Journal of Prostate Cancer

Watkins et al., J Pros Canc 2016, 1:2

Research Article OMICS International

Margin-Positive Radical Prostatectomy: All High Risk? PSA Relapse Risk Subset Identification *via* Recursive Partitioning Analysis

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Received date: October 26, 2016; **Accepted date:** October 27, 2016; **Published date:** November 15, 2016

Abstract

Objectives: To stratify risk of PSA relapse in a large population of men with positive surgical margin(s) at radical prostatectomy for prostate cancer.

Methods: A multi-institutional retrospective analysis of patient-and tumor-specific factor association with PSA (biochemical) relapse-free survival is reported. Eligible patients underwent radical prostatectomy for clinically localized prostate cancer, without pathologic involvement of seminal vesicles or lymph nodes, and >1 site of cancer involvement at the surgical margin. Patients were excluded for pre-prostatectomy PSA >30 or adjuvant (non-salvage) radiotherapy or hormone therapy. PSA failure was defined as PSA >0.10 ng/mL and rising, or at salvage intervention. Kaplan-Meier method was employed for survival estimates; recursive partitioning analysis by conditional inference analysis was applied to identify variables associated with PSA relapse-free survival.

Results: Between 2002 and 2010, 215 patients with margin-positive prostatectomy were eligible for analysis. The median age at diagnosis was 61 years (range, 43 years to 76 years), and median pre-prostatectomy PSA was 5.8 ng/mL (1.6-26.0). At a median follow-up of 78 months (14 months to 155 months; with 42% followed >8 years), 85 patients had experienced PSA relapse. At multivariable analysis, primary Gleason grade, pT-stage, and initial post-prostatectomy PSA were significant. Recursive partitioning analysis yielded 3 discrete risk groups, including a lower-risk group with 78% PSA relapse-free survival at 5 years (initial post-prostatectomy PSA <0.1, Gleason score <7).

Conclusion: Among patients with margin-positive prostatectomy, Gleason score and initial post-prostatectomy PSA permitted risk substratification for PSA relapse-free survival.

Keywords: Prostate neoplasms; Surgical margin; Surgical pathology; Radical prostatectomy; Radiotherapy

Introduction

A positive surgical margin at radical prostatectomy is an established independent high-risk feature for recurrence [1,2]; however, it is also well established that many patients with an involved surgical margin will not experience disease failure [3,4]. This is particularly true in cases without other high-risk features, such as seminal vesicle or lymph node involvement [4,5]. Thus, despite phase III trial evidence demonstrating superior PSA relapse-free survival (bRFS) [6-8], distant metastasis-free survival [6], and overall survival [6] for high-risk patients (inclusive of positive margin) who received immediate post-prostatectomy (adjuvant) radiotherapy, there has been limited adoption of its routine use [9,10]. While the reasons for this are multifactorial [11], difficulty in identifying which men with positive margins are more (or less) likely to fail is likely a critical factor. Thus, clinically applicable models for identification of subpopulations of "high-risk" and "low-risk" margin-positive patients may aid urologic oncologists and radiation oncologists in counseling patients regarding adjuvant therapy. The present investigation seeks to identify risk subgroups within a large population of men with clinically localized, node and seminal-vesicle uninvolved, and adjuvant therapy-naive prostate cancer, following margin-positive prostatectomy, with mature follow-up duration.

Methods

Following Institutional Review Board approval at each study institution, a research database was created with study-specific patient, treatment, and outcome data fields. Eligible cases were identified by review of medical records. After selection for prostate adenocarcinoma cases, patient records were reviewed in order to eliminate patients with advanced or metastatic disease at diagnosis (including pre-prostatectomy evidence of extra prostatic extension, seminal vesicle invasion, 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 scores (GS) of 8-10 or PSA >20 ng/mL. All patients underwent retropubic prostatectomy (open or laparoscopic, with or without robot assistance) as primary curative-intent therapy. Patients with involved seminal vesicles and/or lymph nodes, who received immediate adjuvant therapy (radiation or hormone, prior to salvage setting), or who were lost to urologic oncology follow-up within one year of prostatectomy (no PSA >12 months post-operatively) were excluded from the analysis.

Pathologic specimen preparation technique involved differential inking of the peripheral margins, distinguishing right from left, and 10% buffered formalin fixation for 4 h to 24 h. The apex and base were excised, radially sectioned, and submitted entirely. The remaining tissue was serially sectioned in the transverse plane at 3 mm and 4 mm intervals. Alternate sections were routinely submitted with additional sections near close margins submitted at the discretion of the pathologist. Pathology reports were reviewed in order to identify cases with involvement of one or more surgical margin(s). A margin was considered positive if malignant cells were in contact with the inked margin in the absence of intervening benign tissue. Secondary pathologic review was employed in selected cases.

Post-operative evaluations included physical examination and PSA measurement every 3 months to 6 months for the first 2 years post-prostatectomy, and every 6 months to 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 and oncologist. The principal outcome measure of this retrospective study was PSA relapse-free survival (bRFS) following prostatectomy, measured from date of prostatectomy to date of first rising PSA >0.1 ng/mL or upon salvage intervention for rising PSA. If no PSA rise or intervention occurred, then patients were censored at last follow-up or death if PSA had been drawn within 12 months or on date of most recent PSA if none had been documented within 12 months of last follow-up or death. Patients with detectable post-operative PSAs at ≤ 0.1 ng/mL were not considered disease failures in the absence of salvage intervention. Secondary objectives included analysis of factors associated with bRFS, and identification of low and/or high-risk subsets based upon this.

Statistical analysis

Cox proportional hazard regression was used to assess the effects of pathologic and post-operative variables on bRFS. Using a stepwise selection procedure, variables significantly associated with bRFS at the univariate level were considered for inclusion in the multivariable model. Regression estimates are reported as hazard ratios (HR) and 95% confidence intervals (CI). Plots of survival curves using the Kaplan-Meier method were constructed. Estimates and 95% pointwise confidence intervals were reported for 5th year and 8th year bRFS. To identify potential prognostic groups, a recursive binary partitioning by conditional inference analysis was applied to determine which variables were associated with bRFS. All statistical testing was two-sided and assessed for significance at the 5% level using R (www.r-project.org) and SAS v9.4 (SAS Institute, Cary, NC).

Results

Between years 2002 and 2010, 1,041 patients underwent radical prostatectomy for prostate cancer at the study institutions, and 215 had surgical margin involvement and met study inclusion criteria. Median age was 61 years (range, 43-76), and median highest pre-operative PSA was 5.8 (1.6-26.0). Additional demographic and pre-prostatectomy tumor, staging, and work-up characteristics are outlined in (Table 1). Surgical and pathologic details are demonstrated in (Table 2). No patient underwent post-operative radiation or hormone therapy in the absence of rising PSA.

The overall population, at a median follow-up of 77.6 months (range 13.5 months to 154.6 months, with 70% followed >5 years and 42% followed >8 years), 85 patients (40%) had experienced PSA relapse, and 7 (3%) had died. The 5th year and 8th year bRFS estimates for the entire population were 65% (95% CI, 57% to 71%) and 54% (45% to 62%). The estimated 5th and 8th year overall survivals for the entire population were 99% (95% CI, 96% to 100%) and 95% (87% to 98%). Univariate analysis identified factors associated with bRFS; PSA failure was associated with higher RP primary Gleason grade (GG, >4 *vs.* 3) and total GS (>7 *vs.* 6), pathologic AJCC stage (>III *vs.* II), pT-stage (>3 *vs.* 2), capsule invasion at M+ site, and higher initial post-RP PSA (>0.1 *vs.* <0.1, performed within 6 months of RP), with primary GG, pT-stage, and initial post-RP PSA remaining significant on multivariable analysis (Table 3).

Recursive partitioning analysis was performed, including the following variables: confirmed extraprostatic extension, pathologic T-stage and AJCC stage, initial post-operative PSA (limited to those performed within 6 months post-RP), and primary GG and overall GS at RP. Three terminal nodes were identified, with the first division by initial post-RP PSA, and (for those that were undetectable) the second by GS (6-7 *vs.* 8-9, Table 4). Breakdown of patient numbers by initial post-RP PSA is demonstrated in Table 5, Figures 1 and 2.

Variable	Margin-Positive Prostatectomy (n=215)		
			N (%)
Age	Median	61 years	
	(Range)	(43-76)	
	>70 years		18 (8)
Race	Caucasian		213 (99)
Highest PSA	Median	5.8	
	(Range)	(1.6-26.0)	

	≥ 10 ng/mL		47 (22)
	≥ 20 ng/mL		7 (3)
Clinical T-Stagea	cT1[c]		177 (82)
	cT2[a]		29 (13)
	cT2[b]		6 (3)
	cT2[c]		2 (1)
Gleason Score at Biopsy	3+3		130 (60)
	3+4		58 (27)
	4+3		15 (7)
	3+5		1 (<1)
	4+4		8 (4)
	5+3		0 (0)
	4+5		2 (1)
	5+4		1 (<1)
CT Staging			23 (11)
Bone Scan Staging			71 (33)
PSA=Prostate-Specific Antigen [31]			

Table 1: Patient demographic and pre-operative tumor, staging, and work-up data.

Variable	**Margin-Positive Prostatectomy (n=215)**		
			N (%)
Interval Biopsy to RP	Media Interval	53 days	
	(Range)	(11-512)a	
	>120 days		18 (8)
Prostatectomy Type	NerveSparing	156 (73)	
	RobotAssisted	33 (15)	
Specimen Volume	Median	44 grams	
	(Range)	(16-150)	
Pathologic T-Stage[b]	pT2a		6 (3)
	pT2[b]		3 (1)
	pT2[c]		118 (55)
	pT3a		87 (40)
	pT4		1 (<1)
Pathologic N-Stage[b]	pNx		54 (25)
	pN0		161 (75)
	Median # LN Sampled[c]	4	

	(Range)[c]		
	≥10 LNs excised[c]		20 (9)
Pathology Findings	# Foci of Involved Margin(s)[d]		
	1		140 (68)
	2		48 (23)
	≥ 3		18 (9)
	Perineural Invasion[e]		164 (73)

RP=Radical Prostatectomy; PSA=Prostate-Specific Antigen. [a]All but 8 patients had interval <6 months; reasons for delay included patient decision (n=1), physician-recommended weight loss (1), planned brachytherapy aborted due to peri-rectal abscess (1), and unknown (5). [b]Staging [31]. [c]Includes data from 145 patients had nodes excised, with specific node count reported. [d]For 206 patients with detailed margin foci data, [e]Excludes 27 patients without recorded perineural invasion data.

Table 2: Pathologic data.

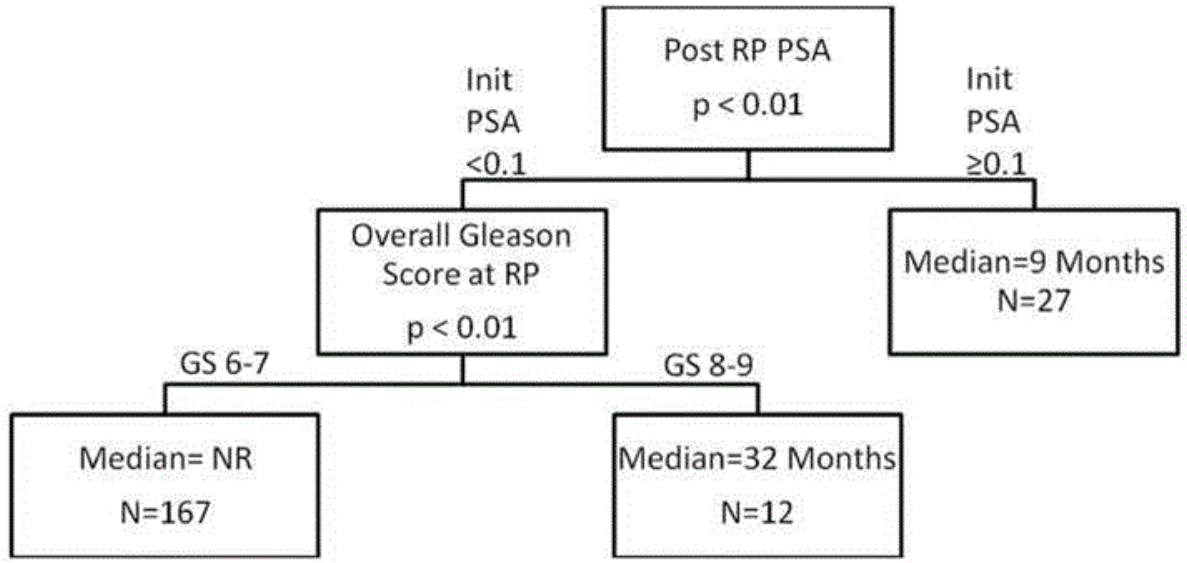

Figure 1: Recursive partitioning analysis for FFF for radical prostatectomy patients with positive margin(s).

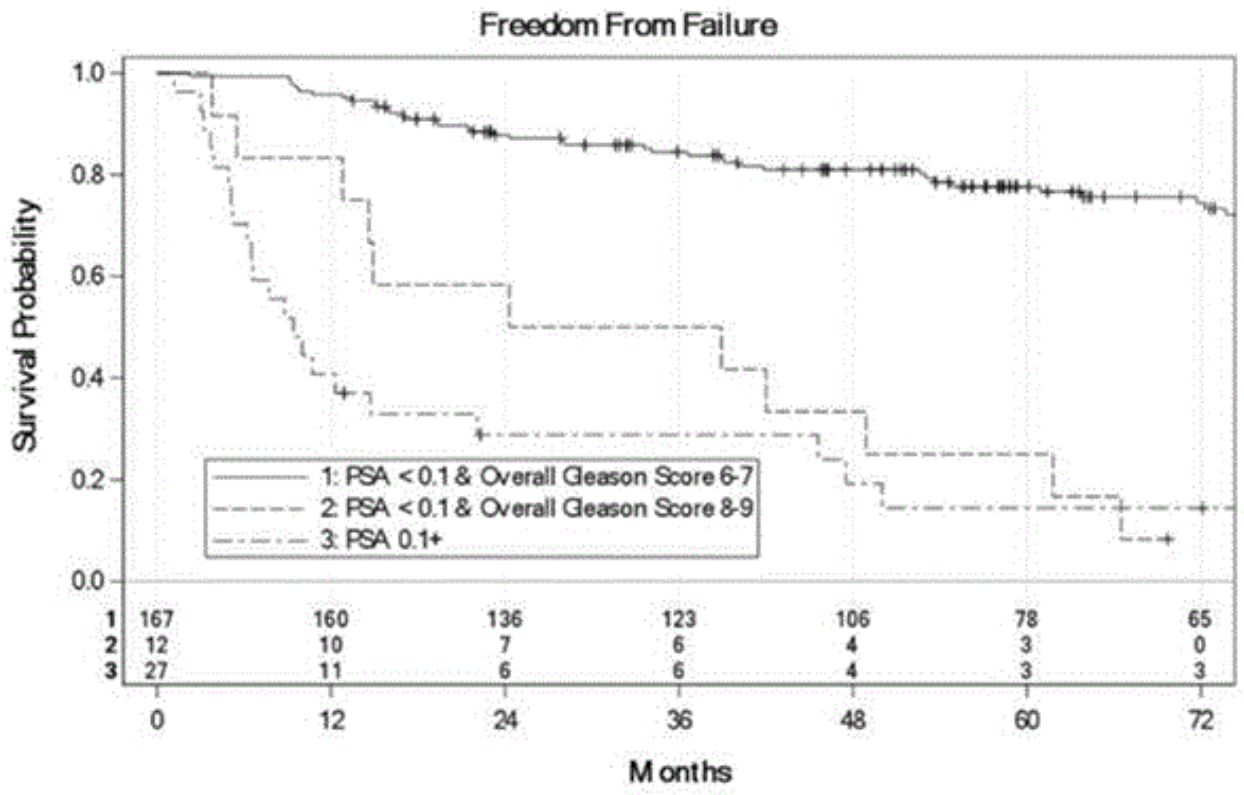

Figure 2: PSA relapse-free survival for patients by RPA subsets.

Variable		Margin-Positive Prostatectomy (n=215)			p
		Comparison	**HR**	**95% CI**	
Univariate Analysis	pT-stage[a]	3-4 vs. 2	1.65	1.08-2.54	0.02
	Pathologic AJCC stage	III-IV vs. II	1.72	1.12-2.65	0.01
	Pseudocapsule Invasion-Intact[b]	Yes vs. No	2.13	1.18-3.84	0.01
	Pseudocapsule Invasion-All Cases	Yes vs. No	1.48	0.96-2.29	0.07
	Primary Gleason Grade at RP[c]	4-5 vs. 3	2.42	1.53-3.84	<0.01
	Overall Gleason Score at RP[d]	7-9 vs. 6	2.54	1.55-4.14	<0.01
	Initial Post-RP PSA[e]	≥ 0.1 vs. <0.1	6.26	3.79-10.34	<0.01
Multivariable Analysis	Primary Gleason Grade at RP	4-5 vs. 3	2.32	1.43-3.77	<0.01
	pT stage	III-IV vs. II	1.62	1.03-2.54	0.04
	Initial Post-RP PSA[e]	≥ 0.1 vs. <0.1	6.47	3.90-10.71	<0.01

RP=Radical Prostatectomy; PSA=Prostate-Specific Antigen. [a]Stratified by pT2 *VS.* pT3-4 [31]. [b]excludes 80 patients with disrupted fibromuscular pseudocapsule at positive margin site, as true pseudocapsule status could not be determined. [c]stratified by grade 3 *VS.* 4-5. [d]stratified by gleason score 6 *vs.*7-9. [e]performed within 26 weeks of RP.

Table 3: Univariate and multivariable analyses of factor association with PSA relapse-free survival.

	bRFS	
	5-Year Estimate	**95% CI**
Initial Post-RP PSA <0.1	78%	70% to 84%
GS6-7		
Initial Post-RP PSA <0.1	25%	6% to 50%
GS 8-9		
Initial Post-RP PSA >0.1	14%	4% to 31%
RP=Radical Prostatectomy; PSA=Prostate-Specific Antigen.		

Table 4: PSA relapse-free survival by subgroup[a].

		Pathologic T-stage[b]	
	GS at RP	**pT2**	**pT3[c]**
Initial Post-RP PSA <0.1	<6	51	20
	7	52	45
	>8	5	7
Initial Post-RP PSA >0.1	<6	5	3
	7	8	7
	>8	2	2
RP=Radical Prostatectomy; PSA=Prostate-Specific Antigen; GS=gleason score, [a]includes n=206 patients, with 8 patients excluded for post-RP to initial surveillance PSA interval >6 months. [b]staging [31].[c]includes one patient with microscopic rectal invasion (pT4).			

Table 5: Individual patient subsets, stratified by initial post-RP PSA.

Discussion

Multiple historic studies have identified cancer involvement at the surgical margin as associated with increased risk for recurrence following prostatectomy [1,2]. However, not all patients with positive margin(s) recur [3,4], with much fewer experiencing prostate cancer-associated symptoms [12,13], and thus do not benefit from immediate adjuvant therapy. In terms of general findings, the 5th year and 8th year bRFS rates of 65% and 54%, respectively, described within the study population, are similar to previously-published series of neoadjuvant and adjuvant therapy-naïve men with positive surgical margins after radical prostatectomy (57% to 66%) [4,14,15]. Specific to factor association with risk substratification, to our knowledge, the present investigation is the first to employ a recursive partitioning analysis to identify a low-risk subgroup. Specifically, the combination of Gleason score (at prostatectomy) and initial post-prostatectomy PSA was identified as a potential clinical decision-making tool for this purpose.

The importance of these findings are twofold; first, current patterns of care studies suggest low rates of adjuvant therapy in prostatectomy patients with high-risk features (including positive margins) [10], despite guideline recommendations by multiple professional societies [16,17]. While reasons for this are multifactorial [11], improved identification of patients most likely to fail (and, thus, potentially benefit), should encourage a multidisciplinary approach. Second, patients unlikely to benefit from adjuvant therapy may be spared the potential adverse effects of hormone or radiation therapy.

Given the improvements in bRFS and distant metastasis-free survival for adjuvant radiotherapy over observation, specific to margin-positive subsets in three major randomized trials [6-8], it is reasonable to extrapolate the potential benefit to the high-risk group of the present study population. This is supported by demonstration of benefit irrespective of Gleason score at prostatectomy [6-8] or presence of detectable PSA [6,7]. While an argument could be made for early salvage radiotherapy (optimally at PSA ≤ 0.5) [18], in the setting of anticipated 5-year recurrence risk exceeding 15% to 20%, the option of adjuvant treatment should be discussed with the patient, as there may be an increased risk of distant metastasis with surveillance [6,15]. Further, contemporary post-operative radiotherapy doses are higher than those employed in the clinical trials (>66 Gy *vs.* 60 to 64 Gy), based upon data suggestive of improved brfs [19] and tolerance with recent technological advances in radiotherapy planning and delivery [20,21].

The present study finding of recurrence risk association with higher Gleason score is also consistent with prior investigations of patients with positive margins. Most recently, a multicenter European retrospective experience of 536 patients with pT3aN0/Nx prostate cancer and positive margin(s) at prostatectomy was reported [22]. None of these patients had received pre- or post-operative therapy. At a median follow-up of 48 months post-prostatectomy, 40% of patients

had experienced PSA relapse. At multivariate analysis, Gleason score remained the only independent prognostic factor for bRFS, with estimated 5-year bRFS rates of 74%, 70%, 38%, and 50% for Gleason score 6, 3+4=7, 4+3=7, and 8-10, respectively. While the European series was significant for the size of its well-defined population, outcomes analysis is limited by the short follow-up.

Aside from Gleason score, several other pathologic factors have been investigated for association with relapse in the margin-positive subpopulation. In particular, several investigations have examined the location, number of foci, and extent of margin involvement for associations with disease control. For location, several reports identified positive margin(s) at the bladder base as an adverse prognostic factor [5,23], though others have failed to confirm this [7,15,24]. Presence of tumor within the pseudocapsule at the margin site has also demonstrated increased risk of failure, over absence of such (i.e., intraparenchymal positive margin, defined as within prostate at site of disrupted pseudocapsule) [25]. With regard to number of foci of margin involvement, several reports have identified increased risk of early PSA failure with multiple margins over single [24], though this is not universally described [15]. Specific to extent of margin involvement, an increasing body of evidence is demonstrating a direct correlation between linear extent of marginal involvement and risk of early PSA failure [22,26,27], particularly in the setting of higher pathologic Gleason score [26].

With regard to patients whose PSA was "detectable" at ≥ 0.1 ng/mL, it must be mentioned that this designation was employed owing to use of multiple laboratories, not all of whom were employing "ultrasensitive" PSA during the years of study inclusion. With increased availability and reduced expense of the ultrasensitive assay, it has become increasingly common to intervene with salvage therapy at lower PSA levels, sometimes at ≤ 0.10 [28]. Specific to the implications of this on the present study population (and future investigations), preliminary single-institution data suggest that early salvage radiotherapy (PSA ≤ 0.5) may result in early PSA control rates approaching that of adjuvant therapy [18].

Despite mature follow-up (median 78 months, with 70% followed ≥ 5 years and 42% followed ≥ 8 years), the present study population experienced low rates of prostate cancer-specific morbidity and mortality. This is in part attributable to specific selection of cases without seminal vesicle invasion or lymph node involvement. Yet, considering the stated objective of defining patients who may be best selected for post-prostatectomy surveillance over immediate adjuvant therapy, the point remains that while patients with Gleason scores ≥ 7 or initial post-operative PSA ≥ 0.1 have high rates of biochemical relapse, deaths at 8 years remain uncommon. This speaks to the demographic and biologic heterogeneity of the margin-involved prostatectomy subpopulation, the generally prolonged natural history of the disease, and the ever-increasing range of systemic salvage intervention options available to patients in the event of late metastatic presentation [29].

As the United States gradually moves into a post-PSA screening era, it is possible that the rate of higher-risk disease at presentation will increase. Thus, expansion of studies such as the present investigation and those referenced above, employing traditional pathologic features (Gleason score, margin involvement) and clinical serologic data (post-prostatectomy PSA), in combination with non-traditional pathologic features (extent, location, and foci of margin involvement), patient-specific factors (age, comorbidity index), and bio molecular data [30], will further advance individualization of therapy so as to maximize value, as measured by outcome over toxicity and expense.

In conclusion, prostate cancer patients with pT2-3aN0 disease who underwent prostatectomy with one or more sites of involved surgical margin(s), multivariate analysis identified an initial post-prostatectomy PSA (within 6 months) of ≥ 0.1, pT-stage, and primary GG as independently associated with subsequent PSA relapse. Employing a recursive partitioning analysis, the post-prostatectomy PSA, in combination with Gleason score at prostatectomy, demonstrated an opportunity for bRFS risk substratification, specific to this margin-positive population. This may assist urologists and oncologists in clinical decision-making, specific to adjuvant therapy interventions. More selective use of adjuvant therapies permits an opportunity for improved disease control while decreasing unnecessary expense and toxicity for patients less likely to experience failure.

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