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Jacobs Journal of Radiation Oncology

Research Article

A Closer Look at Extraprostatic Extension: Evaluation of PSA Relapse Rates Following Prostatectomy for pT3aN0 Prostate Cancer with or without Margin Involvement

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Received: 08-15-2014

Accepted: 09-16-2014

Published: 09-24-2014

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Abstract

Introduction: Extraprostatic extension (EPE) is an established risk factor for recurrence following radical prostatectomy (RP); however, often this is identified in the context of other high-risk features. The present study describes the outcomes and risk factors for pT3aN0 patients with EPE who were followed without adjuvant therapy.

Methods: Retrospective analysis of patient- and tumor-specific factors. Eligible patients underwent RP for biopsy-proven prostate adenocarcinoma and pathologic finding of EPE. Patients with PSA >30 at diagnosis, involved seminal vesicles or lymph nodes at RP, or who received adjuvant therapy (hormone or radiation) were excluded.

Results: Between 2003 and 2010, 544 patients underwent RP, of whom 95 had EPE and were eligible for analysis. The median age was 64 years (range 44-74), and pre-RP PSA 6.1 (1.8-25.4). At median follow-up of 64 months (13.3-136.5), 38 patients had experienced recurrence at a median of 18 months post-RP (1.2-129.8). Overall, the 5-year recurrence rate was 39.2%; associated factors included pre- and post-RP PSA and Gleason score, and margin status. Subset analysis demonstrated no failures at 5 years for Gleason 6 patients with EPE but negative margins, while all other Gleason/margin subsets demonstrated >20% risk.

Conclusion: EPE alone remains a high risk feature for disease failure. Longer follow-up is necessary to determine whether the low-risk group may be safely followed with surveillance. Low-grade EPE cases with involved margin and all Gleason ≥7 patients with EPE (irrespective of margin) have high rates of early PSA relapse, and should be recommended early adjuvant therapy to optimize disease control.

Introduction

Pathologic evidence of extraprostatic tumor is an established risk factor for recurrence following prostatectomy [1,2], and randomized trials including this as a stand-alone criterion for adjuvant radiation therapy have demonstrated improved disease control outcomes [3-5], resulting in recent consensus statements to recommend discussion of these benefits [6]. Unfortunately, in the absence of other high-risk factors (e.g., involved surgical margin and/or seminal vesicle invasion), there has been non-uniformity of adoption of these guidelines for patients with extraprostatic tumor to be referred for adjuvant radiation therapy [7,8]. The present investigation seeks to describe outcomes for a series of node-negative, seminal vesicle-uninvolved prostatectomy patients with extraprostatic extension who were followed without adjuvant therapy, in order to determine whether low- or high-risk subsets exist.

Methods

Following Institutional Review Board approval at the study institutions, a research database was created with study-specific patient, treatment, and outcome data fields. Eligible cases were identified by review of medical records and quality assurance database. After selection for prostate adenocarcinoma cases, a review of patient records was performed in order to eliminate patients with advanced or metastatic disease at diagnosis (including pre-prostatectomy evidence of seminal vesicle or pelvic lymph node involvement) or PSA >30 ng/mL at diagnosis. Pre-operative staging studies were performed at the discretion of the managing urologist, with bone scan and CT scans generally performed for patients with Gleason 8-10 or PSA >20 ng/mL. All patients underwent radical retropubic prostatectomy as primary curative-intent therapy. Patients with involved seminal vesicles and/or lymph nodes, who received immediate adjuvant therapy (radiation or hormone), or who were lost to follow-up within one year of prostatectomy (no PSA >12 months post-operatively) were excluded from the analysis.

Standard pathologic specimen preparation techniques were employed [8], generally consisting of formalin fixation for 4-24 hours, followed by inking of the radial margins. The apex and base are excised and submitted entirely, with a perpendicular sectioning technique, and 3-4mm serial sectioning of the remainder of the gland. Pathology reports were reviewed in order to identify cases with extraprostatic extension, defined as presence of tumor beyond the fibrous stromal layer surrounding the prostate gland. Specimen slides were re-reviewed by a pathologist from each participating institution, who was blinded to patient disease control outcome. Additionally, cases with involved or "close" (≤1mm) margin(s) were also reviewed for accuracy. A margin was considered involved if there was no cell layer or fibrous stroma separating cancer cell(s) from the inked margin.

Post-operative evaluations included physical examination and PSA measurement every 3-6 months for the first 2 years post-prostatectomy, and every 6-12 months thereafter. In the setting of PSA or clinical relapse, re-staging imaging and subsequent intervention(s) were performed at the discretion of the managing urologist.

The principal outcome measure of this retrospective study was freedom from failure, specifically post-prostatectomy PSA, measured from date of prostatectomy to date of first rising PSA >0.15 ng/mL, or last follow-up or death, if no PSA rise occurred. Patients with stable post-operative PSAs at 0.1 ng/mL were not considered disease failures. Secondary objectives included analysis of factors associated with freedom from failure, and identification of low- and/or high-risk subsets based upon this.

Statistical Analysis

The Kaplan-Meier method was employed to estimate freedom from failure for the entire population and subsets. Cox proportional hazards model was used to identify continuous and dichotomous variable association with disease control; categorical variables were analyzed by log-rank analysis. Analyses were performed using SPSS Version 21 (SPSS, Inc.; Chicago, IL, USA).

Results

Between January 2003 and December 2010, 544 patients diagnosed with prostate cancer underwent radical prostatectomy at the study institutions. Of these, 95 were eligible for inclusion in the present study. Of note, 5 patients were excluded on the basis of receiving adjuvant radiation therapy. Patient demographics and pre-operative staging information are outlined in Table 1. Surgical and pathology data are demonstrated in Table 2.

Table 1. Patient Demographics and Tumor Characteristics.

		N	%
Age			
Median	64 yrs		
(Range)	(44-74)		
Race			
White		94	99
PSA*			
Median	6.1 ng/mL		
(Range)	(1.8 – 25.4)		
≤10		77	82
>10-20		13	14
>20-30		4	4
Gleason Score at Biopsy			
6		49	52
7		40	42
8		6	6
Clinical Tumor Stage[$]			
T1c		70	74
T2a		18	19
T2b		4	4
T2c		2	2

**Less one patient without pre-prostatectomy PSA & T-stage. $American Joint Committee on Cancer, TNM Staging Manual, version 7.0;*

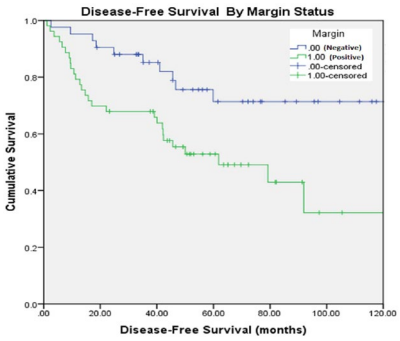
Table 2. Surgical Pathology, Treatment, and Post-Operative Data.

		n	%
Interval Biopsy to RP*			
Median	48 days		
(Range)	(13-512*)		
Nerve-Sparing RP?			
Yes		79	83
Prostate Volume			
Median	43.5 cc		
(Range)	(16-150)		
Pathologic Gleason Score			
6		30	32
7		50	53
8		13	14
9		9	9
Surgical Margin			
Negative		43	63
Positive		52	37
Capsular Involvement			
Focal Penetration		75	79
Extensive/Multifocal		20	21
Lymph Node (LN) Evaluation			
Evaluated		85	89
Median Removed	4 LNs		
(Range)	(0-16)		
Perineural Invasion?			
Yes		79	83
No		4	4
Not recorded		12	13

**RP = radical prostatectomy; all but 2 patients with interval <180 days, owing to cardiac concerns and/or patient decision*

At a median PSA follow-up of 64.0 months (range 13.3-136.5, with 55% followed ≥5 years), 38 patients had experienced disease recurrence at a median of 18.0 months (1.2-129.8). These included 28 of 54 patients (52%) with involved margin(s) versus 10 of 41 (24%) with negative margins (HR 2.775; p=0.006), with 5-year disease control estimates of 52.9% (95% CI, 38.6-67.2%) and 71.4% (55.4-87.4%), respectively (Figure 1).

Figure 1. Disease-Free Survival for Patients with EPE, by Margin Status.



For the entire population of patients with EPE, the 5-year PSA relapse-free survival was 60.8% (50.1-71.5%).

Analysis of factors associated with freedom from failure demonstrated statistically significant associations with pre-prostatectomy PSA and PSA velocity, initial post-prostatectomy PSA, Gleason score at biopsy and prostatectomy, primary Gleason grade at prostatectomy, interval from biopsy to prostatectomy, involved surgical margin(s) (Table 3). Next, a subset analysis was performed in order to determine whether a low or high risk subset could be identified. As demonstrated in Table 4, patients with Gleason 6 and negative surgical margins had no PSA relapses at 5 years. All other subsets, including Gleason 6 with involved margin or Gleason ≥7 with or without margin involvement had PSA relapse >20% at 5 years.

Table 3. Univariate Analysis of Factors Associated with Disease Control and Survival.

	Freedom From Failure	
	exp(b)	p-value
Age	0.963	0.128
Pre-Operative PSA	**1.138**	**0.001**
PSA Velocity	**1.107**	**0.046**
Gleason Score at Biopsy	**1.879**	**0.01**
Interval from Biopsy to RP*	**1.005**	**0.043**
Nerve-Sparing RP?	1.189	0.699
Prostate Volume	1.008	0.34
Primary Gleason at RP	**2.433**	**0.003**
Overall Gleason at RP	**1.972**	**0.001**
Margin Status	**2.775**	**0.006**
Extent of EPE	1.457	0.308
Initial Post-RP PSA	**4.39**	**<0.0001**

**RP = Radical prostatectomy*

Table 4. Five-Year Failure Rates for EPE Population by Gleason Score and Margin Status.

Gleason Score at RP (n)	**Margin**	**5y Failure (95% CI)**
Gleason 6 (30)	-	0% (-)
	+	33.3% (9.9-56.7%)
Gleason 7 (50)	-	28.1% (5.2-51.0%)
	+	50.4% (29.5-71.3%)
Gleason 8-9 (15)	-	62.5% (22.1-100%)
	+	71.4% (29.6-100%)

Discussion

Based upon similar findings from three randomized trials with mature follow-up [3-5], the American Society for Radiation Oncology (ASTRO) and American Urological Association (AUA) released consensus statements recently urging discussion of adjuvant radiation therapy in the setting of one or more of the high-risk features employed in the studies [6]. While the early results of the trials had demonstrated significant improvements in disease control, adoption of early adjuvant radiotherapy has been non-uniform [7,8]. The existence of the sizeable population of the present study exemplifies this issue.

While multivariate analyses have identified extraprostatic extension as an independent high-risk feature for disease recurrence [1,2], there have been few contemporary reports detailing outcomes for uniformly-managed patients with this high-risk feature alone. Within the phase III Southwest Oncology Group (SWOG) 8794 trial, 227 node-negative and seminal vesicle-uninvolved patients were included, of whom 47 had extraprostatic extension only (without involved margin) [9]. The 5-year PSA control rate for this subset was 55%, with benefit of radiotherapy preserved. Similarly, investigators from the University of Western Ontario (Canada) retrospectively described outcomes for a group of heterogeneously-treated, node-negative, seminal vesicle-uninvolved patients with extraprostatic extension and/or involved margins [10]. The study demonstrated a higher rate of PSA failure for patients with extraprostatic extension and involved margin (51.5%) as compared with those who had extraprostatic extension with negative margins (21.8%), similar to our own study findings. The primary weakness of the Western Ontario data is the inclusion of patients treated with various adjuvant therapies (including radiation and/or hormone therapy), including 13 of 28 with extraprostatic extension plus involved margins and 9 of 36 with negative margins.

While the present study findings support extraprostatic extension as a stand-alone risk factor for early PSA relapse, there does remain some consternation regarding the use of adjuvant radiotherapy in the setting of undetectable PSA post-operatively, regardless of other high-risk features. Indeed, our own dataset confirm elevated initial post-prostatectomy PSA as significantly inversely associated with subsequent PSA control. Despite this, subset analyses from the SWOG 8794 and European Organisation for Research and Treatment of Cancer (EORTC) 22911 trials demonstrated similar benefit of adjuvant radiotherapy over observation for patients with "undetectable" PSA (defined as ≤0.2) as compared with detectable (HR=0.6) [11,12]. Additionally, a third randomized trial (ARO 96-02), which included only patients with undetectable post-prostatectomy PSA, demonstrated similar findings (HR=0.5 for radiotherapy) [5]. Thus, patients with extraprostatic extension should be considered for adjuvant radiotherapy regardless of initial post-prostatectomy PSA, particularly as subsequent data have demonstrated additional disease control benefit for radiotherapy doses higher than those employed in the randomized trials [13].

One factor intrinsic to any study evaluating extraprostatic extension or surgical margin status is the pathologic specimen preparation technique employed. Though historically there have been several acceptable preparation, sectioning, and reporting techniques [14], guidelines have been developed to improve uniformity of reporting, processing and reporting prostate biopsies and prostatectomy specimens, based upon recommendations from the College of American Pathologists [15]. While this is an important factor which bears mentioning in any study of high-risk pathologic features, we feel that the techniques employed in the present investigation are representative of those employed in community and academic pathology departments, and thus the findings should translate well into general practice.

Perhaps the most interesting finding of the present investigation is the identification of a low-risk subgroup; specifically, Gleason 6 with negative margins. To our knowledge, this is the first report to identify such a group, though our enthusiasm is tempered by the small sub-population size (n=12) and requirement of longer follow-up. That being stated, if further investigation should bear out a reduced rate or delayed timing of failure, then the next question is whether delayed salvage (rather than immediate adjuvant) radiotherapy may be a safe option for these patients. While no prospective trials on this topic have been reported, a retrospective matched-control study of node-negative, hormone-naive patients treated with adjuvant versus salvage radiotherapy demonstrated improved PSA control for the adjuvant group (90% versus 65% at 3 years) [16]. Interestingly, when the salvage group was subdivided by PSA at the time of intervention, patients treated with "early salvage" (defined as PSA <0.5) had PSA control rates similar to the adjuvant group (86%). Thus, close PSA surveillance of this low-risk group, with early salvage radiotherapy, may be a reasonable option. Other investigators have identified similar findings, with outcomes of early salvage radiotherapy (lower peak post-prostatectomy PSA) approaching that of adjuvant therapy [17-19]. Thus, if the findings of the present investigation are validated in a larger dataset with more mature follow-up, surveillance may be a reasonable option, provided early salvage is employed when indicated.

For the remainder of patients, including those with higher-grade tumors (regardless of margin status) and Gleason 6 with involved margin, early failure rates exceed 20%, and the benefit from early (adjuvant) radiotherapy seems more apparent. While there remains some concern regarding the benefit of adjuvant local therapy in the context of higher-grade disease [20], the long-term SWOG data have demonstrated decreased

distant metastatic failure for the use of adjuvant radiotherapy to the prostate fossa, with benefit most apparent in patients with Gleason score ≥7 [11].

Conclusions

Within the present study, patients with extraprostatic extension have elevated rates of PSA relapse within 5 years of RP. Longer follow-up is necessary to determine whether the low-risk subgroup of Gleason 6 patients with negative margins may be safely observed. Low-grade EPE cases with involved margin and/or higher-risk Gleason score patients with any EPE/margin involvement have high rates of early PSA relapse, and should be recommended early post-operative (adjuvant) therapy in order to optimize PSA control.

Funding Source(s): None.

Conflicts of Interest

None of the authors has potential or actual conflicts of interest with respect to the present investigation.

References

1. Blute ML, Bergstralh EJ, Iocca A, Scherer B, Zincke H. Use of Gleason score, prostate specific antigen, seminal vesicle, and margin status to predict biochemical failure after radical prostatectomy. J Urol. 2001, 165(1):119-125.

2. Swindle P, Eastham JA, Ohori M, Kattan MW, Wheeler T et al. Do margins matter? The prognostic significant of positive surgical margins in radical prostatectomy specimens. J Urol. 2008, 174(5 Suppl): S47-S51.

3.Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G et al. Adjuvant radiotherapy for pathologically advanced prostate cancer. A randomized clinical trial. JAMA. 2006, 296(19): 2329-2335.

4. Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet. 2005, 366(9845): 572-578.

5. Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol. 2009, 27(18): 2924-2930.

6. Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO guideline. J Urol. 2013, 190(2): 441-449.

7. Holmes JA, Wang AZ, Hoffman KE, Hendrix LH, Rosenman JG et al. Is primary prostate cancer treatment influenced by likelihood of extraprostatic disease? A Surveillance, Epidemiology, and End Results patterns of care study. Int J Radiat Oncol Biol Phys. 2012, 84(1): 88-94.

8. Hoffman KE, Nguyen PL, Chen MH, Chen RC, Choueiri TK et al. Recommendations for post-prostatectomy radiation therapy in the United States before and after the presentation of randomized trials. J Urol. 2011, 185(1): 116-120.

9. Swanson GP, Goldman BH, Tangen C, Thompson IM, Chin J et al. Lack of low-risk pathologic findings in SWOG 8794 [Abstract]. Int J Radiat Oncol Biol Phys. 2009, 75(3):S10.

10. Chan SM, Garcia FJ, Chin JL, Moussa M, Gabril MY. The clinical significance of in-depth pathological assessment of extraprostatic extension and margin status in radical prostatectomies for prostate cancer. Prostate Cancer Prostatic Dis. 2011, 14(4): 307-312.

11. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol. 2009, 181(3): 956-962.

12. Van der Kwast TH, Bolla M, Van Poppel H, Van Cangh P, Vekemans K et al. Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy: EORTC 22911. J Clin Oncol. 2007, 25(27): 4178-4186.

13. Bernard JR, Buskirk SJ, Heckman MG, Diehl NN, Ko SJ et al. Salvage radiotherapy for rising prostate-specific antigen levels after radical prostatectomy for prostate cancer: dose-response analysis. Int J Radiat Oncol Biol Phys. 2010, 76(3): 735-740.

14. Desai A, Wu H, Sun L, Sesterhenn IA, Mostofi FK et al. Complete embedding and close step-sectioning of radical prostatectomy specimens both increase detection of extra-prostatic extension, and correlate with increased disease-free survival by stage of prostate cancer patients. Prostate Cancer Prostatic Dis. 2002, 5(3): 212-218.

15. Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of prostate carcinoma. Am J Clin Pathol. 2008, 129: 24-30.

16. Ost P, Cozzarini C, De Meerleer G, Fiorino C, De Potter B et al. High-dose adjuvant radiotherapy after radical prostatecto-

my with or without androgen deprivation therapy. Int J Radiat Oncol Biol Phys. 2012, 83(5): 960-965.

17. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol. 2007, 25(15): 2035-2041.

18. Hagan M, Zlotecki R, Medina C, Tercilla O, Rivera I et al. Comparison of adjuvant versus salvage radiotherapy policies for postprostatectomy radiotherapy. Int J Radiat Oncol Biol Phys. 2004, 59(2): 329-340.

19. Cheung R, Kamat AM, de Crevoisier R, Allen PK, Lee AK et al. Outcome of salvage radiotherapy for biochemical failure after radical prostatectomy with or without hormonal therapy. Int J Radiat Oncol Biol Phys. 2005, 63(1): 134-140.

20. Kamat AM, Babaian K, Cheung MR, Naya Y, Huang SH et al. Identification of factors predicting response to adjuvant radiation therapy in patients with positive margins after radical prostatectomy. J Urol. 2003, 170(5):1860-1863.