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Biopsy Detected Gleason Pattern 5 is Associated with Recurrence, Metastasis and Mortality in a Cohort of Men with High Risk Prostate Cancer

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Abstract

Purpose: We evaluated the relative risk of biochemical recurrence, metastasis and death from prostate cancer contributed by biopsy Gleason pattern 5 among men at high risk with Gleason 8–10 disease in the SEARCH (Shared Equal Access Regional Cancer Hospital) cohort.

Materials and Methods: Men with biopsy Gleason sum 8–10 prostate cancer treated with radical prostatectomy were evaluated. The cohort was divided into men with Gleason 4 + 4 vs those with any pattern 5 (ie Gleason 3 + 5, 5 + 3, 4 + 5, 5 + 4 or 5 + 5). Predictors of biochemical recurrence, metastases, and prostate cancer specific and overall survival were analyzed using Kaplan-Meier, log rank test and Cox proportional hazards models.

Results: We identified 634 men at high risk in the SEARCH database, of whom 394 (62%) had Gleason 4 + 4 and 240 (38%) had Gleason pattern 5 on biopsy. Baseline characteristics did not significantly differ between the groups. On multivariable analysis relative to Gleason 4 + 4 men at high risk with Gleason pattern 5 showed no difference in the risk of biochemical recurrence (HR 1.26, 95% CI 0.99–1.61, p = 0.065). However, they were at significantly greater risk for metastasis (HR 2.55, 95% CI 1.50–4.35, p = 0.001), prostate cancer specific mortality (HR 2.67, 95% CI 0.1.26–5.66, p = 0.010) and overall mortality (HR 1.60, 95% CI 1.09–2.34, p = 0.016).

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Conclusions: Preoperative subclassification of high risk prostate cancer by biopsy Gleason grade (4 + 4 vs any Gleason pattern 5) identified men at highest risk for progression. Any Gleason 5 on biopsy is associated with a greater risk of metastasis, and prostate cancer specific and overall mortality. Grouping all Gleason 8–10 tumors together as high risk lesions may fail to fully stratify men at highest risk for poor outcomes.

Keywords

prostatic neoplasms; prostatectomy; mortality; neoplasm recurrence; local; neoplasm grading

It is estimated that 220,800 men were diagnosed with prostate cancer and 27,540 died of the disease in 2015.[1] Approximately 15% of patients with prostate cancer meet criteria for high risk disease, which includes those with PSA greater than 20 ng/ml, biopsy Gleason grade 8–10 and greater than cT2c findings on digital rectal examination.[2,3] Although men with biopsy Gleason grade 8–10 are at significant risk for clinical progression, this is a heterogeneous population and individual outcomes vary significantly. Traditional risk stratification schemes such as the Kattan nomogram consider Gleason score and PSA as categorical variables and report the probability of disease specific outcomes that result in wide variations.[4]

Biopsy Gleason grading has consistently been one of the strongest predictors of BCR, and disease specific and overall survival.[5–7] However, in many of these studies Gleason sum 8–10 was evaluated as 1 group, thereby losing the ability to differentiate cancer specific outcomes among patients with Gleason pattern 5. Several observational studies have identified patients with any component of Gleason pattern 5 as being at significantly increased risk for clinical progression and adverse outcomes.[8–10] Tertiary Gleason pattern 5 in the setting of intermediate risk disease based on radical prostatectomy specimens was also shown to be an independent risk factor for adverse outcomes.[11] These observations suggest that Gleason pattern 5 represents uniquely aggressive tumor biology.

We sought to substratify men diagnosed with Gleason 8–10 on prostate biopsy to assess outcomes in the SEARCH cohort. We hypothesized that the presence of any Gleason pattern 5 on initial prostate biopsy, even among men who were at clinically high risk and treated with prostatectomy, was an independent predictor of BCR, metastasis, prostate cancer specific mortality and overall survival.

PATIENTS AND METHODS

Characteristics

After approval was obtained from institutional review boards data on patients treated with radical prostatectomy between 1988 and 2015 were combined into the SEARCH database. The patients were treated at Veterans Affairs medical centers in San Diego, West Los Angeles and Palo Alto, California; Augusta, Georgia; and Asheville and Durham, North Carolina.

We excluded from study patients who were treated with preoperative androgen deprivation or radiation therapy. We included men with Gleason sum 8–10 and a primary Gleason score

of 4 or 5 on prostate biopsy who underwent radical prostatectomy. The cohort was divided into 2 groups, including those with Gleason 4 + 4 and those with any pattern 5 (eg Gleason 3 + 5, 4 + 5, 5 + 3, 5 + 4 or 5 + 5). Only 57 men had primary Gleason 5, too few to analyze as a separate group. Thus, those with any pattern 5 were grouped together. Tertiary scores, including tertiary pattern 5, were not routinely reported on prostate needle biopsies and so they were not included in analysis.

BCR was defined as PSA greater than 0.2 ng/ml, 2 values of 0.2 ng/ml or secondary treatment for elevated PSA. All imaging tests (bone scan, magnetic resonance imaging, computerized tomography and x-ray) after surgery were assessed by trained personnel to determine the development of metastases. Any man who had progressive metastatic prostate cancer while on androgen deprivation therapy and who died without another obvious cause of death was considered to have died of prostate cancer.

Statistical Analysis

Clinical and pathological characteristics of patients with high risk prostate cancer were compared among the groups using the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. PSA (logarithmically transformed), age, year of surgery and body mass index in kg/m^2 were examined as continuous variables. Clinical stage (T1, T2–4 or unknown) was examined as a categorical variable. Time to biochemical recurrence, metastasis, death from prostate cancer and overall mortality was analyzed using Kaplan-Meier plots and log rank tests. We constructed univariable and multivariable Cox proportional hazards models, adjusting for year of surgery, medical center and known predictors of a poor outcome, including age, PSA, race and clinical stage. All statistical analyses were performed using STATA®, version 14.1 with $p < 0.05$ considered statistically significant.

RESULTS

Clinical and Pathological Characteristics

Of 5,073 men who underwent prostatectomy in the SEARCH database 634 (10.0%) had high risk prostate cancer, defined as biopsy Gleason grade 8–10. Of these men 394 (62%) had Gleason 4 + 4 and 240 (38%) had any Gleason pattern 5 on biopsy, including Gleason 3 + 5, 4 + 5, 5 + 3,5 + 4 and 5 + 5. Table 1 details baseline the clinicopathological characteristics of the cohort. There were no significant differences in baseline characteristics among the groups except those with any Gleason pattern 5 were more likely to have undergone biopsy and surgery in more recent years ($p = 0.028$).

Biochemical Recurrence

Median followup in men without recurrence was 42 months. There were 293 recurrences (48%). At that point actuarial BCR-free survival was 56% in the Gleason 4 + 4 group vs 43% in patients with any Gleason pattern 5 (log rank $p = 0.008$, fig. 1). On univariable analysis relative to Gleason 4 + 4 men with any Gleason pattern 5 had a higher rate of biochemical recurrence (HR 1.37, 95% CI 1.09–1.74, $p = 0.008$). On multivariable analysis men with any Gleason pattern 5 on preoperative biopsy had a higher rate of biochemical

recurrence (HR 1.26, 95% CI 0.99–1.61, p = 0.065, tables 2 and 3), although this did not reach statistical significance.

Metastasis

Median followup in men without metastasis was 61 months. Metastases developed in 68 patients (11%). At that point the actuarial metastasis-free survival rate was 96% in the Gleason 4 + 4 group vs 85% in patients with any Gleason pattern 5 (log rank p <0.001, fig. 2). On univariable analysis relative to Gleason 4 + 4 men with any Gleason pattern 5 had a shorter time to metastasis (HR 2.63, 95% CI 1.63–4.25, p <0.001). Results remained significant on multivariable analysis (HR 2.55, 95% CI 1.50–4.35, p = 0.001, tables 2 and 3).

Prostate Cancer Mortality

The actuarial disease specific survival rate at a median followup of 62 months was 98% in the Gleason 4 + 4 group vs 91% in men with any Gleason pattern 5 (log rank p <0.001, fig. 3). Overall 42 men died of prostate cancer in the cohort, including 19 (3%) and 23 (4%) in the Gleason 4 + 4 and any pattern 5 groups, respectively. On univariable analysis men with any Gleason pattern 5 were more likely to die of prostate cancer than those with Gleason 4 + 4 (HR 2.67, 95% CI 1.46–4.86, p = 0.001). After adjusting for covariates we found similar results (HR 2.67, 95% CI 1.26–5.66, p = 0.010, tables 2 and 3).

Overall Mortality

There were 147 deaths (23%) during followup. The actuarial overall survival rate at a median followup of 59 months was 91% in the Gleason 4 + 4 group vs 81% in patients with any Gleason pattern 5 (log rank p = 0.007, fig. 4). Compared to Gleason pattern 4 + 4 the presence of any pattern 5 predicted worse overall survival (HR 1.58, 95% CI 1.13–2.21, p = 0.008). These results remained significant on multivariable analysis (HR 1.60, 95% CI 1.09–2.34, p = 0.016, tables 2 and 3).

DISCUSSION

In 1974 Gleason and Mellinger described a grading system for prostate cancer based on the VACURG (Veterans Administration Cooperative Urological Research Group) study.[12] The Gleason scoring system is based on the low power, glandular architectural characteristics of prostate cancer cells.[13,14] Although interobserver variability introduces certain limitations, a well established body of literature supports the consistency of this method.

Since its introduction, the biopsy Gleason score has been a powerful predictor of pathological stage, disease-free survival and adverse outcomes following prostatectomy.[15] Even during a time when there has been a shift in Gleason grading with a trend toward upgrading the final pathological specimen and limited use of grades 1–2, it is remarkable that the assessment of aggressive tumor architecture at initial biopsy remains one of the most powerful predictors of metastases and survival.[16]

Numerous risk factors for PSA recurrence, metastasis, and prostate cancer specific and overall mortality have been identified. Biopsy and pathological Gleason grading remain 2 of

the most significant predictors of outcome, in addition to nodal metastases and seminal vesicle invasion.[17] In the current study using the SEARCH cohort we substratified men with high risk prostate cancer by initial biopsy Gleason grade (4 + 4 vs any Gleason pattern 5 in those with a total grade of 8 or greater). Substratification along these lines identified men with Gleason pattern 5 at initial biopsy as a group at significantly higher risk for adverse cancer related outcomes. After adjusting for known risk factors we found that even in this group of men already at high risk those with any pattern 5 were at significant 2.5-fold greater risk for metastasis and death from prostate cancer and at increased risk for overall mortality. The actuarial disease specific and overall survival rates at a median followup of approximately 62 months were 98% vs 91% and 91% vs 80% in the Gleason 4 + 4 group vs men with any Gleason pattern 5, respectively.

Biopsy detected Gleason grade 5 trended toward significance as a predictor of BCR after prostatectomy (HR 1.26, p = 0.065). There are conflicting data on the effect of Gleason grading on BCR among patients at high risk. Our findings are similar to those of 2 single institution retrospective reviews of post-radical prostatectomy cases in which Gleason pattern 5 on biopsy was associated with biochemical recurrence.[18,19]

Other groups found no association between biopsy Gleason grade and BCR. Nanda et al compared PSA outcomes in a cohort of men with high risk prostate cancer.[8] They studied 312 men who had Gleason sum of 7 with tertiary grade 5, Gleason sum 8 or Gleason sum 9–10 and who underwent primary therapy with prostatectomy or radiotherapy with or without androgen suppression. At a median followup of 5.7 years the investigators found no significant difference in the risk of PSA recurrence in men with any Gleason pattern 5 (p = 0.09). Wambi et al also found no significant difference in biochemical recurrence-free survival among biopsy Gleason 8, 9 and 10 cancers in a total of 368 men treated with robotic prostatectomy.[20]

In 2009 Stephenson et al reported a multiinstitutional model to predict the risk of prostate cancer specific mortality.[4] On multivariable analysis they identified that primary and secondary biopsy Gleason grade 4 or greater (each p <0.001) and increasing PSA (p = 0.021) were associated with increased prostate cancer specific mortality. When applying this model in a hypothetical patient with a biopsy Gleason grade of 4 + 4 = 8, PSA 10 ng/ml and cT1c prostate cancer, the predicted 10-year prostate cancer specific mortality is between 1% and 2%. This nomogram would agree with the actuarial disease specific survival of 98% in the Gleason 4 + 4 group in our study at a median followup of 72 months. However, it does not account for the significant excess mortality observed in those patients with any Gleason pattern 5. In our study those men had nearly 10% prostate specific mortality at 72 months and the multivariable model showed greater than a twofold increase in prostate cancer mortality (tables 2 and 3, and fig. 3).

Our findings also support the recently presented update to the Gleason scoring system by Epstein et al.[21] Citing deficiencies in the Gleason scoring system, they sought to refine the system. Upon reviewing a series of patients with prostate cancer, including 20,845 treated with radical prostatectomy and more than 5,551 treated with radiotherapy, they determined that a 5-grade scoring group (grades 1–5) allowed for the most appropriate prognostic

distinction. Notably in the recommended grading system a Gleason sum of 9 or 10 is given the highest score (worst prognosis) in the newly proposed system as the presence of Gleason pattern 5, regardless of whether it is 4 + 5, 5 + 4 or 5 + 5, appeared to be an independent variable for prostate cancer related outcomes.[21]

In the current series we did not evaluate tertiary patterns because of inconsistent reporting across study sites. Furthermore, according to the 2014 ISUP (International Society of Urological Pathology) conference tertiary patterns should only be recorded for radical prostatectomy specimens with 3 + 4 = 7 or 4 + 3 = 7 with tertiary pattern 5.

We also performed subset analysis of biopsy detected Gleason Grade Group 4 to evaluate the unique risk in each group. Interestingly when evaluating 4 + 4 = 8 vs 3 + 5 = 8 or 5 + 3 = 8, we found no difference in this subgroup in BCR, or metastasis-free, cancer specific or overall survival. This suggests that when Gleason 5 is associated with Gleason 3 on biopsy, the Gleason 5 component may be an over read of the true pathological result. These findings are similar to those of Harding-Jackson et al.[9] Using the most contemporary standards of prostate cancer pathology and repeat review they found that Gleason grades 4 + 4 = 8 and 3 + 5 = 8 had a similar prognosis in terms of metastases and overall survival.

After adjusting for known risk factors men with Gleason pattern 5 at initial biopsy were at significantly greater risk for metastases and death from prostate cancer (HR 1.93 and 2.01, respectively, tables 2 and 3). Many previous studies evaluating the prognostic value of initial biopsy grade among men at high risk have been limited by analyzing all patients with Gleason high grade 8–10 together, by restricting analysis to the final Gleason grading of pathological specimens or by limiting the study to a single institution. Our findings are similar to those of Tsao et al, who also identified that Gleason 9–10 disease treated with definitive local therapy had worse outcomes than biopsy Gleason 8 disease.[10] Similar to the current study, they also noted a trend toward a shorter time to BCR for Gleason 8 vs 9–10 disease (HR 1.13, 95% CI 0.93–1.36) but significantly worse overall survival.

Although a portion of men at high risk will be cured by surgery alone, our data suggest that further stratification by the presence or absence of biopsy detected Gleason grade 5 carries important clinical relevance. Accurate assessment of initial biopsy data is crucial for all men diagnosed with prostate cancer.

This retrospective study has limitations. Several groups have described the lack of consistency between Gleason score in needle biopsies and in subsequent prostatectomy specimens. In a prior study from the SEARCH database Kane et al found that most patients with high risk disease were characterized as such based on Gleason grade alone.[17] However, they also noted that 34% to 55% of biopsy detected Gleason 8–10 cancers were downgraded to Gleason 7 or less at the time of surgery.

Despite possible variations in Gleason grading, our analysis focused on preoperative evaluation of biopsy data to refine how we estimate risk in these patients. Moreover, biopsy Gleason score remains prognostic even after prostatectomy, supporting the idea that biopsy Gleason grade is a vital component of risk stratification.[5]

Also, biopsy schemes and techniques varied throughout the period of analysis and with respect to the location of each hospital.

In addition, the study period spanned the PSA era. The resulting stage migration would have resulted in many higher clinical stage tumors in the early years. To account for these variations with time we adjusted for year of surgery to mitigate the effect of stage migration on our cohort.

Intra-observer and interobserver variability combined with under or over grading of prostate cancer needle biopsy specimens may have introduced some limitations to the analysis. Further, we were unable to perform a centralized pathological review.

These limitations are present in many retrospective reviews and likely reflect actual practice variation. Further validation of our findings with longer followup are required.

Despite these limitations SEARCH is a multicenter, equal access cohort with an intermediate followup and robust findings on multivariable analysis. It should be generalizable to the greater community.

CONCLUSIONS

Prostate biopsy subclassification of high risk disease (Gleason 4 + 4 vs any pattern 5) can identify men at greatest risk for metastasis and prostate cancer mortality. Any Gleason pattern 5 on biopsy portends a poor prognosis, is associated with a significantly greater risk of metastasis and prostate cancer specific mortality, and negatively impacts overall survival. These findings support the concept of a continuum of risk even in these high risk cases. Preoperative risk assessment should consider the presence of Gleason pattern 5 as a uniquely aggressive feature.

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Abbreviations and Acronyms

BCR	biochemical recurrence
PSA	prostate specific antigen
SEARCH	Shared Equal Access Regional Cancer Hospital

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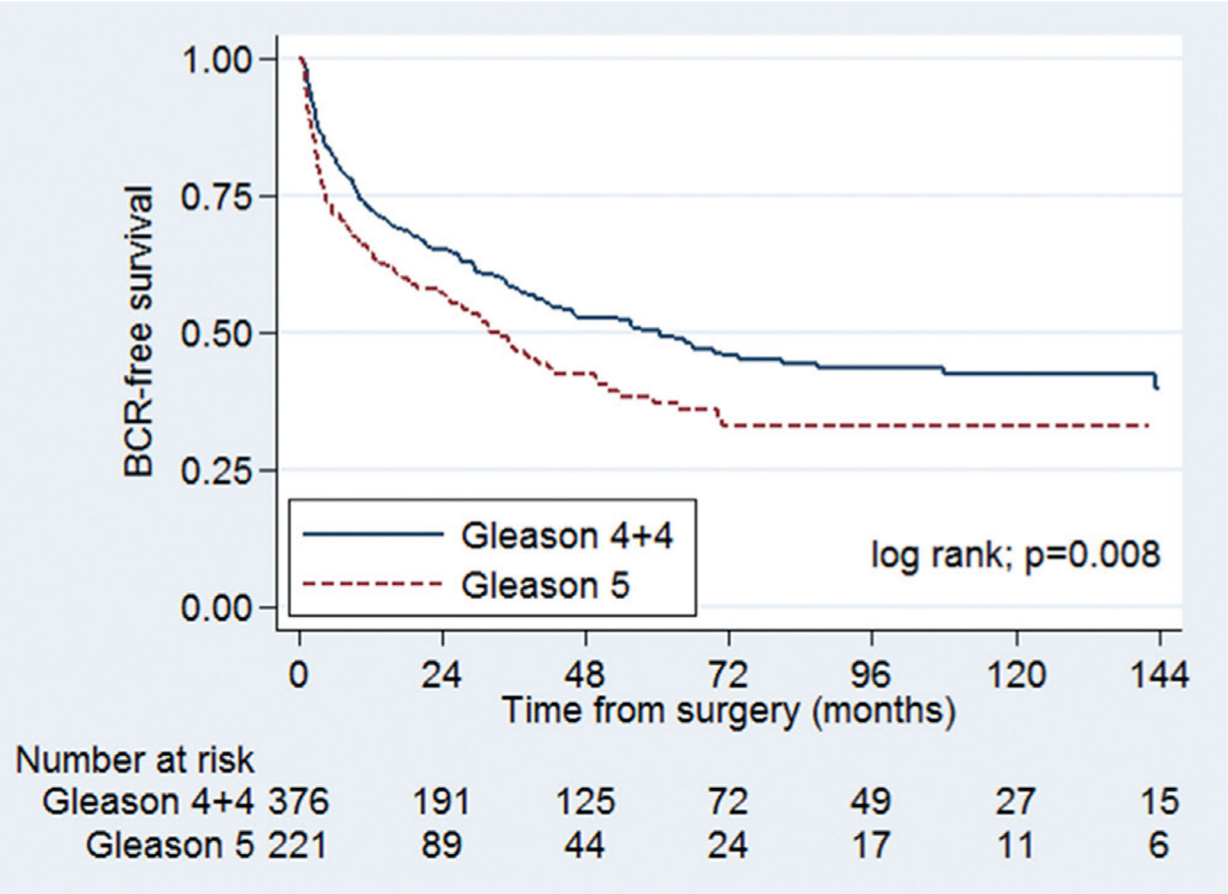

Figure 1.

Kaplan-Meier estimates of freedom from biochemical failure in patients with Gleason 4 + 4 and those with any Gleason 5 (sum 8 or greater). Biochemical recurrence was defined as PSA greater than 0.2 ng/ml, 2 values at 0.2 ng/ml or secondary treatment for elevated PSA.

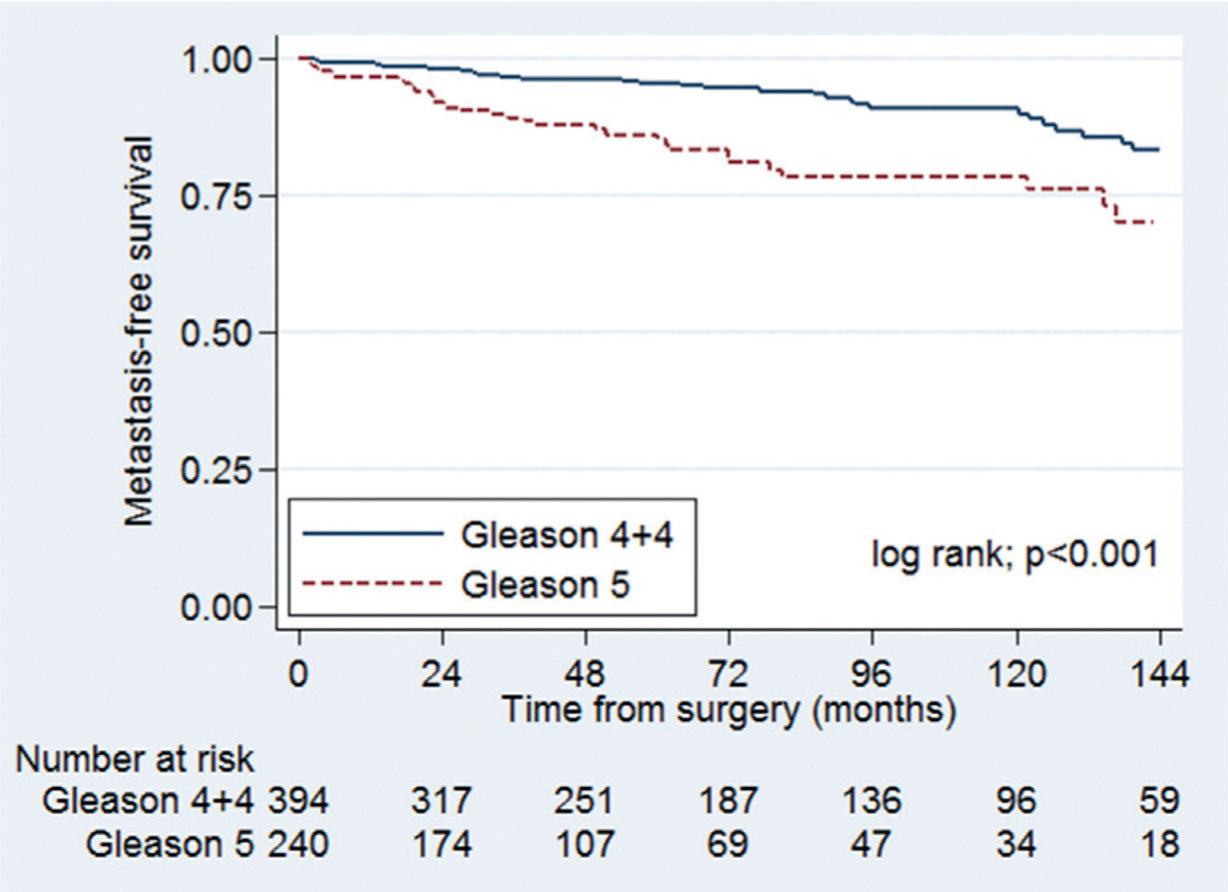

Figure 2.

Kaplan-Meier estimates of freedom from metastasis in men with biopsy Gleason 4 + 4 and those with any biopsy Gleason pattern 5 (sum 8 or greater).

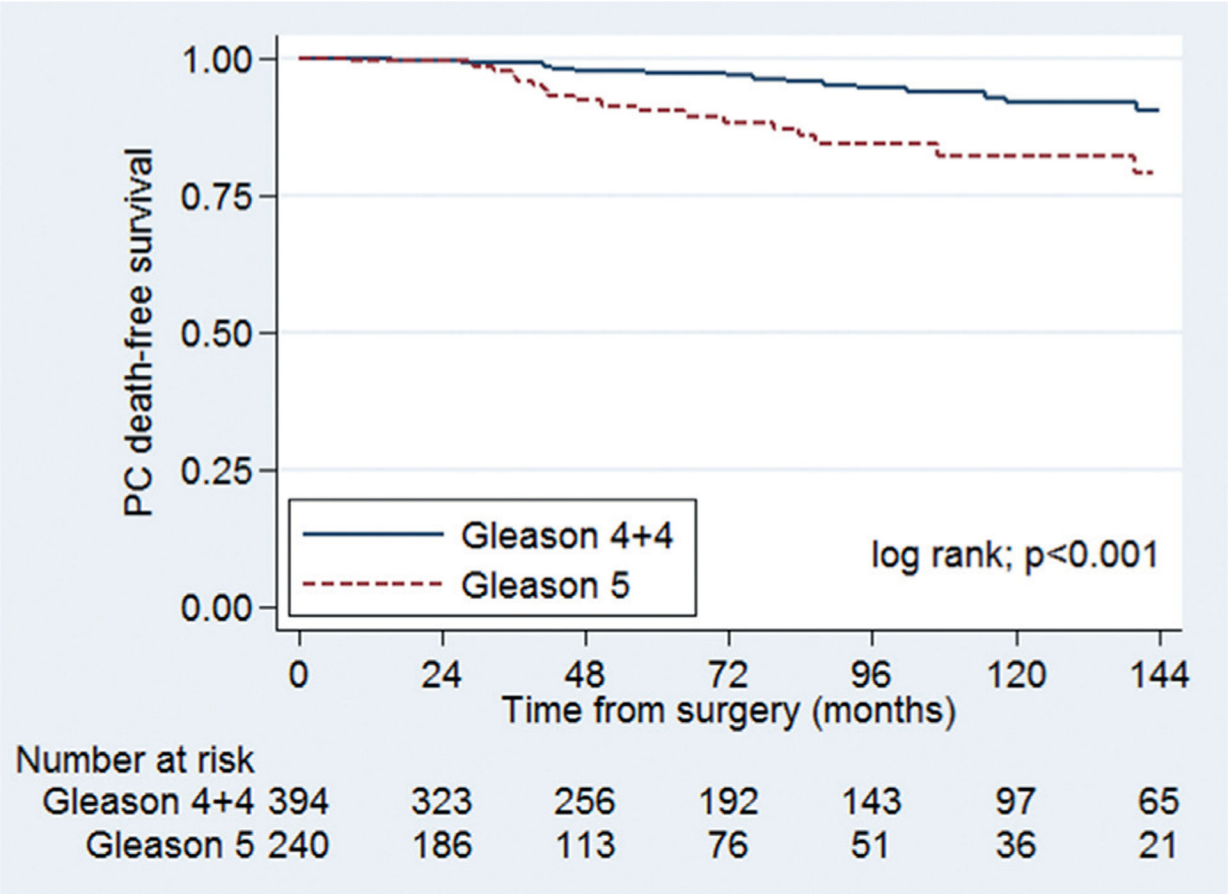

Figure 3.
Kaplan-Meier estimates of prostate cancer (PC) specific survival in men with biopsy Gleason 4 + 4 and those with any biopsy Gleason pattern 5 (sum 8 or greater).

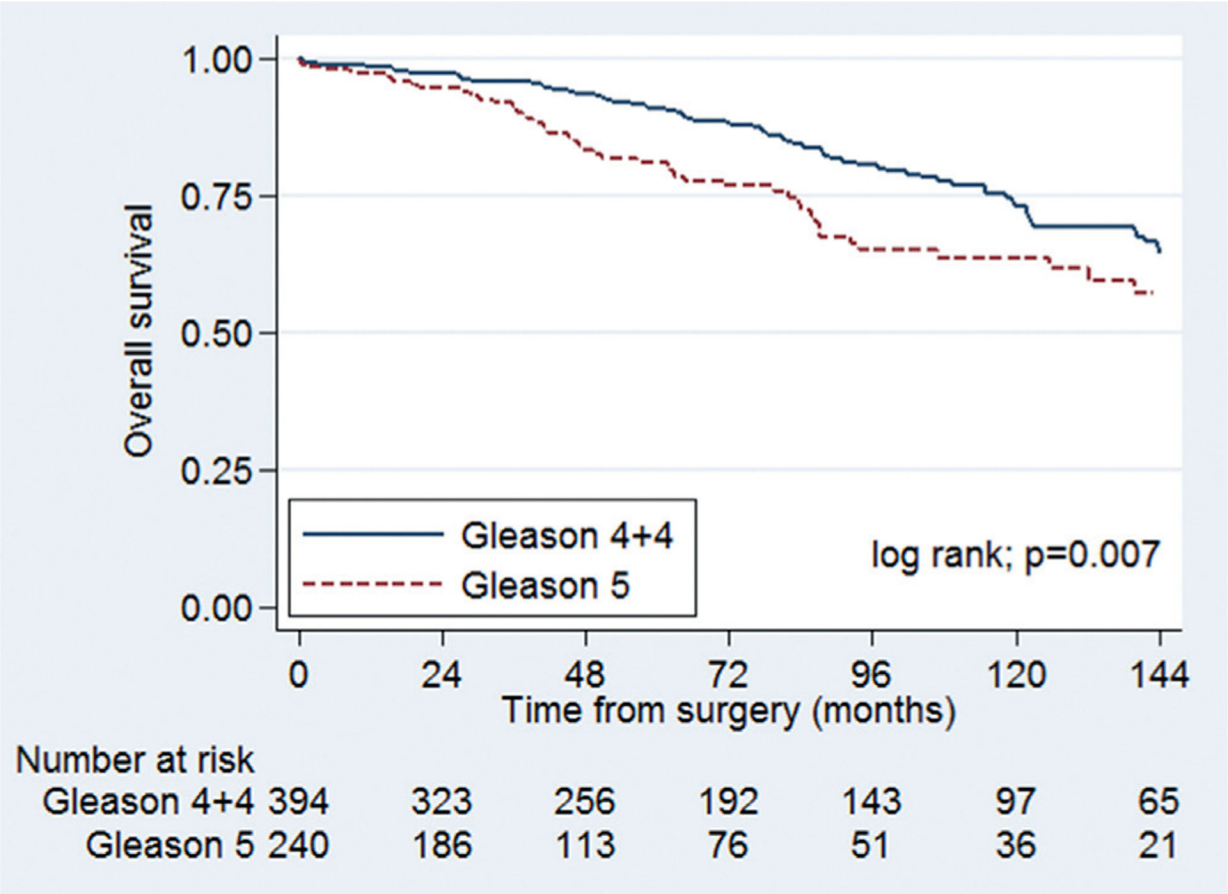

Figure 4.
Kaplan-Meier estimates of overall survival in men with biopsy Gleason 4 + 4 and those with any biopsy Gleason 5 (sum 8 or greater).

Table 1.

Baseline patient characteristics comparing any biopsy Gleason score 5 and Gleason 4 + 4

	Gleason 4 + 4		Any Gleason 5		p Value	
No. pts (%)	394	(62)	240	(38)		-
Median age (IQR)	64	(59–67)	65	(60–68)	0.056	(Wilcoxon rank sum test)
Median ng/ml PSA (IQR)	7.2	(5.0–11.5)	7.8	(5.2–13.6)	0.070	(Wilcoxon rank sum test)
Median kg/m^2 body mass index (IQR) *	28.2	(25.2–31.2)	28.3	(26.0–31.7)	0.388	(Wilcoxon rank sum test)
No. race (%):					0.098	(chi-square test)
White	235	(60)	161	(67)		
Black	142	(36)	74	(31)		
Other	17	(4)	5	(2)		
No. clinical stage (%):					0.410	(chi-square test)
T1	223	(57)	123	(51)		
T2 or greater	158	(40)	109	(46)		
Unknown	13	(3)	8	(3)		
No. biopsy Gleason score (%):						-
4 + 4	394		0			
3 + 5	0		50	(21)		
5 + 3	0		11	(4)		
4 + 5	0		133	(55)		
5 + 4	0		30	(13)		
5 + 5	0		16	(7)		
Median surgery yr (IQR)	2008	(2003–2012)	2010	(2003–2012)	0.028	(Wilcoxon rank sum test)

* Data missing on 31 patients.

Table 2.

Survival by any Gleason pattern 5 vs Gleason 4 + 4

Survival Model	Survival HR (95% CI)*	p Value
Univariable:		
Biochemical recurrence-free	1.37 (1.09–1.74)	0.008
Metastasis-free	2.63 (1.63–4.25)	<0.001
Disease specific	2.67 (1.46–4.86)	0.001
Overall	1.58 (1.13–2.21)	0.008
Adjusted multivariable:†		
Biochemical recurrence-free	1.26 (0.99–1.61)	0.065
Metastasis-free	2.55 (1.50–4.35)	0.001
Disease specific	2.67 (1.26–5.66)	0.010
Overall	1.60 (1.09–2.34)	0.016

*Referent is Gleason 4 + 4.

†Adjusted for age, race, preoperative PSA, medical center, surgery year and clinical stage.

Table 3

	No. Pts
Biochemical recurrence-free survival	618
Biochemical recurrence	293
Metastasis-free survival	632
Metastasis	68
Disease specific survival	633
Prostate Ca death	42
Overall survival	633
All cause death	147