



Platinum Priority – Prostate Cancer

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Radical Prostatectomy for Low-Risk Prostate Cancer Following Initial Active Surveillance: Results From a Prospective Observational Study

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Abstract

Background: Little is known about the outcome of radical prostatectomy (RP) in men initially followed on active surveillance (AS) for low-risk prostate cancer (PCa).

Objective: Evaluate pathology findings after RP in our prospective AS cohort.

Design, setting, and participants: All men participated in the Prostate Cancer Research International: Active Surveillance (PRIAS) study. Eligible men were initially diagnosed with low-risk PCa (clinical stage \leq T2, prostate-specific antigen [PSA] \leq 10 ng/ml, PSA density $<$ 0.2 ng/ml per ml, one or two positive biopsy cores, and Gleason score \leq 6) and underwent RP between December 2006 and July 2011. The study protocol recommends RP in case of risk reclassification on repeat biopsy (Gleason score $>$ 6 and/or more than two positive cores) or a PSA doubling time \leq 3 yr.

Measurements: Descriptive statistics were used to report on pathology findings for staging and grading.

Results and limitations: Pathology results were available in 167 out of 189 RP cases (88.4%). Median time to RP was 1.3 yr (range: 1.1–1.9). Protocol-based recommendations led to deferred RP in 143 men (75.7%); 24 men (12.7%) switched because of anxiety, and 22 (11.6%) had other reasons. Pathology results showed 134 (80.8%) organ-confined cases and 32 (19.2%) cases with extracapsular extension. Gleason scores \leq 6, 3 + 4, 4 + 3, and 8 were found in 79 (47.3%), 64 (38.3%), 21 (12.6%), and 3 (1.8%) cases, respectively. Unfavourable RP results (pT3–4 and/or Gleason score \geq 4 + 3) were found in 49 patients (29%), of whom 33 (67%) had a biopsy-related reason for deferred RP.

Conclusions: RP results in men initially followed on AS show organ-confined disease and favourable Gleason grading in a majority of cases. Most men in our cohort had a protocol-based reason to switch to deferred RP. A main focus for AS protocols should be to improve the selection of patients at the time of inclusion to minimise reclassification of risk and preserve the chance for curative treatment, if indicated.

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1. Introduction

The use of active surveillance (AS) as a treatment option for low-risk prostate cancer (PCa) is increasing in response to high rates of overdiagnosis in the contemporary prostate-specific antigen (PSA) era. AS protocols aim to select patients with favourable disease characteristics by applying strict criteria for inclusion and follow-up. Systematic monitoring of these men serves to provide timely identification of any risk reclassification or disease progression, so that radical treatment can be applied within the window of curability to those who need it and AS can be continued in those with persisting low-risk features. However, in the absence of markers selectively differentiating low-risk from significant disease, it remains challenging to exclusively select those men in whom PCa will never lead to symptoms, let alone death, which has led to a variation of criteria for eligibility and risk reclassification or disease progression in different AS studies [1–6]. In addition to tumour characteristics, competing risks for mortality should be considered when deciding on the best treatment for a patient [7]. Because AS is a fairly new treatment strategy, relatively few studies have long-term results available, and criteria for inclusion and follow-up have not yet been validated.

Prevention of overtreatment by AS protocols should not be at the cost of potentially preventable unfavourable outcomes, which can lead to poor prognosis in the case of delayed radical therapy. However, so far, little is known about the outcome of radical prostatectomy (RP) in men initially followed on AS for low-risk PCa. To get better insight into the effectiveness of protocol-based active therapy recommendations and into the nature of the disease at RP after initial AS, we evaluated the reasons for deferred treatment and reported on the pathologic outcome in patients who underwent RP in our prospective AS cohort.

2. Methods

The Prostate Cancer Research International: Active Surveillance (PRIAS) study offers an AS protocol that urologists worldwide are using via a Web-based instrument [8]. Eligible men were initially diagnosed with low-risk PCa (clinical stage \leq T2, PSA \leq 10 ng/ml, PSA density $<$ 0.2 ng/ml per ml, one or two positive biopsy cores, and Gleason score \leq 6). PSA was measured every 3 mo, and volume-based ($<$ 40-ml, 8 cores; 40- to 60-ml, 10 cores; $>$ 60-ml, 12 cores) repeat biopsies were applied according to protocol (at least after 1, 4, and 7 yr). Deferred radical treatment was advised in case of risk reclassification towards higher risk on repeat biopsy (Gleason score \geq 7 or \geq 3 biopsy cores) or a PSA doubling time (DT) \leq 3 yr. PSA DT was calculated by plotting the base 2 logarithm of the PSA value against the time since diagnosis; the DT can be calculated as the reciprocal value of the slope of the regression line through these points. The PSA DT was used for recommendation only after a minimum of four follow-up visits (ie, the first protocol-based recommendation to switch to active treatment normally was after 1 yr of follow-up).

Men who underwent RP between December 2006 and July 2011 were eligible for this study. The reason for switching to RP was recorded on the PRIAS Web site [8]. Information on pathology findings on T stage, lymph node status, Gleason score, and surgical margins was requested from the attending physicians. A favourable RP result was defined as pT stage \leq 2 and Gleason score \leq 3 + 4; unfavourable disease was defined as pT stage 3–4 and/or Gleason score \geq 4 + 3 [9,10]. An observational descriptive

analysis was performed to summarise data and report absolute numbers, proportions, and median values. Statistical analyses were performed using SPSS v.17.0 statistical software (IBM Corp., Armonk, NY, USA).

3. Results

Of 2079 men included in PRIAS up to July 2011, 446 men (22%) underwent deferred treatment, of which 189 men (42%) underwent RP. Pathology results were available in 167 men (88.4%). Median follow-up for patients who remained on AS was 1.6 yr (range: 0.8–2.8). Median time to RP was 1.3 yr (range: 1.1–1.8) after diagnosis. Table 1 shows the clinical characteristics at time of diagnosis. Protocol-based recommendations led to deferred RP in 143 men (75.7%); 24 men (12.7%) switched because of anxiety, and 22 (11.6%) had other reasons (Table 2).

Pathology results showed 134 (80.8%) organ-confined cases and 32 (19.2%) cases with extracapsular extension (ECE). Gleason scores \leq 6, 3 + 4, 4 + 3, and 8 were found in 79 (47.3%), 64 (38.3%), 21 (12.6%), and 3 (1.8%) cases, respectively (Table 3). The latter group consisted of two patients with Gleason score 3 + 5 and one with Gleason score 5 + 3. Upgrading in the RP specimen compared to the last (repeat) biopsy was seen in 31%, while downgrading was present in 8%; 61% had an unchanged Gleason score (Table 4). Negative lymph nodes were reported in 45 patients, while an NX status was reported in 122 cases.

Table 1 – Baseline cohort characteristics (n = 189)

Parameter	Median	25–75th percentile
Age, yr	63.2	59.6–67.2
PSA, ng/ml	5.8	4.8–7.1
Prostate volume, ml	41	34–59
PSA density, ng/ml per ml	0.14	0.10–0.17
No. of cores	10	8–12
	No.	%
Clinical T stage:		
T1C	162	85.7
T2A	27	14.3
No. of positive cores:		
1	118	62.4
2	71	37.6
Gleason score:		
\leq 6	19	10.1
6	170	89.9

PSA = prostate-specific antigen.

Table 2 – Reason for deferred radical prostatectomy (n = 189)

	No.	%	Time to surgery, yr (25–75th percentile)
Protocol recommendation	143	75.7	1.3 (1.2–1.9)
Anxiety	24	12.7	0.7 (0.5–1.3)
Other*	22	11.6	1.0 (0.6–2.2)

* Other reasons included increase in prostate-specific antigen, increase in lower urinary tract symptoms, patient's desire, and unknown reasons.

Table 3 – Radical prostatectomy results after initial active surveillance (n = 167)

Parameter	Median	25–75th percentile
Time to surgery, yr	1.3	1.1–1.8
	No.	%
Pathologic T stage:		
HGPIN	1	0.6
All T2:	134	80.2
T2	6	3.6
T2A	17	10.2
T2B	13	7.9
T2C	98	59.8
All T3:	30	18.0
T3	7	4.2
T3A	20	12.0
T3B	3	1.8
T4A	2	1.2
Gleason score:		
≤3 + 3 = 6	79	47.3
3 + 4 = 7	64	38.3
4 + 3 = 7	21	12.6
8	3	1.8
Margin status:		
Negative	123	75.5
Positive:	40	24.5
T2	25	18.9
T3–4	15	51.6
Positive lymph nodes*	0	0
RP outcome**:		
Favourable	118	70.7
Unfavourable	49	29.3

HGPIN = high-grade prostatic intraepithelial neoplasia; RP = radical prostatectomy.
 * Negative lymph nodes (N0) were reported in 45 cases, while an Nx status was reported in 122 cases.
 ** Favourable outcome was defined as pT stage ≤2 and Gleason score 3 + 4; unfavourable outcome was defined as pT stage 3–4 and/or Gleason score ≥4 + 3.

Unfavourable RP results (pT3–4 and/or Gleason score ≥4 + 3) were found in 49 patients (29%). Forty (82%) of these patients had a protocol-based reason for deferred RP; in 33 (67%) cases, the reason was biopsy related. Of the 118 cases (71%) with favourable RP results (pT2 and Gleason score ≤3 + 4), 88 (75%) had been given protocol-based advice to undergo radical treatment. The number of favourable and unfavourable RP results per protocol-based reason is shown in Table 5. Having more than three positive biopsy cores

was the most frequent trigger to switch to RP, while a combination of both biopsy-related features shows the highest percentage (52%) of unfavourable outcomes. In patients in whom anxiety was the trigger for RP, only 1 out of 17 (6%) had an unfavourable RP result. Pathology results for patients with biopsy-based indications for RP are shown again separately in Table 6; the proportion of favourable and unfavourable RP outcomes in this subgroup was 71 of 104 (68.8%) versus 33 of 104 (31.7%) respectively.

4. Discussion

AS is emerging as a treatment option for low-risk PCa, but because of relatively short follow-up, little is known about the outcome of RP after initially being followed on AS. In the present analysis, we report on the largest prospective cohort of men receiving RP after initial AS. It was shown that most men switch to RP on the basis of the protocol. Most of their pathology results show organ-confined disease and favourable Gleason grading.

Regarding the short amount of time from diagnosis to surgery in the current study (median: 1.3 yr) and the slow-growing nature of PCa, true disease progression is less likely than actual reclassification of risk because of understaging and/or undergrading at diagnosis. It is the basic principle of AS that patients with more aggressive disease will eventually be selected to undergo treatment. Timely identification of risk reclassification could attenuate the risk of a potentially worsened prognosis resulting from a delay in curative therapy. Early repeat biopsy potentially could have decreased the amount of unfavourable RP outcomes in this cohort by up to 67%, because 33 out of 49 patients with unfavourable disease had a biopsy-related reason to undergo RP. Thus, it is important to improve the selection of patients by means of extended biopsy schemes, immediate repeat biopsy, or risk stratification to prevent patients from being included in an AS programme when they are probably better off receiving immediate treatment. Future studies on new biomarkers [11] will hopefully add to the selective identification of suitable patients.

One of the main questions in evaluating AS as a treatment strategy is what price has to be paid for delaying or avoiding radical treatment. In an attempt to address this issue, several previous studies examined oncologic outcomes in RP series comparing delayed to immediate

Table 4 – Gleason score on last (repeat) biopsy compared to Gleason score on final pathology (n = 167)

Gleason score on last (repeat) biopsy*	Gleason score on RP				
	No PCa	≤6	3 + 4	4 + 3	8
No PCa	1	4	–	2	–
≤6	–	67	32	7	2
3 + 4	–	7	28	4	1
4 + 3	–	–	2	7	–
8	–	–	1	1	–
9	–	–	1	–	–

RP = radical prostatectomy; PCa = prostate cancer.
 * In 137 patients, at least 1 repeat biopsy was taken; in 30 patients, the biopsy at diagnosis was the last.

Table 5 – Number of men with protocol-based reasons to switch to deferred radical prostatectomy stratified by outcome

Protocol-based reason to switch to deferred RP [†]	No.	Favourable RP outcome (n = 118) pT2 and Gleason score ≤3 + 4			Unfavourable RP outcome (n = 49) pT3–4 and/or Gleason score ≥4 + 3		
		No.	Reason for RP, %	Favourable RP outcome, %	No.	Reason for RP, %	Unfavourable RP outcome, %
Any protocol-based reason	128	88	69	75	40	31	82
(1) Only Gleason score ≥7 on repeat biopsy	23	18	78	15	5	22	10
(2) Only ≥3 positive cores on repeat biopsy	35	27	77	23	8	23	16
(3) Only PSA DT ≤3 yr [*]	24	17	71	14	7	29	14
Combination 1 + 2	21	10	48	8	11	52	22
Combination 1 + 3	4	2	50	2	2	50	4
Combination 2 + 3	17	12	71	10	5	29	10
Combination 1 + 2 + 3	4	2	50	2	2	50	4

RP = radical prostatectomy; PSA DT = prostate-specific antigen doubling time.
[†] Includes patients with the particular protocol-based reason in the absence of any other reason.
^{*} PSA DT was used for recommendations only after a minimum of four follow-up visits.

therapy in men with low-risk features at diagnosis, which did not lead to significant differences in outcome between both cohorts in most series.

Dall'Era et al. [12] reported no difference in Gleason upgrading, positive surgical margins (PSM), or ECE between men undergoing primary RP and a surveillance cohort. Van den Bergh et al. [13] found similar results as well as

comparable tumour volume and biochemical recurrence (BCR) rates in a similar setting. Warlick et al. [14] also showed that a >75% risk of “non-curable” cancer was not significantly different for delayed and immediate intervention groups. Accordingly, in a Swedish study [15], among low- and intermediate-risk patients, no difference was observed for any one or more of three adverse pathology features of Gleason score upgrading, PSM, and ECE. Furthermore, two studies [16,17] found no effect of treatment delay on biochemical progression rates in an RP cohort receiving surgery within 1 yr after diagnosis. Also, a nationwide cohort study in the United States showed similar rates for PCa mortality among men with low-risk disease who opted for deferred treatment and those who were initially treated [18].

Conflicting results have been reported by others who showed increased rates of PSA progression [19,20] and Gleason score upgrading in low-risk patients undergoing deferred therapy before or after 6 mo, while no difference was found for ECE, PSM, and positive lymph nodes [19]. However, both studies identified low-risk patients according to the D’Amico classification, which results in less strict criteria to define low-risk disease than those used in most contemporary AS studies.

Although the aforementioned studies attempt to throw light on the risk of applying AS, it should be kept in mind that selection bias in the deferred treatment groups is likely because reasons for switching from AS to active treatment often include signs of risk reclassification (eg, on repeat biopsy). Another downside of these studies is their retrospective and nonrandomised nature. To be able to evaluate whether a delay in treatment after risk reclassification or true disease progression will compromise cure, prospective randomised trials comparing AS to radical treatment are essential but not yet available [21].

Other studies have evaluated the pathologic RP outcomes of men who would have been eligible for AS [22–26]. Rates of upgrading in these studies varied between 21% and 36%, with Gleason score 8–10 in 3–4%, ECE found in 5–19%, PSA progression in 11–23%, and PSM in 14–35%. These results show that a considerable amount of men who are thought to have low-risk PCa according to clinical features at diagnosis harbour more aggressive disease on RP.

Table 6 – Radical prostatectomy results after initial active surveillance and any biopsy-based reason for surgery (n = 104)

Parameter	Median	25–75th percentile	
Time to surgery, yr	1.3	1.1–1.6	
	No.	%	
Pathological T stage:			
All T2:	81	77.9	
T2	3	2.9	
T2A	9	8.7	
T2B	8	7.7	
T2C	61	58.7	
All T3:	22	21.2	
T3	5	4.8	
T3A	16	15.4	
T3B	1	1.0	
T4A	1	1.0	
Gleason score:			
≤3 + 3 = 6	36	34.6	
3 + 4 = 7	53	51.0	
4 + 3 = 7	13	12.5	
8	2	1.9	
Margin status:			
Negative	73	73.7	
Positive:	26	26.3	
T2	15	18.5	
T3–4	11	47.8	
Positive lymph nodes [*]	0	0	
RP outcome:			
Favourable	71	68.3	
Unfavourable	33	31.7	

RP = radical prostatectomy.
^{*} Negative lymph nodes (N0) were reported in 38 cases, while an Nx status was reported in 66 cases.
^{**} Favourable outcome was defined as pT stage ≤2 and Gleason score ≤3 + 4; unfavourable outcome was defined as pT stage 3–4 and/or Gleason score ≥4 + 3.

Compared to these immediate RP series in patients with AS-suitable clinical features, the rate of unfavourable characteristics in RP specimens of this AS cohort might be considered relatively high. Again, this might be explained by the self-selection of men who start on AS and receive RP because of reclassification to higher risk during follow-up, which leaves the true low-risk patients undisturbed and singles out men at higher risk and worse prognosis among those selected for AS to undergo RP. It can also be argued that the follow-up protocol in this study is able to ensure that those with aggressive disease are not left untreated. This is also illustrated by the observation that all protocol-based reasons led to relatively high rates of unfavourable RP outcomes (Table 5), especially when compared to the rate in patients switching to RP based on anxiety (1 of 17; 6%). Moreover, the majority of this cohort had a favourable RP outcome, and as the number of unfavourable outcomes is only 3% of the original AS population—which is still being followed on AS—it still seems to be acceptable compared with upfront RP in all patients.

Prospective data on RP results after initial AS is scarce. Khatami et al. [27] presented the RP results of 70 patients who had initially been managed expectantly. They found upgrading in 21%, organ-confined disease in 86%, and PSM in 23%. PSA DT was the only predictive factor of PSA relapse in their study, with no PSA relapses in cases with PSA DT >4 yr after a median follow-up of 63 mo. However, inclusion and follow-up of patients in this cohort was not executed according to a strict AS protocol. Seiler et al. [28] reported 79% organ-confined cases, 56% Gleason score >6, and 31% PSM in 61 cases. They found more favourable results in patients fulfilling the Epstein criteria [29] for low-risk disease. In another study by Duffield et al. [30], a total of 48 RP cases after AS and progression on biopsy were evaluated. Mean time to RP was 29.5 mo; organ-confined disease was present in 65%, of which 52% was Gleason score 6. Potentially clinically insignificant tumours (according to Epstein [29]) were found in 27%, while 71% showed at least one of the criteria of ECE, any Gleason score 4, or tumour volume >1 cm³. Although no tumour volume was available in our study, we found a comparable rate of 28% with no ECE and no Gleason score 4 for the group with biopsy-related reasons for RP and even 41% for the complete cohort. This result indicates that at least a portion of these men was overtreated, but we would rather stay on the safe side as opposed to not treating men with higher-risk disease. It should also be kept in mind that a vast majority of the total AS cohort has not received any treatment until now, contributing to the aim of AS: minimising overtreatment.

Limitations of this study include the heterogeneity in medical centres participating in PRIAS and their surgery experience, which might also be reflected in the relatively high rate of PSM. It can be argued that this is more of a true reflection of PSM rates than those presented in most high-volume centres. Furthermore, interobserver variations in pathologic diagnosis might have slightly affected pathologic outcomes and data on tumour volume, and localisation was not routinely reported. Because follow-up for prospective AS cohorts is still limited, adverse pathologic features are often

used as surrogate markers, which do not necessarily translate to poorer outcomes instead of hard end points such as metastatic disease and PCa-specific death. Follow-up after RP in this cohort was too short to report clinically relevant details on BCR, metastatic disease, and PCa death. Longer follow-up will provide essential insight into these outcome measures.

5. Conclusions

Pathology results in men who were initially followed with AS show organ-confined disease and favourable Gleason grading in a majority of cases; however, the amount of unfavourable outcomes could not be neglected. Therefore, it remains an important focus for AS protocols to improve the selection of patients at the time of inclusion to minimise reclassification of risk during follow-up; early repeat biopsy in this cohort could have identified up to 67% of the unfavourable PCa cases. Until biomarkers become available that reliably predict significant disease, strict follow-up of men on AS with repeated PSA tests and regular repeat biopsies is warranted to preserve the chance for curative treatment, if indicated, and to avoid side-effects of invasive treatment in those with persisting low-risk features.

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Study concept and design: Bul.

Acquisition of data: Bul.

Analysis and interpretation of data: Bul, Zhu.

Drafting of the manuscript: Bul.

Critical revision of the manuscript for important intellectual content: Bul, Zhu, Rannikko, Staerman, Valdaghi, Pickles, Bangma, Roobol.

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