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Pathologic Outcomes in Favorable-risk Prostate Cancer: Comparative Analysis of Men Electing Active Surveillance and Immediate Surgery

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Abstract

Background: It remains unclear whether men selecting active surveillance (AS) are at increased risk of unfavorable longer term outcomes as compared with men who undergo immediate treatment.
Objective: To compare adverse pathologic outcomes in men with favorable-risk prostate cancer who underwent delayed prostatectomy after surveillance (DPAS) to those who elected immediate prostatectomy (IRP).
Design, setting, and participants: We conducted a retrospective analysis of a prospective AS registry from 2004 to 2014. From the Johns Hopkins AS program ($n = 1298$), we identified a subset of men who underwent DPAS ($n = 89$) and was representative of the entire cohort, not just those that were reclassified to higher risk. These men were compared with men who underwent IRP ($n = 3788$).
Outcome measurements and statistical analysis: We measured adverse pathologic features (primary Gleason pattern ≥ 4, seminal vesicle invasion [SVI], or lymph node [LN] positivity). Multivariable models were adjusted for age, prostate-specific antigen density, and baseline risk classification.
Results and limitations: Delayed prostatectomy occurred at a median of 2.0 yr (range: 0.6–9.0) after diagnosis. The DPAS and IRP cohorts demonstrated similar proportions of men with primary Gleason pattern ≥ 4 (17% vs 20%; $p = 0.11$), SVI (3.3% vs 3.2%; $p = 0.53$), LN positivity (2.3% vs 1.2%; $p = 0.37$), and overall adverse pathologic features (21.3% vs 17.0%; $p = 0.32$). The adjusted odds ratio of adverse pathology was 1.33 (95% confidence interval, 0.82–2.79; $p = 0.13$) for DPAS as compared with IRP. Limitations include a modest cohort size and a limited number of events.
Conclusions: In men with favorable-risk cancer, the decision to undergo AS is not independently associated with adverse pathologic outcomes.
Patient summary: This report compares men with favorable-risk prostate cancer who elected active surveillance with those who underwent immediate surgery accounting for evidence that approximately one-third of men who choose surveillance will eventually undergo treatment. Our findings suggest that men who are closely followed with surveillance may have similar outcomes to men who elect immediate surgery, but additional research is needed.

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1. Introduction

Curative intervention of prostate cancer (PCa) is associated with side effects that are likely to have an impact on quality of life [1,2]. Although morbidity may be accepted in the setting of life-extending therapy, the treatment of indolent nonlethal tumors exposes men to unnecessary negative effects [3]. Despite improvements in diagnostic and imaging techniques, it remains difficult to predict which cancers will and will not prove harmful during a man's lifetime [4]. Active surveillance (AS) has been proposed as a potential solution to this problem [5].

Although an increasing proportion of men are being managed with AS [6,7], variability in utilizing this approach is large and depends more on physician practice patterns than tumor metrics [8]. One factor contributing to the limited uptake of AS is a fear that failure to treat a localized cancer while in a curable stage could prove costly over a long-term follow-up [9]. The vast majority of favorable-risk cancers demonstrate a prolonged, indolent course [10], but approximately a third will eventually demonstrate higher risk features [11]. In the absence of prospective trials comparing various management strategies [12], previous studies have compared surgical outcomes of men undergoing immediate radical prostatectomy (IRP) with subjects initially managed on AS who subsequently underwent delayed prostatectomy after an interval on surveillance [13–15].

A major limitation of this approach, however, is that most men on AS who proceed to surgery do so based on worrisome findings such as biopsy reclassification or increasing prostate-specific antigen (PSA) [15,16]. Thus delayed radical prostatectomy (RP) cohorts have been composed of the highest risk AS patients who ultimately failed this approach. Although informative to this subgroup of patients who fail AS during follow-up, such comparisons provide minimal insight to the newly diagnosed man who does not know whether he will later exhibit high-risk disease. As such, others have proposed that an ideal study design would compare an immediate surgery population with a similar cohort that selected AS at the same time—including both the minority of AS patients who progressed to treatment and the majority of AS patients who remained on surveillance [14]. Because this third group does not undergo treatment, however, treatment outcomes are not available for assessment. By incorporating a population of men who elected to undergo treatment in the absence of progression, however, we uniquely compared pathologic outcomes from a risk-representative delayed surgery after surveillance cohort with a similar cohort that underwent IRP.

2. Methods

2.1. Active surveillance cohort

Starting in 1995, men with favorable-risk (ie, very low risk [VLR] or low risk [LR]) PCa were offered enrollment in AS [17]. VLR criteria include clinical stage T1c disease, prostate-specific antigen density (PSAD) $<$0.15 ng/ml, biopsy Gleason score (GS) $\leq$6, two or fewer positive biopsy cores, and $\leq$50% involvement of any core with cancer. We have not used PSA (eg, $>$10 ng/ml) to exclude men from VLR classification if PSAD was $<$0.15 because our experience has not identified a clinically meaningful PSA cut-off to predict higher risk disease [18]. LR cancer was defined as clinical stage $\leq$T2a, PSA $<$10 ng/ml, and GS $\leq$6. Our protocol includes semiannual PSA and digital rectal examination, and annual prostate biopsy in most cases. As previously described, adherence to our protocol approximates 90% annually [19]. Curative intervention is recommended upon disease reclassification, defined as biopsy findings no longer meeting inclusion criteria. Based on our experience, PSA kinetics are not used as a trigger for intervention in this program [20]. As such, interventions not due to biopsy reclassification are due to changes in patient preference.

Of 1298 men enrolled in AS during the study period, 926 men (71.3%) met VLR and 372 (28.7%) met LR classification criteria. During follow-up (median: 5.0 yr; range: 0.01–18.0), 467 men (36.0%) underwent reclassification at a median of 2.0 yr after diagnosis; conversely, 831 men (64% of the overall cohort) did not undergo reclassification and were eligible to remain on AS. Of those who reclassified, 81 (6.5%) reclassified based on grade, 234 (18.0%) reclassified based on volume, and 149 (11.5%) reclassified based on grade and volume.

2.2. Study design

We sought to assess an intermediate end point (ie, surgical pathology) in the AS population for comparison with men who underwent immediate treatment. Comparing the entire delayed RP population, however, with men who undergo IRP is inherently biased against AS; the delayed RP cohort does not represent all men who select AS, but rather those men who select AS and then demonstrate higher risk disease during follow-up (Fig. 1). This bias has been described in the setting of AS by multiple authors and is a well-recognized limitation of previous comparative studies [14]. To mitigate this limitation, we aimed to identify a delayed prostatectomy after surveillance (DPAS) population that represented the *overall* AS cohort in terms of demographic factors, reclassification rate during follow-up (36%), and type of reclassification observed (6.5% by grade, 18% by volume, and 11.5% by grade and volume). To ensure modern pathologic grading, the study was limited to men who underwent surgery after 2004.

2.3. Patient population

2.3.1. Delayed prostatectomy after surveillance (study cohort)

From January 2005 to September 2014, a total of 185 men underwent delayed prostatectomy after initial management on AS. Sixty-one men elected to undergo RP in the absence of clinical or pathologic evidence of disease progression. Four of these men (6.6%) were excluded due to age (median age: 45.5 yr; range: 44–46 yr) discordant with the AS population, yielding 57 study-eligible men who underwent delayed RP without a trigger for intervention. Consistent with our AS experience, these 57 men were designated to represent 64% of the DPAS study cohort, and the total DPAS cohort was calculated to equal 89 subjects. The study design is illustrated in Figure 2.

Corresponding to reclassification event rates in the overall AS cohort, the remaining 36% (n = 32) of the DPAS study group was composed of 6 men (6.7%) who underwent grade reclassification, 16 (18%) who underwent volume reclassification, and 10 (11.3%) who underwent grade plus volume reclassification. To minimize selection bias, subjects were selected from eligible men within each reclassification group using simple random sampling after stratification by year of surgery. Patient characteristics were similar between the DPAS cohort and overall AS cohort, confirming representative sampling (Supplementary Table 1).

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