Risk Group and Death From Prostate Cancer
Implications for Active Surveillance in Men With Favorable Intermediate-Risk Prostate Cancer

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IMPORTANCE  Active surveillance (AS), per the National Comprehensive Cancer Network (NCCN) guidelines, is considered for patients with low-risk prostate cancer (PC) and a life expectancy of at least 10 years. However, given the grade migration following the 2005 International Society of Urologic Pathology consensus conference, AS may be appropriate for men presenting with favorable intermediate-risk PC.

OBJECTIVE  To estimate and compare the risk of PC-specific mortality (PCSM) and all-cause mortality (ACM) following brachytherapy among men with low and favorable intermediate-risk PC.

DESIGN, SETTING, AND PARTICIPANTS  Prospective cohort study of 5580 consecutively treated men (median age, 68 years) with localized adenocarcinoma of the prostate treated with brachytherapy at the Prostate Cancer Foundation of Chicago between October 16, 1997, and May 28, 2013.

INTERVENTION  Standard of practice per the NCCN guidelines.

MAIN OUTCOMES AND MEASURES  Fine and Gray competing risks regression and Cox regression analyses were used to assess whether the risks of PCSM and ACM, respectively, were increased in men with favorable intermediate-risk vs low-risk PC. Analyses were adjusted for age at brachytherapy, year of treatment, and known PC prognostic factors.

RESULTS  After median follow-up of 7.69 years, 605 men had died (10.84% of total cohort), 34 of PC (5.62% of total deaths). Men with favorable intermediate-risk PC did not have significantly increased risk of PCSM and ACM compared with men with low-risk PC (adjusted hazard ratio [HR], 1.64; 95% CI, 0.76-3.53; P = .21 for PCSM; adjusted HR, 1.11; 95% CI, 0.88-1.39; P = .38 for ACM). Eight-year adjusted point estimates for PCSM were low: 0.48% (95% CI, 0.23%-0.93%) and 0.33% (95% CI, 0.19%-0.56%) for men with favorable intermediate-risk PC and low-risk PC, respectively. The respective estimates for ACM were 10.45% (95% CI, 8.91%-12.12%) and 8.68% (95% CI, 7.80%-9.61%).

CONCLUSIONS AND RELEVANCE  Men with low-risk PC and favorable intermediate-risk PC have similarly low estimates of PCSM and ACM during the first decade following brachytherapy. While awaiting the results of ProtecT, the randomized trial of AS vs treatment, our results provide evidence to support AS as an initial approach for men with favorable intermediate-risk PC.

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Treatment recommendations for men with localized prostate cancer (PC) are based on risk stratification. Men with low-risk PC who have a life expectancy of at least 10 years may be offered radical prostatectomy (RP), external-beam radiotherapy (EBRT), brachytherapy, or active surveillance (AS) as an initial treatment. Active surveillance involves monitoring the course of PC with the expectation to initiate curative treatment if the cancer progresses. Follow-up of AS consists of annual transrectal ultrasonographically guided needle biopsies of at least 12 cores, semiannual prostate-specific antigen (PSA) measurements, and annual digital rectal examinations (DREs). Progression on surveillance can include any of the following: Gleason grade 4 or 5 PC found on repeat biopsy; PC found in a greater number biopsy cores or occupying a greater amount of the prostate biopsy cores; or a new nodule felt on DRE. In earlier experience with AS, PSA kinetics were used as a marker of disease progression; however, the clinical utility of PSA measurement for predicting progression has since been questioned: a rapid rise in PSA alone is no longer considered a reason to initiate curative treatment. Given the data from the Prostate Cancer Intervention Trial vs Observation Trial (PIVOT) suggesting a lack of benefit in men with low-risk PC when managed with RP vs watchful waiting, AS has become the preferred option for these men. While men in the PIVOT study were considered less healthy than men in the Surveillance, Epidemiology and End Results (SEER)-Medicare population, the results suggested that men with low-risk PC might not be at an increased risk of death from PC during the first decade after diagnosis if actively monitored.

The intermediate-risk group is heterogeneous with respect to the risk of PSA recurrence and PC-specific mortality (PCSM) following treatment with RP, EBRT, or brachytherapy. Therefore, Zumsteg and colleagues divided intermediate-risk patients into favorable and unfavorable categories based on recurrence risk following accepted standards of care. They defined men with favorable intermediate-risk PC as those with a Gleason score of 3 + 4 or less, a percentage of positive biopsy cores (PPB) less than 50%, and at most 1 National Comprehensive Cancer Network (NCCN) determinant of intermediate-risk PC. Recent data by Keane and colleagues suggest that favorable intermediate-risk patients may not benefit from androgen deprivation therapy (ADT) in addition to radiation therapy, whereas unfavorable intermediate-risk patients appear to require ADT to reduce their risk of PCSM.

To date, no direct comparison has been made between favorable intermediate-risk and low-risk PC with respect to PCSM or all-cause mortality (ACM) following high-dose radiotherapy such as brachytherapy. Such comparisons are clinically relevant because AS, per the NCCN guidelines, is currently considered appropriate for patients who have low-risk PC and a life expectancy of at least 10 years. Moreover, following the 2005 meeting of the International Society of Urologic Pathology consensus conference, the reporting of secondary pattern Gleason grade 4 became more prevalent, and grade migration from Gleason score 3 + 3 to 3 + 4 has been observed. Thus, in our current era of grade migration, we should consider the possibility that men with favorable intermediate-risk PC have low risks of PCSM and ACM similar to those of men with low-risk PC. If so, AS may also be an appropriate initial option for men with favorable intermediate-risk PC. Fortunately, the randomized phase 3 United Kingdom ProtecT trial (NCT02044172) comparing AS with definitive local therapy included men with favorable intermediate-risk PC for AS, as did the Canadian phase 2 AS protocol. To gain insight into whether AS may be an appropriate option for men with favorable intermediate-risk PC, we estimated and compared the risks of PCSM and ACM following brachytherapy among men with low-risk and favorable intermediate-risk PC.

At a Glance
- More than 5000 men with low-risk or favorable intermediate-risk prostate cancer were treated with brachytherapy.
- At a median follow-up of 7.69 years, 11% of men had died, 6% from prostate cancer.
- There were no significant differences in prostate-specific mortality between low-risk or favorable intermediate-risk prostate cancer.
- There were no significant differences in all-cause mortality between the groups.
- Pending results of ProtecT, active surveillance may be appropriate for men diagnosed with favorable intermediate-risk prostate cancer.

Methods
This study was performed with the approval of the independent institutional review board IntegReview, which is fully accredited by the Association for the Accreditation of Human Research Protection Programs. Each participant provided written informed consent at the time of initial consultation, allowing his deidentified clinical and PC-related information to be collected and entered into a secure, password-protected database for subsequent outcomes analysis.

Patient Population and Treatment
We studied a prospective cohort of 5580 men (median age, 67.50 years; interquartile range [IQR], 61.45-72.71 years) with localized adenocarcinoma of the prostate who were consecutively treated with brachytherapy at the Prostate Cancer Foundation of Chicago between October 16, 1997, and May 28, 2013. Baseline and outcome data were prospectively collected, and participants were categorized into low-risk and intermediate-risk PC groups based on NCCN guidelines. Men in the intermediate category were further subdivided into favorable and unfavorable intermediate-risk groups based on the definition outlined by Zumsteg and colleagues. Men with favorable intermediate-risk PC and PPB of 50% or less were included in the study.

All participants were treated according to accepted standards of practice per the NCCN guidelines. Specifically, men with low-risk and favorable intermediate-risk PC were treated with prostate brachytherapy alone. The technical aspects of the brachytherapy have been previously described.
Follow-up and Determination of Cause of Death
The primary end point of the study was the risk of PCSM. The risk of ACM was a secondary end point. Follow-up began on the date of prostate brachytherapy after the completion of treatment and continued to the date of death or the date of last data set update, June 1, 2013, whichever was earlier. Follow-up involved serial PSA measurements followed by a DRE every 3 months for 2 years, every 6 months for an additional 3 years, and then annually thereafter. To be classified as having died of PC, men had to have radiographic documentation of metastatic PC and a rising PSA despite salvage ADT and in most men cytotoxic chemotherapy.

Statistical Analysis

Distribution of Patient Clinical Characteristics at Presentation, Stratified by Risk Group

Descriptive statistics were used to characterize clinical factors at the time of diagnosis stratified by favorable intermediate-risk vs low-risk PC group. Wilcoxon rank sum tests were used to compare the distributions about the median values of the continuous clinical factors of PSA level, age, and year of brachytherapy. A log-rank test was used to compare the distributions of follow-up times. The Fisher exact test was used to compare the distributions of the categorical clinical factors of Gleason score (by categories of 6 and 3 + 4) and the 2012 American Joint Commission on Cancer (AJCC) tumor (T) category (T1c, T2a, T2b, T2c, or higher).

Competing Risks and Cox Regressions for PCSM and ACM

Univariable and multivariable Fine and Gray competing risks regression and Cox regression analyses were used to assess whether the risk of PCSM and ACM (the dependent variables) were increased in men with favorable intermediate-risk PC compared with men with low-risk PC. Analyses were adjusted for age, year of brachytherapy, risk group, PSA level, biopsy Gleason score (3 + 4 vs ≤6), and AJCC clinical tumor stage (T2 vs T1c). We elected to use the logarithm of the PSA measurement given that the PSA level in men with favorable intermediate-risk PC varied from greater than 0 to 19.9 ng/mL, and we wanted to ensure a normal distribution of the covariate and avoid having extreme values of PSA drive the model. Adjusted and unadjusted hazard ratios (HRs) with 95% CIs were calculated, and significance was set at \( P \leq 0.05 \).

Fine and Gray competing risks regression analyses were used to account for the competing risks of non-PCSMM in our estimates that men with PC have a high competing risk of mortality due to cardiovascular disease in addition to other non-PCSMM causes. A Cox regression power analysis revealed 75% power to detect an effect size of an adjusted HR of 1.64 for favorable intermediate-risk vs low-risk PC in this study of 5580 men, with an event rate of 34 per 5580 (0.60%) at a significance level of 0.05.

Patient age and year of treatment were included because both increasing age and earlier year of treatment have previously been shown to be associated with increased risk of PCSM. Given that a protopathic bias may exist when treatment is inadvertently initiated before diagnosis (or in the current study, before AS) and that all men in the current study were treated, we performed sensitivity analyses using left truncation durations of 6, 9, and 12 months to see whether our results would differ.

Adjusted Estimates of PCSM and ACM

Cumulative incidence estimates of PCSM and ACM were calculated and adjusted for patient age at brachytherapy and year of treatment (given that these factors were significant on the multivariable analysis). They were graphically displayed for the purpose of illustration, stratified by low-risk and favorable intermediate-risk PC. Point estimates of PCSM and ACM associated with 95% CIs were calculated and reported for each risk group. These estimates were compared using the multivariate Fine and Gray regression model for PCSM and Cox regression model for ACM, adjusting for patient age and year of brachytherapy, the only significant covariates in the model. We used R software, version 2.12.0 (R Foundation for Statistical Computing) for calculations pertaining to the Fine and Gray regression analyses. All other statistical analyses were performed using SAS software, version 9.3 (SAS Institute).

Results

Distribution of Patient Clinical Characteristics at Presentation, Stratified by Risk Group

Compared with men who had low-risk PC, men with favorable intermediate-risk PC were significantly older (median age, 68.84 vs 66.89 years; \( P < 0.001 \)), had a higher median PSA level (8.98 vs 5.92 ng/mL; \( P < 0.001 \)), were less likely to have AJCC T1c disease (74.94% vs 82.25%; \( P < 0.001 \)) (Table 1). In addition, the median follow-up time (7.43 vs 7.73 years; \( P = 0.06 \)) was slightly shorter, as reflected in the distribution of the year of brachytherapy being later in the current study, before AS, and that all men in the current study were treated, we performed sensitivity analyses using left truncation durations of 6, 9, and 12 months to see whether our results would differ.

Competing Risks and Cox Regressions for PCSM and ACM

After a median follow-up of 7.69 years (IQR, 5.42-10.55 years), a total of 605 men died (10.84% of total cohort), 34 of PC (5.62% of total deaths). Men with favorable intermediate-risk PC did not have significantly increased risk of PCSM or ACM compared with men with low-risk PC (adjusted HR, 1.64; 95% CI, 0.76-3.53; \( P = 0.21 \) for PCSM; adjusted HR, 1.11; 95% CI, 0.88-1.39; \( P = 0.38 \) for ACM) (Table 2). Under the traditional definition of favorable intermediate-risk PC with PBP less than 50%, men with favorable intermediate-risk PC did not have significantly increased risks of PCSM or ACM compared with men with low-risk PC (adjusted HR, 1.87; 95% CI, 0.81-4.31; \( P = 0.13 \) for PCSM; adjusted HR, 1.06; 95% CI, 0.82-1.37; \( P = 0.65 \) for ACM). Sensitivity analyses using left truncations of 6, 9, and 12 months all showed similar nonsignificant adjusted HRs for PCSM ranging from 1.64 to 1.65 (\( P = 0.20 \) to \( P = 0.21 \)) for men with favorable intermediate-risk PC compared with men with low-risk PC.
In addition, increasing age was associated with increased risks of PCSM (adjusted HR, 1.07; 95% CI, 1.02-1.13; \( P = .01 \)) and ACM (adjusted HR, 1.09; 95% CI, 1.07-1.10; \( P < .001 \)), whereas later year of brachytherapy was associated with decreased risks of PCSM (adjusted HR, 0.80; 95% CI, 0.71-0.90; \( P < .001 \)) and ACM (adjusted HR, 0.90; 95% CI, 0.87-0.93; \( P < .001 \)). The PC prognostic factors of PSA level, Gleason score, and T category did not reach statistical significance for the endpoints of PCSM (\( P \geq .06 \)) and ACM (\( P \geq .33 \)).

**Adjusted Estimates of PCSM and ACM**

After adjusting for patient age and year of brachytherapy, men with favorable intermediate-risk disease did not have significantly higher estimates of PCSM (\( P = .63 \)) or ACM (\( P = .18 \)) compared with men with low-risk PC (Figure). Eight-year adjusted point estimates for PCSM were 0.48% (95% CI, 0.23%-0.93%) and 0.33% (95% CI, 0.19%-0.56%) for men with favorable intermediate-risk PC and low-risk PC, respectively. The respective estimates for ACM were 10.45% (95% CI, 8.91%-12.12%) and 8.68% (95% CI, 7.80%-9.61%).

**Discussion**

We found that men with favorable intermediate-risk PC undergoing brachytherapy had 8-year point estimates of PCSM that were low: 0.48% (95% CI, 0.23%-0.93%) and 0.33% (95% CI, 0.19%-0.56%) for men with favorable intermediate-risk PC and low-risk PC, respectively, for an absolute difference of 0.15%, and had a risk of PCSM not significantly different from that of men with low-risk PC (adjusted HR, 1.64; 95% CI, 0.76-3.53; \( P = .21 \)). This lack of a significant difference in the risk of PCSM was evident even though men with low-risk PC had lower median PSA levels, did not have Gleason 3 + 4 disease, and were more likely to have AJCC T1c disease (Table 1), all of which could have caused men with favorable intermediate-risk PC to have a higher risk of PCSM. Moreover, while the median follow-up was slightly (although not significantly) longer (3.6 months; \( P = .06 \)) for men with low-risk PC than for those with favorable intermediate-risk PC, this was adjusted for in the model by including year of brachytherapy as a covariate. Similarly,
men with favorable intermediate-risk PC did not have significantly increased risk of ACM compared with men with low-risk PC (adjusted HR, 1.11; 95% CI, 0.88-1.39; \( P = 0.38 \)).

The clinical significance of our findings is that men with favorable intermediate-risk PC may also be candidates for AS. Currently, per the NCCN guidelines, only men with low-risk PC and a life expectancy of at least 10 years are candidates for AS. However, given that the risk of PCSM in men with favorable intermediate-risk PC does not appear to be significantly different than that in men with low-risk PC undergoing prostate brachytherapy after a median follow-up of 7.69 years, men with favorable intermediate-risk PC may also be candidates for AS. However, we found a trend toward an increased risk of PCSM in men with AJCC clinical tumor stage T2 vs T1c PC (Table 2), and while the trend was not statistically significant (\( P = 0.06 \)), it is possible that only men with clinical category T1c low-risk PC or favorable intermediate-risk PC would be ideal candidates for AS.

Several points deserve further consideration. First, our results suggesting a nonsignificant difference in the risk of PCSM in men with low-risk and favorable intermediate-risk PC should be interpreted cautiously because they are based on data from a single institution and not a randomized clinical trial. Moreover, showing a nonsignificant difference in the risk of PCSM among men with favorable intermediate-risk PC vs low-risk PC who were treated may not translate into the same nonsignificant results among men in similar risk groups who undergo AS. Fortunately, prospective phase 2 AS studies have been performed,12,13,30-38 some of which included men with favorable intermediate-risk PC.12,13,30,31,34 While these phase 2 trials will be able to ascertain whether similar low death rates from PC of treated men with favorable intermediate-risk PC also exist in men with favorable intermediate-risk PC who initially underwent AS using historical controls, the level 1 evidence to support or refute AS in men with favorable intermediate-risk PC will come from the randomized ProtecT trial, scheduled to report its initial findings in 2016.11

That said, the data in the current study were prospectively collected; the sample size is large; and the median follow-up approaches 8 years. Therefore, given only a 0.15% absolute increase of PCSM at 8 years for treated men with
favorable intermediate-risk vs low-risk PC, it is likely that even if results of a very large prospective randomized trial could ascertain a 0.15% difference that was statistically significant, the clinical significance of such a small difference could be questioned. Moreover, the present study began in 1997, so some participants who were classified as having low-risk PC based on a Gleason score of 3 + 3 would be classified today as having a Gleason score of 3 + 4 based on the 2005 International Society of Urologic Pathology consensus conference guidelines. This further supports the lack of a significant difference in the risk of PCSM observed in the present study among men with favorable intermediate-risk PS vs low-risk PC.

Second, further follow-up of this study is necessary to determine whether AS is an appropriate option for healthy men with favorable intermediate-risk PC who have a life expectancy in excess of the reporting times in the current study. Third, it is important to note that men with intermediate-risk PC enrolled in prospective AS studies could have had either favorable or unfavorable intermediate-risk disease. For instance, the Canadian AS experience included men older than 70 years with PSA levels as high as 15 ng/mL or Gleason scores up to 3 + 4. Since the protocol allowed inclusion of men with both of these factors, the study could have enrolled some men with unfavorable intermediate-risk PC. Therefore, it is important to note that estimates of PCSM for men with intermediate-risk PC in prospective AS surveillance studies may not be representative of PCSM rates for the subset of men with favorable intermediate-risk PC. The recently reported long-term results of the phase 2 Canadian AS protocol showed a 10-year PCSM estimate of 1.9% vs 0.71% for men with favorable intermediate-risk PC and 0.44% for men with low-risk PC in the present study.

Fourth, a probable reason for increasing age being significantly associated with an increased risk of PCSM in the adjusted competing risks regression analysis is the known association of increasing age and high-grade PC. Given the sampling error that is associated with prostate biopsies and that older men tend to have larger prostates than younger men secondary to benign prostatic hyperplasia, older men are more likely than younger men to experience undergrading due to increased biopsy sampling error. Therefore, further workup to rule out clinically occult high-grade PC with multiparametric magnetic resonance imaging could be considered before managing PC in older men (age >65 years) with AS.

Finally, given that our study only had a power of 75% to detect a significant difference in the risk of PCSM when comparing men with favorable intermediate-risk PC with those who had low-risk PC, there is a 25% chance that a difference exists that we did not observe or that a type 2 error occurred.

Conclusions

Despite potential study limitations, we found that men with low-risk PC and favorable intermediate-risk PC have similar and very low estimates of PCSM and ACM during the first decade following brachytherapy. While awaiting the results of ProtecT, the randomized trial of AS vs treatment, our results provide evidence to support AS as an initial approach for men with favorable intermediate-risk PC.

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Study concept and design: D’Amico.

Acquisition, analysis, or interpretation of data: Raldow, Zhang, Chen, Braccioforte, Moran, D’Amico.

Drafting of the manuscript: Raldow, Chen, D’Amico.

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REFERENCES


Active Surveillance in Prostate Cancer
How Far Should We Go?
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The risk of overtreatment in localized prostate cancer has become a subject of paramount importance and is one of the major reasons behind some of the negative perceptions of screening. Although treatment today has less morbidity than in the past, there is still significant risk associated with all available treatment options. To dissociate screening from treatment, the concepts of watchful waiting (WW) and active surveillance (AS) have gained widespread attention and appeal.

The concept of WW implies that patients are followed up without intervention until symptoms manifest or clinical or metastatic progression becomes apparent. The concept of WW has become less attractive, especially for younger patients, given that a large randomized clinical trial demonstrated that radical prostatectomy significantly improved metastasis-free and overall survival compared with WW.

A compromise between WW and immediate intervention has given rise to the concept of AS. Given the low risk of 10-year cancer-specific mortality, AS has become a recommended option for selected patients diagnosed with apparently low-risk cancer. Low-risk disease is generally defined as Gleason grade 6 cancers with prostate-specific antigen (PSA) findings below 10 ng/mL and nothing more than clinical T2a disease on digital rectal examination (DRE). The subclassification of very-low-risk cancer is defined as 2 or fewer positive biopsy findings with less than 50% of any core being cancerous. These cases are often considered optimal for AS. Patients under AS are followed up regularly with PSA measurements and DREs and usually biopsied at variable time points. The plan is to intervene if and when progression to a more aggressive phenotype occurs.

Whether we can safely expand the concept of AS to some patients with intermediate-risk prostate cancers has become a subject of interest to both physicians and patients. The study in this issue of JAMA Oncology by Braidot et al compares low-risk to favorable intermediate-risk prostate cancer and shows that brachytherapy was equally effective, with a very low risk of mortality, in both groups. According to the authors, the findings suggest that some intermediate-risk patients may actu-