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Adverse pathology and undetectable ultrasensitive prostate-specific antigen after radical prostatectomy: is adjuvant radiation warranted?

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Objectives

To determine if men with adverse pathology but undetectable ultrasensitive (<0.01 ng/mL) PSA are at high-risk for biochemical recurrence (BCR), or if there is a subset of patients at low-risk for whom the benefit of adjuvant radiation therapy might be limited.

Patients and Methods

We evaluated 411 patients treated with RP from 2001 to 2013 without adjuvant radiation who had an undetectable (<0.01 ng/mL) PSA level after RP but with adverse pathology [positive surgical margins (PSMs), extraprostatic extension (EPE), and/or seminal vesicle invasion (SVI)]. Multivariable Cox regression analyses tested the relationship between pathological characteristics and BCR to identify groups of men at highest risk of early BCR.

Results

On multivariable analysis, only pathological Gleason 7 (4 + 3), Gleason ≥ 8 , and SVI independently predicted BCR

($P = 0.019$, $P < 0.001$, and $P = 0.001$, respectively), although on two-way analysis men with Gleason 7 (4 + 3) did not have significantly higher rates of BCR compared with patients with Gleason ≤ 6 (log-rank, $P = 0.074$). Men with either Gleason ≥ 8 (with PSMs or EPE) or SVI (15% of the cohort) defined a high-risk group vs men without these characteristics (3-year BCR risk of 50.4% vs 11.9%, log-rank, $P < 0.001$).

Conclusions

Among men with adverse pathology but an undetectable (<0.01 ng/mL) PSA level after RP, the benefits of adjuvant radiation are probably limited except for men with Gleason 8–10 (with PSMs or EPE) or SVI who are at high-risk of early BCR.

Keywords

adjuvant radiotherapy, prostate, prostatic neoplasm, prostate-specific antigen, recurrence

Introduction

Although radical prostatectomy (RP) provides excellent control of prostate cancer, about one-third of men will develop a PSA biochemical recurrence (BCR) within 10 years

of surgery [1]. Additionally, men with adverse pathological features including extraprostatic extension (EPE), positive surgical margins (PSMs), and seminal vesicle invasion (SVI) have as high as 60% risk of developing BCR within 3 years, leading to an increased risk of prostate cancer death [2–12].

To reduce BCR risk, the AUA working with the American Society for Radiation Oncology (ASTRO) developed a guideline for adjuvant radiation for men with adverse pathology after RP. The guideline states that ‘Physicians should offer adjuvant radiotherapy to men with adverse pathologic findings at prostatectomy, including seminal vesicle invasion, positive surgical margins, or extraprostatic extension because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression’ [10].

Beyond adverse pathological features portending an increased risk of BCR [2–8,13–16], postoperative PSA nadir is an important risk stratification tool after RP [17]. A prior study from the Shared Equal Access Regional Cancer Hospital (SEARCH) database showed that adding postoperative PSA nadir to established post-RP nomograms increased their ability to predict BCR by 7% [17]. Additionally, not only do men with undetectable ultrasensitive PSA (<0.01 ng/mL) have considerably lower BCR rates compared with men with elevated postoperative PSA levels [17], but there is also evidence to suggest ultrasensitive assays provide better BCR risk stratification vs less sensitive PSA assays (i.e. detection limit <0.1 ng/mL) [17–21]. While men with an undetectable (<0.01 ng/mL) postoperative PSA level have lower overall BCR rates [17–21], outcomes of men with adverse pathology and undetectable ultrasensitive PSA levels after RP are unknown.

To address this gap, we assessed men with adverse pathology but an undetectable postoperative ultrasensitive PSA (<0.01 ng/mL), who are candidates for adjuvant radiation based on the AUA/ASTRO guidelines. As men with undetectable ultrasensitive PSA have lower BCR rates overall [17,19,21], we hypothesised most men with ‘adverse’ pathology and undetectable ultrasensitive PSA (<0.01 ng/mL) would be at low risk of early BCR (3-years), defining a population for which adjuvant radiation may provide only modest benefits. Conversely, we hypothesised that using certain pathological characteristics, we could identify a small subset of men at high risk of early BCR despite an undetectable ultrasensitive PSA, defining a population for which adjuvant radiation may provide greater benefit [9]. To test our hypothesis we examined a racially diverse multicentre population of men who underwent RP at one of the six equal-access hospitals represented in the SEARCH database [22].

Patients and Methods

After obtaining Institutional Review Board approval, data from men undergoing RP between 2001 and 2013 at six Veteran Affairs hospitals (West LA, Palo Alto and San Diego, CA; Augusta, GA; Durham and Asheville, NC) were combined into SEARCH [22]. Men treated with preoperative androgen deprivation or radiation therapy were excluded.

Within SEARCH, ultrasensitive PSA nadir (detection limit <0.01 ng/mL) was available starting in 2001 in two centres, 2002 in one centre, and 2005 in the last three centres. Using these limits, we identified 2 802 men from the initial 5 073 men, treated after the introduction of ultrasensitive PSA testing at their centre. As our goal was to identify risk factors for BCR among men with adverse pathology and undetectable ultrasensitive postoperative PSA who are adjuvant radiation candidates, we excluded men with a detectable PSA nadir after RP (PSA level of ≥ 0.01 ng/mL; 1 657 men), as well as men who received adjuvant radiation (45). We excluded men with lymph node involvement (nine), as this group represented a small portion of our population (2%). Of the remaining men, we excluded those (663 men) who were not adjuvant radiation candidates using the AUA/ASTRO guidelines (i.e. men with organ-confined, SM negative disease) [10]. Finally, we excluded men with missing data for preoperative PSA level, SM status, SVI, pathological Gleason score, EPE, and follow-up (17 men). This resulted in a study population of 411 men (Fig. S1). All men were followed with serial PSA level determinations and clinical visits at intervals according to attending physician’s discretion. BCR was defined as a single PSA concentration of >0.2 ng/mL, two concentrations at 0.2 ng/mL, or secondary treatment for elevated PSA as this definition delineates men at highest risk of further PSA progression compared with higher PSA level thresholds (i.e. 0.5 ng/mL) [23].

Our primary outcome was to identify men at high-risk for early BCR for whom adjuvant radiation may be most appropriate. We evaluated the association between each potential risk-factor and BCR using Kaplan–Meier plots and the log-rank test. Patients were stratified by 3- and 5-year BCR-free rates to assess early BCR, as BCR within 3 years after RP is associated with worse prostate cancer-specific survival [9]. Variables included in the multivariable models included surgical centre (categorical), age (continuous), surgery year (continuous), race (categorical), body mass index (BMI; categorical), preoperative PSA level (<10 , 10–19.9, ≥ 20 ng/mL), pathological Gleason sum [2–6, 7 (3 + 4 and 4 + 3), and 8–10], EPE (categorical), PSM (categorical), and SVI (categorical).

Multiple Cox models were created by first entering all covariates into the model, and subsequently removing the variable most strongly associated with BCR [highest hazard ratio (HR) and lowest *P* value] and repeating the analysis until no significant predictors remained. All assumptions for the Cox models were tested and met for all covariates.

Statistical analysis was performed using Stata, version 11.0 (Stata Corp, College Station, TX, USA). Statistical significance was two-sided, with $P < 0.05$ considered to indicate statistical significance.

Results

The demographic and pathological characteristics of our population are shown in Table 1. In all, 46% of patients were non-White men. The median patient age was 61 years. The predominant adverse pathological characteristic was PSM, present in 86% of men; followed by EPE (30%), and SVI (10%). In all, 58% of men had pathological Gleason 7, 32% Gleason ≤ 6 , and 10% Gleason 8–10.

Kaplan–Meier Estimates of BCR-Free Rates for Pathological and Demographic Characteristics

Among the 411 men with adverse pathology and undetectable ultrasensitive postoperative PSA, 70 (17%) developed BCR with a median follow-up of 63 months among non-recurrent men. Table 2 shows the 3- and 5-year Kaplan–Meier estimates for BCR-free rates by demographic and pathological characteristics. Men with SVI and Gleason 8–10 had the lowest 3-year BCR-free rates, with rates of 36.8% ($P < 0.001$) and 55.0% ($P < 0.001$), respectively. Men with EPE also had a lower 3-year BCR-free rate compared to those without EPE (79.1% vs 85.9%, $P = 0.022$). No differences in BCR-free rates were noted in men with PSM vs negative SM, or when men were stratified by race, BMI, or preoperative PSA level (Table 2).

BCR

To identify independent BCR predictors, we conducted multivariable Cox regression analyses (Table 3). In model 1,

which included all patients, Gleason 8–10 (HR 3.53, $P < 0.001$) was the strongest BCR predictor defined as the highest HR and lowest P value. SVI (HR 2.94, $P = 0.001$) and Gleason 7(4 + 3) (HR 2.21, $P = 0.019$) were also independent BCR predictors. Based upon relatively high rates of early BCR (Fig. 1), we determined that men with Gleason 8–10 may be good candidates for adjuvant radiation. Thus, we excluded men with Gleason 8–10 in subsequent analyses to identify additional high-risk groups.

In model 2, which excluded men with Gleason 8–10, we found SVI was the strongest independent BCR predictor (HR 3.39, $P = 0.002$), with Gleason 7(4 + 3) (HR 2.61, $P = 0.005$) also remaining an independent predictor. This was confirmed even when excluding men with Gleason 8–10 disease, those with SVI were at high-risk of early BCR as shown by 3-year BCR-free rates of 37.2% ($P < 0.001$; Fig. 2). Therefore, we determined that men with SVI may be good candidates for adjuvant radiation and we thus excluded these men in subsequent analyses to identify additional high-risk groups.

In model 3, which excluded men with Gleason 8–10 or SVI, Gleason 7(4 + 3) was the only independent BCR predictor. However, 3-year BCR was not significantly different in patients with Gleason 7(4 + 3) (80.0%) when compared with those with Gleason ≤ 6 (88.6%, $P = 0.074$). Nevertheless, as Gleason 7(4 + 3) was the strongest predictor of BCR in model 3, we excluded these men from the subsequent analysis to identify additional groups at high-risk.

Table 2 Kaplan–Meier estimates for BCR by pathological and demographic characteristics.

Characteristics	3-year BCR-free rate, % (95% CI)	5-year BCR-free rate, % (95% CI)	P (log rank)
Race			0.886
White	81.7 (75.7–86.4)	78.4 (71.9–83.6)	
Non-white	84.6 (78.1–89.2)	75.4 (67.7–81.6)	
BMI, kg/m ²			0.419
<25	84.0 (78.8–88.0)	77.3 (71.2–82.2)	
25–29.9	80.1 (70.5–86.8)	73.6 (62.6–81.9)	
≥ 30	84.2 (66.0–93.1)	84.2 (66.0–93.1)	
Preoperative PSA level, ng/mL			0.121
<10	84.4 (79.9–88.0)	78.5 (73.3–82.9)	
10–19.99	76.5 (62.3–86.0)	70.8 (55.3–81.8)	
≥ 20	72.9 (36.8–90.5)	60.8 (25.0–83.6)	
Pathological Gleason sum			<0.001
2–6	88.8 (81.7–93.2)	85.9 (78.2–91.0)	
7 [3 + 4]	86.9 (80.8–91.2)	79.1 (71.6–84.9)	
7 [4 + 3]	73.1 (57.4–83.9)	62.5 (44.5–76.1)	
8–10	55.0 (36.9–70.0)	50.8 (33.5–66.5)	
PSM			0.089
No	71.4 (55.7–82.4)	68.3 (52.0–80.1)	
Yes	84.6 (80.2–88.1)	78.2 (73.0–82.5)	
EPE			0.022
No	85.9 (81.1–89.6)	75.6 (66.1–82.8)	
Yes	79.1 (73.4–83.8)	71.7 (61.6–79.6)	
SVI			<0.001
No	85.9 (81.8–89.1)	79.5 (74.6–83.6)	
Yes	36.8 (17.0–56.8)	36.8 (17.0–56.8)	

The bold font indicates statistically significant values.

Table 1 Demographic, clinical, and pathological characteristics.

Variable	Value
Number of patients	411
Mean (SD) age at surgery, years	61.0 (6.1)
Median (IQR) year of surgery	2006 (2004–2009)
N (%):	
Race	
White	224 (54)
non-White	187 (46)
BMI, kg/m ²	
<25	269 (65)
25–29.9	106 (26)
≥ 30	36 (9)
Preoperative PSA level, ng/mL	
<10	343 (83)
10–19	56 (14)
≥ 20	12 (3)
Pathological Gleason sum	
2–6	130 (32)
7 (3 + 4)	186 (45)
7 (4 + 3)	52 (13)
8–10	43 (10)
PSM	353 (86)
EPE	124 (30)
SVI	29 (10)

IQR, interquartile range.

Table 3 Multivariable Cox proportional hazard analysis of factors predicting BCR after RP.

Pathological characteristics	Model 1			Model 2			Model 3			Model 4		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Race (vs non-white)												
White	0.84	0.53–1.29	0.403	0.73	0.44–1.20	0.217	0.77	0.46–1.30	0.338	0.91	0.51–1.61	0.746
BMI (vs <25 kg/m ²)												
25–29.9	1.28	0.80–2.05	0.303	1.23	0.73–2.09	0.431	1.24	0.71–2.14	0.448	1.28	0.69–2.36	0.438
≥30	0.91	0.38–2.18	0.831	0.72	0.28–1.87	0.499	0.36	0.09–1.53	0.168	0.40	0.09–1.67	0.209
Preoperative PSA level (vs PSA <10 ng/mL)												
10–19.99	1.46	0.84–2.54	0.179	1.21	0.65–2.26	0.544	1.23	0.63–2.40	0.542	1.51	0.75–3.07	0.249
≥20	2.06	0.72–5.87	0.181	1.91	0.56–6.48	0.302	1.60	0.36–7.05	0.532	0.87	0.11–6.73	0.893
Gleason sum (vs Gleason ≤6)												
Gleason 7(3 + 4)	1.05	0.61–1.80	0.863	1.17	0.68–2.00	0.575	1.14	0.65–1.98	0.643	1.15	0.65–2.02	0.633
Gleason 7(4 + 3)	2.21	1.14–4.30	0.019	2.61	1.33–5.12	0.005	2.14	1.03–4.47	0.042	–	–	–
Gleason 8–10	3.53	1.76–7.10	<0.001	–	–	–	–	–	–	–	–	–
PSM	1.02	0.53–1.96	0.957	0.91	0.43–1.94	0.809	1.30	0.54–3.16	0.561	0.81	0.30–2.22	0.682
EPE	1.26	0.75–2.11	0.376	1.20	0.65–2.22	0.555	1.50	0.79–2.84	0.214	1.22	0.57–2.61	0.603
SVI	2.94	1.59–5.43	0.001	3.39	1.59–7.24	0.002	–	–	–	–	–	–

Model 1: all patients (411 men). Model 2: Patients with Gleason 8–10 excluded (368 men). Model 3: Patients with Gleason 8–10 excluded and SVI excluded (348 men). Model 4: Patients with Gleason 8–10, SVI, and Gleason 7(3 + 4) excluded (303 men). All models were mutually adjusted for surgical centre, year of surgery, age, race, BMI, reoperative PSA level, Gleason score, PSMs, EPE, and SVI. The bold font indicates statistically significant values.

Fig. 1 Kaplan–Meier curve for freedom from BCR by Gleason score.

In model 4, which excluded men with Gleason 8–10, SVI and Gleason 7(4 + 3), no risk factor was significantly related to BCR (Table 3). In other words, surgical centre, age, surgery year, race, BMI, preoperative PSA level, Gleason ≤7(3 + 4), PSMs, and EPE were unrelated to BCR once men with Gleason 8–10, SVI, and Gleason 7(4 + 3) were excluded.

Based upon the above, among men who all had an undetectable postoperative ultrasensitive PSA and adverse pathology, the men at highest risk for early BCR included those with Gleason 8–10 disease (with PSMs or EPE) and SVI (63 men, 15% of the cohort). Indeed these men had significantly lower 3-year BCR-free rates of 49.6% vs 88.1%

Fig. 2 Kaplan–Meier curve for freedom from BCR by SVI in patients with pathological Gleason ≤7 (43 patients with Gleason 8–10 excluded).

for men with lower risk disease (i.e. Gleason ≤7 with PSMs or EPE) (log-rank, $P < 0.001$; Fig. 3).

Discussion

Given the importance of pathological features at RP predicting BCR [1,4–6,10,12], the AUA/ASTRO recommend men with adverse pathology be offered adjuvant radiation after RP to reduce BCR risk [10]. However, another tool in assessing BCR risk is the postoperative PSA nadir [17,19]. As the risk of BCR in men with an undetectable ultrasensitive (<0.01 ng/mL) postoperative PSA is low, the risk of and risk

Fig. 3 Kaplan–Meier curve for freedom from BCR by patients with Gleason ≤ 7 (with EPE or PSMs) vs patients with SVI or Gleason 8–10 (with EPE or PSMs).

Number of patients at risk

Gleason ≤ 7 , SVI–	348	325	286	252	203	167	134	104	71
Gleason 8–10, SVI+	63	41	29	20	19	14	12	7	3

factors for BCR in men with a mismatch, adverse pathology but an excellent PSA response after RP, is unknown. To examine this issue, we examined outcomes among 411 men with a mismatch between pathology and postoperative PSA level. Among these men with undetectable ultrasensitive PSA (<0.01 ng/mL), the presence of either Gleason 8–10 (with EPE or PSMs) or SVI defined a group (15%) at high-risk for early BCR. Alternatively, men with Gleason ≤ 7 (with EPE or PSMs) and without SVI identified a group with a nearly 90% 3-year BCR-free rate. If validated in other studies, these findings provide useful information about the risk of BCR in men with undetectable ultrasensitive PSA and adverse pathology, giving insight to potential benefits of adjuvant radiation.

The AUA/ASTRO guideline was largely based on three randomised clinical trials that assessed adjuvant radiation in men with adverse pathology after RP [10]. All trials showed BCR risk reduction; however, they exhibited subtle differences in inclusion criteria and subset analyses [24–26]. The European Organisation for the Research and Treatment of Cancer (EORTC) 22 911 trial was comprised of 1 005 men with stage pT3 disease and/or PSMs [26]. In the treatment arm, there was a 50% reduction in BCR overall, as well as in men with a postoperative PSA level of ≤ 0.2 ng/mL, suggesting a benefit for adjuvant radiation in men with lower postoperative PSA levels [26]. In the Southwest Oncology Group (SWOG) S8794 trial, comprised of 425 men with pT3N0M0, a similar BCR risk reduction to the EORTC trial was achieved [24]. Although this trial did not specifically assess men with low PSA levels postoperatively, most of the men in the study (66.2%), had a PSA level of ≤ 0.2 ng/mL [24]. It also should be noted, that long-term follow-up has

shown treatment resulted in an $\approx 30\%$ reduction in metastasis risk [27]. In the ARO 96-02 trial, comprised of 307 men with pT3N0M0 tumours, eligibility for treatment required an undetectable postoperative PSA level of <0.1 ng/mL [25]. Again, a BCR risk reduction of 50% was seen [25]. Although these trials definitively suggest a benefit to adjuvant radiation in men with adverse pathology and lower postoperative PSA levels, outcomes among men using ultrasensitive PSA assay with detection of <0.01 ng/mL was not analysed [24–26]. This is an important distinction as men with undetectable (<0.01 ng/mL) ultrasensitive PSA have a low risk of BCR compared with men with an undetectable PSA determined by less sensitive assays [19].

While those trials showed a 50% relative risk reduction when examining their populations as a whole, the benefit of adjuvant radiation became less clear when examining individual pathological features [25–27]. For instance, the SWOG trial showed that only men with Gleason ≥ 7 had significant benefit from adjuvant radiation, while men with SVI did not benefit [27]. The EORTC trial reported similar findings, in that SVI was not predictive of adjuvant radiation benefit, while higher Gleason score, PSMs, and EPE were predictive of adjuvant radiation benefit [26]. Although in the ARO trial, SVI was not specifically addressed on sub-group analysis, Gleason score >6 and PSMs were predictive of benefit with adjuvant radiation [25]. These three trials suggest that there is certainly a benefit of adjuvant radiation in patients with adverse pathology; however, when examining which specific feature more strongly predicts benefit with adjuvant radiation, the interpretation becomes less clear. Although there is a uniform relative risk reduction overall, the absolute risk reduction of adjuvant therapy could be less pronounced in populations that have lower risk of BCR (i.e. Gleason <7). Additionally, the differences between the trials could be due to their study population, as men had varying ranges of postoperative PSA levels. This assumption relates to our present study, as men with undetectable ultrasensitive PSA had a large variability in BCR rates dependent on pathological features. As such, our population has the potential to have varying benefit from adjuvant radiation therapy. For instance, men with higher rates of early BCR and undetectable ultrasensitive PSA (men with SVI and Gleason 8–10 with other adverse pathological features) may benefit more from adjuvant radiation than men without those features. While our present study based on observational data cannot specifically address which patients that meet current AUA/ASTRO guidelines for adjuvant radiation receive the most treatment benefit from adjuvant therapy, it illustrates the large differences in BCR that can be seen in a population with undetectable ultrasensitive PSA.

Although the current AUA/ASTRO guideline employs a straightforward approach to patients with any adverse pathological characteristics, the approach to patients with

adverse pathology after RP in the clinical setting is not as straightforward. Even though this guideline is in place, physicians are currently not treating all patients with adverse pathology uniformly [28]. This is demonstrated by physician surveys that show a substantial difference in treatment recommendations when comparing urologists to radiation oncologists, with radiation oncologists favouring more aggressive adjuvant therapy and urologists favouring salvage radiation in most instances [28,29].

While our present study focused on men who could potentially benefit from adjuvant radiation, it still remains unclear if adjuvant radiation is actually superior to salvage radiation. While prior observational data suggests that early salvage therapy (PSA level of <0.5 ng/mL) in men with pT3N0 disease is equivalent to adjuvant therapy in terms of BCR-free survival [30] and early salvage therapy (within 2 years after recurrence) has been correlated with improved survival [12], the Radiotherapy and Androgen Deprivation in Combination after Local Surgery (RADICALS) and the Radiotherapy – Adjuvant Versus Early Salvage (RAVES) trials are attempting to further answer this question [31,32]. Until these studies are concluded, this will remain a hotly debated topic.

The strengths of the present study include a well-established, multicentre database with detailed outcome data. Our present study was limited by its retrospective design. Follow-up was modest precluding us from examining later outcomes such as prostate cancer death. This reflects the fact that our inclusion criterion was an undetectable ultrasensitive PSA assay and these assays were only introduced at our centres in the past $10 \pm$ years. To overcome this, we specifically chose early BCR (3-years) as our primary outcome because this has been shown to predict a higher risk of prostate cancer death [9]. We acknowledge the definition of ‘excellent’ PSA response is unclear. Prior work from our group found that any level of detectable PSA (i.e. ≥ 0.01 ng/mL) increases the risk of BCR [17]. Thus, we chose the more conservative definition of excellent PSA response. Exploring alternative definitions of ‘excellent’ PSA response is beyond the scope of the present paper. Finally, it is possible that other pathological features that we did not examine, such as prostate size or number of extent of PSMs, may help predict the risk of BCR. Future studies are needed to address this. There was no central pathology review and thus pathological interpretation may have varied by centre. However, this is also a strength, in that it better reflects community practice where most pathological review is not done by dedicated genitourinary pathologists. Finally, as the number of men was modest, future studies are needed to validate our present findings.

In conclusion, most men with adverse pathology (PSMs or EPE) with Gleason <8 and an undetectable (<0.01 ng/mL) postoperative PSA nadir have a low risk of early BCR and

therefore, the benefit of adjuvant radiation could be small. Alternatively, men with Gleason 8–10 (with PSMs or EPE) and SVI with undetectable PSA levels (<0.01 ng/mL) are at high-risk of early BCR, and therefore stand to benefit more from adjuvant radiation. To confirm our present results, further studies are required to test which men actually derive the most benefit from adjuvant radiation, as well as to determine if postoperative PSA nadir and pathological Gleason sum should be included in future radiation treatment guidelines.

Conflicts of Interest

There are no financial disclosures, conflicts of interest, and/or acknowledgements for the authors, and/or no funding sources for the manuscript. This statement includes all co-authors.

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Abbreviations: ASTRO, American Society for Radiation Oncology; BCR, biochemical recurrence; BMI, body mass index; EORTC, European Organisation for the Research and Treatment of Cancer; EPE, extraprostatic extension; HR, hazard ratio; RP, radical prostatectomy; SEARCH, Shared Equal Access Regional Cancer Hospital; (P)SM, (positive) surgical margin; SVI, seminal vesicle invasion; SWOG, Southwest Oncology Group.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Consort flow diagram of men in our cohort study addressing adverse pathology in patients with undetectable ultrasensitive (<0.01 ng/mL) PSA.