Published in final edited form as:

Urology. 2008 September ; 72(3): 654–658. doi:10.1016/j.urology.2007.11.020.

Residual Prostate Cancer Following Radiotherapy: A Study of Radical Cystoprostatectomy Specimens

David J. Kaplan¹, Paul L. Crispen¹, Richard E. Greenberg¹, David Y.T. Chen¹, Rosalia Viterbo¹, Mark K. Buyyounouski², Eric M. Horwitz², and Robert G. Uzzo^{1,*}

¹Department of Urologic Oncology, Fox Chase Cancer Center, Philadelphia, PA

²Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA

Abstract

Objective—The incidence of histologic prostate cancer (CaP) following definitive radiation therapy (RT) for localized disease is rarely quantitated. Here we investigate the relationship between PSA and histologically residual CaP following definitive RT in patients undergoing radical cystoprostatectomy (RCP) for unrelated indications.

Methods—We reviewed our prostate cancer database to identify patients undergoing RCP who previously received definitive RT for localized CaP. Pre-radiation variables examined include PSA, Gleason score, radiation modality and dose. Post-radiation variables reviewed include PSA, time to RCP, the presence of histologically proven prostate cancer, and Gleason score.

Results—We identified 21 patients who underwent RCP at a median of 60 months following RT for localized CaP. Pre-radiation Gleason scores were low (≤ 6) to intermediate risk (3+4) in 82% (14/17), intermediate (4+3) to high (≥ 8) in 18% (3/17), and unavailable in 4 patients. Median pre-radiation PSA was 9 ng/ml. Median PSA prior to RCP in all patients was 0.8 ng/ml. 52% (11/21) of patients demonstrated active CaP in the RCP specimen. Although 89% (16/18) of patients met the Phoenix definition of biochemical freedom from disease, 50% (8/16) of these patients had histologically residual CaP at the time of RCP. Median PSA was not significantly different between patients with and without active CaP.

Conclusions—Histologic evidence of CaP was noted in 50% of patients demonstrating biochemical freedom from disease at the time of RCP. While the biological significance of active CaP in this select population is uncertain, our findings demonstrate the limitations of PSA in monitoring CaP disease activity following definitive RT.

Keywords

Prostate Cancer; Radiation Therapy; Biochemical Failure; PSA

Introduction

Modalities utilized in the definitive treatment for clinically organ confined prostate cancer (CaP) include radical prostatectomy, radiation therapy (RT), and cryotherapy. Following

*Correspondence: Robert G. Uzzo, MD, Department of Urologic Oncology, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA, Email: r_uzzo@fccc.edu, Phone: 215-728-3501, Fax: 215-214-1734.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

treatment, surveillance for disease recurrence is based on physical exam and serial measurements of serum prostate specific antigen (PSA). While contemporary series have shown similar outcomes as measured by biochemical control or “PSA success,” the definition of disease recurrence differs between treatment modalities.^{1,2}

Although PSA should be undetectable following prostatectomy, several definitions of PSA failure have been proposed for these patients. A recent comprehensive literature search of the CaP data revealed 53 varying definitions for biochemical recurrence in patients treated with radical prostatectomy. While the most common definition of this phenomenon was a PSA ≥ 0.2 ng/ml, a consensus has not been reached.³

The assessment of biochemical recurrence after RT however, may be more difficult due to the prolonged therapeutic effect of this modality as well as the presence of residual benign prostate tissue, which produces PSA. The difficulty in defining disease recurrence following RT is reflected in the need to redefine biochemical recurrence on several occasions. The 1996 criteria by the American Society of Therapeutic and Radiation Oncologists (ASTRO) defined biochemical recurrence after RT for CaP as three consecutive PSA rises from the biochemical nadir with the time of recurrence being backdated halfway between the date of the nadir and the first rise in PSA.⁴ These criteria were modified in 2005 and are known as the Phoenix definition.⁵ The current definition of biochemical recurrence after RT is PSA elevation greater than 2ng/ml from the PSA nadir with the date of failure being that of the first rise in PSA. Importantly, the Phoenix definition has been shown to predict clinical outcomes including; systemic progression and cancer specific mortality.

Unfortunately, PSA is an imperfect measure of CaP disease activity following RT.^{6,7} Additionally, existing post-radiation biopsy data may in fact underestimate the true incidence of active CaP in this population of patients due to the inherent limitations of transrectal biopsies in demonstrating recurrent CaP. The goal of this study is to evaluate the presence of histologically residual CaP following RT in patients without evidence of biochemical failure. To this end, we evaluated radical cystoprostatectomy (RCP) specimens for the presence of histological CaP in a group of patients previously treated with RT for non-metastatic disease.

Materials and Methods

A retrospective review of the Fox Chase Cancer Center tumor registry was performed to identify patients having undergone RT for localized CaP with curative intent, who subsequently required RCP for bladder pathology from January 1990 to June 2007. Eligible patients received either definitive brachytherapy or external beam radiation and subsequently underwent RCP for a non-CaP related disease at a later date. Patients undergoing radical retropubic prostatectomy followed by adjuvant or salvage radiation therapy prior to RCP were excluded from analysis. No patient had undergone RCP for palliation or disease specific control of known recurrent local or systemic CaP.

Patients meeting inclusion criteria were evaluated for the following variables prior to radiation therapy: Gleason score, PSA, and mode/dose of radiation received. Patients were further categorized as having low, intermediate, or high risk CaP at the time of presentation.⁸ Radiation therapy techniques were categorized as external beam or brachytherapy. Post-radiation variables examined included: CaP pathologic stage at RCP, Gleason score in RCP specimen, PSA prior to RCP, bladder pathology and time from RT to RCP. Clinical and pathologic stage was assigned according to the 2002 AJCC TNM staging criteria. Definition of biochemical failure following RT was assigned using the Phoenix definition (PSA nadir + 2).⁵

Data were collated and analyzed to assess differences between PSA prior to RCP in patients with and without active prostate cancer in RCP specimens. Statistical analysis was performed

using Graph Pad InStat software, San Diego, California. Statistical significance was considered with $p < 0.05$.

Results

A total of 21 patients were identified meeting our inclusion criteria (Table 1). The median age at diagnosis of prostate cancer was 71 years (mean 69, range 54-80). Initial PSA at the time of diagnosis of prostate cancer was 9.0 ng/ml (mean 14.5, range 3.13-80). The median Gleason score at time of diagnosis was 6 (range 5-9). 19% (4/21) had definitive brachytherapy while 81% (17/21) had undergone external beam RT. The median dose external beam dose was 7200 cGy (range 6800-8100). Radiation dose information for the brachytherapy patients was only available for two of the 4 patients. Individual and summary data are presented in Tables 1 and 2 respectively. The majority of patients 83% (15/18) had low to intermediate risk localized disease while only 17% (3/18) had high risk clinically localized prostate cancer.

The median duration between RT and RCP was 60 months (mean 71, range 15-156). Indications for RCP following definitive radiation therapy for CaP included: bladder cancer (N=19), radiation cystitis (N=1), and local invasion of rectal cancer (N=1). Prior to RCP, median PSA was 0.8 ng/ml (mean 1.36, range 0-6.8). 86% (18/21) of patients had post-radiation PSA data available to evaluate biochemical failure. 89% (16/18) of patients met the Phoenix definition for biochemical freedom from disease. Histologically residual CaP was noted in 52% (11/21) of all RCP specimens despite a history of definitive RT. Figure 1 demonstrates irradiated prostatic tissues without (Panel A) and with (Panel B) active CaP at the time of RCP. In the patients considered free of disease according to the Phoenix definition, 50% (8/16) had histologically residual CaP at the time of RCP. The median PSA in patients with residual CaP at the time of RCP was 1.0 ng/ml (mean 1.86, range 0.1-6.8), while it was 0.6 ng/ml (mean 0.71, range 0-2.3) in patients without evidence of CaP. PSA values were not statistically different between these groups, $p=0.44$. Moreover, the time interval between RT and RCP did not differ significantly between patients with (median 94, mean 87, range 18-156) and without (median 36, mean 55, range 15-144) residual CaP at time of RCP, $p=0.11$. Gleason score was upgraded in 57% (4/7) of patients who had both pre and post RCP data available.

Discussion

The ability of post-treatment surveillance to detect disease recurrence and/or persistence is critical in assessing treatment success and the planning of salvage therapy. Our study suggests that PSA alone does not accurately assess CaP activity in patients following RT. We observed that PSA prior to RCP was not significantly different between patients with and without histologically residual CaP in RCP specimens following definitive RT. Furthermore, 50% of patients had active CaP at the time of RCP despite meeting the Phoenix definition of biochemical success. Although, it is difficult to quantify the clinical significance of histologic CaP following RT, it is likely that the residual CaP represents persistent and/or under-treated disease. There are several possible explanations for poor predictive value of PSA for active CaP following RT. These include misclassification of active CaP, timing of CaP disease assessment, and the decreased ability of PSA to reflect locally persistent CaP following RT.

The differentiation between active CaP and post-RT changes may be histologically challenging. Ongoing controversy exists for determining the best way to follow patients who were initially treated with RT. This difficulty is in large part due to the prolonged effects of RT for destroying viable cancer cells, as well as the presence of residual prostate tissue architecture and glandular function, which can continue to produce PSA. Of primary importance is the ability to differentiate prostatic carcinoma from radiation treatment effects in the appropriate setting, and to identify small residual foci of disease. Pathologic examination

of post-RT prostate specimens may demonstrate cellular atrophy, decreased number and size of glandular acini, and squamous metaplasia.⁹ The most common finding in irradiated prostate tissue is atypical basal cell hyperplasia, which can often be identified by cytoplasmic clearing and atypical nuclei in the same glandular acini that contain more typical appearing cells.^{9,10} Additionally, while vascular changes such as narrowing of vessel lumens from intimal hyperplasia may be seen in irradiated specimens, it is rare to identify vascular ectasia and fibrinoid necrosis which can be present in specimens with active CaP. Conversely, one of the hallmarks of malignancy is peri-neural invasion, which should not be seen in specimens with post-RT effects alone. In difficult cases, CaP can be identified with the finding of “retraction artifact” in high-power fields as well as the presence of intraluminal crystalloids and blue mucin, which are more common findings in malignant glands.¹⁰

Another confounding factor when evaluating CaP activity is the timing of disease assessment in relation to the completion of RT. Following RT, complete treatment effect is not expected for at least 12-18 months or longer, as radiation treatment does not kill cells immediately upon exposure. Prior series investigating the role of post-RT biopsy in evaluating CaP activity recommend waiting at least 24-36 months to avoid false positive biopsies. This point is supported by repeat biopsy data which demonstrated regression of disease on subsequent biopsies.⁶ The median duration of time between RT and RCP in the current series was 60 months. Additionally, with the known relationship between preoperative PSA and tumor volume in prostatectomy series, patients with clinically occult active CaP and a low PSA may simply have small volume disease.¹¹⁻¹³ Such patients may go on to demonstrate biochemical failure with extended follow-up due to subsequent tumor growth. This concept is supported by the known natural history and PSA kinetics of small volume CaP observed in active surveillance series.^{14,15}

There are several disparities in opinion on how to follow patients treated with definitive RT for CaP by serial assessment of PSA. Controversy surrounding the use of PSA monitoring post-RT is derived primarily from its inability to differentiate between local and distant disease recurrence, as well as the “bounce” effect commonly seen after RT. The ability of post-RT prostate biopsies to predict biochemical recurrence is a topic that has been previously investigated. Several series have demonstrated that patients meeting the criteria for biochemical failure have a higher rate of residual CaP on post-RT biopsy specimens.¹⁶⁻¹⁸

In a report defining biochemical recurrence by the Phoenix definition (PSA nadir + 2), it was found that 52% of patients without evidence of biochemical recurrence had an abnormal prostate biopsy 24 months following RT.⁷ Abnormal biopsies were defined as atypical cells (35%), malignant cells (15%), or biopsies with treatment effect (50%). The authors noted two important points. First, patients who were shown to have an abnormal biopsy had a significantly greater likelihood of developing biochemical recurrence compared to patients with a normal biopsy. Second, multivariate analyses showed that biopsy results were independent of PSA status in predicting biochemical recurrence. In a study by Crook et al., the incidence of active CaP following RT was 15%, despite meeting the 1996 ASTRO criteria for biochemical success.⁶ A third study by Pollack et al., revealed residual CaP in 30% of patients which were prospectively biopsied 2 years following RT without evidence of biochemical failure¹⁹. Although the occurrence of active CaP following RT in patients who are biochemically NED following RT has been documented in the past, the reported rates are lower than the observed rate in the current series of 50%. The most likely explanation for this discrepancy is the manner in which residual CaP was evaluated. In our series, RCP specimens were evaluated which allowed complete histopathologic evaluation of the entire prostate, while the other described series relied on transrectal biopsy evaluation. The limitations of transrectal biopsy in evaluating the presence of CaP are well described, with sampling error being of significant concern.⁶

There are several limitations of the current series. Because a subset of patients had their CaP treated at outside institutions, complete clinical and pathologic data including the details of their radiation treatment were not available on all patients. In addition, our series was retrospective and made up of a relatively small population of patients. With the small sample size presented, the study may be underpowered to detect a significant difference between PSA values in patients with and without active CaP at the time of RCP. However, the need for RCP following RT for CaP is infrequent and a prospective approach to evaluating this question is impractical. Despite these limitations, our series provides a unique look at the occurrence of histological CaP following RT in patients who meet the current definition of biochemical success.

Conclusions

CaP disease surveillance following RT based on PSA does not capture all patients with recurrent or persistent disease. The true incidence of active CaP following RT in prior series may have been underestimated secondary to the sampling error associated with transrectal biopsy. The current series demonstrates 50% of RCP specimens containing active CaP despite meeting the Phoenix definition of biochemical success. Identification and development of novel methods in monitoring CaP disease activity following RT warrant future investigation.

References

1. Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, Spangberg A, Busch C, Nordling S, Garmo H, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005;352:1977–84. [PubMed: 15888698]
2. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, von Eschenbach AC, Kuban DA, Rosen I. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53:1097–105. [PubMed: 12128107]
3. Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico AV, Dmochowski RR, Eton DT, Forman JD, Goldenberg SL, Hernandez J, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol* 2007;177:540–5. [PubMed: 17222629]
4. Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997;37:1035–41. [PubMed: 9169810]
5. Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, Sandler H. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65:965–74. [PubMed: 16798415]
6. Crook J, Malone S, Perry G, Bahadur Y, Robertson S, Abdoell M. Postradiotherapy prostate biopsies: what do they really mean? Results for 498 patients. *Int J Radiat Oncol Biol Phys* 2000;48:355–67. [PubMed: 10974448]
7. Vance W, Tucker SL, de Crevoisier R, Kuban DA, Cheung MR. The predictive value of 2-year posttreatment biopsy after prostate cancer radiotherapy for eventual biochemical outcome. *Int J Radiat Oncol Biol Phys* 2007;67:828–33. [PubMed: 17161554]
8. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, Tomaszewski JE, Renshaw AA, Kaplan I, Beard CJ, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *Jama* 1998;280:969–74. [PubMed: 9749478]
9. Magi-Galluzzi C, Sanderson H, Epstein JI. Atypia in nonneoplastic prostate glands after radiotherapy for prostate cancer: duration of atypia and relation to type of radiotherapy. *Am J Surg Pathol* 2003;27:206–12. [PubMed: 12548167]

10. Cheng L, Cheville JC, Bostwick DG. Diagnosis of prostate cancer in needle biopsies after radiation therapy. *Am J Surg Pathol* 1999;23:1173–83. [PubMed: 10524518]
11. Stamey TA, Caldwell M, McNeal JE, Nolley R, Hemenez M, Downs J. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years? *J Urol* 2004;172:1297–301. [PubMed: 15371827]
12. Miyake H, Sakai I, Harada K, Hara I, Eto H. Prediction of potentially insignificant prostate cancer in men undergoing radical prostatectomy for clinically organ-confined disease. *Int J Urol* 2005;12:270–4. [PubMed: 15828954]
13. Alschibaja M, Wegner M, Massmann J, Funk A, Hartung R, Paul R. Prostate cancer volume -- can it be predicted preoperatively? *Urol Int* 2005;75:354–9. [PubMed: 16327306]
14. Zhang L, Loblaw A, Klotz L. Modeling prostate specific antigen kinetics in patients on active surveillance. *J Urol* 2006;176:1392–7. [PubMed: 16952640]discussion 1397-8
15. Warlick CA, Allaf ME, Carter HB. Expectant treatment with curative intent in the prostate-specific antigen era: triggers for definitive therapy. *Urol Oncol* 2006;24:51–7. [PubMed: 16414495]
16. Dugan TC, Shipley WU, Young RH, Verhey LJ, Althausen AF, Heney NM, McManus PL, Abraham EH. Biopsy after external beam radiation therapy for adenocarcinoma of the prostate: correlation with original histological grade and current prostate specific antigen levels. *J Urol* 1991;146:1313–6. [PubMed: 1719244]
17. Gaudin PB, Zelefsky MJ, Leibel SA, Fuks Z, Reuter VE. Histopathologic effects of three-dimensional conformal external beam radiation therapy on benign and malignant prostate tissues. *Am J Surg Pathol* 1999;23:1021–31. [PubMed: 10478661]
18. Stone NN, Stock RG, White I, Unger P. Patterns of local failure following prostate brachytherapy. *J Urol* 2007;177:1759–63. [PubMed: 17437808]discussion 1763-4
19. Pollack A, Zagars GK, Antolak JA, Kuban DA, Rosen II. Prostate biopsy status and PSA nadir level as early surrogates for treatment failure: analysis of a prostate cancer randomized radiation dose escalation trial. *Int J Radiat Oncol Biol Phys* 2002;54:677–85. [PubMed: 12377318]

Abbreviations

CaP	prostate cancer
cGy	centigray
EBRT	external beam radiation therapy
n/a	not available
NED	no evidence of disease
PSA	prostate specific antigen
RCP	radical cystoprostatectomy
RT	radiation therapy

Figure 1.

Histologic appearance of irradiated prostate with and without active CaP at the time of RCP. Panel A demonstrates benign glands with radiation effect. The represented specimen was treated with EBRT for low risk CaP. RCP was performed 48 months following RT for recurrent pTis of the bladder. Panel B demonstrates active CaP at the time of RCP following EBRT. Gleason pattern 3 CaP is apparent within the previously irradiated prostate. The patient presented with intermediate risk CaP with a PSA of 14.9 ng/ml and Gleason 3+3=6 on transrectal biopsy. Following RT the patient did not demonstrate biochemical recurrence with a PSA nadir of 0.3 ng/ml. RCP was performed 106 months following RT for invasive urothelial carcinoma.

Table 1
Histologically Residual CaP in RCP Specimens Following RT

Pre-RT PSA	Pre-RT Gleason	Type of RT	Dose of RT (cGy)	Time from RT to RCP (months)	PSA at RCP	Residual CaP (Y/N)	Gleason at RCP	Initial CaP Stage	CaP Stage at RCP	Bladder Pathology
5.6	6	EBRT	7020	48	0.9	N	0	T1c	T0	T1
9.9	5	EBRT	7200	97	0.8	N	0	T2a	T0	T2
n/a	7	EBRT	n/a	36	5.7	Y	8	T3	T4	T3b
n/a	n/a	EBRT	6840	144	6.8	Y	9	n/a	T3	T3b
n/a	6	EBRT	6800	36	1.4	Y	7	T3	T3	Tis
3.7	6	EBRT	n/a	97	0.2	N	0	T2b	T0	T3a
n/a	n/a	EBRT	6840	60	0.4	N	0	n/a	T0	T1
80	6	EBRT	n/a	n/a	0	Y	6	T2c	n/a	Tis
n/a	n/a	EBRT	7200	84	0.1	Y	n/a	T3	n/a	T3a
14.9	6	EBRT	n/a	106	1.0	Y	7	T1c	T4	T2
5.3	6	BT	7200	28	n/a	Y	n/a	T1c	T2a	Tis
7.8	7	EBRT	7200	126	0.9	N	0	T2b	T0	T3a
18.9	6	EBRT	n/a	15	3.1	Y	5	T1c	T2b	T2
3.13	7	BT	5800	30	0.1	Y	8	T3	T3	T3b
4.1	7	EBRT	n/a	21	0.4	Y	6	T2a	T2a	T4
n/a	9	EBRT	n/a	49	0	Y	n/a	n/a	T2a	T3a
9.0	5	BT	n/a	156	0.5	N	0	T1c	n/a	Rectal ca.
n/a	n/a	EBRT	n/a	128	n/a	N	0	n/a	T0	T4
14	6	EBRT	8100	48	n/a	N	0	n/a	T0	Tis
n/a	7	BT	n/a	18	0.2	N	0	n/a	T0	Cystitis
12	7	EBRT	7800	90	2.0	N	0	T1c	T0	T4

Table 2

Prostate and Bladder Cancer Pathology

Age at Diagnosis	Median	71
	Mean	69
	Range	54-80
Initial PSA (ng/ml)	Median	9.0
	Mean	14.5
	Range	3.13 – 80
Initial Gleason Sum	≤7(3+4)	14 (82%)
	≥7(4+3)	3 (18%)
Risk Category	Low	6
	Intermediate	9
	High	3
	n/a	3
Mode of Radiation	External Beam	17
	Conventional	8
	3D Conformal	6
	IMRT	3
	Brachytherapy	4
Dose of Radiation (cGy)	Median	7200
	Mean	7042
	Range	5800-8100
Post-RT Gleason Sum	≤7(3+4)	4 (50%)
	≥7(4+3)	4 (50%)
Time from RT to RCP	< 2 years	3 (15%)
	2-5 years	8 (40%)
	> 5 years	9 (45%)
Bladder Cancer Histology	Urothelial	16 (84%)
	Squamous	3 (16%)
Bladder Cancer Pathologic Stage	T1/CIS	6 (32%)
	T2	3 (16%)
	T3a	4 (21%)
	T3b	3 (16%)
	T4	3 (16%)
%Total Patients with Residual CaP		52% (11/21)

n/a= not available