRT on long-term potency.

Our retrospective review reinforces what many clinicians practice—allow patients to become continent prior to administering XRT. However, data from multiple authors support giving XRT prior to significant PSA elevation, making waiting for continence to return potentially risky. A theoretical compromise is to start hormonal therapy while waiting for continence to recover but this has not been tested and would require a randomized trial to prove its efficacy. Radiation after prostatectomy adversely affects urinary continence even in those fully continent when starting radiation therapy. Men who have had nerve sparing RP are more likely to preserve their continence after XRT. Multivariate analysis showed that pathologic stage T2 and T3c, Gleason score 8–10 and post-RP PSA > 2.0 ng/ml were predictive of PSA recurrence after salvage XRT. Extensive use of hormonal therapy and low potency rates after RP precluded any definitive conclusions on the effect of radiation on potency in this select population.

Acknowledgements

This research was supported by the following: The Center for Prostate Disease Research, a program of the Henry M Jackson Foundation for the Advancement of

Military Medicine, 1401 Rockville Pike, Suite 600, Rockville, MD 20852-3001, funded by the US Army Medical Research and Materiel Command. This research was approved through the Department of Clinical Investigation, Walter Reed Army Medical Center, Washington, DC, WU# 2857-98 and WU#2852-98.

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