Characterization of a "Low-Risk" Cohort of

Gleason 7 Prostate Cancer Patients

By

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1.1 Literature Review

ABSTRACT

Purpose

Evaluate the outcomes of men with Gleason 7 prostate cancer followed on active surveillance in the published literature.

Methods

We conducted a PubMed search including variations of the terms prostate cancer, active surveillance, and Gleason 7 disease. We supplemented this search with a detailed review of cited references. We analyzed and critiqued relevant articles for study design, sample size, eligibility criteria, outcomes, length of follow-up, data sources, statistical methods, and risk of bias.

Results

After title and abstract review of 125 articles identified by our PubMed search and the addition of four articles discovered during our detailed References review, we identified five relevant studies. Conclusions from these studies are different, as are the measures, outcomes, and study inclusion criteria. Risk of bias is high and generalizability is severely limited.

Conclusion

Little reliable data about the safety of following men with Gleason 7 prostate cancer on active surveillance can be extrapolated from published studies.

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer among men in the developed world.[1] In the United States this year, an estimated 220,800 men will receive a new diagnosis of prostate cancer and 27,540 will die of the disease.[2] Among men newly diagnosed with prostate cancer, approximately 90% will pursue definitive treatment (surgery or radiation therapy)[3, 4] and the majority will experience at least one long-term adverse effect due to this treatment.[5] The disease's high incidence, treatment morbidity, and long natural history have provoked extensive public health discussions about overdiagnosis and overtreatment.

To reduce the overtreatment of low-risk prostate cancer (Appendix A, Table 1.1),[6-8] active surveillance protocols began in the late 1990's. On protocol, enrolled patients with low-risk prostate cancer undergo biannual PSA testing, an annual digital rectal exam, and a repeat prostate biopsy as frequently as every 12 months. Worsening PSA kinetics, progression of clinical stage on rectal exam, or changing biopsy characteristics trigger definitive treatment. The reported mortality for prostate cancer is <1% among men with low-risk prostate cancer on active surveillance protocols with long-term follow-up.[9]

The qualifying criteria for intermediate-risk prostate cancer (Appendix A, Table 1.1) includes Gleason 7 disease (Appendix A, Table 1.2), which, is the most common Gleason sum on prostate biopsy.[10] With the objective of further mitigating prostate cancer overtreatment, we examined the literature for studies including men with Gleason 7 disease followed on active surveillance.

METHODS

Search Strategy

To identify published studies addressing our question of how men with Gleason 7 prostate cancer fare on active surveillance, we conducted an advanced PubMed search combining MeSH and text word terms on June 9, 2015 following consultation with a Cancer Information Librarian in the Health Sciences Library at the University of North Carolina, Chapel Hill. We did not apply any limitations on language or publication date. Our specific search strategy was:

> (Prostatic Neoplasms[mesh] OR prostatic neoplasms[tw] OR prostatic neoplasm[tw] OR Prostate Cancer[tw] OR Prostate Cancers[tw] OR Cancer of the Prostate[tw] OR Prostatic Cancers[tw] OR Prostatic Cancer[tw]) AND active surveillance[tw] OR surveillance[tw]) AND (Gleason 7[tw] OR Gleason Score 7[tw] OR Gleason Score=7[tw] OR Gleason Score<7 OR Gleason score 3+4[tw])

The search yielded 125 articles for review. We supplemented this search with a detailed examination of cited references from the retrieved articles, which yielded an additional 4 relevant studies for review.

Study Selection

We reviewed the titles and abstracts of all articles to identify the publications most likely to address the study question. We further reviewed the Methods and Results section of 10 articles to determine relevance to our study question. Our inclusion criteria required the articles review clinically- or oncologically-significant outcomes for men with localized Gleason 7 prostate cancer followed on active surveillance. Clinically- or oncologically-significant outcomes included Gleason score progression on repeat biopsy, progression to radical treatment, time to radical treatment, prostate cancer specific survival, and overall survival. We excluded prostate cancer review articles and expert opinion pieces, choosing to focus our review upon

original research. We excluded studies of men with localized prostate cancer followed exclusively on watchful waiting protocols. In contrast to active surveillance, which involves close monitoring and administration of curative treatment in response to disease progression detected by PSA kinetics, a change in disease characteristics identified on repeat biopsy, or a palpable change on digital rectal exam, watchful waiting advises androgen deprivation when prostate cancer becomes symptomatic,[11] most commonly from osseous metastases or urinary obstruction.[12] The objective of active surveillance is selective delayed intervention with curative intent among men meeting specific disease criteria, whereas symptom palliation is the goal in watchful waiting. For this reason, expectations for prostate cancer-specific survival and overall survival are quite different between men followed on modern active surveillance protocols and men followed on watchful waiting.

Data Abstraction and Quality Assessment

We analyzed the articles relevant to our study question for the following details: study design, sample size, study outcome(s), length of follow-up, study participants and eligibility criteria, relevant demographic data including age and baseline PSA, data sources, measurement, statistical methods, main results, and any study funding or author conflicts of interest.

Extrapolating key study quality assessment items from the STROBE criteria,[13] we graded each study based upon the strength of the design, study size (with a focus upon the number of men with Gleason 7 prostate cancer included in the study), study outcome data, length of follow-up, and risk of bias. Each study received a grade of 1 (lowest) to 3 (highest) in each of these five categories, for a total score of 3-15. For study design: case series received 1 point, single cohort studies received 2 points, and cohort studies with a control group received 3 points. For study

size: studies with <50 men with Gleason 7 prostate cancer received 1 point, 50-100 men with Gleason 7 disease received 2 points, and studies with >100 men with Gleason 7 prostate cancer received 3 points. For oncological relevance and evaluation of study outcomes: studies limited to progression to radical treatment received 1 point, studies of intermediate outcomes such as biochemical recurrence among those receiving curative intervention received 2 points, and studies evaluating overall or prostate-cancer specific survival received 3 points. Length of follow-up was graded: 1 point for <3 years follow-up, 2 points for ≥3 years but <6 years follow-up, and 3 points for ≥6 years of follow-up. Finally, points were inversely assigned in relation to the perceived risk of bias within the study: studies at the highest risk of bias received 1 point, studies with an intermediate risk of bias received 2 points, and studies with little perceived bias received 3 points.

RESULTS

After title and abstract review of 125 articles identified by our PubMed search and the addition of four articles identified during our detailed References review, we identified a total of seven relevant articles[14-20] (Appendix B, Figure 1.1). Upon comprehensive review of the seven relevant articles, three captured the same active surveillance source population from the University of Toronto.[14, 15, 18] Accordingly, we chose the most recent publication from this group for data abstraction and quality assessment, as this publication captured the longest clinical follow-up period.[18] In total, we performed complete data abstraction and quality assessment for five studies[16-20] (Appendix C, Tables 1.1 and 1.2). The studies varied significantly in overall quality, ranging from a score of 6 to 13 on a 15-point scale designed for grading observational studies.[13]

The included studies reported various outcomes of men with Gleason 7 prostate cancer followed over time on active surveillance.[7, 17-20] The study designs, measures, population size, length of follow-up, evaluated outcomes, and findings are quite variable.

Three studies report findings from single institution prospective active surveillance databases with detailed measures and triggers for curative treatment.[17, 18, 20] Of these three cohort studies, only Cooperberg et al.'s study of men with intermediate-risk prostate cancer followed on active surveillance at the University of California, San Francisco provides a control group.[17] The remaining studies from the University of Toronto[18] and Royal Marsden Hospital in the United Kingdom[20] are single cohort studies reporting the outcomes of men enrolled on institutional active surveillance protocols, a fraction of whom had intermediate risk disease. The two final studies in this review from Stattin et al.[19] and van den Bergh et al.[16] include data generated from larger studies; within these studies, the authors abstracted data on men with intermediate risk disease followed on an uncertain combination of active surveillance and watchful waiting.[16, 19] Stattin et al. used data collected during the National Prostate Cancer Register of Sweden Follow-up Study to retrospectively evaluate the outcomes of men diagnosed with localized prostate cancer, some of whom had Gleason 7 disease.[19] van den Bergh et al. compiled a case series of men enrolled in the European Randomized Study of Screening for Prostate Cancer with screen-diagnosed Gleason 7 disease followed expectantly.[16]

Despite the large studies from which several of the included articles draw their study populations, the number of men with Gleason 7 disease in the studies is small, ranging from 29 to 93 men.[17, 19] Follow-up of these small numbers of men ranges from 22 months to 8.2 years.[19, 20]

Three studies evaluated the oncologically-critical outcomes of overall survival or prostate-cancer specific survival.[16, 18, 19] The first study, van den Bergh et al.'s case series of men with Gleason 7 prostate cancer, reported 68% 6-year overall survival and 100% 6-year cancer-specific survival, leading the authors to suggest that active surveillance might be an option for selected patients with screen-detected Gleason 3+4 disease.[16] The second study, Stattin et al.'s study of men with localized prostate cancer from the National Prostate Cancer Register of Sweden Follow-up Study, reported that men with intermediate-risk disease followed on surveillance were more than twice as likely to die of prostate cancer as were men with low-risk disease followed on surveillance (5.2% [95% CI: 3.7-6.9%] vs. 2.4% [95% CI: 1.2-4.1%]).[19] While the third study from Klotz et al. at the University of Toronto did not provide specific survival data for men with intermediate-risk disease, the study reported that men with Gleason 3+4 disease were nearly twice as likely to transition from active surveillance to radical treatment (OR 1.83 [95%CI: 1.086-3.097]; p=0.0233) compared to men with Gleason ≤6 disease.[18] The remaining two active surveillance cohort studies also evaluated the transition to curative treatment.[17, 20] On univariate analysis, van As et al. identified an association between Gleason 7 disease and a shorter time to radical treatment in the Royal Marsden active surveillance cohort (HR 2.43 [95% CI 1.39-4.25]; p=0.002). On multivariate analysis adjusted for initial PSA, clinical T stage, free/total PSA ratio, PSA density, percent positive cores, number of positive scores, prostate volume, and maximum percentage cancer involvement in any core, this association was no longer significant. Finally, in the University of California, San Francisco active surveillance cohort, Cooperberg et al. reported that men with intermediate risk disease were no more likely to progress to active treatment than men with low-risk disease.[17]

DISCUSSION

We identified five studies that include men with Gleason 7 prostate cancer followed on active surveillance. Drawing any conclusions from these studies presents a challenge, as the included study populations, length of follow-up, and evaluated outcomes are quite different. At face value, two studies suggest that active surveillance is appropriate for men with Gleason 7 or intermediate risk prostate cancer.[16, 17] In contrast, two studies report that men with Gleason 7 disease followed on active surveillance do not fare well, with markedly higher rates of prostate-cancer specific death[19] and transitions to curative treatment.[18] The final study reports an association between Gleason 7 disease and a shorter time to radical treatment on univariate analysis; however, this association loses significance upon multivariate analysis.[20] The risks of various biases and the influence of these biases upon study findings are critical to understand before determining whether men with Gleason 7 prostate cancer can be safely followed on active surveillance.

Of the studies captured in this review, the National Prostate Cancer Register of Sweden Follow-up Study provides the highest quality statistical analysis, has the longest follow-up, includes the largest number of men with Gleason 7 prostate cancer followed on active surveillance, and has the most generalizable study population, including 90% of all patients in Sweden 70 years or younger with a low- or intermediate-risk prostate cancer diagnosed from January 1, 1997, through December 31, 2002.[19] The study evaluated the oncologically-critical outcomes of prostate-cancer specific mortality and overall survival, concluding that men with low-risk prostate cancer may be safely followed on active surveillance. In contrast, men with intermediate-risk disease followed on surveillance were more than twice as likely to die of prostate cancer as were men with low-risk disease.

While the study[19] has multiple strengths, fundamental flaws in study group composition and the definition of surveillance used in the research design limit extrapolation of study findings to our review question. The intermediate-risk group defined in the study included men with a Gleason score ≤7 and a PSA <20 ng/mL. In total, this group included 936 men; however, only 93 of these men had a Gleason score of 7. Analyses were stratified by risk-level, rather than by Gleason score. The influence of disease aggressiveness (as reflected by the Gleason score) vs. total disease burden (as reflected by PSA value) upon the outcomes of men with intermediate risk disease followed on active surveillance cannot be determined from the provided data. Additionally, an inherent selection bias that affects overall and prostate-cancer specific survival exists in this observational cohort, as healthy patients with intermediate-risk prostate cancer were likely counseled to undergo curative treatment, whereas men with multiple comorbidities were likely encouraged to pursue surveillance or watchful waiting. The influence of this bias would positively skew the magnitude of the study results. Finally, treatment for men on surveillance in this nationwide observational cohort was a mixture of active surveillance and watchful waiting. As previously reviewed, prostate cancer-specific survival and overall survival is quite different among men on modern active surveillance protocols as compared to men followed on watchful waiting. The ratio of men followed on active surveillance compared to watchful waiting in the study population is uncertain.

Similar to the National Prostate Cancer Register of Sweden Follow-up Study[19], van den Bergh et al.'s case series of 50 men with screen-detected Gleason 7 prostate cancer also included men followed on both active surveillance and watchful waiting.[16] However, in stark contrast to the lower prostate cancer- specific survival rates among intermediate-risk men reported in the Swedish study, van den Bergh et al. reported 100% 6-year prostate cancer-specific survival

among men with Gleason 7 prostate cancer who were followed expectantly. No prostate cancer-specific deaths in a population of men with Gleason 7 disease managed with a mixture of active surveillance and watchful waiting is quite remarkable and raises concerns for selection bias. In total, the European Randomized Study of Screening for Prostate Cancer, which is the source population for this case series, enrolled 162,387 men in seven European centers.[21] From four participating sites, van den Bergh et al. identified 50 men with Gleason 7 prostate cancer followed expectantly. The authors omit specific information concerning the identification of these men and any applied exclusion criteria, which severely hampers interpretation and generalizability of the study's findings.

While the studies from Stattin et al.[19] and van den Bergh et al.[16] lack uniform follow-up for men with Gleason 7 prostate cancer, the remaining studies included in our review follow men on single-institution active surveillance protocols with well-defined follow-up measures and triggers for curative treatment.[17, 18, 22] Unfortunately, each study is also plagued by significant deficits limiting application to our study question regarding how men with Gleason 7 prostate cancer fare on active surveillance.

Klotz et al.'s cohort of men on active surveillance at the University of Toronto includes 72 men with Gleason 3+4 disease followed for a median of 6.8 years. Unfortunately, while the study is well presented and examines the oncologically-critical outcomes of overall survival and prostate-cancer specific survival, these outcomes are not stratified by risk group or Gleason score. On univariate logistic regression analysis, men with Gleason 3+4 prostate cancer are nearly twice as likely to transition from active surveillance to radical treatment compared to men with Gleason ≤6 disease. Whether this finding would persist on multivariable analysis when

adjusted for PSA, clinical stage, age, race, PSA density, or percentage core involvement, is uncertain. This uncertainty limits the generalization of the study's findings.

Cooperberg et. al's cohort of men on active surveillance at the University of California, San Francisco includes 90 men with intermediate-risk disease, though only 29 of these men had Gleason 7 disease.[17] While this is the only study to directly compare the outcomes of men with intermediate-risk prostate cancer followed on a well-defined active surveillance protocol to a control group of low-risk prostate cancer patients followed on the same active surveillance protocol, the authors' classification of low- and intermediate-risk disease restricts extrapolation to our study question. The authors' included men with Gleason score 2-6 (Appendix A, Table 1.2) and CAPRA score 0-2 (Appendix A, Table 1.4) as low-risk and men with Gleason score 7 and CAPRA score 3-5 as intermediate risk. By CAPRA score, men with higher volume Gleason 6 disease fit in the intermediate-risk category and, in fact, compose the majority of the study's intermediate-risk group. The oncologic acceptability of this classification is debatable.[23, 24] As a result, Cooperberg et al.'s conclusion of no difference in cancer progression, PSA doubling time, or progression to active treatment between low- and intermediate-risk men followed on active surveillance may not apply specifically to men with Gleason 7 disease.

The last prospective active surveillance cohort in our review includes 39 men with Gleason 7 prostate cancer followed on protocol at the Royal Marsden Hospital. van As et al. found Gleason 7 disease was associated with a shorter time to radical treatment on univariate analysis, though not on multivariate analysis. With a time-dependent solitary outcome, the study's significant limitation is its 22 month median follow-up, which is far too short to draw any generalizable conclusions. Additionally, the study fails to account for personal preference as the reason for discontinuation of active surveillance. As 20% of men followed on active

surveillance transition to curative treatment over time because of personal preferences or anxiety,[25] this is a significant confounder which requires measurement and adjustment.

CONCLUSION

We identified five studies that included men with Gleason 7 prostate cancer followed on active surveillance. Conclusions from these studies are different, as are the measures, outcomes, and study inclusion criteria. Weighing the risk of bias and generalizability of these studies, little reliable data about the safety of following men with Gleason 7 prostate cancer on active surveillance can be extrapolated. Further research, with more rigorous study designs and statistical analyses, is needed before offering active surveillance as a management strategy to men with Gleason 7 disease.

1.2 Appendix A: Prostate Cancer Risk Stratification

Table 1.1: Most widely used risk strata for newly diagnosed prostate cancer.[6-8]

Risk Category	**PSA**		**Gleason Score**		**Clinical Exam**
Low	≤ 10 ng/mL	*and*	≤ 6[*]	*and*	T1c, T2a[^]
Intermediate	PSA > 10 to 20 ng/mL	*or*	7 (3+4 or 4+3)[*]	*or*	T2b[^]
High	PSA > 20 ng/mL	*or*	8-10[*]	*or*	T2c or higher[^]

[*]Refer to Table 1.2
[^]Refer to Table 1.3

Table 1.2: Gleason scoring for prostate carcinoma.[26]

Gleason Pattern	Description
1	Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini that are larger than Gleason pattern 3 glands.
2	Fairly circumscribed nodules; may have minimal infiltration of glands at the edge of the tumor nodule; Glands are more loosely arranged and not quite as uniform as Gleason pattern 1 glands.
3	Discrete glandular units; Typically smaller glands than seen in Gleason pattern 1 or 2; Infiltrates in and amongst non-neoplastic prostate acini; Marked variation in size and shape; Smoothly circumscribed small cribriform nodules of tumor.
4	Fused micro-acinar glands; Ill-defined glands with poorly formed glandular lumina; Large cribriform glands; Cribriform glands with an irregular border; Hypernephromatoid
5	Essentially no glandular differentiation: composed of solid sheets, cords, or single cells; Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

When evaluated by pathology, each prostate cancer biopsy specimen receives a primary and secondary Gleason pattern score of 1-5; added together, these numbers provide the total Gleason biopsy score of 2-10. The first number represents the most common pattern in the specimen, while the second number represents the highest grade tumor in the specimen.

For example, if a prostate biopsy specimen has 80% Gleason 3 prostate cancer and 20% Gleason 4 prostate cancer visible within the biopsy core on low-power magnification, the patient is diagnosed with Gleason 3 + 4 = 7 prostate cancer.

Table 1.3: Clinical staging of prostate cancer.[27]

Clinical Stage	Interpretation
T1a	Prostate cancer detected in ≤ 5% of resected tissue from a transurethral resection of the prostate; no palpable tumor on digital rectal exam (DRE) and no visible tumor on imaging
T1b	Prostate cancer detected in > 5% of resected tissue from a transurethral resection of the prostate; no palpable tumor on DRE and no visible tumor on imaging
T1c	Prostate cancer identified on prostate needle biopsy; no palpable tumor on DRE and no visible tumor on imaging
T2a	Palpable tumor in ≤ ½ of one side of the prostate on DRE and/or visible tumor ≤ ½ of one side of the prostate on imaging
T2b	Palpable tumor in > ½ of one side of the prostate on DRE and/or visible tumor in > ½ of one side of the prostate on imaging
T2c	Palpable tumor, or visible tumor on imaging, involving both lobes
T3a	Palpable tumor, or visible tumor on imaging, extends beyond the prostate capsule
T3b	Palpable tumor, or visible tumor on imaging, invades the seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures (external sphincter, rectum, bladder, levator muscles, and/or pelvic wall)

Table 1.4: The University of California, San Francisco Cancer of the Prostate Risk Assessment (CAPRA) score.[28]

Variable	Range	Points
PSA (ng/mL)	2.0-6.0	0
	6.1-10.0	1
	10.1-20.0	2
	20.1-30.0	3
	> 30.0	4
Gleason score (primary/secondary)	1-3/1-3	0
	1-3/4-5	1
	4-5/1-5	3
Clinical stage	T1/T2*	0
	T3a*	1
% positive biopsy cores	<34% positive	0
	≥34% positive	1
Age	<50 years old	0
	≥50 years old	1

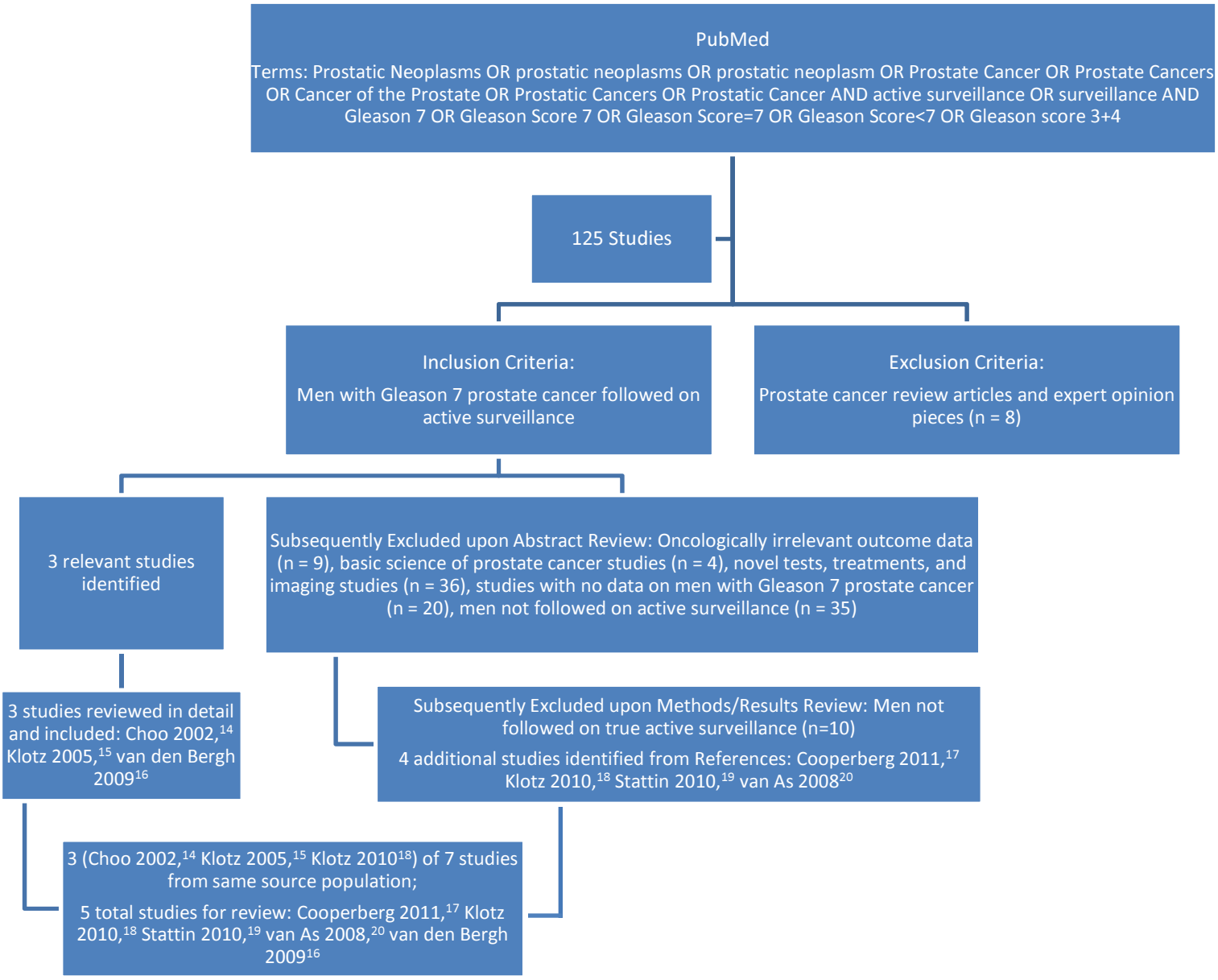
*Refer to Table 1.3.

The overall CAPRA score is determined by adding the points for each variable category. Men are then classified as low-, intermediate-, or high-risk as follows:[29]

Risk Category	CAPRA Score
Low-risk	0-2
Intermediate-risk	3-5
High-risk	6-10

1.3 Appendix B: Study Selection Methodology

Figure 1.1: Overview of study selection methodology.



1.4 Appendix C: Quality and Evidence Tables

Table 1.1: Description of included studies.

Citation	Study Population	Data Source/ Measures	Analysis	Outcome(s)/Results	Funding/ COI
Cooperberg MR, et al. 2011[17]	*Inclusion Criteria:* Men with low (Gleason score 2-6 AND CAPRA score 0-2) (Appendix A, Table 1.4) or intermediate-risk (Gleason score 7 OR CAPRA score 3-5) prostate cancer followed on active surveillance at UCSF; Minimum of 1 follow-up biopsy or PSA value 6-18 months after diagnosis. *Exclusion Criteria:* CAPRA score 6-10, Gleason score 8-10, or cT3 disease; <1 year follow-up. *Demographics:* Mean age at diagnosis: 62.8 ± 8.1 yrs; Intermediate risk group older (64.9 *vs.* 62.3 years; *P*<.01), higher PSA (10.9 *vs.* 5.1 ng/mL; *P*<.01), and greater tumor involvement (20.4% *vs.* 15.3% positive biopsy cores; *P* < .01) compared to low-risk men.	*Source:* Data from UCSF urologic oncology database. *Measures:* Patients followed with DRE and PSA every 3 months, transrectal ultrasound every 6-12 months, and follow-up prostate biopsy every 12-24 months. PSA doubling time calculated as the time after the first measurement until the patient's logPSA increased by a factor of 2.	Demographic and disease characteristics between the low- and intermediate-risk groups compared using chi-square or *t*-tests. Kaplan-Meier analysis used to estimate progression-free survival. Poisson regression used to estimate the Gleason upgrade incidence rate per group.	*Cancer progression (upgrading on repeat biopsy):* No difference: 111/313 (35%) low-risk men vs. 19/63 (30%) intermediate-risk men upgraded on repeat biopsy; p=0.42. *PSA doubling time:* No difference: ≤ 2 years: 7% low-risk vs. 5% intermediate-risk; p=0.52; ≤ 3 years: 10% low-risk vs. 11% intermediate-risk; p=0.80. *Progression to active treatment (radical prostatectomy, radiation, or androgen deprivation therapy):* No difference: 30% low-risk vs. 35% intermediate-risk within 4 years of diagnosis; log-rank p=0.88. *Subsequent nodal involvement or biochemical recurrence among men progressing to radical prostatectomy:* None at 3 year follow-up among 58 low-risk and 16 intermediate-risk men undergoing radical prostatectomy.	*Funding:* UCSF Special Program of Research Excellence Grant; National Institutes of Health/ National Cancer Institute Grant. *COI*: Greene KL: stock ownership

Citation	Study Population	Data Source/ Measures	Analysis	Outcome(s)/Results	Funding/ COI
Klotz L, et al. 2010 [18]	*Inclusion Criteria:* Prostate cancer diagnosed within 12 months of study entry confirmed by central pathologic review; No previous treatment for prostate cancer; Men <70 years old with "favorable-risk" disease = Gleason ≤6, PSA ≤10 ng/mL, and clinical stage T1b-T2b; Men ≥70 years old with "favorable-risk" or intermediate risk disease = Gleason score ≤7 (3+4 only) or PSA ≤15 ng/mL, and clinical stage T1b-T2b. *Exclusion Criteria:* Clinical stage ≥T2c, nodal or metastatic disease *Demographics:* Median age: 70.3 years; 71% of patients "favorable risk" & 29% intermediate-risk and either >70 years of age or with significant comorbidity.	*Source:* Data from prospectively collected database at Sunnybrook Health Sciences Centre, University of Toronto. *Measures:* PSA every 3 months for 2 years and then every 6 months in stable patients; Confirmatory biopsy 6-12 months after initial biopsy and then every 3-4 years until age 80. Patients re-classified as higher risk and offered radical intervention for	Kaplan-Meier survival analysis and log-rank test used to analyze overall survival, cause-specific survival, time to stopping active surveillance, and time to PSA failure. Cox proportional hazards regression analysis used to determine the hazard ratio between non–prostate cancer mortality and prostate cancer mortality. Univariate logistic regression analysis used to determine the likelihood of being treated based upon PSA	*KM Analyses:* *Overall survival for entire cohort*: 353/450 (78.6%) at median follow-up of 6.8 years; 10-year overall survival 68% (95% CI: 62-74%). *Prostate cancer-specific survival for entire cohort*: 5-year cancer-specific survival: 99.7%; 10-year cancer-specific survival: 97.2%. *Time to PSA failure for entire cohort:* Median 48 months in 117 patients treated with radical therapy after stopping active surveillance. *Time to stopping active surveillance for entire cohort:* At 2, 5, and 10 years, the likelihood that a patient remained on surveillance was 84, 72, and 62%, respectively. *Cox Proportional Hazards analysis for the entire cohort:* Hazard ratio for non-prostate cancer to prostate cancer mortality = 18.6 (95% CI 7.6-45.7) at 10 years.	None

Citation	Study Population	Data Source/ Measures	Analysis	Outcome(s)/Results	Funding/ COI
Klotz L, et al. 2010 [18]		PSA doubling time <3 years, histologic upgrade on repeat prostate biopsy, or development of a palpable nodule. Biochemical recurrence defined as PSA >0.2 ng/mL for patients who underwent surgery and the PSA nadir + 2 ng/mL for patients who received radiation.	at baseline (>10 ng/mL vs. ≤10 ng/mL), stage at baseline (≥T2 vs. <2), and Gleason score at baseline (> 6 vs. ≤ 6).	*Univariate logistic regression analysis:* Likelihood of proceeding for radical treatment related to Gleason score (odds ratio, 1.83, 95% CI 1.086-3.097); *P* =.0233) and T stage ≥T2a (odds ratio, 2.02; 95% CI 1.305-3.133; *P*= .0016).	
Stattin P, et al. 2010[19]	*Inclusion Criteria:* Men enrolled in the National Prostate Cancer Register of Sweden Follow-up Study diagnosed with clinical stage T1–2 prostate cancer between 1/1/97 and 12/31/2002 with a Gleason score ≤7, PSA <20 ng/mL, no lymph node	*Sources:* National Prostate Cancer Registry, Swedish Population Register, Cause of Death Register, and review of death certificates.	Distribution of patient characteristics by treatment group compared using chi square and *t*-tests. Pepe and Mori test used to	*Death from prostate cancer:* Death was attributed to prostate cancer in 58/2021 (2.9%) patients in the surveillance group, 56/3339 (1.7%) patients in the prostatectomy group, and 40/1429 (2.8%) patients in the radiation therapy group. Within the surveillance group, 14 men with low-risk disease (1.3%)	*Funding:* Swedish Research Council; Väster-botten County Council; Swedish Cancer

Citation	Study Population	Data Source/ Measures	Analysis	Outcome(s)/Results	Funding/ COI
Stattin P, et al. 2010[19]	or bone metastases, and treated with surveillance (including active surveillance and watchful waiting) or curative intent (including radical prostatectomy or radiation). *Exclusion Criteria:* Primary hormonal treatment, Gleason 8-10 tumors, missing PSA, stage, grade, or treatment data. *Demographics:* Mean age of surveillance group 64.7 ± 4.6 vs. 61.2 ± 5.3 for prostatectomy group vs. 63.4 ± 4.9 years for the radiation group; In total, 2021 men in the surveillance group (93 with Gleason 7 disease), 3399 in the surgery group (601 with Gleason 7 disease), and 1429 in the radiation group (280 with Gleason 7 disease).	Treatment data and surveillance termination information extracted from individual medical records by research nurses a median of 4 years after the date of diagnosis. *Measures:* No surveillance protocol; "active surveillance" group a mixture of men followed on surveillance and watchful waiting by individual physicians across Sweden. No defined triggers for transition to curative treatment.	analyze the difference in the cumulative incidence of mortality between treatment groups. Cox proportional hazards model and competing-risks regression models used to determine relative risk of low- (clinical stage T1a-c, Gleason score ≤6 [or WHO grade I-II], and serum PSA <10 ng/mL) vs. intermediate-risk (clinical stage T2 or Gleason score 7 or serum PSA ≥10 ng/mL) groups.	died of prostate cancer, compared to 44 (4.7%) men with intermediate risk disease. The calculated cumulated prostate cancer–specific mortality after 10 years of follow-up was 3.6% (95% CI: 2.7- 4.8%) in the surveillance group vs. 2.4% in the prostatectomy group (95% CI: 1.8- 3.3%) vs. 3.3% (95%CI: 2.5-5.7%) in the radiation therapy group. Among those with low-risk disease, prostate cancer–specific mortality was 2.4% (95% CI: 1.2- 4.1%) in the surveillance group, 0.4% in the prostatectomy group (95% CI: 0.13-0.97%) and 1.8% in the radiation therapy group (95% CI: 0.65- 4.0%). Among those in the intermediate-risk category, prostate cancer–specific mortality was 5.2% (95% CI: 3.7-6.9%) in the surveillance group, 3.4% (95% CI: 2.5- 4.7%) in the prostatectomy group, and 3.8% (95% CI: 2.6-5.4%) in the radiation therapy group. Among patients with intermediate risk disease, the risk of calculated	Foundation *COI:* None

Citation	Study Population	Data Source/ Measures	Analysis	Outcome(s)/Results	Funding/ COI
	After a median follow-up time of 4 years, 692/2021 (34%) patients on surveillance received deferred treatment, which was radical prostatectomy for 277 men, radiation therapy for 207 men, and hormonal therapy for 208 men.			cumulative prostate cancer–specific death was significantly lower among patients in the prostatectomy group than among patients in the surveillance group (RR 0.49, 95% CI: 0.34-0.71). After multivariable adjustment, there was a lower risk of prostate cancer–specific mortality among those in the prostatectomy group than among those in the surveillance group (RR 0.49, 95% CI: 0.34-0.71), and among those in the radiation therapy group than among those in the surveillance group (RR 0.70, 95% CI: 0.45-1.09). *Death from competing causes:* 413/2021 (20.4%) patients on active surveillance died in follow-up vs. 286/3399 (8.4%) of the surgery patients vs. 196/1429 (13.7%) of the radiation therapy patients. The 10-year cumulative risk of dying of competing causes differed significantly by treatment received: 19.2% (95% CI 17.2-21.3%) in the surveillance group vs. 8.5% (95% CI: 7.3-9.8%) in the prostatectomy	

Citation	Study Population	Data Source/ Measures	Analysis	Outcome(s)/Results	Funding/ COI
				group, and 14.2% (95% CI: 11.7-16.9%) in the radiation therapy group. *Death from all causes:* Calculated all-cause mortality at 10 years of follow-up was 23.4% (95% CI: 21.3-25.8%) in the surveillance group, 11.3% (95% CI: 10.0-12.9%) in the radical prostatectomy group, and 18.3% (15.7-21.3%) in the radiation therapy group.	
van As NJ et al. 2008[20]	*Inclusion Criteria:* Men ages 50-80 years old with clinical stage T1–T2a, N0–NX, M0–MX adenocarcinoma of the prostate with serum PSA <15 ng/ml, Gleason score ≤7, primary Gleason grade ≤ 3, and ≤50% positive biopsy cores. All men were required to be of adequate health and fitness to undergo radical treatment. *Exclusion Criteria:* None specified. *Demographics:*	*Source:* Data from prospectively collected database at Royal Marsden Hospital. *Measures:* Serum PSA monthly in year 1, every 3 months in year 2, and every 6 months thereafter. DRE every 3 months for 2 years, then every	Univariate and multivariate Cox regression analysis used to compare baseline clinical variables (initial PSA level, Gleason score, clinical T stage, free/total PSA ratio, PSA density, % positive cores, number of positive cores, prostate volume, and maximum core involvement) and	*Time to radical treatment:* At a median follow-up of 22 months (range: 1–56 months), 238/336 patients (73%) remained on active surveillance, 65/336 (20%) underwent radical treatment, 16/336 (5%) switched to watchful waiting because of increasing comorbidity, and 7/336 (2%) died of other causes. 15/39 patients with Gleason 7 disease proceeded for radical treatment, compared to 50/287 patients with Gleason ≤3+3 disease. Median time to treatment was 15 (range: 1–40) months. Among those undergoing treatment,	*Funding:* Royal Marsden NHS Trust; NHS Executive; Institute of Cancer Research; Cancer Research UK Section of Radio-therapy; Pelican Foundation *COI:* None

Citation	Study Population	Data Source/ Measures	Analysis	Outcome(s)/Results	Funding/ COI
	Median patient age 67 (range 50-79) years, median initial PSA 6.4 ng/ml (range 0.2-14.9), and 17% median biopsy cores involvement (range 4-50%).	6 months thereafter. Repeat biopsy at 18 -24 months and then every 2 years. Indications for radical treatment included a PSA velocity >1 ng/ml/yr, a Gleason score ≥4+3, or >50% core involvement on repeat biopsy. Biochemical failure after radical treatment was defined as a PSA > 0.2 ng/ml after radical prostatectomy, or nadir + 2 after radiation therapy.	time to radical treatment.	4/65 experienced biochemical recurrence; no metastases or prostate cancer deaths have occurred. Univariate analysis showed that initial PSA level (HR 1.15, 95% CI: 1.07-1.23; p< 0.001), free/total PSA ratio (HR 0.87, 95% CI: 0.83-0.92; p< 0.001), PSA density (HR 55.67, 95% CI: 8.71-355.83; p<0.001), Gleason score (HR 2.43, 95% CI 1.39-4.25; p=0.002); maximum percentage involvement of any core (HR 2.21, 95% CI: 1.34-3.65;p = 0.002), % positive cores (HR 1.74, 95% CI 1.06-2.86; p=0.03), clinical T stage (HR 1.86, 95% CI: 1.06-3.25, p=0.03), number of positive cores (HR 1.64, 95% CI1.00-2.69; p=0.04), and prostate volume (HR 0.98, 95% CI 0.97-0.99; p=0.04) were associated with time to radical treatment. On multivariate analysis, free/ total PSA ratio (HR 0.88, 95% CI: 0.84-0.93; p< 0.001) and clinical T stage (HR 2.63, 95% CI 1.32-5.23; p=0.006) remained statistically significant determinants of time to radical treatment.	

Citation	Study Population	Data Source/ Measures	Analysis	Outcome(s)/Results	Funding/ COI
van den Bergh RCN, et al. 2009[16]	*Inclusion criteria:* Dutch, Swedish, and Finnish men 50-75 years of age participating in the European Randomized Study of Screening for Prostate Cancer who had screen-detected prostate cancer with Gleason 7 disease (3+4 or 4+3) on biopsy. Patients self-selected expectant management. *Exclusion criteria:* Men with positive lymph nodes or distant metastatic disease. *Demographics:* Mean age 69.5 (range: 59.6-76.2) years; 44/50 (88%) with Gleason 3+4 disease; 6/50 (12%) with Gleason 4+3 disease; Mean PSA 5.7 ng/mL (range: 2.5-15.9); Mean PSA density 0.18 (range: 0.05-0.54); 40/50 (80%) cT1c; 9/50 (18%) cT2; 32/50 (64%) with 1 or 2 positive	*Source:* Follow-up data collected from patient charts; mortality information obtained from National Registries. *Measures:* Men followed "expectantly" were followed with a mixture of active surveillance and watchful waiting by individual physicians at four centers participating the the European Randomized Study of Screening for Prostate Cancer in Sweden, Finland, and the Netherlands.	Kaplan-Meier method and log-rank test used to analyze prostate cancer-specific survival, overall survival and treatment-free survival. In a subgroup analysis, men with favorable risk Gleason 7 disease (PSA ≤10.0 ng/mL, cT1c/T2, PSA density <0.2 ng/mL/mL, and two or fewer positive biopsy cores) were compared to men with less favorable risk Gleason 7 disease using the Kaplan-Meier method and log-rank test.	*Prostate cancer-specific survival*: 6-year cancer-specific survival: 100% *Overall survival*: 6-year overall survival: 68%; *Treatment-free survival:* 6-year treatment-free survival: 59% Median time to deferred active therapy was 1.4 (IQR 0.7-3.0) years. Subgroup Analysis: Men with less favorable risk Gleason 7 disease (29/50 men) were more likely to transition to deferred active therapy than were men with favorable risk Gleason 7 disease (log-rank p<0.001).	*Funding:* Beckman Coulter Ltd.; Dutch Cancer Society; Netherlands Organization for Health Research and Development; 6th Framework Program of the EU; Europe against Cancer; Swedish Cancer Society; Schering Plough; Abbot; Gunvor and Ivan Svensson's Foundation; Af Jochnick's Foundation; Academy of Finland; Cancer Society of Finland; Sigrid Juselius Foundation; Competitive Research Funding of the Pirkanmaa Hospital District; Helsingin Sanomat Centenarian Fund; Hybritech Corp; Foundation for Finnish Culture

Citation	Study Population	Data Source/ Measures	Analysis	Outcome(s)/Results	Funding/ COI
	cores; 10/50 (20%) with 3 or 4 positive cores; Mean 6.7 total biopsy cores (range 5-12).	No defined triggers for transition to curative treatment.			*COI:* Schröder FH: Ferring Ltd; Glaxo-Smith Kline; Bayer; Schering; Cougar Biotechnology; Genprobe

Table 1.2: Quality assessment of included studies.

Author	Study Design	Points	Sample Size	Points	Primary Outcome(s)	Points	Follow-up	Points	Bias	Points	Total
Cooperberg MR, et al. 2011[17]	Single institution prospective cohort with control group	3	Total: 466 men *Subset of Gleason 7 men*: 29	1	- Gleason score progression on repeat biopsy - PSA kinetics - Progression to active treatment	1	Mean: 51 months (range: 14-140 months) months for intermediate risk men	2	++	2	**9**
Klotz L, et al. 2010[18]	Single institution prospective cohort	2	Total: 450 men *Subset of Gleason 7 men*: 72	2	- Overall survival - Prostate-cancer specific survival	3	Median: 6.8 years (range: 1-13 years)	2	++	2	**10**
Stattin P, et al. 2010[19]	National population-based retro-spective cohort	2	Total: 6849 men; *Subset of Gleason 7 men*: 93	2	- Prostate-cancer specific mortality - Risk of death from competing causes - Death from all causes	3	Median: 8.2 years (IQR 7.1-9.7 years)	3	++	3	**13**

Author	Study Design	Points	Sample Size	Points	Outcome(s)	Points	Follow-up	Points	Bias	Points	Total
van As NJ, et al.[20]	Single institution prospective cohort	2	Total: 326 men *Subset of Gleason 7 men*: 39	1	- Time to radical treatment	1	Median: 22 months (range 1-56 months)	1	++	2	**7**
van den Bergh RCN, et al. 2009[16]	Case series	1	Total: 50 men, all with Gleason 7 prostate cancer	1	- Cancer-specific survival - Overall survival - Treatment-free survival	3	Mean: 3.4 years (range: 0.0-11.6 years)	1	+++	1	**6**

The above table displays the quality rating for each study included in this review. Each category was graded on scales of 1 (lowest) to 3 (highest). Combining scores for study design, sample size, outcome measures, length of follow-up, and risk of bias, the quality score for each study could range from 5 (lowest quality) to 15 (highest quality).

2.1 Original Manuscript

Characterization of a "Low-Risk" Cohort of Gleason 7 Prostate Cancer Patients: Results from the Shared Equal Access Regional Cancer Hospital (SEARCH) Database

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ABSTRACT

Purpose

To examine if there is a subset of men with Gleason 7 (3+4) prostate cancer who may be potential candidates for active surveillance.

Materials and Methods

We used the SEARCH database to identify 870 men undergoing radical prostatectomy from 2001-13 with >8 biopsy cores and complete clinical information. We compared characteristics of men who fulfilled low-risk disease criteria (clinical stage T1c/T2a; biopsy Gleason ≤6; PSA ≤10 ng/mL) with the exception of biopsy Gleason 7 (3+4) vs. men who met all 3 low-risk criteria. Logistic regression was used to test the association between biopsy Gleason and pathological features. Biochemical recurrence was examined using Cox hazards analysis. To examine whether there was a subset of men with low-volume Gleason 7 with comparable outcomes to low-risk men, we repeated all analyses limiting the percentage positive cores to ≤33% and positive cores to ≤4, ≤3, or ≤2.

Results

Gleason 7 low-risk men had increased risk of pathological Gleason ≥4+3 ($p<0.001$), positive margins ($p=0.070$), extracapsular extension ($p<0.001$), seminal vesicle invasion ($p=0.005$), and higher biochemical recurrence (HR 1.65, $p=0.006$). Using increasingly strict definitions of low-volume disease, at ≤3 positive cores there was no difference in adverse pathology between groups (all $p>0.1$), except higher pathological Gleason score ($p<0.001$). Biochemical recurrence was similar in men with Gleason 6 or Gleason 7 (3+4) (HR 1.39; $p=0.254$).

Conclusion

Among men with PSA≤10 ng/mL and clinical stage T1c/T2a, those with Gleason 7 (3+4) in ≤3 total positive cores have similar rates of adverse pathology and biochemical recurrence as men with Gleason ≤6.

INTRODUCTION

Active surveillance is an attractive option to avoid overtreatment for men with low-risk disease typically defined as Gleason score ≤6, PSA ≤10 ng/mL, clinical stage ≤T2a,[30] low disease volume on biopsy (limited by percentage or total number of positive cores),[31-34] and low PSA density.[35, 36] Among men meeting these criteria, prostate cancer specific mortality is low and radical treatment is avoided.[9] Limited data exist on the inclusion of men with intermediate-risk prostate cancer, including Gleason 7, into active surveillance protocols. In the University of Toronto's active surveillance cohort, 72 (17%) men had Gleason 3+4. Relative to men with Gleason score ≤6, those with Gleason 3+4 were 1.8 times more likely to undergo radical treatment.[30] Conversely, Cooperberg et al. reported that among 90 men with intermediate-risk disease undergoing active surveillance at UCSF, there was no difference in progression-free survival or the proportion of men undergoing treatment within a four year period versus men with low-risk disease.[37] Most recently, Musunuru et al. presented an abstract reporting lower overall survival and cause-specific survival in 237 patients with PSA>10ng/mL or Gleason score 7 or clinical stage T2b/2c followed on active surveillance at a single institution.[38]

As Gleason 7 is now the most common score on biopsy,[10] we examined if there was a subset of men with Gleason 7 (3+4) who would be reasonable candidates for active surveillance. We hypothesized that by defining PSA, clinical stage, and volume criteria on biopsy, we could identify a group of men with Gleason 7 (3+4) who would be candidates for active surveillance, thereby further reducing prostate cancer overtreatment.

MATERIALS AND METHODS

Study population

After obtaining IRB approval, data from patients at Veterans Administration (VA) Medical Centers (Palo Alto, CA; West Los Angeles, CA; San Diego, CA; Durham, NC; Augusta, GA) were combined into the Shared Equal Access Regional Cancer Hospital Database (SEARCH). As few men treated prior to 2001 had adequate prostate sampling (defined as >8 cores), we limited analyses to men treated in 2001 or later biopsied per physician standard practice (n=2,810). We excluded men with missing data on race (n=3), PSA (n=16), biopsy Gleason (n=24), pathological Gleason (n=15), clinical stage (n=170), number of cores taken (n=282), number of positive cores (n=39), positive margins (n=14), extracapsular extension (n=14), seminal vesicle invasion (n=6), and surgical technique (n=10). Of the remaining 2,217 men, 870 met our study criteria of PSA ≤10 ng/mL, biopsy Gleason ≤7 (3+4), clinical stage T1c or T2a, and >8 cores on biopsy. In a subset analysis, we further excluded men with missing PSA density data (n=132). In this subset, 738 men met study inclusion criteria.

We compared men who fulfilled the criteria of AUA low-risk disease (clinical stage T1c/T2a, biopsy Gleason ≤6 and PSA ≤10 ng/mL)[6-8] with the exception of biopsy Gleason 7 (3+4) (henceforth "Gleason 7 low-risk") versus men who met all 3 criteria for AUA low-risk. We used this definition of low-risk disease for comparison because active surveillance is a recommended treatment option for men meeting these criteria in the National Comprehensive Cancer Network Guidelines.[8]

Statistical analysis

Differences in demographic and clinicopathological features between the Gleason 7 low-risk and AUA low-risk group were examined using *t*-tests for normally distributed continuous

variables, Wilcoxon rank-sum tests for non-normally distributed continuous variables, chi-square tests for categorical variables, and Fisher's exact test for categorical variables with any cell count ≤5.

Crude and adjusted logistic regression models were used to test the association between risk group (Gleason 7 low-risk vs. AUA low-risk) and pathological features (pathological Gleason score [≤6 vs. ≥4+3], positive margins, extracapsular extension, and seminal vesicle invasion). Models were adjusted for age at surgery (continuous), surgery year (continuous), race (white vs. black vs. other), number of biopsy cores (continuous), surgical center, surgical technique, clinical stage (T1c vs. T2a), and PSA (log-transformed, continuous).

On average, men were evaluated every 3 months in the first year post-operatively, every 6 months in years 2-3, and annually thereafter. Biochemical recurrence was defined as a single PSA >0.2 ng/mL, two consecutive PSAs of 0.2 ng/mL, or secondary treatment for elevated PSA in the post-operative period. Hazard ratios (HR) for biochemical recurrence between Gleason 7 low-risk and D'Amico low-risk were analyzed using Cox proportional hazards analysis, adjusting for age at surgery (continuous), surgery year (continuous), race (white vs. black vs. other), surgical center, surgical technique, clinical stage (T1c vs. T2a), PSA (log-transformed, continuous), and biopsy cores taken (continuous). Biochemical recurrence was examined using the Kaplan-Meier method and comparisons between the groups were performed using the log-rank test.

All analyses were repeated with matching of the percentage or number of positive biopsy cores between the Gleason 7 low-risk and the D'Amico low-risk group, including positive cores ≤33%, ≤4 positive cores, ≤3 positive cores, and ≤2 positive cores.

In a subset analysis including men with PSA density data, all analyses were repeated limiting the PSA density threshold between the Gleason 7 low-risk and the D'Amico low-risk group at ≤0.30, ≤0.25, ≤0.20, ≤0.15, and ≤0.10 ng/mL/g.

Statistical analyses were performed using Stata 13.1 (Stata, Corp., College Station, TX, USA). Statistical significance was two-sided with $p<0.05$.

RESULTS

D'Amico Low-Risk Patients vs. Gleason 7 Low-Risk Patients

Baseline characteristics of the 870 men who met inclusion criteria are shown in Table 2.1. Among them, 495 (57%) had D'Amico low-risk and 375 (43%) had Gleason 7 low-risk. The Gleason 7 low-risk group had a more recent median surgery year versus the D'Amico low-risk group (2011 vs. 2008; $p<0.001$), were more likely to have a robotic prostatectomy (47% vs. 32%; $p<0.001$), and undergo a pelvic lymph node dissection (PLND) (67% vs. 38%; $p<0.001$). Among men whose cancer did not recur, median post-operative follow-up was significantly shorter in the Gleason 7 low-risk group (22.0 vs. 48.8 months; $p<0.001$). As expected, Gleason 7 low-risk men had higher pre-surgery PSA (5.6 vs. 5.3 ng/mL; $p=0.011$), more positive cores (4 vs. 2; $p<0.001$), and higher rates of extracapsular extension (15 vs. 7%; $p<0.001$), seminal vesicle invasion (8 vs. 2%, $p<0.001$), and positive lymph nodes (2 vs. <1%; $p=0.024$) versus D'Amico low-risk men. Consistent with Gleason grading on prostate biopsy, Gleason 7 low-risk men were more likely to have higher pathological grade versus D'Amico low-risk men (13 vs. 46% Gleason 2-6; 62 vs. 44% Gleason 3+4; 24 vs. 10% Gleason ≥4+3; $p<0.001$). There were no significant differences in patient age, race, or clinical stage.

The Gleason 7 low-risk group had higher pathological Gleason scores, more extracapsular extension, and more seminal vesicle invasion, in both crude and adjusted models (all $p<0.01$) (Table 2.2). The risk of positive margins was not significantly different between

groups. Gleason 7 low-risk men had higher rates of biochemical recurrence than D'Amico low-risk men (log-rank, p=0.003; Figure 2.1a).

In order to identify if there were subsets of men with Gleason 7 low-risk disease with outcomes similar to D'Amico low-risk men, we assessed the effect of limiting the analysis to men with low-volume disease, using varying definitions of "low-volume". As the definition of low-volume became increasingly strict (i.e. fewer cores positive), the HR for biochemical recurrence between the Gleason 7 low-risk group and the D'Amico low-risk group became increasingly smaller (i.e. closer to 1) (Table 2.3). At ≤3 positive cores, the difference in biochemical recurrence risk between the Gleason 7 low-risk and the D'Amico low-risk group lost statistical significance (HR 1.39; p=0.254).

Analysis of Gleason 7 Low-Risk Patients vs. D'Amico Low-Risk Patients with ≤3 Total Positive Cores

As biochemical recurrence risk was comparable between the Gleason 7 low-risk and D'Amico low-risk group when restricted to men with ≤3 total positive cores, we repeated the analysis comparing baseline characteristics (Table 2.4), risk of adverse pathology (Table 2.5), and biochemical recurrence risk (Figure 2.1b) between these groups. There were 334 men (68%) with D'Amico low-risk disease and ≤3 positive biopsy cores and 157 men (32%) with Gleason 7 low-risk disease and ≤3 positive biopsy cores. Consistent with the larger cohort of men previously reviewed, the Gleason 7 low-risk group with ≤3 total positive cores had a more recent median year of surgery than the D'Amico low-risk group (2010 vs. 2007; p <0.001), were more likely to undergo a robotic prostatectomy (47% vs. 27%; p<0.001), and PLND (64% vs. 35%; p<0.001). Median post-operative follow-up was significantly shorter in the Gleason 7 low-risk group compared to the D'Amico low-risk group (22.9 vs. 51.4 months; p<0.001). While

limiting the number of positive cores to ≤3, men in the Gleason 7 low-risk group were more likely to have 2 or 3 positive cores versus the D'Amico low-risk group ($p<0.001$). Consistent with biopsy Gleason grading, pathological Gleason scores were higher in the Gleason 7 low-risk group compared to the D'Amico low-risk group (17 vs. 53% Gleason 2-6; 61 vs. 38% Gleason 3+4; 22 vs. 9% Gleason ≥4+3; $p<0.001$). There were no significant differences in patient age, race, PSA at diagnosis, clinical stage, or rates of extracapsular extension, seminal vesicle invasion, positive margins, or positive nodes between groups.

The likelihood of the Gleason 7 low-risk group having a pathological Gleason score ≥4+3 remained statistically greater than the D'Amico low-risk group ($p=0.005$) (Table 2.5). However, the risk of positive margins, extracapsular extension, and seminal vesicle invasion were similar between the Gleason 7 low-risk and the D'Amico low-risk group. There was no significant difference in biochemical recurrence risk between the two groups (log-rank, $p=0.331$; Figure 2.1b).

Supplementary Table 2.1 shows the stratification of D'Amico low-risk and biopsy Gleason 3+4 low-risk men by year of surgery. Over time, the number of Gleason 7 low-risk men undergoing surgery is increasing.

Subset Analysis: D'Amico Low-Risk Patients vs. Gleason 7 Low-Risk Patients with PSA Density Data

An alternative means to select "low-risk" men with Gleason 7 is to limit to men with low PSA density. To address this, we evaluated progressively lower PSA density thresholds, and found that men with Gleason 7 low-risk had significantly higher biochemical recurrence risk than the D'Amico low-risk group, until the PSA density was ≤0.10 ng/mL/g, when results were similar (HR 1.44; $p=0.451$) (Supplementary Table 2.2).

DISCUSSION

Limited and conflicting data on the outcomes of men with intermediate-risk prostate cancer on active surveillance exist. As Gleason 7 disease is now the most common score on biopsy,[10] we examined if a subset of Gleason 7 prostate cancer patients had similar outcomes to low-risk patients and thus could be reasonable potential active surveillance candidates. Using the SEARCH database of men undergoing radical prostatectomy, we compared men who fulfilled the D'Amico low-risk disease criteria versus men with Gleason 7 low-risk prostate cancer, but who otherwise fulfilled the D'Amico low-risk disease criteria. We explored associations between risk group, pathological features, and biochemical recurrence, with matching of PSA density (subset analysis) and the percentage or number of positive cores between the Gleason 7 low-risk and the D'Amico low-risk group. We found that among men with PSA≤10 ng/mL and clinical stage T1c/T2a, those with Gleason 7 (3+4) prostate cancer and a PSA density ≤0.10 ng/mL/g had similar rates of adverse pathology and biochemical recurrence as men with Gleason ≤6. The number of men meeting this PSA density threshold was ~2% of SEARCH over the study time period. We found that among men with PSA≤10 ng/mL and clinical stage T1c/T2a, those with Gleason 7 (3+4) prostate cancer in ≤3 positive cores had similar rates of adverse pathology and biochemical recurrence as men with Gleason ≤6. The number of men meeting this cutoff was ~6% of SEARCH. The inclusion of these men on active surveillance protocols would reduce prostate cancer overtreatment, and additional study is warranted to assess the safety of this approach.

Previous studies established higher rates of biochemical recurrence, metastases, and cancer specific death[39-41] in men with Gleason 7 versus those with Gleason ≤6. The heterogeneity of prostate cancer outcomes in men with Gleason 7 disease is recognized to

strongly correlate with primary Gleason grade (3 vs. 4).[30, 42] While active surveillance for low-risk disease has made progressive in-roads to mitigate prostate cancer overtreatment, a decrease in non-curative initial management among men with intermediate-risk prostate cancer has been observed in U.S. population level datasets.[3]

Our interest in the possible expansion of active surveillance to a defined population of men with intermediate-risk prostate cancer is shared. In a European multi-institutional dataset, Gandaglia et al. reported no significant biochemical recurrence difference between 564 men with Gleason 3+4 organ-confined disease and 926 men with Gleason 3+3 organ-confined disease who preoperatively met PRIAS criteria for active surveillance.[43] In a single-institution radical prostatectomy dataset, Kwon et al. identified 217 men with Gleason 3+4 disease who otherwise fulfilled at least one common active surveillance protocol criteria (Hopkins,[35] MSKCC,[32] PRIAS,[44] Miami,[33] UCSF,[45] or Toronto[30]). They found the rate of pathologically aggressive disease would not significantly increase with expansion of active surveillance criteria to include Gleason 3+4 under most contemporary protocols.[46]

In a retrospective review of 2,323 men who underwent radical prostatectomy for Gleason 3+4 at six European institutions, Ploussard et al. determined that 46% had unfavorable disease at final pathology. However, by narrowing their selection criteria to men with PSA ≤10 ng/mL, PSA density ≤0.15 ng/mL/g, clinical stage T1c, and ≤2 positive cores, the rate of adverse disease was 19%, leading the authors to conclude that expanding active surveillance to these men may be acceptable provided strict adherence to selection criteria.[47]

Similar to Ploussard's analysis, we explored a PSA density of ≤0.15 ng/mL/g and ≤2 positive cores as cut-points. While pathologic outcomes and biochemical recurrence were

similar between Gleason 7 low-risk and D'Amico low-risk group with ≤2 positive cores in our cohort, we found a threshold PSA density of ≤0.10 ng/mL/g was needed to achieve similar outcomes between the groups. In SEARCH, <4% of men had Gleason 7 low-risk disease and ≤2 positive cores on biopsy. However, by increasing our cut-point to ≤3 total positive cores, we nearly doubled the number of men included as "low-risk" while still maintaining no significant difference in pathological outcomes or biochemical recurrence. With the objective of minimizing overtreatment, we elected to proceed with the less stringent criterion of ≤3 total positive cores.

Including men with Gleason 7 (3+4), PSA ≤10 ng/mL, clinical stage T1c/T2a, and ≤3 total positive cores would considerably expand the population eligible for active surveillance. In our study, among men with Gleason 7 low-risk disease, 42% had ≤3 total positive cores on biopsy. Men meeting our Gleason 7 low-risk disease criteria with ≤3 total positive cores comprised 10+% of the entire SEARCH population over the past two years.

Our study has the inherent limitations of all retrospective analyses. While our dataset included men from five VA centers, central pathology review was not completed. Changes in Gleason grading during our study period may limit study validity. Pathologic findings serve as intermediate endpoints for aggressive disease and may not predict disease-specific or overall survival; overall survival was not included as few deaths occurred in the cohort. Year of surgery and follow-up length between our D'Amico low-risk and Gleason 7 low-risk groups were significantly different and introduce possible bias. As SEARCH is a radical prostatectomy database, an inherent selection bias exists. Finally, as all men with Gleason 3+4 low-risk in our dataset underwent radical prostatectomy, it is unknown if their outcomes with intervention reflect the natural history of Gleason 3+4 low-risk monitored on active surveillance.

CONCLUSION

Among men with PSA≤10 ng/mL and clinical stage T1c/T2a, those with Gleason 7 (3+4) prostate cancer in ≤3 total positive cores have similar rates of adverse pathology and biochemical recurrence as men with Gleason ≤6 disease. This finding, if confirmed in additional cohorts, may expand active surveillance protocol inclusion criteria to further reduce prostate cancer overtreatment.

EXTERNAL FUNDING

None

2.2 Manuscript Tables and Figures

Table 2.1: Baseline characteristics between D'Amico low-risk* and biopsy Gleason 3+4 low-risk patients

	D'Amico low-risk N=495 (57%)	Gleason 7 low-risk N=375 (43%)	p-value
Age, mean ± SD	60.6 ± 5.8	61.4 ± 6.2	0.070†
Year of surgery	2008 (2005, 2010)	2011 (2007, 2012)	<0.001‡
Race, n (%)			0.100§
White	252 (51)	164 (44)	
Black	212 (43)	181 (48)	
Other	31 (6)	30 (8)	
PSA (ng/ml)	5.3 (4.3, 7.0)	5.6 (4.6, 7.0)	0.011‡
Clinical Stage (%)			0.333§
T1c	405 (82)	297 (79)	
T2a	90 (18)	78 (21)	
# Cores	12 (10, 12)	12 (11, 12)	<0.001‡
Positive cores	2 (1, 4)	4 (3, 6)	<0.001‡
Follow-up (months)	48.8 (23.4, 84.5)	22.0 (8.1, 50.3)	<0.001‡
Surgical Technique, n (%)			<0.001§
Open RRP	286 (58)	172 (46)	
Perineal prostatectomy	32 (6)	17 (5)	
Laparoscopic prostatectomy	21 (4)	9 (2)	
RARP	156 (32)	177 (47)	
Pathological Gleason score, n (%)			<0.001§
2 – 6	229 (46)	50 (13)	
3+4	216 (44)	234 (62)	
4+3, 8 – 10	50 (10)	91 (24)	
Extracapsular extension, n (%)	35 (7)	56 (15)	<0.001§
Seminal vesicle invasion, n (%)	10 (2)	30 (8)	<0.001§
Positive margins, n (%)	178 (36)	157 (42)	0.074§
PLND performed, n (%)	186 (38)	253 (67)	<0.001§
Positive lymph nodes, n (%)	1 (<1)	7 (2)	0.013#

Cells display median (25^{th} percentile, 75^{th} percentile) unless otherwise noted
P-value calculated using † t-test, ‡ rank sum test, § chi-square test, or # Fisher's exact test

*D'Amico low-risk patients had PSA≤10, clinical stage T1c-T2a, biopsy Gleason ≤6, and more than 8 cores taken on biopsy.
Biopsy Gleason 3+4 low-risk patients had PSA ≤10, clinical stage T1c-T2a, biopsy Gleason 3+4, and more than 8 cores taken on biopsy.

RRP = Radical retropubic prostatectomy
RARP = Robotic assisted radical prostatectomy
PLND = Pelvic lymph node dissection

Table 2.2: Odds ratios for risk group predicting pathological features between D'Amico low-risk and biopsy Gleason 3+4 low-risk patients.

	OR	95% CI	p –value
Pathological Gleason ≥ 4 + 3			
Crude	2.85	1.96 – 4.15	< 0.001
Adjusted*	2.22	1.47 – 3.36	< 0.001
Positive margins			
Crude	1.28	0.97 – 1.69	0.076
Adjusted*	1.32	0.98 – 1.79	0.070
Extracapsular extension			
Crude	2.31	1.48 – 3.60	< 0.001
Adjusted*	2.60	1.60 – 4.23	< 0.001
Seminal vesicle invasion			
Crude	4.22	2.03 – 8.74	< 0.001
Adjusted*	3.10	1.42 – 6.78	0.005

* Adjusted for age, year, race, surgical center, surgical technique, clinical stage, number of biopsy cores taken, and PSA

Table 2.3: Hazard ratios for risk of biochemical recurrence for biopsy Gleason 3+4 low risk group relative to D'Amico low-risk group* stratified by number of positive biopsy cores.

Entry Criteria	Number of D'Amico low risk patients	Number of Gleason 7 low risk patients	HR	95% CI	p-value
All	495	375	1.65	1.15 – 2.36	0.006
<33% positive cores	376	202	1.86	1.16 – 3.00	0.011
≤ 4 positive cores	394	208	1.80	1.14 – 2.84	0.012
≤ 3 positive cores	334	157	1.39	0.79 – 2.45	0.254
≤ 2 positive cores	248	88	1.29	0.59 – 2.81	0.519

* D'Amico low-risk patients had PSA≤10, clinical stage T1c-T2a, biopsy Gleason ≤6, and more than 8 cores taken on biopsy.
Biopsy Gleason 3+4 low-risk patients had PSA ≤10, clinical stage T1c-T2a, biopsy Gleason 3+4, and more than 8 cores taken on biopsy.

Table 2.4: Baseline characteristics between D'Amico low-risk* and biopsy Gleason 3+4 low-risk patients with ≤3 total positive biopsy cores.

	D'Amico low-risk N=334 (68%)	Gleason 7 low-risk N=157 (32%)	p-value
Age, mean ± SD	61.0 ± 5.7	62.2 ± 6.1	0.037†
Year of surgery	2007 (2004, 2010)	2010 (2007, 2012)	<0.001‡
Race, n (%)			0.069§
White	174 (52)	67 (43)	
Black	142 (42)	75 (48)	
Other	18 (5)	15 (10)	
PSA (ng/ml)	5.3 (4.3, 6.8)	5.5 (4.5, 6.6)	0.285‡
Clinical Stage (%)			0.582§
T1c	279 (84)	128 (82)	
T2a	55 (16)	29 (18)	
# Cores	12 (10, 12)	12 (11, 12)	0.005‡
Positive cores	2 (1, 3)	2 (2, 3)	<0.001‡
Follow-up (months)	51.4 (27.4, 85.6)	22.9 (11.7, 51.7)	<0.001‡
Surgical Technique, n (%)			<0.001§
Open RRP	201 (60)	76 (48)	
Perineal prostatectomy	25 (7)	6 (4)	
Laparoscopic prostatectomy	17 (5)	2 (1)	
RARP	91 (27)	73 (47)	
Pathological Gleason score, n (%)			<0.001§
2 – 6	177 (53)	26 (17)	
3+4	127 (38)	96 (61)	
4+3, 8 – 10	30 (9)	35 (22)	
Extracapsular extension, n (%)	21 (6)	12 (8)	0.576§
Seminal vesicle invasion, n (%)	6 (2)	6 (4)	0.175§
Positive margins, n (%)	102 (31)	57 (36)	0.203§
PLND performed, n (%)	116 (35)	100 (64)	<0.001§
Positive lymph nodes, n (%)	1 (<1)	1 (1)	0.538#

Cells display median (25th percentile, 75th percentile) unless otherwise noted
P-value calculated using † t-test, ‡ rank sum test, § chi-square test, or # Fisher's exact test

*D'Amico low-risk patients had PSA≤10, clinical stage T1c-T2a, biopsy Gleason ≤6, more than 8 cores taken on biopsy, and ≤ 3 positive biopsy cores.
Biopsy Gleason 3+4 low-risk patients had PSA ≤10, clinical stage T1c-T2a, biopsy Gleason 3+4, more than 8 cores taken on biopsy, and ≤ 3 positive biopsy cores.

RRP = Radical retropubic prostatectomy
RARP = Robotic assisted radical prostatectomy
PLND = Pelvic lymph node dissection

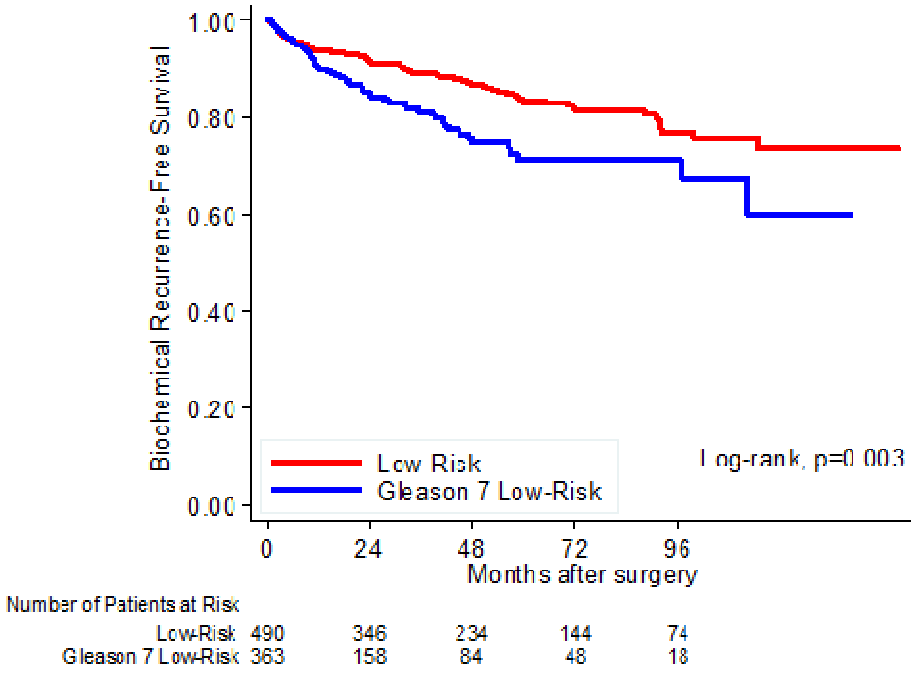
Table 2.5: Odds ratios for risk group predicting pathological features between D'Amico low-risk and biopsy Gleason 3+4 low-risk patients with ≤3 total positive biopsy cores.

	OR	95% CI	p –value
Pathological Gleason ≥ 4 + 3			
Crude	2.91	1.71 – 4.94	< 0.001
Adjusted*	2.36	1.30 – 4.29	0.005
Positive margins			
Crude	1.30	0.87 – 1.93	0.203
Adjusted*	1.55	0.99 – 2.42	0.057
Extracapsular extension			
Crude	1.23	0.59 – 2.58	0.576
Adjusted*	1.48	0.65 – 3.38	0.347
Seminal vesicle invasion			
Crude	2.17	0.69 – 6.85	0.185
Adjusted*	2.18	0.60 – 7.98	0.238

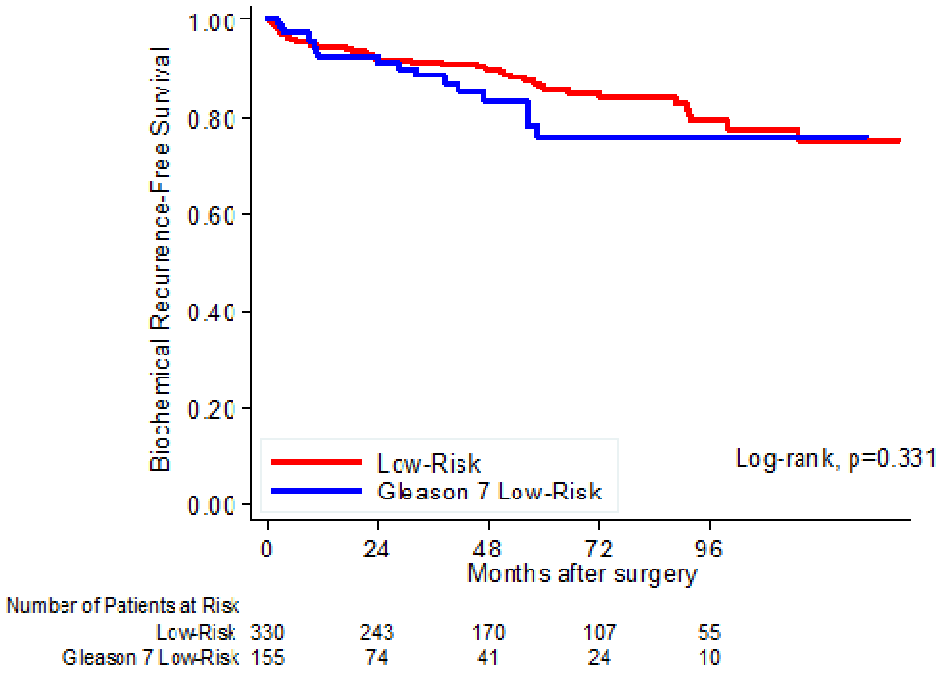
* Adjusted for age, year, race, surgical center, surgical technique, clinical stage, number of biopsy cores taken, and PSA

Figure 2.1:

a. Kaplan-Meier curves comparing biochemical recurrence-free survival for D'Amico low-risk and Gleason 7 (3+4) low-risk prostate cancer.



b. Kaplan-Meier curves comparing biochemical recurrence-free survival for D'Amico low-risk and Gleason 7 (3+4) low-risk prostate cancer ≤3 total positive biopsy cores.



SUPPLEMENTARY MATERIAL:

Table 2.1:

a. Stratification of D'Amico low-risk* and biopsy Gleason 3+4 low-risk patients by year of surgery.

Year of Surgery	SEARCH database N = 2810	D'Amico low-risk N=495	Gleason 7 low-risk N=375
2001, n (% of SEARCH)	165	19 (12)	8 (5)
2002	184	31 (17)	6 (3)
2003	211	38 (18)	7 (3)
2004	222	34 (15)	20 (9)
2005	200	40 (20)	23 (12)
2006	204	39 (19)	22 (11)
2007	196	34 (17)	18 (9)
2008	194	48 (25)	16 (8)
2009	230	48 (21)	30 (13)
2010	220	41 (19)	35 (16)
2011	254	52 (20)	42 (17)
2012	290	46 (16)	78 (27)
2013	240	25 (10)	70 (29)

b. Stratification of D'Amico low-risk* and biopsy Gleason 3+4 low-risk patients with ≤3 total positive biopsy cores by year of surgery.

Year of Surgery	SEARCH database N = 2810	D'Amico low-risk N=334	Gleason 7 low-risk N=157
2001, n (% of SEARCH)	165	15 (9)	4 (2)
2002	184	24 (13)	3 (2)
2003	211	26 (12)	4 (2)
2004	222	25 (11)	9 (4)
2005	200	26 (13)	7 (4)
2006	204	32 (16)	10 (5)
2007	196	22 (11)	3 (2)
2008	194	29 (15)	7 (4)
2009	230	36 (5)	17 (7)
2010	220	29 (13)	15 (7)
2011	254	33 (13)	17 (7)
2012	290	21 (7)	38 (13)
2013	240	16 (7)	23 (10)

* D'Amico low-risk patients had PSA≤10, clinical stage T1c-T2a, biopsy Gleason ≤6, and more than 8 cores taken on biopsy.
Biopsy Gleason 3+4 low-risk patients had PSA ≤10, clinical stage T1c-T2a, biopsy Gleason 3+4, and more than 8 cores taken on biopsy.

SUPPLEMENTARY MATERIAL:

Table 2.2: Hazard ratios for risk of biochemical recurrence for biopsy Gleason 3+4 low risk group relative to D'Amico low-risk* group stratified by PSA density.

Entry Criteria	Number of D'Amico low risk patients	Number of Gleason 7 low risk patients	HR	95% CI	p-value
All	404	334	1.78	1.22 – 2.61	0.003
≤ 0.30 ng/mL/g	372	299	1.70	1.13 – 2.58	0.012
≤ 0.25 ng/mL/g	341	269	1.63	1.04 – 2.53	0.032
≤ 0.20 ng/mL/g	289	219	2.28	1.38 – 3.76	0.001
≤ 0.15 ng/mL/g	219	151	2.46	1.35– 4.51	0.003
≤ 0.10 ng/mL/g	116	67	1.44	0.56– 3.70	0.451

* D'Amico low-risk patients had PSA≤10, clinical stage T1c-T2a, biopsy Gleason ≤6, and more than 8 cores taken on biopsy.
Biopsy Gleason 3+4 low-risk patients had PSA ≤10, clinical stage T1c-T2a, biopsy Gleason 3+4, and more than 8 cores taken on biopsy.

2.3 Appendix D: Detailed Methods

A. Regulatory Approval

The research contained in the original manuscript was prepared under the auspices of the Durham Veterans Affairs (VA) Medical Center Research Institutional Review Board (protocol ID# 01827, "Predictors of Prostate Cancer and Prostate Cancer Outcomes in a National VA Cohort").

The supporting documentation for completion of this Master's Paper was deemed exempt from Institutional Review Board approval by the Office of Human Research Ethics, University of North Carolina at Chapel Hill (study # 15-0718).

B. Study Population

1. Shared Equal Access Regional Cancer Hospital Database

The Shared Equal Access Regional Cancer Hospital (SEARCH) Database is a national prostate cancer registry that includes retrospective data from consecutive prostate cancer patients at eight Veterans Administration (VA) medical centers (West Los Angeles, CA; Palo Alto, CA; San Diego, CA; San Francisco, CA; Augusta, GA; Birmingham, AL; Asheville, NC; and Durham, NC). SEARCH includes detailed pre-operative clinical information, pathologic data, and follow-up information for >5000 men undergoing radical prostatectomy at these eight sites between 1982 and 2013.

All data abstraction is performed using only medical record data from the Corporate Data Warehouse, VA Informatics and Computing Infrastructure (VINCI), and other VA sources. Medical records are reviewed for data relevant to prostate cancer; no direct patient contact occurs. Information from identified patients is recorded in an electronic database housed on VINCI and the VA

server. The database and associated information is maintained behind the VA firewall.

2. Inclusion Criteria for Study

Men 18 years or older diagnosed with prostate cancer following an adequate prostate biopsy, defined as a minimum of 8 cores, and undergoing a radical prostatectomy using any surgical technique at five VA medical centers (Palo Alto, CA; West Los Angeles, CA; San Diego, CA; Durham, NC; and Augusta, GA) between January 1, 2001 and December 31, 2013 were combined into SEARCH. These five centers were chosen based upon radical prostatectomy volume and the reliability of pathology results from these centers, as determined from previous studies. A study start date of January 1, 2001 was selected as few men treated prior to this year had adequate prostate sampling at the time of biopsy. The latest medical records complete data abstraction included information through December 31, 2013.

To address our study question, we narrowed this large population of men with prostate cancer to those with low- to intermediate-risk disease characteristics diagnosed at the time of prostate biopsy (Appendix A, Table 1.1). Specifically, we included men with a PSA ≤10.0 ng/mL, a Gleason score ≤7 (Appendix A, Table 1.2), and clinical stage T1c or T2a (Appendix A, Table 1.3). As we sought to define a subset of men with pre-operatively defined intermediate-risk disease that had similar outcomes to men with low-risk disease, we further narrowed our eligible population to men with Gleason 3+4 or less disease diagnosed at the time of prostate biopsy, as primary Gleason 4 tumors are known to be an aggressive

subset of Gleason 7 prostate cancer with more advanced clinical and pathologic stages[37] and higher rates of biochemical recurrence.[30]

3. Exclusion Criteria for Study

Men with missing data on our variables of interest were excluded from the study. Our variables of interest included: race, PSA, clinical stage, total number of prostate biopsy cores, number of positive prostate biopsy cores, Gleason score, radical prostatectomy pathologic information (Gleason score, positive margins, extracapsular extension, seminal vesicle invasion), surgical technique, and PSA density. PSA density was explored in a subset analysis of the study, as >15% of men in the dataset were missing information on this variable.

Additionally, men who received pre-operative hormonal or radiation therapy were excluded from the cohort, as these treatments prior to prostatectomy can affect pathologic Gleason grading.[48]

C. Statistical Analysis

We compared men who fulfilled the criteria of low-risk prostate cancer (clinical stage T1c/T2a, biopsy Gleason ≤6 and PSA ≤10 ng/mL)[6-8] with the exception of biopsy Gleason 7 (3+4) (henceforth "Gleason 7 low-risk") versus men who met all 3 criteria for low-risk disease. Once analyses were completed for all men meeting study inclusion criteria, increasingly strict definitions of low-volume disease were applied to the two groups. The number or percentage of positive biopsy cores and PSA density were selected as ways to define low-volume disease; this selection was driven by the inclusion criteria of common active surveillance protocols for men with low-risk prostate cancer.[33, 35, 36, 49]

To assess if there was a cut-point of low volume disease with comparable outcomes among men with Gleason 7 low-risk disease and low-risk disease, all analyses evaluating differences in demographic and clinicopathologic variables, pathologic features, and biochemical recurrence between the two groups were repeated with matching of the percentage or number of positive biopsy cores or PSA density between them, including ≤33% positive cores, ≤4 positive cores, ≤3 positive cores, and ≤2 positive cores, and PSA density ≤0.30, ≤0.25, ≤0.20, ≤0.15, and ≤0.10 ng/mL/g. In total, we performed the analysis eleven times: 4 iterations limiting the groups by percentage or number of positive biopsy cores as compared to the entire cohort, and 5 times in a subset analysis limiting the groups by PSA density thresholds compared to the entire cohort with PSA density information.

Statistical analyses were performed using Stata 13.1 (Stata, Corp., College Station, TX, USA). Statistical significance was two-sided with $p<0.05$.

1. **Demographic and Clinicopathologic Variables**

   Demographic factors of interest included patient age, year of surgery, and race. In the SEARCH database, age and year of surgery are continuous variables, while race is a categorical variable defined as white, black, or other. To begin, we assessed the distribution of the continuous variables in the dataset, patient age and surgery year, using histograms. Patient age was normally distributed; thus, we reported mean age ± standard deviation in years. We examined the difference in age between the Gleason 7 low-risk and D'Amico low-risk group using a *t*-test, as age was a normally distributed continuous variable in the dataset. In contrast to age, surgery year was a non-normally distributed continuous variable, noted to be skewed left. Accordingly, we reported the median year of surgery for each group,

along with the 25th and 75th percentiles. As surgery year was a non-normally distributed continuous variable in the dataset, we examined the difference in year of surgery between the Gleason 7 low-risk and D'Amico low-risk group using a Wilcoxon rank-sum test. To test the association of our categorical variable, race, across our low-risk and Gleason 7 low-risk patient populations, we used chi-square tests.

Clinicopathologic variables of interest included PSA, clinical stage, total number of biopsy cores and number of positive biopsy cores, surgical technique, pelvic lymph node dissection performance, pathological Gleason score, extracapsular extension, positive surgical margins, seminal vesicle invasion, positive pelvic lymph nodes, and length of follow-up. To begin, we again assessed the distribution of our continuous variables of interest using histograms. PSA, total number of biopsy cores, number of positive biopsy cores, and length of follow-up were all non-normally distributed continuous variables that were skewed right in our patient sample. Accordingly, we reported the median value for each variable with the 25th and 75th percentiles and examined differences between the Gleason 7 low-risk and D'Amico low-risk groups using the Wilcoxon rank-sum test. Within SEARCH, surgical technique is classified into one of four categories (open radical retropubic prostatectomy, perineal prostatectomy, laparoscopic prostatectomy, and robotic assisted laparoscopic prostatectomy). We classified pathological Gleason score into one of three categories (2-6, 3+4, and 4+3/8-10). By study inclusion criteria, all men had clinical stage T1c or T2a prostate cancer. The remaining clinicopathologic

variables of interest were binary variables, including pelvic lymph node dissection performance (completed or not completed), extracapsular extension (yes or no), positive surgical margins (yes or no), seminal vesicle invasion (yes or no), and positive pelvic lymph nodes (yes or no). To test the association of these categorical variables across our low-risk and Gleason 7 low-risk patient populations, we used chi-square tests. For any categorical variable with a cell count ≤5, we used Fisher's exact test.

2. Pathologic Features

We used logistic regression models to test the association between risk group (Gleason 7 low-risk vs. D'Amico low-risk) and pathological features, including pathological Gleason score, positive surgical margins, extracapsular extension, and seminal vesicle invasion. As previously noted, surgical margins, extracapsular extension, and seminal vesicle invasion are recorded as binary variables in SEARCH. To enable logistic regression analysis, pathological Gleason score was categorized as ≤6 vs. ≥4+3.

We used an exposure-disease logistic regression model, controlling for all variables that were unequally distributed among the men in our low-risk and Gleason 7 low-risk groups as well as variables known to be associated with pathologic outcomes. The fully adjusted model included age at surgery, surgery year, race, number of biopsy cores, surgical center, surgical technique, clinical stage, and PSA (log-transformed). While the number of positive biopsy cores was unevenly distributed between the groups on our initial analysis, which included all men in the cohort, we subsequently stratified by the maximum number of positive

biopsy cores and repeated analyses, thereby controlling for this potential confounder.

3. Biochemical Recurrence

Given the prolonged natural history of prostate cancer following radical prostatectomy,[50] we evaluated the intermediate outcome of biochemical recurrence as our clinical endpoint of interest, rather than overall or prostate-cancer specific survival. Biochemical recurrence commonly triggers secondary treatment for prostate cancer post-prostatectomy, including salvage radiation and/or androgen deprivation therapy,[8] and can significantly affect health-related quality of life.[51-53] In SEARCH, biochemical recurrence is defined as a single PSA >0.2 ng/mL, two consecutive PSAs of 0.2 ng/mL, or secondary treatment for elevated PSA in the post-operative period.

We analyzed the hazard ratios for biochemical recurrence between the Gleason 7 low-risk and D'Amico low-risk groups using Cox proportional hazards analysis. Our final model included adjustment for the independent prognostic factors of age, surgery year, race, surgical center, surgical technique, clinical stage, PSA (log-transformed), and total number of prostate biopsy cores.

We visually explored biochemical recurrence free survival using the Kaplan-Meier method and quantified the difference between our two groups using the log-rank test.

2.4 Appendix E: Strengths and Limitations

The primary strengths of our study stem from the reliability and thoroughness of our data source. SEARCH is one of the premier multi-institutional prostate cancer databases in the world; researchers have generated over 100 peer-reviewed manuscripts from the database since 2002. Information within the database is exceptionally detailed, as access to patients' complete medical records, including all physician notes, laboratory results, and imaging, is readily available.

SEARCH captures all men diagnosed with prostate cancer in participating VA centers across the United States. Accordingly, selection biases that may occur in single institutional registries are mitigated. Access difficulties due to insurance or financial limitations that are encountered in private centers and limit the participation or follow-up of patients do not exist within the VA system, as the system is designed to be equal access. Additionally, once a patient is within the system, the care that is delivered is independent of institutional or financial motivation, removing a potential for provider bias. Finally, compared to other prostate cancer databases, SEARCH includes a large number of minority patients, increasing the external validity of research findings from the database.

In order to maximize the reliability of our findings, we selected VA centers for study inclusion with known expertise in urologic care. In recent years, many VA hospitals have been accused of providing substandard care and employing deficient physicians.[54] As the reliability of our study results depends upon timely treatment following prostate biopsy and pre-operative staging, reproducible surgical results, detailed post-operative follow-up, and consistent pathology reporting, we chose five academically affiliated VA centers with strong reputations, fellowship-trained urologic oncologists, and established pathologists on staff for study inclusion.

Our study has the inherent limitations of all retrospective analyses. While our dataset included men from five VA centers, central pathology review was not completed. As central pathology review may change biopsy Gleason score in up to 15% of cases, this introduces significant possible variation in our study.[55] Changes in Gleason grading during our study period[56] may limit study validity. Pathologic findings serve as intermediate endpoints for aggressive disease and may not predict disease-specific or overall survival; overall survival was not included as few deaths occurred in the cohort. Year of surgery and follow-up length between our low-risk and Gleason 7 low-risk groups were significantly different and introduce possible bias. As SEARCH is a radical prostatectomy database, an inherent selection bias exists. Finally, and most importantly, as all men with Gleason 3+4 low-risk in our dataset underwent radical prostatectomy, it is unknown if their outcomes with intervention reflect the natural history of Gleason 3+4 low-risk monitored on active surveillance. Prospective study is required to address this limitation.

2.5 Appendix F: Study Implications

Prostate cancer is the most commonly diagnosed cancer among men in the developed world.[1] In the United States this year, an estimated 220,800 men will receive a new diagnosis of prostate cancer and 27,540 will die of the disease.[2] An estimated 2.9 million American men are prostate cancer survivors.[57] Active treatment for the newly diagnosed and follow-up care for prostate cancer survivors will cost the U.S. health care system approximately $14.1 billion dollars in 2015.[58]

Among men newly diagnosed with prostate cancer, approximately 90% will pursue definitive treatment (surgery or radiation therapy)[3, 4] and the majority will experience at least one long-term adverse effect due to this treatment.[5] The disease's high incidence, tremendous costs, treatment morbidity, and long natural history have provoked extensive public health discussions on overdiagnosis and overtreatment.

To reduce the overtreatment of low-risk prostate cancer,[7] active surveillance protocols began in the late 1990's. On protocol, enrolled patients with low-risk prostate cancer are monitored with PSA testing every six months, an annual digital rectal exam, and a repeat prostate biopsy as frequently as every 12 months. If worsening PSA kinetics, clinical stage progression on rectal exam, or changing biopsy characteristics are identified, then definitive treatment is advised. With this management strategy, reported prostate cancer specific mortality is <1% among men on active surveillance protocols with long-term follow-up.[9]

Active surveillance is a recommended treatment strategy for men with low-risk prostate cancer per National Comprehensive Cancer Network Guidelines.[8] Limited and conflicting data exist on the outcomes of men with intermediate-risk prostate cancer,[6-8] including Gleason 7 disease, on active surveillance protocols.[17, 18, 20, 38] As Gleason 7 disease is now the most

common score on prostate biopsy,[10] we examined if a subset of Gleason 7 prostate cancer patients had similar outcomes to low-risk patients and thus could be reasonable potential active surveillance candidates.

Using the SEARCH database of men undergoing radical prostatectomy between 2001 and 2013, we compared men who fulfilled all three low-risk disease criteria[6-8] to men with Gleason 7 prostate cancer who otherwise fulfilled the PSA and clinical stage low-risk disease criteria. We explored associations between risk group, pathological features, and biochemical recurrence, with matching of PSA density (subset analysis) and the percentage or number of positive cores between the Gleason 7 low-risk and the D'Amico low-risk group. We found that among men with PSA≤10 ng/mL and clinical stage T1c/T2a, those with Gleason 7 (3+4) PC in ≤3 positive cores had similar rates of adverse pathology and biochemical recurrence as men with Gleason ≤6.

Including men with Gleason 7 (3+4), PSA ≤10 ng/mL, clinical stage T1c/T2a, and ≤3 total positive cores would considerably expand the population eligible for active surveillance. Approximately 6% of all men undergoing a radical prostatectomy from 2001-2013 at the five VA centers included in our study had Gleason 7 low-risk disease. Interestingly, when studied over time, men with Gleason 7 low-risk disease comprise a growing percentage of the SEARCH database. Since 2011, over 10% of men undergoing a radical prostatectomy in our centers had Gleason 7 low-risk disease with ≤3 total positive cores. As our research indicates the pathological and biochemical recurrence outcomes of men with Gleason 7 low-risk disease are similar to those men with low-risk prostate cancer in our study population, inviting these men to monitor their disease on active surveillance may further reduce prostate cancer overtreatment.

As we created the Gleason 7 low-risk criteria for our study, the number of men nationally with prostate cancer meeting these criteria is unknown. However, as Gleason 7 disease is the most commonly diagnosed prostate cancer score on biopsy,[10] the likely increase in potential candidates for active surveillance with adoption of these criteria is significant. As we strive to minimize prostate cancer overtreatment, continued retrospective study of outcomes among men with Gleason 7 disease undergoing definitive treatment, and careful prospective study of men with Gleason 7 disease on active surveillance protocols, is warranted.

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