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**New prostate cancer grade grouping system predicts survival after radical prostatectomy**

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Running head: Grade grouping in prostate cancer survival prediction

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**Abstract**

Histological Gleason grading of prostate cancer has been through modifications and conjoined into a Grade Grouping system recently. The aim of this study was to determine whether the new Grade Grouping system predicts disease-specific and all-cause mortality after radical prostatectomy. We constructed a clinical database consisting of all consecutively radical prostatectomy treated men between 1983 and 1998 and between 2000 and 2005 at the Helsinki University Hospital and at the Turku University Hospital, respectively. Patients' all-cause and prostate cancer-specific mortality information were updated in November 2015 from the Finnish Cancer Registry. Secondary therapy information was also available from the patients' records at Helsinki. Univariate and multivariate statistical analyses were performed to assess predictive significance of the Grade Grouping system. Grade Grouping associated independently with increased risk of prostate cancer-specific mortality within 15 years of follow-up in a multivariable model containing age at operation, diagnostic prostate-specific antigen, pathological stage and lymph node status at operation. Additionally, the all-cause mortality free survival time and time to secondary therapies were different between the Grade Groups, emphasized in the sub-analysis of Grade Group 1-2 versus Grade Group 3-5. We can conclude that the new Grade Grouping system is feasible in predicting prostate cancer specific survival after radical surgical treatment. Grade Grouping offers a simpler way to interpret the predicted course of the disease to individual patients and thus may help in justifying more conservative follow-up approaches, especially in the lower Grade Group patients.

Key words: Grade Group, Gleason grade, prostate cancer, survival

## 1. Introduction

Gleason grading holds the position as the strongest predictor of survival after initial treatment of prostate cancer. Since the introduction of the Gleason grade patterns and score in 1966, the modifications done to the overall Gleason score (GS) over the years have led to clustering of new prostate cancer diagnoses mainly into GS 6 and 7 [1–3]. The current consensus is that no GS 2-4 should be assigned in biopsies and even GS 5 is very rare [4]. There is strong evidence that GS 3+4 = 7 and 4+3 = 7 differ in terms of survival [5,6]. As a whole, the aforementioned 'grade inflation' and sources of confusion for the patients have led to a consensus work-up for a new Grade Group (GG) system recently introduced in the World Health Organization classification for prostate cancer [4,7–9]. Histologically, the variable adaptation of the modifications to Gleason grading after the International Society of Urological Pathology (ISUP) 2005 consensus meeting have now been incorporated into a consensus statement with uniform acceptance and grading is performed with more unified criteria (Fig. 1). The new grading system allows for easier counseling of patients and has potentially increased predictive value over GS. GGs are formed from the contemporary GS criteria (Table 1). Tertiary patterns, now suggested to be referred to as minor high-grade patterns (MHGP), have also been considered in the context of GG's as recent studies have shown that MHGP can potentially add prognostic value to GG. MHGP, however, are not currently considered as an integral part of the GG and are only assessed in radical prostatectomy (RP) specimens [10]. The validation studies for GG have thus far have shown the relation of GG to biochemical recurrence-free survival (BRFS) and prostate cancer specific mortality (PCSM) in RP cohorts, using biopsy and/or RP grades [11–13]. Registry based re-analyses have shown the strength of GG in predicting PCSM and metastasis-free survival [14]. Also recently, a radiation treated cohort was analyzed for biopsy GG as

predictor of BRFs and PCSM [15]. However, none of the studies have shown that the new GG system has increased predictive with respect to GS, and most of the studies are hampered by short follow-up times and BRFs as the end-point for the analysis.

The weakness for BRFs as end-point is its surrogate nature [16–18]. Altogether 30-40% of RP treated patients experience BRFs during post-operative follow-up [19–21]. However, assumedly by the survival-prolonging effect of secondary treatments, only approximately 10% of the patients experience disease-specific mortality in 10 to 15 years after RP [22,23]. Cohorts with an adequate number of patients and sufficient follow-up time for PCSM are rarely available. In addition, pre-magnetic resonance imaging (MRI)-era transrectal ultrasound-guided (TRUS) biopsies are prone to significant sampling error, thus higher grade prostate cancer foci are missed in up to 30% of GS 3+3 biopsies [24,25]. Validation of the GG system in predicting the all-cause mortality (ACM) and PCSM compared to conventional Gleason grade pattern scores is essential in order to facilitate its use in patient communication. Here, we have validated the predictive significance of the new GG system after RP in a large patient set with substantially long follow-up time. In addition to the most important outcome, i.e. survival, secondary treatment information was incorporated into the analysis.

## **2. Materials and methods**

### **2.1. Patient cohort**

The study cohort consisted of patients with comprehensive clinical data and accompanying RP specimens operated on between 1983 and 1998 at Helsinki University Hospital and between 2000 and 2005 at Turku University Hospital. Limited pelvic lymph node dissection accompanied most of the

RPs in both cohorts. The clinical databases were combined and updated in November 2015 with the Finnish Cancer Registry's data on patients' all-cause and disease-specific mortality, resulting in a median follow-up time of 15.7 years for the Helsinki cohort (range 0.7-28.6) and 9.5 years (range 0.2-14.0) for the Turku cohort. The median post-RP follow-up time for the entire cohort for PCSM and ACM was 11.9 years and the median age at RP was 62.4 years. For more detailed demographics of the separate Helsinki and Turku cohorts and the whole cohort, see Table 2.

The Helsinki and Turku cohorts originally included 478 and 532 patients respectively. For both cohorts, the original clinical RP specimen slides were re-evaluated between years 2005 and 2010 by experienced uropathologists according to the GS criteria of ISUP 2005 consensus meeting and taking into account the commonly applied recommendations thereafter, to form the classes currently recognized as GGs (the criteria that were approved in the consensus of 2014) (Table 1) [1,2,26]. To avoid possible interference of accompanied treatments on [1] tissue interpretation, patients who had received neoadjuvant therapies prior to RP were excluded, leading to 401 and 503 patients in the Helsinki and Turku cohorts, respectively. Complete follow-up data were available for a total of 374 and 457 patients, who were included in the final analysis. Post-operative follow-up was conducted by clinical examinations and prostate-specific antigen (PSA) measurements at least three times during the first year after surgery and at least once a year during the following years. For the Helsinki cohort, also the complete information of the commencement dates for secondary therapies was available (Supplementary Table 1).

The ethical committees of the corresponding hospital districts approved the use of clinicopathological data (Hospital District of Helsinki and Uusimaa, 445/E6/02, and Hospital District of Southwest

Finland). Approval for the use of clinical and registry data was obtained from the National Authority for Welfare and Health (Valvira 394/05.01.00.06/2009) and the use of the Finnish Cancer Registry's data was approved by the National Institute for Health and Welfare (THL/1549/5.05.00/2013).

Patients' personal information was de-identified prior to analyses.

## 2.2 Statistical analysis

The primary outcomes in this study were PCSM and ACM within the first 15 years of follow-up. If outcome events occurred after 15 years, the patient's follow-up was encoded as 15 years, and censored. The secondary outcome, analyzed only in the Helsinki cohort, was initiation of secondary therapy. Kaplan-Meier survival analysis with Mantel-Haenzel log-rank test for time to PCSM, time to ACM or time to secondary therapies were performed. Additionally, univariable and multivariable Cox regression analyses were performed to assess risk for outcome events, and included age at operation, PSA at diagnosis, GG, pathological T-stage (pT), and lymph node status in the models. Competing risk analysis was performed comparing the risk of mortality by any causes and by prostate cancer, as stratified by GG. Receiver operating characteristic (ROC) area under the curve (AUC) analyses were performed for the new 5-tiered GG and 3-tiered GS (<7, 7, >7) to compare the predictive accuracy of the two grading systems. Decision curve analyses comparing net benefit of Grade Grouping versus Gleason scoring in the decision making was also performed. All statistical analyses were performed using R Statistical Software v.3.3.3 (Foundation for Statistical Computing, Vienna, Austria) using the packages *survival*, *survminer*, *pROC*, *cmprsk*, and *rms*.

### 3. Results

#### 3.1 Univariable survival analysis

Amongst the study population, half of the patients were originally graded as GS7 and almost one third as GS $\leq$ 6. After stratifying patients into GGs, GG2 and GG3 formed almost equally sized groups (Table 2). In Kaplan-Meier survival analyses for ACM and PCSM outcomes, remarkably, GG2 stratified patients similarly to GG1, while the survival profile of patients with GG3 was similar to those patients with GG4 or GG5 ( $P < .0001$ , Fig. 2A&B). Each unit increase in GG was significantly associated with shorter median secondary therapy treatment-free survival ( $P < .0001$ , Supplementary Fig. 1).

In univariable cox proportional hazard analysis for probability of death after surgical treatment, the hazard ratio for PCSM ranged from 8.015 ( $P = .052$ , 95% CI = 0.986-65.14) to 55.799 ( $P < .001$ , 95% CI 6.717-463.52) when GG2 to GG5 were compared to reference of GG1. Similarly, increased GG was associated with increased risk of ACM and initiation of secondary therapy (Table 3).

#### 3.2 Multivariable survival analysis

In testing cox-proportional hazards assumption for a multivariable model with PCSM as the outcome, the lymph node status at RP was found to violate the assumption, and was assessed in a time dependent manner of less than or equal to 6 years follow-up, or greater than 6 years follow-up.

Additionally, due to the low number of PCSM events in GG1 ( $n=1$ ), our multivariable model did not converge, and thus we conducted pooled analysis of GG1 and 2 together as the reference group.

In the multivariable cox regression analysis, pT stage and lymph node positivity predicted significant differences in PCSM. Interestingly, the increased risk of outcome events due to lymph node positivity



was observed to be time-dependent, with it no longer being associated with PCSM after the first 6 years of follow-up (Table 3A).

### 3.3. Competing risk analysis of cause of mortality

Gray's competing risk analysis was conducted to analyze the predicted risk of patients with GG 1 and 2, vs GG 3-5 PC progressing to PCSM in comparison to patients who experienced ACM or survival.

There was a significant difference of cumulative incidence by GG in patients who experienced PCSM ( $P < .0001$ ) and ACM ( $P = .046$ ) (Fig. 2C).

### 3.4. Benefits of Grade Grouping in outcome prediction

In order to study the additive effect of GG in survival prediction, ROC-AUC analyses were performed to address the discriminatory power of three-tier GS (<7, 7, >7) and the five-tier GG with outcomes. The receiver-operating curve discriminatory analysis showed increased area under the curve (AUC) values for GG in all of the study outcomes when compared with the three-tier GS (Supplementary Fig. 2A-C).

Lastly, decision curve analyses were performed to compare the net benefit of GG and GS in predicting outcome. Decision curve analysis plots the net benefit of predictors against all probabilities of an event occurring. This allows for comparison of different predictors in assessing the harm-to-benefit ratio for clinical decision of an intervention. For all measured outcomes (PCSM, ACM and secondary therapy free survival), across all threshold probabilities of outcome events occurring, GG performed better than, or as well as, GS (Supplementary Fig. 3).

#### 4. Discussion

A new predictive prostate cancer grading system has recently been proposed by authors at Johns Hopkins Hospital led by the pathologist Jonathan Epstein using a fairly simple division of Gleason grade pattern sums into GG (Table 1) [4]. The predictive value has been validated in studies of prostate cancer patients treated with different modalities as well as in separate cohorts of RP and radiation treated patients [12,14,27]. Despite studies assessing the predictive value of GG to predict hard outcomes such as PCSM [13], few studies have comprehensively conducted rigorous discriminatory analysis of GS and GG in the same patient cohort.

Previous studies have compared GG and GS in prediction of BRFs [15,27,28] and have found GG to be a better predictor of outcome than GS. The strengths of these studies include large sample sizes, multi-center analyses, and diverse study populations. The studies, however, suffer from short median follow-up times, and the use of BRFs, which is considered as a surrogate endpoint. Additionally, as commented by Dell'Oglio et al., these studies did not address the most crucial unmet clinical need; assessing the possible superiority of GG over GS with regard to harder outcomes, namely PCSM [29].

In order to address these problems, two other recently published studies, have analyzed harder endpoints [30,31]. In the study by Dell'Oglio et al., no additive benefit for GG over GS could be shown. The authors assessed performance with respect to clinical recurrence (CR), defined as detection of metastasis after BRFs, as an endpoint and a median follow-up of 5.8 years [30]. The authors speculated that a lack of plateau in their Kaplan-Meier curves might suggest increased differences between GGs with longer follow-up. The study by Grogan et al., compared the predictive power of GG and GS for BRFs, CR, and PCSM in a single-center cohort. The study cohort featured a rigorous re-evaluation of GS to the ISUP 2005 standard, and a long median follow-up time of 15 years. While their

study found GG to be superior to GS in predicting BRFS, CR and PCSM, the authors did not report whether GG remained an independent predictor of PCSM in multivariable analysis for PCSM, despite reporting such data for other study outcomes [31].

To our knowledge, our study is the first multicenter study, with long term follow-up, to demonstrate increased predictive value of GG over GS in predicting PCSM and ACM. Our study, with a median of 11.1 years follow-up, affirms the power of GG to predict long-term survival in a RP treated cohort. Our patients had not received neoadjuvant treatments, but had been treated with adjuvant or secondary therapies at any given era according to treating urologist's discretion. Given the fact that GG remarkably associated with probability of receiving secondary therapies and stratified each group to separate survival curves, only patients in GGs 3 to 5 progressed to prostate cancer-specific death to significant numbers. It is also obvious that the greater adjuvant therapy with each successive GG likely lessened the separation of the curves in the cancer-specific mortality Kaplan Meier curves (Fig. 2A) since adjuvant therapy is associated with delaying the time to death.

One of the strengths of our study compared to other contemporary cohorts is the long median follow-up time needed to study survival endpoints [14]. Only by long follow-up the significant variables independently associated with PCSM can be assessed, those being age, diagnostic, pT stage, lymph node status and GG in our multivariable analysis. Regardless of the local extent of the disease, GG predicted PCSM after RP. Especially the clear depression in survival probability seen between GG2 and GG3 emphasizes the importance of volume of Gleason grade pattern 4 predominance in long-term for contributing to disease progression and mortality, despite secondary therapies. All of our patients have been diagnosed before 2005 and thus the treatment decisions were based on the

Gleason criteria at that time. Importantly, as we aimed for long follow-up to allow survival endpoints to be studied, we chose a historical cohort but re-evaluation of the slides was conducted according to 2005 ISUP consensus meeting, supplemented by the modifications later approved in 2014. Our study with re-evaluated RP specimens further states the use of GG in differentiation of Gleason score 7 tumors into groups with significantly different prognosis.

In addition to being a retrospective analysis, other weaknesses of our study include lack of thorough PSA-data for BRFs-analysis and the lack of information on the tertiary Gleason pattern in RP specimens. A recent study has evaluated how the existence of tertiary higher-grade pattern along with the new GG affects the prognosis after RP [32]. Also, as the biopsies are now more often taken under MRI-TRUS fusion guidance, the issues of undersampling can be better avoided [24]. Based on our results on RP treated cohorts, we can postulate that GG2 patients react to adjuvant treatments better and can possibly be treated more conservatively post-operatively, or followed-up less frequently as GG  $\geq 3$  patients. Addition of tissue biomarkers, such as PTEN, to the analysis might further help stratify patients into proper follow-up or adjuvant therapies [33,34].

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**Figure Legends**

Fig. 1. Histological examples of the growth patterns that had been adopted to variable extent after the ISUP 2005 consensus meeting but unanimously incorporated into distinct Gleason grades and Grade Groups in 2014 ISUP consensus meeting. A. Separate glands should be assigned a Gleason grade pattern 3, regardless of the size or, for example mucinous excretion (arrowheads). Fusing glands of Gleason grade pattern 4 shown on the right, partially perineurally (arrows). B. Cribriform and glomeruloid glands are assigned as Gleason grade pattern 4 (open arrows), regardless of the size (Gleason grade pattern 3 glands shown in comparison, arrowheads). Intraductal carcinoma (asterisk) should not be given a Gleason grade.

Fig. 2. Survival analysis of new Grade Group system and outcomes. Kaplan-Meier analyses for probability of survival during follow-up for prostate cancer specific mortality (PCSM)-free survival (A), any cause mortality (ACM)-free survival (B). To evaluate the new Grade Grouping system with regards to significance in predicting competing outcomes, Gray's competing risk analysis (C) was performed of low (1-2) vs high (3-5) and cumulative incidence of any cause mortality within 15 years of follow-up (ACM15) and prostate cancer-specific mortality within 15 years of follow-up (PCSM15).



## Highlights

- New Grade Grouping associates with mortality and secondary treatment after radical prostatectomy
- Grade Grouping outperforms Gleason scoring in predictive significance
- Individual post-operative follow-up should be conducted according to the Grade Group

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**Table 1. Gleason Score vs Grade Group**

<b>Gleason Score</b>	<b>Grade Group</b>
≤6	1
3+4	2
4+3	3
4+4	4
5+3	
3+5	
4+5	5
5+4	
5+5	

**Table 2.** Characteristics of the 2 study cohorts and combined study population

Characteristics	Helsinki cohort (1982-1998)	Turku cohort (2000-2005)	Total
Age at RP, years (n = 831) (median, range)	64 (45-76)	62 (40-73)	63 (40 - 76)
Diagnostic PSA, ng/ml (n = 715) (n, %)			
≤10.0	145 (50.0)	294 (69.2)	439 (61.4)
10.1-20.0	92 (31.7)	96 (22.6)	188 (26.3)
>20.0	53 (18.3)	35 (8.2)	88 (12.3)
Gleason score at RP (n = 831) (n, %)			
≤6	97 (25.9)	168 (36.8)	265 (31.9)
7	217 (58.0)	197 (43.1)	414 (49.8)
8-10	60 (16.0)	92 (20.1)	152 (18.3)
Grade Group at RP (n = 831) (n, %)			
1	97 (25.9)	168 (36.8)	265 (31.9)
2	95 (25.4)	134 (29.3)	229 (27.6)
3	122 (32.6)	63 (13.8)	185 (22.3)
4	47 (12.6)	70 (15.3)	117 (14.1)
5	13 (3.5)	22 (4.8)	35 (4.2)
pT (n = 784) (n, %)			
2	208 (60.5)	233 (53.0)	441 (56.2)
3	136 (39.5)	207 (47.0)	343 (43.8)
Lymph node status (n = 822) (n, %)			
N0	358 (97.3)	434 (95.6)	792 (96.4)
N1	10 (2.7)	20 (4.4)	30 (3.6)
Follow-up time after RP, years (n = 831) (median, range)	15.7 (0.1-28.6)	9.5 (0.2-14.0)	11.1 (0.1-28.6)
Death from any cause (n = 831) (n, %)	183 (48.9)	73 (16.0)	256 (30.8)
Death from prostate cancer (n = 831) (n, %)	36 (9.6)	19 (4.2)	55 (6.6)
Patients receiving secondary therapy (n = 812) (n, %)	128 (34.2)	136 (31.1)	264 (31.8)

**Abbreviations:** RP=radical prostatectomy, PSA=prostate-specific antigen, pT=pathological stage

**Table 3.** Uni- and multivariate Cox regression analysis of clinicopathological variables and outcome

	Univariate Cox Regression			Multivariate Cox Regression		
	HR	95% CI	P-value	HR	95% CI	P-value
<b>A. Uni- and multivariate Cox regression analysis of clinicopathological variables and prostate cancer specific mortality within 15 years of follow-up</b>						
Age at RP ≤ 60 Years	-	-	Ref	Age at RP ≤ 60 Years	-	Ref
		(0.599 -			(0.799 -	
Age at RP 60.1 - 70 Years	1.137	2.156)	0.695	Age at RP 60.1 - 70 Years	1.908	4.553)
		(0.603 -			(0.075 -	0.146
Age at RP > 70 Years	1.660	4.568)	0.327	Age at RP > 70 Years	0.616	5.054)
PSA at Diagnosis 0 - 10.0	-	-	Ref	PSA at Diagnosis 0 - 10.0	-	-
PSA at Diagnosis 10.1-20.0	1.902	(0.806 -	0.142	PSA at Diagnosis 10.1-20.0	1.514	(0.623 -
		4.486)	0.027			3.678)
PSA at Diagnosis > 20	2.913	7.528)	*	PSA at Diagnosis > 20	1.145	3.188)
Grade Group 1	-	-	Ref	Grade Group 1&2	-	-
		(0.986 -				(0.861 -
Grade Group 2	8.015	65.14)	0.052	Grade Group 3	2.699	8.464)
	27.31	(3.656 -	0.001			(2.215 -
Grade Group 3	5	204.06)	*	Grade Group 4	6.692	20.218)
	37.13	(4.905 -	<0.00			(2.037 -
Grade Group 4	6	281.16)	1*	Grade Group 5	7.797	29.843)
	55.79	(6.717 -	<0.00			
Grade Group 5	9	463.52)	1*	pT Stage 2	-	-
pT Stage 2	-	-	Ref	pT Stage 3&4	6.224	21.247)
	16.54		<0.00	LN Negative in first 6	-	-
pT Stage 3&4	4	(5.088 - 53.8)	1*	years	-	-
LN Negative	-	-	Ref	LN Positive in first 6	17.48	(4.883 -
LN Positive in first 6	16.06	(6.018 -	<0.00	years	1	62.582)
years	8	42.90)	1*	LN Positive after first 6	1.917	(0.24 -
LN Positive after first 6	4.624	(1.399 -	0.012	years	15.289)	0.539
years		15.28)	*			
<b>B. Uni- and multivariate Cox regression analysis of clinicopathological variables and any cause mortality within 15 years of follow-up</b>						
Age at RP ≤ 60 Years	-	-	Ref	Age at RP ≤ 60 Years	-	-
		(0.882 -				-
Age at RP 60.1 - 70 Years	1.217	1.681)	0.232	Age at RP 60.1 - 70 Years	1.281	(0.887 - 1.85)
		(1.918 -	<0.00			(1.664 -
Age at RP > 70 Years	2.933	4.486)	1*	Age at RP > 70 Years	2.807	4.737)
PSA at Diagnosis 0 - 10.0	-	-	Ref	PSA at Diagnosis 0 - 10.0	-	-
PSA at Diagnosis 10.1-20.0	0.967	(0.667 -	0.858	PSA at Diagnosis 10.1-20.0	0.879	(0.599 - 1.29)
		1.402)				(0.553 -
PSA at Diagnosis > 20	1.515	2.302)	0.052	PSA at Diagnosis > 20	0.886	1.421)
Grade Group 1	-	-	Ref	Grade Group 1	-	-
		(0.772 -				(0.569 -
Grade Group 2	1.181	1.807)	0.444	Grade Group 2	0.928	1.513)
Grade Group 3	2.025	(1.368 -	<0.00	Grade Group 3	1.291	(0.784 -
						0.315

		2.997)	1*			2.126)	
Grade Group 4	2.749	(1.805 - 4.188)	<0.001*	Grade Group 4	1.784	(1.044 - 3.047)	0.034*
Grade Group 5	2.861	(1.536 - 5.331)	<0.001*	Grade Group 5	1.823	(0.864 - 3.845)	0.115
pT Stage 2	-	-	Ref	pT Stage 2	-	-	Ref
pT Stage 3&4	1.940	(1.447 - 2.601)	<0.001*	pT Stage 3&4	1.520	(1.056 - 2.188)	0.024*
LN Negative	-	-	Ref	LN Negative	-	-	Ref
LN Positive	3.649	(2.247 - 5.925)	<0.001*	LN Positive	3.492	(1.899 - 6.419)	<0.001*
<b>C. Uni- and multivariate Cox regression analysis of clinicopathological variables and initiation of secondary therapy</b>							
Age at RP ≤ 60 Years	-	-	Ref	Age at RP ≤ 60 Years	-	-	Ref
Age at RP 60.1 – 70 Years	0.832	(0.481 – 1.439)	0.510	Age at RP 60.1 – 70 Years	1.226	(0.786 – 1.911)	0.369
Age at RP > 70 Years	0.876	(0.376 – 2.043)	0.760	Age at RP > 70 Years	1.556	(0.830 – 2.917)	0.168
PSA at Diagnosis 0 – 10.0	-	-	Ref	PSA at Diagnosis 0 – 10.0	-	-	Ref
PSA at Diagnosis 10.1-20.0	2.152	(1.162 – 3.983)	0.015*	PSA at Diagnosis 10.1-20.0	1.896	(1.041 - 3.454)	0.037*
PSA at Diagnosis > 20	4.047	(2.235 - 7.327)	<0.001*	PSA at Diagnosis > 20	6.942	(3.957 – 12.177)	<0.001*
Grade Group 1	-	-	Ref	Grade Group 1	-	-	Ref
Grade Group 2	1.676	(0.626 – 4.487)	0.304	Grade Group 2	3.376	(1.442 – 7.903)	0.005
Grade Group 3	2.920	(1.139 – 7.487)	0.026*	Grade Group 3	7.566	(3.421 - 16.735)	<0.001*
Grade Group 4	6.799	(2.455 - 18.828)	<0.001*	Grade Group 4	6	(5.396 - 29.172)	<0.001*
Grade Group 5	26.20	(7.785 - 88.23)	<0.001*	Grade Group 5	25.59	(9.478 - 69.097)	<0.001*
pT Stage 2	-	-	Ref	pT Stage 2	-	-	Ref
pT Stage 3&4	2.959	(1.747 - 5.012)	<0.001*	pT Stage 3&4	4.586	(3.039 - 6.919)	<0.001*
LN Negative	-	-	Ref	LN Negative	-	-	Ref
LN Positive	1.406	(0.404 - 4.895)	0.593	LN Positive	4.87	(2.128 - 11.14)	<0.001*

**Abbreviations:** RP=radical prostatectomy, PSA=prostate-specific antigen, pT=pathological stage, LN=lymph node.

\* Statistically significant *p*-value, 2-tailed

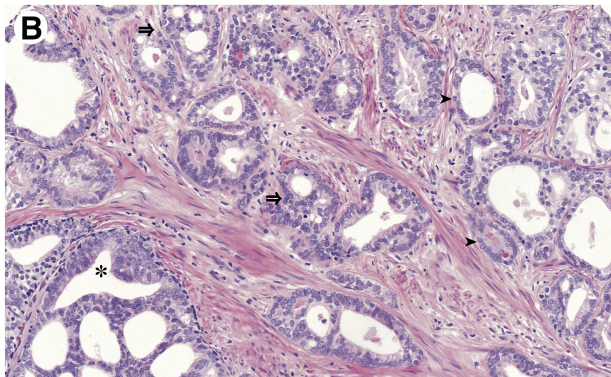
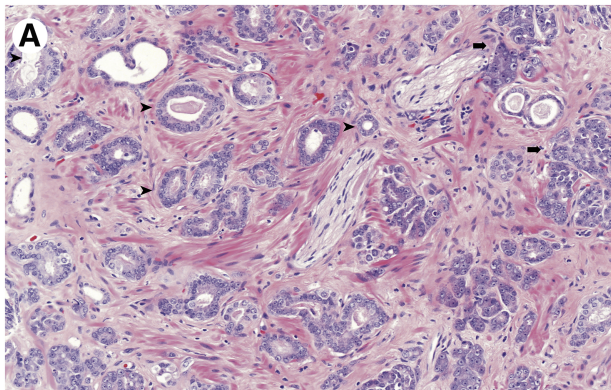


Figure 1

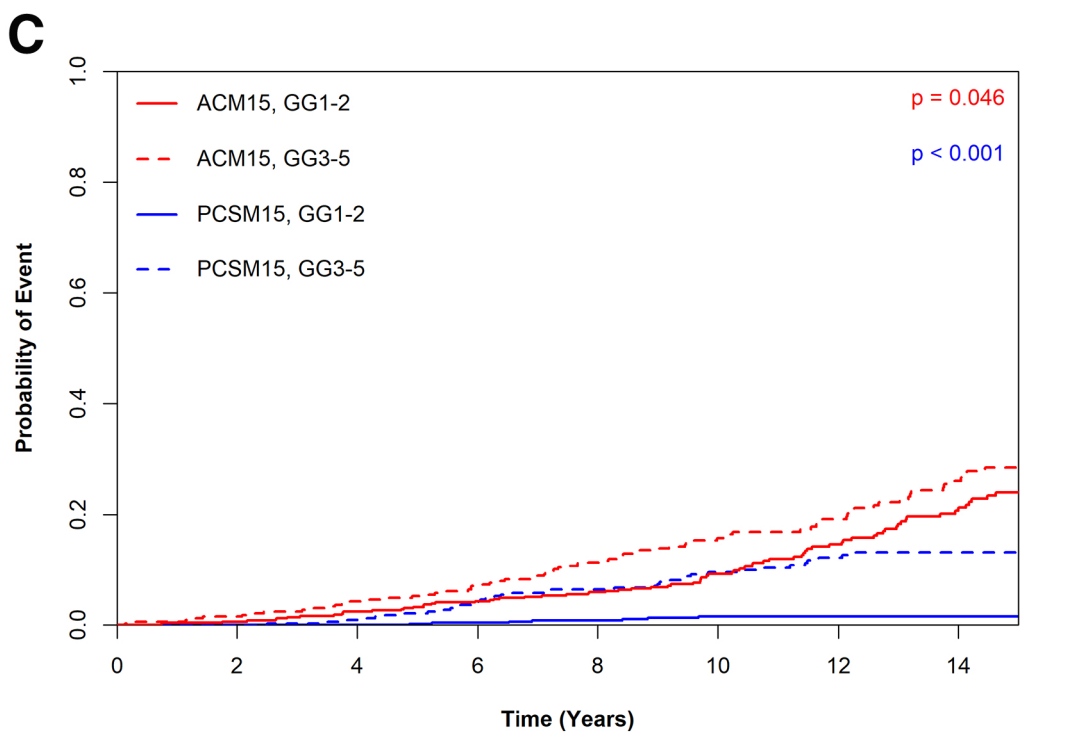
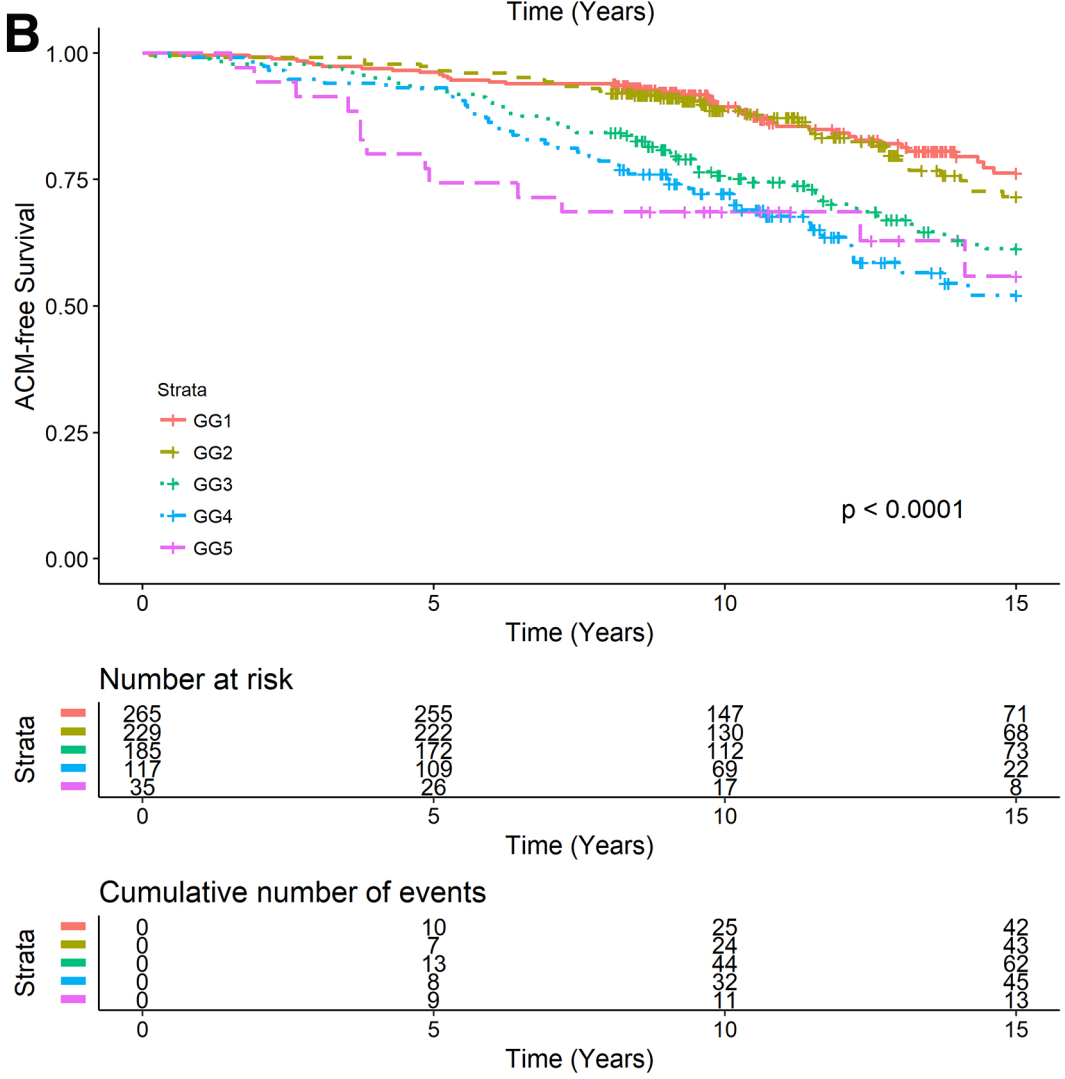
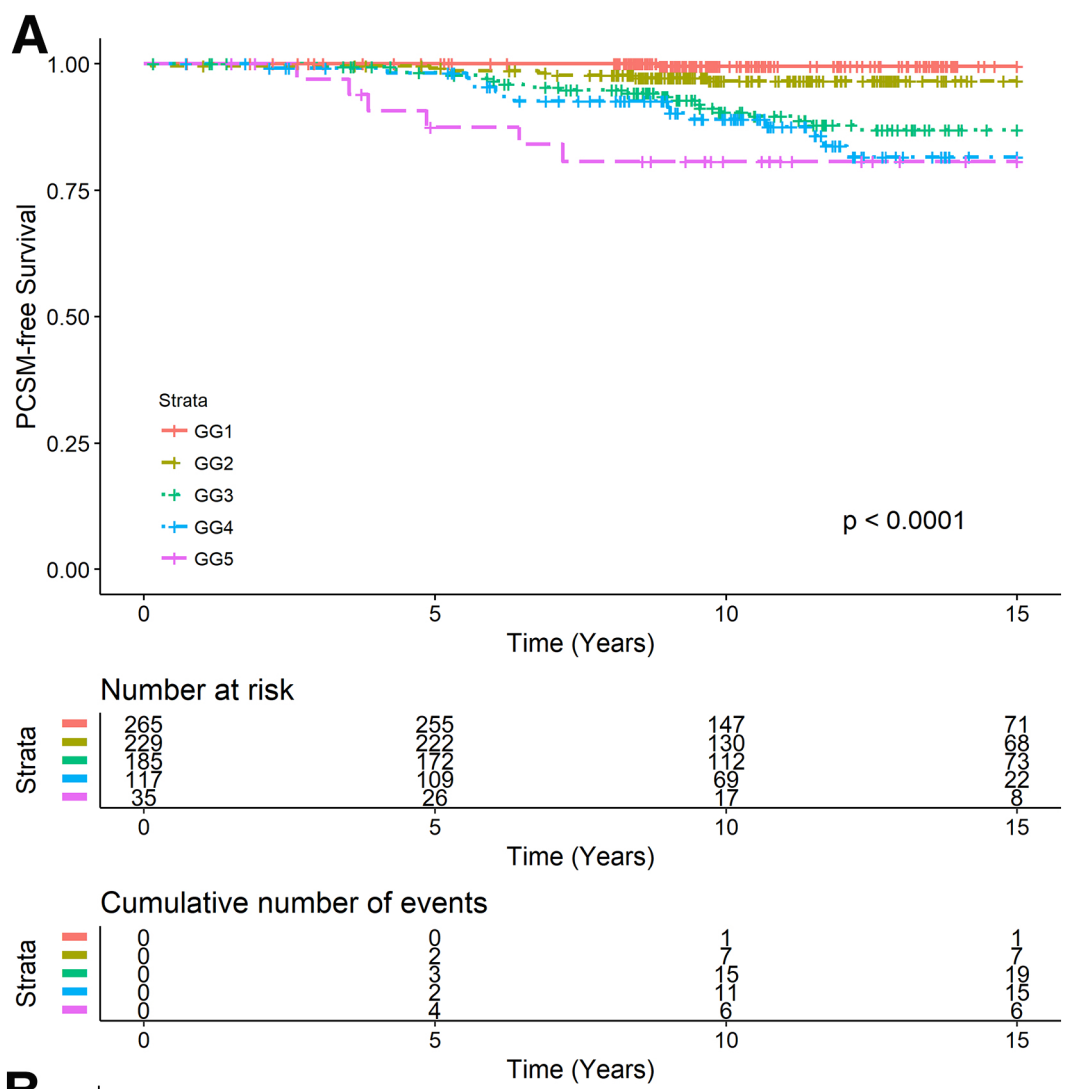
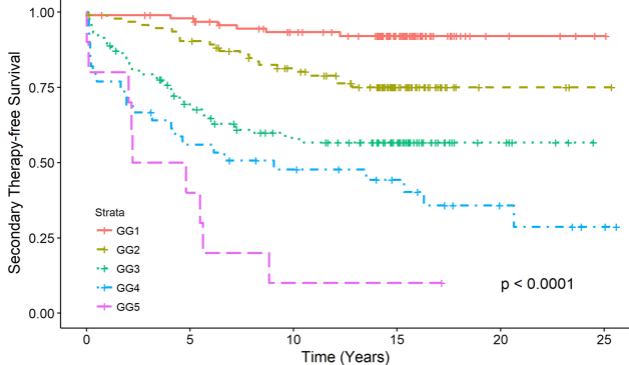


Figure 2



Number at risk

Strata	0	5	10	15	20	25
GG1	96	91	77	45	5	1
GG2	94	84	68	29	3	1
GG3	117	74	54	32	6	0
GG4	39	21	16	11	5	2
GG5	10	4	9	0	0	0

Time (Years)

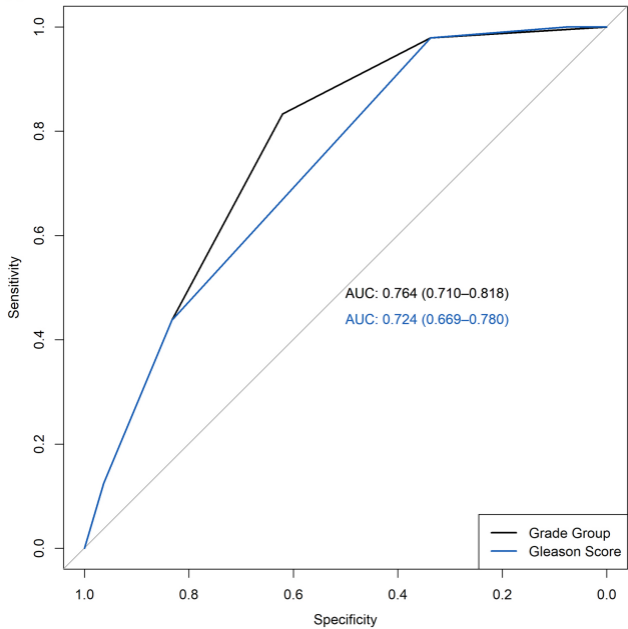
Cumulative number of events

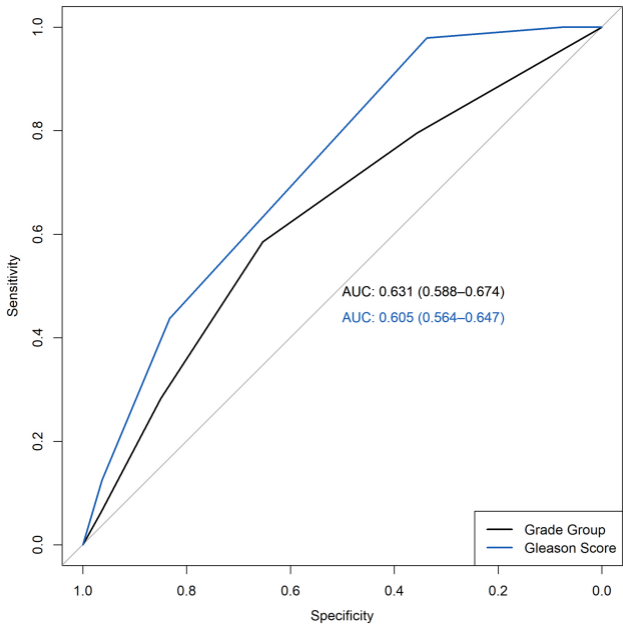
Strata	0	5	10	15	20	25
GG1	0	2	6	7	7	7
GG2	0	9	17	22	22	22
GG3	0	36	47	48	48	48
GG4	0	17	20	21	23	24
GG5	0	6	9	9	9	9

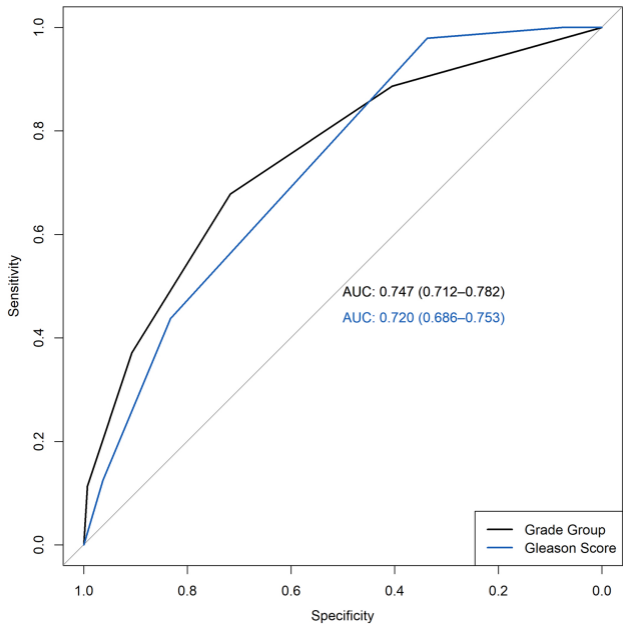
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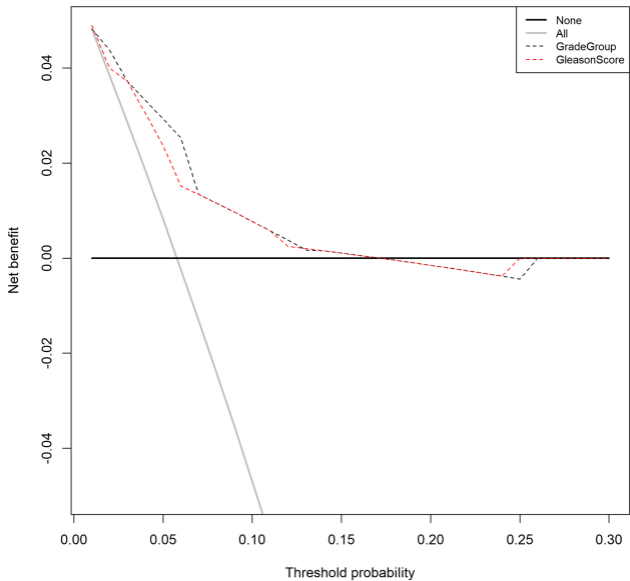
Figure 3

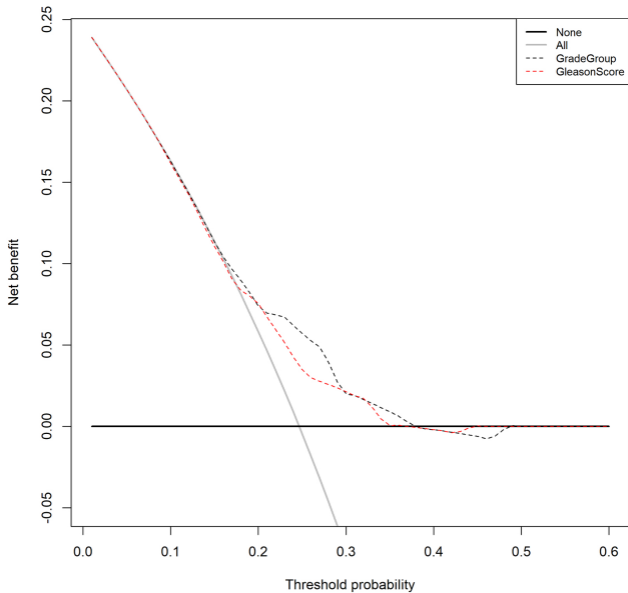


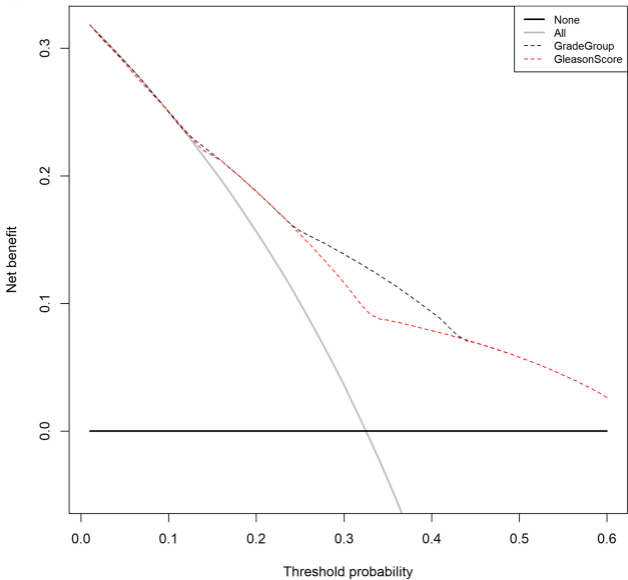
**A****Figure 4**

**B****Figure 5**

**C****Figure 6**

**A****Figure 7**

**B****Figure 8**

**C****Figure 9**