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The Impact of Differing Gleason Scores at Biopsy on the Odds of Upgrading and the Risk of Death from Prostate Cancer

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Abstract

Background—The Gleason score (GS) is an established prostate cancer (PCa) prognostic factor. Whether the presence of differing GS's at biopsy (e.g. 4 + 3 and 3 + 3), which we term ComboGS, improves the prognosis that would be predicted based on the highest GS (e.g. 4 + 3) due to decreased upgrading is unknown. Therefore, we evaluated the odds of upgrading at radical prostatectomy (RP) and the risk of prostate cancer-specific mortality (PCSM) when ComboGS was present versus absent.

Methods—Logistic and competing risks regression were performed to assess the impact ComboGS had on the odds of upgrading at RP in the index (n=134) and validation cohorts (n=356) and the risk of PCSM following definitive therapy in a long-term cohort (n=666), adjusting for known predictors of these endpoints. We calculated and compared the area under the

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Conflict of Interest Statement

The authors of this manuscript state that there are no conflicts of interest relative to this work.

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curve using a receiver operating characteristic analysis when ComboGS was included versus excluded from the upgrading models.

Results—ComboGS was associated with decreased odds of upgrading (Index: Adjusted Odds Ratio (AOR): 0.14 [95% CI: 0.04–0.50], $p = 0.003$; Validation: AOR: 0.24 [95% CI: 0.11–0.51], $p < 0.001$) and added significantly to the predictive value of upgrading for the in-sample index ($p = 0.02$), validation ($p = 0.003$) and out-of-sample prediction models ($p = 0.002$). ComboGS was also associated with a decreased risk of PCSM (AHR: 0.40 [95% CI: 0.19–0.85], $p = 0.02$).

Conclusions—Differing biopsy Gleason scores are associated with both a lower odds of upgrading and risk of PCSM. If validated, future randomized non-inferiority studies evaluating de-escalated treatment approaches in men with ComboGS could be considered.

Keywords

Gleason score; radical prostatectomy; upgrading; prostate cancer-specific mortality

Introduction

The biopsy Gleason score (GS)¹, defined as the sum of the 2 most predominant Gleason grades (GG), is a prognostic factor significantly associated with the risk of prostate cancer-specific mortality (PCSM) following conservative² or curative management.^{3, 4} Studies have established the association of the commonly used GS levels (i.e. 8 to 10 vs. 7 vs. 6 or less) with an increased risk of PCSM after adjusting for known prognostic factors.⁵

Approximately 1/3 of men with clinically localized prostate cancer (PCa) will be upgraded at radical prostatectomy (RP) due to under-sampling of occult high grade PCa at transrectal ultrasound-guided prostate needle biopsy (TRUS PNB) and therefore have a worse prognosis than would have been predicted based on the highest biopsy GS.^{6–9} In order to improve counseling regarding prognosis, investigators have identified predictors of upgrading based on information available at diagnosis.^{6–16} However, only a single study¹⁷ has observed that the presence of differing Gleason scores (i.e. a lower in addition to the highest GS) at biopsy (termed ComboGS in the current study) lowered the odds of upgrading at RP. No study to date, however, has investigated the impact of differing Gleason scores on the risk of PCSM. Therefore, in the current study we evaluated the impact that the presence of ComboGS had on the odds of upgrading and the risk of PCSM.

Methods

Index and Validation Study Cohorts

The index cohort consisted of 134 consecutive men with localized PCa diagnosed between April 2008 and September 2011 using a 12-core TRUS PNB. Clinically localized PCa was defined as clinical tumor category (T)1c–T2c based on the 2009 American Joint Committee on Cancer (AJCC) PCa staging guidelines.¹⁸ Men underwent an RP at the Brigham and Women's Hospital (BWH) performed by a single surgeon.

The validation cohort consisted of 356 men distinct from the index cohort with localized PCa diagnosed between January 2005 and December 2008 using a median of 12-cores

[Interquartile range (IQR): 10 to 12] via a TRUS PNB who underwent RP at the BWH. Of note, 44% of these men had a less than 12-core sample. The index and validation cohorts overlap in time but not in patients treated between April 2008 and December 2008. All men from the index cohort were operated on by a single urologic oncologist (JR) whereas men from the validation cohort were operated on by any of the urologic oncologists at the BWH. This study and the prospective acquisition of the data were approved by the Dana Farber Cancer Institute (DFCI) Institutional Review Board (IRB).

The long-term study cohort consisted of 666 consecutive men with localized or locally advanced PCa diagnosed via a TRUS PNB (median of 6 cores, IQR 5–6 cores). The men were referred to Saint Anne's Hospital (SAH, Fall River, MA), a DFCI/BWH affiliated regional community-based cancer center and treated definitively between October 1989 and July 2000 with either surgery ($N = 44$) if radiation (RT) was declined, 70 Gray of RT ($N = 533$) or 6 months of androgen suppression therapy (AST) and 70 Gray of RT ($N = 89$). All patient data was collected prospectively into a database that was approved by SAH IRB.

Assignment of Gleason Score and Definition of Upgrading

Biopsy and RP GS were assigned by a single genitourinary pathologist in the index cohort whereas any staff genitourinary pathologist at the BWH (Boston, MA) assigned the biopsy and RP GS in the validation cohort. For the 666 men in the long-term study cohort, biopsy GS was assigned by community pathologists associated with St. Anne's Hospital. For men in the index and validation cohorts, GS was assigned per the 2005 International Society of Urological Pathology Consensus Conference (ISUPCC) on Gleason Grading.¹⁹ Since all men in the long-term cohort were diagnosed prior to the 2005 ISUPCC, GS in this cohort was assigned using the conventional grading scale of 2 through 10.¹ Upgrading was defined as the presence of a higher GS at RP when compared to the biopsy GS (e.g. prostatectomy 4 + 4 vs biopsy 4 + 3). However for numerically equal Gleason scores, an increase in the proportion of the predominant GG component conferred a grade change. For example, a GS of 4+3=7 at RP compared to a GS of 3+4=7 at biopsy was considered upgrading.

Definition of ComboGS

ComboGS was defined as present when the biopsy revealed a GS in at least one core that was lower than the highest GS observed in the entire biopsy sample (e.g. 3 + 3 and 4 + 4) or in the case of GS 7 when both 3 + 4 and 4 + 3 were present.

Statistical Methods

Comparison of the Distribution of Baseline Characteristics

A comparison of the distribution of clinical characteristics stratified by whether the patient was in the index, validation, or long-term cohort and by the presence or absence of ComboGS was performed using a Mantel-Haenszel²⁰ chi-square metric for categorical factors and a non-parametric Wilcoxon test for continuous covariates.²¹

Comparison of Upgrading by Biopsy Gleason Score and Presence of ComboGS

A comparison of the odds of upgrading stratified by both biopsy Gleason score and presence or absence of ComboGS was performed for men in both the index and validation cohorts using a Mantel-Haenszel²⁰ chi-square metric.

Logistic Regression and the Odds of Upgrading at RP

The primary endpoint of the study is the adjusted odds of upgrading. For both the index and validation cohorts, logistic regression multivariable analysis²² was performed to assess the impact that ComboGS had on the odds of upgrading at RP adjusting for the continuous covariates of age, PSA level at diagnosis and percent positive biopsies (ppb), and the categorical covariate of clinical T-category (T2 vs. T1c as reference). Adjusted odds ratios (AOR) and 95% confidence intervals (CI) with two-sided p-values were calculated. Given that men with both a high ppb and PSA level at diagnosis were more likely to have higher biopsy GS and therefore would have less opportunity for upgrading as compared to men with either a high ppb or high PSA level but not both, the possibility of an interaction existed between ppb and PSA level. Therefore, an interaction term between ppb and PSA level was included in the model.

Model Validation

We calculated and compared the area under the curve (AUC) value using a receiver operating characteristic (ROC) analysis²³ when ComboGS was included versus excluded from the logistic regression model for both the index and validation cohorts which is termed an “in-sample” analysis. We assessed model validation by performing a prediction ROC analysis²³ where we compared the AUC’s obtained when ComboGS was included in the model versus excluded using the coefficients for each clinical covariate from the index model to calculate a prediction of upgrading using the data from the validation cohort which is termed an “out-of-sample” analysis.

Long-Term Cohort

Competing Risks Regression and the Risk of PCSM

The second primary endpoint of this study was the risk of PCSM. A Fine and Gray competing risks multivariable regression²⁴ was performed to assess the impact of ComboGS on the risk of PCSM adjusting for known prognostic factors in the long-term cohort. Time 0 was defined as the date of treatment. The median (IQR) time from date of diagnosis to treatment was 2.2 months (IQR: 1.8 to 2.9). Continuous covariates in the model included PSA and age at diagnosis. Categorical covariates included treatment (RP vs. RT vs. RT and AST as reference), highest GS (8 to 10 vs. 7 vs. 6 or less as reference), and T-category (T3, T4 vs. T2 vs. T1c as reference). Adjusted hazard ratios (AHR) and 95% CI with two-sided p-values were calculated.

Estimates of PCSM stratified by Highest Gleason Score and the Presence or Absence of ComboGS

Cumulative incidence estimates of PCSM stratified by the presence or absence of ComboGS were generated for men with highest GS 6 or less, 7 and 8 to 10²⁵ and compared using a k-sample test.²⁶ A Bonferroni correction was applied for multiple comparisons. SAS version 9.3 was used for all statistical analyses (SAS Institute, Cary, NC) except for the competing risks analysis, which was performed using R version 2.15.2⁹ (R Foundation for Statistical Computing, Vienna, Austria).

Results

Comparison of the Distribution of the Baseline Characteristics

As shown in Table 1, the percent of men with ComboGS was not significantly different between the index and validation cohort being 20% (27/134) and 24% (87/356) respectively ($p = 0.32$). Among the 27 men with ComboGS in the index cohort, 4 (15%), 12 (44%) and 11 (41%) were upgraded, unchanged or downgraded respectively. These respective values were 9 (10%), 44 (51%) and 34 (39%) for the 87 men with ComboGS in the validation cohort. Amongst men with and without ComboGS in the index and validation cohorts, the median [IQR] prostate gland volume was not significantly different being 49.8 cc [44, 55] versus 48 cc [42, 60]; ($p = 0.86$) and 50 cc [43, 59] and 53 cc [44, 64]; ($p = 0.22$) respectively.

Comparison of Upgrading by Biopsy Gleason Score and Presence of ComboGS

Table 2 shows the impact that ComboGS had on decreasing the likelihood of upgrading for men in the index and validation cohorts before adjustment for other clinical and tumor characteristics. The comparison in the subgroup of men with biopsy Gleason score 4 + 4 or higher in the index cohort is limited by a very small event rate of upgrading.

Logistic Regression and the Odds of Upgrading at RP

As shown in Table 3, ComboGS was associated with a decreased odds of upgrading (AOR: 0.14 [95% CI: 0.04–0.50], $p = 0.003$; AOR: 0.24 [95% CI: 0.11–0.51], $p < 0.001$); whereas increasing ppb (AOR: 1.10 [95% CI: 1.05 to 1.16], $p < 0.001$; AOR: 1.03 [95% CI: 1.002 to 1.05], $p = 0.03$); and PSA level (AOR: 1.43 [95% CI: 1.14 to 1.80], $p = 0.002$; AOR: 1.17 [95% CI: 1.01 to 1.34], $p = 0.03$) were associated with an increased odds of upgrading in the index and validation cohorts respectively. There was a significant interaction between PSA level and ppb ($p = 0.003$) in the index cohort.

Model Validation

Adding ComboGS significantly improved the ability of the model to predict the odds of upgrading in both the index (AUC: 0.70 to 0.78; $p = 0.02$) and validation (AUC: 0.58 to 0.67; $p = 0.003$) cohorts. Using the data from the validation cohort with and without ComboGS, a significant improvement was observed (AUC 0.57 to 0.64; $p = 0.002$) in the ability to predict the odds of upgrading in the model optimized for the index cohort.

Long-Term Cohort

Comparison of the Distribution of the Clinical Characteristics

As shown in Table 4, men with and without ComboGS did not have significant differences in the distribution of treatment, median age, or PSA level at the start of treatment. However, men with ComboGS had a higher proportion of men with highest GS 7 or 8 to 10 PCa as compared to men without ComboGS ($p < .001$).

Competing Risks Regression and the Risk of PCSM

After a median follow up of 4.6 years (IQR 2.5–6.7 years), 168 men (25.2%) had died, 41 (24.4%) of PCa. As shown in Table 5, ComboGS was associated with a decreased risk of PCSM (AHR: 0.40 [95% CI: 0.19–0.85], $p = .02$). In addition, the established prognostic factors of increasing PSA (AHR: 2.63 [95% CI: 1.71–4.06], $p < 0.001$) and highest GS 8 to 10 (AHR: 10.73 [95% CI: 3.57–32.31], $p < 0.001$) and 7 (AHR: 3.59 [95% CI: 1.27–10.16], $p = 0.02$) were associated with an increased risk of PCSM.

Estimates of PCSM stratified by Highest Gleason Score and the Presence or Absence of ComboGS

For the purpose of illustration, estimates of PCSM are shown in Figures 1A–C and are higher in men without versus with ComboGS when the highest GS was 8 to 10 ($p = 0.02$) or 7 ($p = 0.02$) but not 6 or less ($p = 0.71$) respectively. Specifically, these respective 5-year estimates (95% CI) were 27.3% (7.4, 52.2) versus 14.8% (6.2, 26.9), 7.3% (1.2, 21.0) versus 1.4% (0.3, 4.5) and 1.9% (0.2, 8.7) versus 2.7% (0.7, 7.2) for men with highest GS 8 to 10, 7, and 6 or less respectively.

Discussion

Currently available clinical and pathologic factors are insufficiently predictive for upgrading at RP and are therefore of limited clinical utility.²⁷ In the current study we define, test and validate that ComboGS, a factor available at diagnosis following a standard PNB, is associated with a significant reduction in the odds of upgrading at RP and a decreased risk of PCSM. The effect on the odds of upgrading does not appear to be explained by an improved sampling in men with versus without ComboGS in that the median number of cores sampled was 12 and the distribution of prostate gland volumes was not significantly different amongst men with and without ComboGS in the index and validation cohorts.

Given the known association of prostatectomy Gleason score with the risk of recurrence, metastasis and death from prostate cancer,^{3–5} men with ComboGS who have a lower odds of upgrading at RP should have a more favorable prognosis than expected based on the highest biopsy GS. We provide evidence for this hypothesis by showing that men with ComboGS had a 60% reduction in the risk of PCSM after adjusting for known prognostic factors. Moreover, this reduction in PCSM was only observed in men with clinically significant PCa corresponding to highest biopsy GS 7 to 10 PCa (Figure 1). The clinical relevance of these data is that the presence of ComboGS may allow physicians to counsel men with highest biopsy GS 7 or higher PCa at presentation and prior to definitive treatment that their

prognosis is better than the highest biopsy GS suggests. If validated, the presence of ComboGS could be used to design future non-inferiority randomized trials to assess de-escalated therapies such as RT and short course hormonal deprivation as opposed to RT and long course hormonal deprivation in men with highest GS 8 to 10 PC.

Several points require further discussion. First, it is important to note that the number of men in the index and validation cohorts with ComboGS is limited to less than 25%. However despite this small proportion, a significant reduction in the risk of upgrading was observed across biopsy Gleason score categories in both the index and validation cohorts after adjusting for known predictors of upgrading as illustrated in Table 3.

Second, it is of note that the absolute magnitude of the AUC for the base model was lower for cases where the validation cohort data was used for the “in-sample” or “out-of sample” analyses as compared to the “in-sample” index cohort analysis. This can be explained by the fact that ppb, which is a significant predictor in both the index and validation cohorts and known to be significantly associated with upgrading from prior studies,^{8, 14} was less well defined in the validation cohort (only 56% had a 12-core biopsy). Given that a 12-core PNB has been shown to increase the detection rate of PCa and the concordance of the biopsy with the prostatectomy Gleason score²⁸, the 12-core biopsy was standard by 2008 when the index but not validation cohort began. This may also explain why the interaction term did not reach significance in the logistic regression model for the validation cohort but did in the index cohort. Given that today most men have a 12-core PNB performed for diagnosis, we would expect performance characteristics for upgrading to be consistent with the index model in our study with an AUC value of 0.78 when ComboGS was included. This is one of the highest AUC values in the literature.²⁷ Additionally, the median number of cores sampled in the long-term cohort was 6 as a 12-core biopsy became standard of practice after men in the long-term cohort were diagnosed. However given the long natural history of prostate cancer, using this data set provided the follow-up necessary to evaluate the endpoint of PCSM. Third, when illustrating graphically the prognostic significance of ComboGS within subgroups of men stratified by highest Gleason score, significance was just achieved for men with highest GS 7 or 8 to 10. Therefore additional follow up is needed to ascertain whether significance within these subgroups is maintained.

Finally, advances in identifying novel prognostic factors have come from genomic-based studies^{29, 30} that evaluated the impact of genomic profiling on the risk of upgrading. While potentially of great value, the importance of the results in the current study is that upgrading odds can be better assessed using the information obtained from the standard 12-core PNB using the ComboGS construct. Therefore, assessing whether genomic profiling can improve upon the information provided by ComboGS in detailing the odds of upgrading and subsequent risk of PCSM deserves further study.

In conclusion, these data provide evidence to support that men whose PNB shows differing biopsy Gleason scores (ComboGS) have both a lower odds of upgrading at RP and a lower risk of PCSM. If validated, future randomized non-inferiority studies evaluating de-escalated treatment approaches in men with ComboGS could be considered.

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Clinical Practice Points

1. The presence of differing Gleason scores at biopsy (ComboGS) is associated with approximately an 80% reduction in the odds of upgrading at radical prostatectomy.
2. The presence of ComboGS reduced the risk of prostate cancer-specific mortality by 60% following definitive therapy. If validated, the presence of ComboGS at biopsy should allow physicians to counsel patients that their overall prognosis is better than the highest Gleason score would otherwise indicate.
3. A future randomized non-inferiority study evaluating de-escalated treatment approaches such as RT and short course hormone deprivation versus RT and long course androgen deprivation in men with ComboGS and highest GS 8 to 10 PCa could be considered.

Figure 1.

Figure 1A–C: Cumulative incidence estimate²⁶ of PCSM stratified by the presence or absence of **ComboGS** for men in the long-term cohort with highest Gleason score of 8 to 10 (Panel A), 7 (Panel B), or 6 or less (Panel C).

k-sample p-value²⁶ = 0.02 for Panel A and B, and 0.71 for Panel C. Significant p-value after applying the Bonferroni correction and rounding to 2 significant digits = 0.02.

Table 1
Comparison of the distribution of the baseline characteristics among the 134 and 356 men in the index and validation cohorts

Clinical Factor	Index Cohort (N = 134)	Validation Cohort (N = 356)	P-value
ComboGS			
Present	27 (20%)	87 (24%)	0.32
Absent	107 (80%)	269 (76%)	
Median age in years (IQR)	57.3 [52.5, 62.3]	59.7 [54.4, 63.9]	0.02
Median PSA in ng/ml (IQR)	5.2 [3.8, 7.4]	4.8 [3.8, 6.0]	0.05
Median ppb in percentage (IQR)	33.3 [20.0, 50.0]	25.0 [12.5, 40.0]	<0.001
Tumor(T) Category			
T2	31 (23%)	62 (17%)	0.15
T1c	103 (77%)	294 (83%)	
Highest Gleason Score			
8–10	14 (10%)	26 (7%)	0.002
4 + 3	21 (16%)	35 (10%)	
3 + 4	45 (34%)	86 (24%)	
6 or less	54 (40%)	209 (59%)	

Abbreviations: IQR: Interquartile Range; PSA: Prostate-Specific Antigen; ppb: percent positive biopsies

Table 2

Unadjusted illustration of the impact of ComboGS on the likelihood of upgrading amongst men in the index and validation cohorts

Biopsy Gleason score	Index Cohort		Validation Cohort		p-value
	ComboGS present	ComboGS absent	ComboGS present	ComboGS absent	
3 + 4 or less	2/11 (18.2%)	38/88 (43.2%)	4/44 (9.1%)	76/251 (30.3%)	0.0048
4 + 3	1/10 (10%)	3/11 (27.3%)	2/26 (7.7%)	1/9 (11.1%)	
4 + 4 or higher	1/6 (16.7%)	1/8 (12.5%)	3/17 (17.6%)	2/9 (22.2%)	

p-value calculated using a Mantel-Haenszel chi-square²⁰ metric

Table 3

Logistic regression ²² unadjusted and adjusted odds ratios and associated 95% confidence intervals and p-values representing the impact of clinical factors have on upgrading at radical prostatectomy, among the 134 and 356 men in the index and validation cohorts

Clinical Factor at Diagnosis	Number of Men	Number (%)upgraded	Odds Ratio [95% CI]	p-value	Adjusted Odds Ratio [95% CI]	p-value
INDEX COHORT						
ComboGS Present	27	4 (15%)	0.27 [0.09–0.83]	0.02	0.14 [0.04–0.50]	0.003
ComboGS Absent	107	42 (39%)	1.0 (ref.)	--	1.0 (ref.)	--
PSA in ng/ml	134	46 (34%)	1.38 [1.11–1.72]	0.004	1.43 [1.14–1.80]	0.002
ppb	134	46 (34%)	1.07 [1.02–1.12]	0.005	1.10 [1.05–1.16]	<0.001
Age in years	134	46 (34%)	1.01 [0.96–1.07]	0.69	0.99 [0.92–1.05]	0.65
Clinical Tumor(T) Category						
T1c	103	40 (39%)	1.0 (ref.)	--	1.0 (ref.)	--
T2	31	6 (19%)	0.38 [0.14–1.0]	0.05	0.23 [0.07–0.74]	0.01
PSA*ppb	134	46 (34%)	0.992 [0.985–0.998]	0.01	0.99 [0.98–0.997]	0.003
VALIDATION COHORT						
ComboGS Present	87	9 (10%)	0.28 [0.13–0.58]	<0.001	0.24 [0.11–0.51]	<0.001
ComboGS Absent	269	79 (29%)	1.0 (ref.)	-	1.0 (ref.)	-
PSA in ng/ml	356	88 (25%)	1.17 [1.02–1.34]	0.03	1.17 [1.01–1.34]	0.03
ppb	356	88 (25%)	1.02 [0.99–1.04]	0.12	1.03 [1.002–1.05]	0.03
Age in years	356	88 (25%)	1.03 [0.99–1.06]	0.18	1.03 [0.99–1.07]	0.18
Clinical Tumor(T) Category						
T1c	294	76 (26%)	1.0 (ref.)	-	1.0 (ref.)	-
T2	62	12 (19%)	0.69 [0.35–1.36]	0.28	0.81 [0.39–1.67]	0.57
PSA*ppb	356	88 (25%)	0.997 [0.994–1.001]	0.12	0.998 [0.994–1.001]	0.14

Abbreviations: CI: Confidence Interval; PSA: prostate-specific antigen; ppb: percent positive biopsies PSA*ppb = interaction factor between PSA and ppb.

Table 4

Baseline characteristics among the 666 men in the long-term cohort in patients with and without ComboGS

Clinical Factor	ComboGS absent (N=195)	ComboGS present (N=471)	P-value
Median age in years (IQR)	72.57 [68.11, 75.53]	72.08 [68.24, 75.26]	0.66
Median PSA in ng/ml (IQR)	10.25 [5.90, 15.69]	9.10 [6.20, 14.90]	0.46
Tumor(T) Category			0.95
T3 or T4	14 (7.2%)	31 (6.6%)	
T2	108 (55.4%)	268 (56.9%)	
T1c	73 (37.4%)	172 (36.5%)	
Highest Gleason Score			<0.001
8–10	22 (11.3%)	67 (14.2%)	
7	49 (25.1%)	232 (49.3%)	
6 or less	124 (63.4%)	172 (36.5%)	
Treatment			0.39
Radical Prostatectomy	10 (5.1%)	34 (7.2%)	
Radiation Therapy	159 (81.5%)	374 (79.4%)	
Radiation + AST	26 (13.3%)	63 (13.4%)	

Abbreviations: IQR: Interquartile Range; PSA: Prostate-Specific Antigen; AST: Androgen Suppression Therapy

Table 5

Fine and Grays regression ²⁴ unadjusted and adjusted Hazard ratios and associated 95% confidence intervals and p-values representing the impact clinical factors have on the risk of PCSM among the 666 men in the long-term cohort.

Clinical Factor	Number of Men	Number of PCa Deaths	HR [95% CI]	p-value	AHR [95% CI]	p-value
ComboGS						
Present	471	27	0.68[0.36, 1.28]	0.23	0.40[0.19, 0.85]	0.02
Absent	195	14	1.0	-	1.0	-
Treatment						
Radiation	533	34	0.65[0.23, 1.89]	0.43	0.94[0.34, 2.65]	0.91
Radical Prostatectomy	44	3	0.61[0.13, 2.82]	0.53	1.21[0.23, 6.43]	0.82
Radiation + AST	89	4	1.0	-	1.0	-
PSA in ng/ml	666	41	2.70[1.90, 3.84]	<0.001	2.63[1.71, 4.06]	<0.001
Highest Gleason Score						
8–10	89	15	9.68[3.68, 25.46]	<0.001	10.73[3.57, 32.31]	<0.001
7	281	20	3.54[1.44, 8.71]	0.006	3.59[1.27, 10.16]	0.02
6 or less	296	6	1.0	-	1.0	-
Tumor category						
T3–4	45	6	3.46[1.24, 9.64]	0.02	0.67[0.17, 2.68]	0.57
T2	376	27	1.62[0.75, 3.51]	0.22	1.12[0.51, 2.46]	0.78
T1c	245	8	1.0	-	1.0	-
Age in years	666	41	1.02[0.97, 1.08]	0.40	1.04[0.98, 1.10]	0.22

Abbreviations: AHR: Adjusted Hazard Ratio; PCa: Prostate Cancer; PCSM: Prostate Cancer-Specific Mortality; PSA: Prostate-Specific Antigen; AST: Androgen Suppression Therapy