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Prognostic implications of 2005 Gleason grade modification. Population-based study of biochemical recurrence following radical prostatectomy

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Abstract

Objective—To assess the impact of the 2005 modification of the Gleason classification on risk of biochemical recurrence (BCR) after radical prostatectomy (RP).

Patients and Methods—In the Prostate Cancer data Base Sweden (PCBaSe), 2,574 men assessed with the original Gleason classification and 1,890 men assessed with the modified Gleason classification, diagnosed between 2003 and 2007, underwent primary RP. Histopathology was reported according to the Gleason Grading Groups (GGG): GGG1 = Gleason score (GS) 6, GGG2 = GS 7(3+4), GGG3 = GS 7(4+3), GGG4 = GS 8 and GGG5 = GS 9–10. Cumulative incidence and multivariable Cox proportional hazards regression models were used to assess difference in BCR.

Results—The cumulative incidence of BCR was lower using the modified compared to the original classification: GGG2 (16% vs. 23%), GGG3 (21% vs. 35%) and GGG4 (18% vs. 34%),

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respectively. Risk of BCR was lower for modified versus original classification, GGG2 Hazard ratio (HR) 0.66, (95%CI 0.49–0.88), GGG3 HR 0.57 (95%CI 0.38–0.88) and GGG4 HR 0.53 (95%CI 0.29–0.94).

Conclusion—Due to grade migration following the 2005 Gleason modification, outcome after RP are more favourable. Consequently, outcomes from historical studies cannot directly be applied to a contemporary setting.

Keywords

prostate cancer; radical prostatectomy; biochemical recurrence; Gleason classification; ISUP

Introduction

Tumour differentiation assessed by the Gleason grading system is the strongest predictor for prostate cancer progression and prostate cancer-specific death [1–4]. Since first introduced in 1966 [5], the Gleason classification system has only undergone one major revision prior to 2005 [6]. The classification grades the glandular architecture from 1 through 5, where Gleason pattern 1 is the least aggressive and 5 is the most aggressive. Originally, the Gleason score (GS) was obtained by adding the most commonly observed pattern and the second most commonly observed pattern [6]. In 2005, the Gleason classification was updated by the International Society of Urological Pathology (ISUP) [7]. The most important changes included modified definitions of Gleason patterns 3 and 4, where regular cribriform glands, previously considered pattern 3, were now graded as pattern 4 [7]. Also, the Gleason classification in a biopsy specimen was changed to be the sum of the most common pattern and the most aggressive pattern. In cases where the most common pattern was also the most aggressive pattern, a secondary lower pattern should only be reported if the volume was more than 5% of the total tumour volume in the specimen. These changes have resulted in a subsequent increase in the proportion of cancers graded as Gleason pattern 4 and a decrease of Gleason pattern 3 [8].

The aim of this study was to quantify the change in risk of biochemical recurrence (BCR) after radical prostatectomy (RP) caused by the ISUP 2005 modification of the Gleason classification.

Material and methods

This study was conducted within The Prostate Cancer data Base Sweden (PCBaSe) 3.0 [9]. PCBaSe contains information on cancer characteristics at diagnosis and primary treatment obtained from The National Prostate Cancer Register (NPCR) of Sweden as well as other patient characteristics such as the Charlson Comorbidity Index (CCI) [10] based on discharge diagnosis from the Patient Register [11], and education level, income and marital status from the Longitudinal Integration Database for health insurance and labour market (LISA) [12].

For men diagnosed in 2003–2007, the NPCR performed a Five-Year Follow-Up Study of men age ≥ 70 diagnosed with localised prostate cancer (prostate-specific antigen, PSA < 20

ng/ml and clinical tumour category cT1/cT2) [13]. In the present study, we included all of these men who underwent RP within 6 months from diagnosis.

We used the five-tier terminology for the Gleason classification which has recently been adopted by the ISUP, World Health Organization and a consensus of journal editors to be included in reporting [14–17]. The new terminology has the advantage of simplified distinction between cases with primary Gleason pattern 3 and secondary Gleason patterns 4 versus those with primary Gleason pattern 4 and secondary Gleason pattern 3. In the new classification Gleason Grading Group (GGG), 1 corresponds to Gleason score 6, GGG 2 corresponds to GS 7 (3+4), GGG 3 corresponds to GS 7 (4+3), GGG 4 corresponds to GS 8 and GGG 5 corresponds to GS 9–10 [15,18]. In addition, the new terminology has the pedagogical value of denoting the least aggressive cancer as GGG 1, which compared with the previous term ‘Gleason score 6’, makes it easier to convey the good prognosis of these cancers [19,20]. Men with GGG 5 on biopsy were excluded from analysis because of few cases (original: n=20, modified: n=21).

The following preoperative information was used: age at diagnosis, serum level of PSA (Log₂-scale), clinical tumour category (cT1 vs. cT2), biopsy GGG, proportion of biopsy cores positive for cancer (33%, 34–50%, >50%), CCI, educational level, and marital status. Postoperative information included RP specimen GGG 1, GGG 2, GGG 3, pathological tumour stage (pT, pT2 vs. pT3 or higher) and surgical margin status (negative vs. positive vs. indeterminate). Finally, adjuvant or salvage radiotherapy prior to BCR was recorded. BCR was defined as two PSA measurements >0.2 ng/ml after RP. Outcome was assessed by chart review at 5 years after diagnosis. The Research Ethics Board at Umeå University Hospital approved the study.

Guideline Applied for Gleason Classification Reporting

We used the Gleason classification from routine assessment by the local pathologist. Standard practice in Sweden for prostate biopsies is to submit each specimen in a separate container and to separately embed each specimen. Several efforts have been made to standardize Gleason classification in Sweden, for example, by use of reference images [21,22]. Each core is then assigned a score and the entire specimen is assigned one global score. For RP, the specimen is completely embedded, usually with a whole mount preparation to facilitate identification of individual tumour foci.

Statistics

Based on the assumption that the occurrence of biopsy GS 2–5 (which are no longer used for reporting biopsy specimen [15]) would decrease and that GGG 2 and 3 would increase after the 2005 revision, adherence to the modification of the Gleason classification was assessed in a change point analysis of the proportion of men diagnosed with GS 2–5 and GGG 2 and 3 on biopsy in each county [8]. Taylor’s cumulative sum change point analysis approach was used by 1,000 bootstrap samples [23,24]. A significant change was considered to have occurred if it had a corresponding confidence level of 95% or higher. If the change in GS 2–5 did not coincide with the change in GGG 2 and 3, a midpoint between these change points was used. A period of 6 months surrounding each change point was used as a transition

period; men diagnosed in the pertinent county during the transition period were excluded from the analyses. Fourteen Swedish counties had a sufficiently large change to be included in the analyses, including all six counties with university hospitals.

Mann-Whitney U-tests were used to compare continuous data and a χ^2 test was used to test for independence. Cumulative incidence of BCR was estimated for men graded according to the original and modified Gleason classification, and compared using Gray's test. Radiotherapy after RP and death were treated as competing events. Cox proportional hazards regression was used to compare BCR-free survival by estimating hazard ratios (HR) with 95% confidence intervals (CI), adjusted for baseline covariates. In multivariable analyses, multiple imputation was used to replace missing values [25]. All tests were two sided and the significance level was set to $p < 0.05$. Statistical analysis was performed with R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 4,464 men were included in the analysis and the GGG was reported according to the original classification in 2,574 men, while it was reported according to the modified classification in 1,890 men. Men in these groups had similar preoperative PSA, clinical tumour category and percentage positive biopsy cores, Supplemental Table SI. When stratified according to preoperative biopsy GGG men classified according to the original and modified Gleason classification had comparable preoperative characteristics, such as age, percentage positive biopsy cores, marital status, and CCI, Table I. A shift towards lower PSA ($p=0.003$) and fewer cT2 tumours ($p=0.002$) in men with GGG 2 according to the new classification compared to men with GGG 2 according to the old classification were the only significant differences. Supplemental Table SII demonstrates the postoperative findings and Table II demonstrates postoperative findings stratified according to biopsy GGG. The only significant differences were a higher percentage of men diagnosed with biopsy GGG 1 according to the new classification who had GGG 2 in the prostatectomy specimen ($p<0.001$) while fewer of these men had pT3 tumours ($p<0.001$).

The cumulative incidence of BCR was significantly lower in men classified with modified compared to the original classification: modified vs. original GGG 2, 16% and 23%, GGG 3 21% and 35%, and GGG 4, 18% and 34%, Figure 1.

In multivariable analysis, the risk of BCR increased with higher PSA, clinical tumour category and proportion of positive biopsy cores (Table III) as well as with higher prostatectomy Gleason grades, non organ-confined disease and positive surgical margins, Table IV. Adjusting for preoperative characteristics, men assessed with the modified Gleason classification had a significantly lower risk of BCR compared to men with similar Gleason grades from the original Gleason classification: modified vs original GGG 2 HR 0.66 (95% CI 0.49–0.88), GGG 3 HR 0.57 (95% CI 0.38–0.88) and GGG 4 HR 0.53 (95% CI 0.29–0.94). Also when adjusting for postoperative characteristics, men with modified GGG had a significantly lower risk of BCR compared to men with similar GGG from the original Gleason classification: modified vs original GGG 2 HR 0.65 (95% CI 0.49–0.87), GGG 3 HR 0.62 (95% CI 0.40–0.95) and GGG 4 HR 0.54 (95% CI 0.30–0.98).

In order to assess if men with GGG 2 could be candidates for active surveillance, we compared the risk of BCR between men with original GGG 1 and modified GGG 2. Overall men with original GGG 1 had a lower risk of BCR compared to men with modified GGG 2, Figure 2. However, the difference was not significant when adjusting for preoperative PSA, clinical tumour category and ratio of positives cores, HR 1.29 (95% CI 0.98–1.69) or postoperative pathological stage and surgical margins, HR 1.30 (0.99–1.71). In order to assess if there had also been a stage migration, we then assessed BCR in the full study cohort by merging all GGG. The cumulative incidence of BCR at 4 years was 16% for men with the original GGG and 12% in men with the modified GGG, $p=0.002$ (Supplemental figure SI).

When we grouped men with original GGG 1 and modified GGG 2 in subgroups based on pre- and postoperative characteristics most subgroups had similar risk of biochemical recurrence, that is, HR close to 1 and 95% CI including 1 (Tables V and VI). The exceptions were men with PSA <10 ng/ml, cT1 and 33% positive cores (HR 2.33, 95% CI 1.32–4.13), men with PSA 10–20 ng/ml, cT2 and >50% positive cores (HR 5.05, 95% CI 1.04–24.49) and men with PSA 10–20 ng/ml, negative surgical margins and pT2 (HR 2.08, 95% CI 1.17–3.69). The 4-year cumulative incidence of BCR was 14% (95% CI 7–21) for men with modified GGG 2, PSA <10 ng/ml, cT1 and 33% positive cores.

Discussion

In this population-based study in Sweden of men treated with RP for localised prostate cancer, risk of BCR was significantly lower for men classified with the modified 2005 Gleason classification compared with the original classification. Thus, outcome for men assessed by use of the original Gleason classification [26,27] cannot directly be applied to contemporary men assessed by the current modified Gleason classification.

The most important consequence of this modification is the decreased risk of BCR for men with GGG 2 following RP, with a likely improved cancer-specific survival [28,29]. In the current study, 1,771 men with original GGG 1 and 458 men with modified GGG 2 had similar BCR following RP, also when accounting for pre- and postoperative factors known to affect risk of BCR. The higher cancer-specific mortality in men with GGG 2 compared to GGG 1 in the original Gleason classification [3] that has previously led many active surveillance programmes to exclude men with GGG 2 [30,31], is unlikely to be applicable to men with modified GGG 2. Although men with PSA <10 ng/ml, cT1, 33% positive cores and modified GGG 2 had an increased risk of BCR compared to men with original GGG 1, the low cumulative incidence of BCR for these men with limited cancer on biopsy and modified GGG 2 indicates that this increased risk has minimal clinical implications. Thus, our results strongly suggest that modified GGG 2 should not be an absolute exclusion criterion for active surveillance.

One of the reasons for the modification of the Gleason classification was to improve the concordance between the Gleason assessment in the biopsy and RP specimen [7]. However, in the present study, there was a higher proportion of upgrading from modified biopsy GGG 1 to RP GGG 2 than for original biopsy GGG 1 to RP GGG 2, in contrast to what was

expected [7]. In contrast, other researchers have reported that a lower proportion of men diagnosed with modified GGG 1 are upgraded in the RP specimen compared to men with original GGG 1 [32]. Still, more than one in three men diagnosed with modified GGG 1 have T3 and/or GGG 2 or greater in their RP specimen [32,33]. Our data are in accordance with the only previous study comparing BCR after RP for men graded with the original and modified Gleason classification [34]. Together, these studies indicate that men with modified GGG 2 have a prognosis closer to men with GGG 1 than to men with GGG 3.

The main limitations of our study are the short follow-up and the use of Gleason classification from routine clinical assessment [35]. The use of real-world data will result in a less uniform assessment compared to a centralized reassessment and will dilute an association between grade and outcome. Speculatively, departments that rapidly adapted the modified classification may have produced higher quality assessments, resulting in a high precision in this study. Strengths of our study includes the 98% capture of all prostate cancer cases in Sweden compared to the Cancer Registry and the documented data quality in NPCR [36,37].

To date, there are still limited data on outcome in men graded with the modified Gleason classification [14,38,39]. In a recent publication, 4-year BCR after RP was lower both for men with original and modified GGG 1 and 2 than in our study [38]. A likely reason for the difference in outcome is that these results were from five selected academic centres with lower preoperative PSA levels and a higher proportion of cT1 cancers compared to our cohort, which was population-based and included men also treated in non-academic hospitals in Sweden.

In parallel with the modification of the Gleason classification, there has been an increase in the number of men diagnosed with low-risk prostate cancer in Sweden [40,41]. The more favourable outcome in the full study group after the modification is most likely explained by an underlying “true” continuing stage and grade migration. An increasing proportion of men in Sweden are diagnosed with low-risk prostate cancer [41]. In 2014, 74% of low- risk and 90% of men with very low-risk disease received active surveillance [42] and as a consequence, the risk of BCR after RP according to the modified Gleason classification could be overestimated as currently fewer men with very low-risk cancer undergo primary RP.

Conclusion

The 2005 modification of the Gleason classification caused a grade migration resulting in a more favourable outcome after RP when using the modified classification compared to the original classification. Consequently, outcomes from historical studies cannot directly be applied to a contemporary setting and our data suggests that GGG 2 (former GS 7 (3+4)) should no longer be considered an absolute contraindication for active surveillance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Epstein JI, Pizov G, Walsh PC. Correlation of pathologic findings with progression after radical retropubic prostatectomy. *Cancer*. 1993; 71:3582–93. [PubMed: 7683970]
2. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998; 280:969–74. [PubMed: 9749478]
3. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA*. 2005; 293:2095–101. [PubMed: 15870412]
4. Eggener SE, Scardino PT, Walsh PC, Han M, Partin AW, Trock BJ, et al. Predicting 15-year prostate cancer specific mortality after radical prostatectomy. *J Urol*. 2011; 185:869–75. [PubMed: 21239008]
5. Gleason DF. Classification of prostatic carcinomas. *Cancer Chemother Rep*. 1966; 50:125–8. [PubMed: 5948714]
6. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol*. 1974; 111:58–64. [PubMed: 4813554]
7. Epstein JI, Allsbrook WC, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol*. 2005; 29:1228–42. [PubMed: 16096414]
8. Danneman D, Drevin L, Robinson D, Stattin P, Egevad L. Gleason Inflation 1998–2011. A Registry Study of 97 168 Men. *BJU Int*. 2014 Epub ahead of print.
9. Van Hemelrijck M, Wigertz A, Sandin F, Garmo H, Hellström K, Fransson P, et al. Cohort Profile: the National Prostate Cancer Register of Sweden and Prostate Cancer data Base Sweden 2.0. *Int J Epidemiol*. 2013; 42:956–67. [PubMed: 22561842]
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40:373–83. [PubMed: 3558716]
11. Berglund A, Garmo H, Tishelman C, Holmberg L, Stattin P, Lambe M. Comorbidity, treatment and mortality: a population based cohort study of prostate cancer in PCBaSe Sweden. *J Urol*. 2011; 185:833–9. [PubMed: 21239002]
12. Longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym) - Statistiska centralbyrån. n.d.
13. Loeb S, Folkvaljon Y, Makarov DV, Bratt O, Bill-Axelsson A, Stattin P. Five-year nationwide follow-up study of active surveillance for prostate cancer. *Eur Urol*. 2015; 67:233–8. [PubMed: 24993868]
14. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. *BJU Int*. 2013; 111:753–60. [PubMed: 23464824]
15. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol*. 2016; 40:244–52. [PubMed: 26492179]

16. Zietman A, Smith J, Klein E, Droller M, Dasgupta P, Catto J. Describing the Grade of Prostate Cancer: Consistent Use of Contemporary Terminology Is Now Required. *Eur Urol.* 2016; 70:6716.
17. Humphrey P, Moch H, Cubilla A, Ulbright T, Reuter V. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. *Eur Urol.* 2016; 70:106–19. [PubMed: 26996659]
18. Loeb S, Folkvaljon Y, Robinson D, Lissbrant IF, Egevad L, Stattin P. Evaluation of the 2015 Gleason Grade Groups in a Nationwide Population-based Cohort. *Eur Urol.* 2016; 69:1135–41. [PubMed: 26707871]
19. Loeb S, Curnyn C, Sedlander E. Perspectives of Prostate Cancer Patients on Gleason Scores and the New Grade Groups: Initial Qualitative Study. *Eur Urol.* 2016; S0302–2838:30247–0.
20. Berney DM, Beltran L, Fisher G, North BV, Greenberg D, Møller H, et al. Validation of a contemporary prostate cancer grading system using prostate cancer death as outcome. *Br J Cancer.* 2016; 114:1078–83. [PubMed: 27100731]
21. Egevad L, Ahmad AS, Algaba F, Berney DM, Boccon-Gibod L, Compérat E, et al. Standardization of Gleason grading among 337 European pathologists. *Histopathology.* 2013; 62:247–56. [PubMed: 23240715]
22. Egevad L. Reproducibility of Gleason grading of prostate cancer can be improved by the use of reference images. *Urology.* 2001; 57:291–5. [PubMed: 11182339]
23. Kass-Hout TA, Xu Z, McMurray P, Park S, Buckeridge DL, Brownstein JS, et al. Application of change point analysis to daily influenza-like illness emergency department visits. *J Am Med Informatics Assoc.* 2012; 19:1075–81.
24. Taylor W. Change-point analysis: a powerful new tool for detecting changes. 2010
25. Buuren, S. Flexible Imputation of Missing Data. London: Chapman and Hall/CRC; 2012.
26. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med.* 2014; 370:932–42. [PubMed: 24597866]
27. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med.* 2012; 367:203–13. [PubMed: 22808955]
28. Albertsen PC, Hanley JA, Barrows GH, Penson DF, Kowalczyk PDH, Sanders MM, et al. Prostate cancer and the Will Rogers phenomenon. *J Natl Cancer Inst.* 2005; 97:1248–53. [PubMed: 16145045]
29. Rider JR, Sandin F, Andrén O, Wiklund P, Hugosson J, Stattin P. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. *Eur Urol.* 2013; 63:88–96. [PubMed: 22902040]
30. Klotz L. Active surveillance for prostate cancer: for whom? *J Clin Oncol.* 2005; 23:8165–9. [PubMed: 16278468]
31. Thomsen FB, Brasso K, Klotz LH, Andreas Røder M, Berg KD, Iversen P. Active surveillance for clinically localized prostate cancer--A systematic review. *J Surg Oncol.* 2014; 109:830–5. [PubMed: 24610744]
32. Van Praet C, Libbrecht L, D'Hondt F, Decaestecker K, Fonteyne V, Verschuere S, et al. Agreement of Gleason score on prostate biopsy and radical prostatectomy specimen: is there improvement with increased number of biopsy cylinders and the 2005 revised Gleason scoring? *Clin Genitourin Cancer.* 2014; 12:160–6. [PubMed: 24361055]
33. Vellekoop A, Loeb S, Folkvaljon Y, Stattin P. Population based study of predictors of adverse pathology among candidates for active surveillance with Gleason 6 prostate cancer. *J Urol.* 2014 Feb.;350–7.
34. Berg KD, Thomsen FB, Nerstrøm C, Røder MA, Iversen P, Toft BG, et al. The impact of the 2005 International Society of Urological Pathology consensus guidelines on Gleason grading - a matched-pair analysis. *BJU Int.* 2016; 117:883–9. [PubMed: 26823232]
35. Berney DM, Algaba F, Camparo P, Compérat E, Griffiths D, Kristiansen G, et al. The reasons behind variation in Gleason grading of prostatic biopsies: areas of agreement and misconception among 266 European pathologists. *Histopathology.* 2014; 64:405–11. [PubMed: 24102975]

36. Tomic K, Berglund A, Robinson D, Hjälm-Eriksson M, Carlsson S, Lambe M, et al. Capture rate and representativity of The National Prostate Cancer Register of Sweden. *Acta Oncol.* 2015; 54:158–63. [PubMed: 25034349]
37. Tomic K, Sandin F, Wigertz A, Robinson D, Lambe M, Stattin P. Evaluation of data quality in the National Prostate Cancer Register of Sweden. *Eur J Cancer.* 2015; 51:101–11. [PubMed: 25465187]
38. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. *Eur Urol.* 2015; doi: 10.1016/j.eururo.2015.06.046
39. Samaratunga H, Delahunt B, Gianduzzo T, Coughlin G, Duffy D, LeFevre I, et al. The prognostic significance of the 2014 International Society of Urological Pathology (ISUP) grading system for prostate cancer. *Pathology.* 2015; 47:515–9. [PubMed: 26325670]
40. Ohmann EL, Loeb S, Robinson D, Bill-Axelson A, Berglund A, Stattin P. Nationwide, population-based study of prostate cancer stage migration between and within clinical risk categories. *Scand J Urol.* 2014
41. Bratt O, Folkvaljon Y, Loeb S, Klotz L, Egevad L, Stattin P. Upper limit of cancer extent on biopsy defining very low-risk prostate cancer. *BJU Int.* 2015; 116:213–9. [PubMed: 25053197]
42. Loeb S, Folkvaljon Y, Curnyn C, Robinson D, Bratt O, Stattin P. Almost Complete Uptake of Active Surveillance for Very Low-Risk Prostate Cancer in Sweden. *JAMA Oncol.* 2016 In press.

Figure 1. Cumulative incidence of biochemical recurrence (BCR) following radical prostatectomy (RP) for men graded according to the original Gleason classification (blue) and men graded according to the modified Gleason classification (orange) stratified according to biopsy Gleason Grade Group (GGG).

Figure 2.
Cumulative incidence of biochemical recurrence (BCR) following radical prostatectomy (RP) for men with original Gleason Grade Group (GGG) 1 (blue) and men with modified GGG 2 (orange).

Table 1

Preoperative characteristics and demographics of men who underwent a primary RP graded according to the original and modified Gleason classification, in the 5-year follow-up study in PCBaSe 3.0, by biopsy Gleason Grade Group (GGG)

	Biopsy GGG 1			Biopsy GGG 2			Biopsy GGG 3			Biopsy GGG 4		
	Original	(%)	Modified	(%)	Original	(%)	Modified	(%)	Original	(%)	Modified	(%)
Men	1771	(100)	1168	(100)	551	(100)	458	(100)	153	(100)	175	(100)
Age (years)												
Median (IQR)	61.9	(58–66)	62.3	(58–66)	62.9	(59–66)	62.9	(59–66)	63.2	(60–67)	63.9	(60–67)
<60	618	(35)	417	(36)	159	(29)	138	(30)	35	(23)	44	(25)
60–64	613	(35)	402	(34)	194	(35)	157	(34)	52	(34)	62	(35)
65–70	540	(30)	349	(30)	198	(36)	163	(36)	66	(43)	69	(39)
Serum PSA (ng/mL)												
Median (IQR)	6.4	(4.6–9.2)	6.3	(4.7–9.0)	7.0	(5.1–10.0)	6.3	(4.5–9.2)	7.9	(5.5–11.3)	8.1	(5.8–11.2)
Clinical tumour category												
cT1	1263	(71)	851	(73)	296	(54)	291	(64)	80	(52)	93	(53)
cT2	508	(29)	317	(27)	255	(46)	167	(36)	73	(48)	82	(47)
Ratio of positive cores												
33%	1062	(60)	672	(58)	246	(45)	183	(40)	56	(37)	73	(42)
34–50%	386	(22)	242	(21)	129	(23)	128	(28)	55	(36)	55	(31)
50–100%	247	(14)	130	(11)	157	(28)	117	(26)	35	(23)	27	(15)
Missing data	76	(4)	124	(11)	19	(3)	30	(7)	7	(5)	20	(11)
Marital status												
Not married	446	(25)	299	(26)	147	(27)	115	(25)	36	(24)	50	(29)
Married	1325	(75)	869	(74)	404	(73)	343	(75)	117	(76)	125	(71)
Educational level*												
Low	489	(28)	317	(27)	185	(34)	122	(27)	48	(31)	53	(30)
Middle	764	(43)	497	(43)	226	(41)	190	(41)	62	(41)	78	(45)
High	511	(29)	352	(30)	139	(25)	145	(32)	42	(27)	44	(25)
Missing data	7	(0)	2	(0)	1	(0)	1	(0)	1	(1)	0	(0)
Charlson Comorbidity Index												
CCI 0	1601	(90)	1062	(91)	497	(90)	416	(91)	139	(91)	153	(87)
									84	(85)	83	(93)

	Biopsy GGG 1				Biopsy GGG 2				Biopsy GGG 3				Biopsy GGG 4			
	Original		Modified		Original		Modified		Original		Modified		Original		Modified	
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
CCI 1	109	(6)	72	(6)	33	(6)	26	(6)	4	(3)	16	(9)	9	(9)	4	(4)
CCI 2+	61	(3)	34	(3)	21	(4)	16	(3)	10	(7)	6	(3)	6	(6)	2	(2)

Gleason Grade Group (GGG) 1 = Gleason score (GS) 6, GGG 2 = GS 7(3+4), GGG 3 = GS 7(4+3), GGG 4 = GS8. RP = Radical prostatectomy, IQR = Interquartile range, PSA = Prostate-specific antigen, CCI = Charlson comorbidity index
* Educational level: low = compulsory school (<10 years), middle = upper secondary school (10–12 years), high = college or university (>12 years)

Table II

Postoperative characteristics of men in table 1

	Biopsy GGG 1				Biopsy GGG 2				Biopsy GGG 3				Biopsy GGG 4			
	Original	(%)	Modified	(%)	Original	(%)	Modified	(%)	Original	(%)	Modified	(%)	Original	(%)	Modified	(%)
Men	1771	(100)	1168	(100)	551	(100)	458	(100)	153	(100)	175	(100)	99	(100)	89	(100)
Prostatectomy																
GGG 1	1208	(68)	713	(61)	104	(19)	101	(22)	15	(10)	20	(11)	7	(7)	8	(9)
GGG 2	453	(26)	345	(30)	349	(63)	268	(59)	52	(34)	48	(27)	18	(18)	16	(18)
GGG 3	58	(3)	76	(7)	75	(14)	78	(17)	63	(41)	85	(49)	35	(35)	34	(38)
GGG 4	14	(1)	16	(1)	13	(2)	8	(2)	11	(7)	11	(6)	26	(26)	18	(20)
GGG 5	6	(0)	0	(0)	4	(1)	2	(0)	8	(5)	6	(3)	11	(11)	12	(13)
Missing data	32	(2)	18	(2)	6	(1)	1	(0)	4	(3)	5	(3)	2	(2)	1	(1)
Pathological stage																
pT2	1286	(73)	820	(70)	323	(59)	254	(55)	78	(51)	94	(54)	47	(47)	39	(44)
pT3 or higher	365	(21)	189	(16)	197	(36)	121	(26)	64	(42)	52	(30)	45	(45)	32	(36)
Missing data	120	(7)	159	(14)	31	(6)	83	(18)	11	(7)	29	(17)	7	(7)	18	(20)
Surgical margins																
Negative	1163	(66)	779	(67)	347	(63)	258	(56)	77	(50)	95	(54)	52	(53)	43	(48)
Positive	351	(20)	152	(13)	121	(22)	83	(18)	49	(32)	36	(21)	31	(31)	22	(25)
Indeterminate	225	(13)	121	(10)	67	(12)	46	(10)	24	(16)	23	(13)	12	(12)	8	(9)
Missing data	32	(2)	116	(10)	16	(3)	71	(16)	3	(2)	21	(12)	4	(4)	16	(18)

GGG = Gleason Grade Group

Table III

Biochemical recurrence after prostatectomy according to biopsy classification and preoperative characteristics

	GGG 1		GGG 2		GGG 3		GGG 4	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Biopsy classification								
Original	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
Modified	0.84	(0.67–1.06)	0.66	(0.49–0.88)	0.57	(0.38–0.88)	0.53	(0.29–0.94)
PSA (log₂-scale)	1.75	(1.49–2.07)	1.63	(1.33–1.99)	1.63	(1.17–2.27)	1.48	(0.97–2.25)
Clinical tumour category								
cT1	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
cT2	1.56	(1.24–1.96)	1.19	(0.90–1.58)	1.53	(1.00–2.34)	1.39	(0.77–2.50)
Ratio of positive cores								
33%	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
34–50%	1.55	(1.19–2.01)	1.50	(1.05–2.13)	1.58	(0.94–2.63)	0.85	(0.42–1.72)
50–100%	1.43	(1.03–1.98)	1.30	(0.91–1.85)	1.88	(1.04–3.40)	1.87	(0.82–4.30)

Multivariable Cox regression with hazard ratios (HR) and 95% confidence intervals (CI). PSA at date of diagnosis was also included in the models. GGG = Gleason Grading Groups. PSA = Prostate-specific antigen.

Table IV

Biochemical recurrence (BCR) after prostatectomy according to biopsy classification and postoperative characteristics

	GGG 1		GGG 2		GGG 3		GGG 4	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Biopsy grading								
Original grading	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
Modified grading	0.86	(0.68–1.08)	0.65	(0.49–0.87)	0.62	(0.40–0.95)	0.54	(0.30–0.98)
Prostatectomy grading								
GGG 1	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
GGG 2	1.65	(1.30–2.11)	1.41	(0.90–2.21)	1.67	(0.67–4.18)	3.54	(0.45–27.55)
GGG 3 or higher	3.14	(2.21–4.45)	2.27	(1.38–3.74)	2.35	(0.97–5.68)	4.25	(0.64–28.39)
Pathological stage								
pT2	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
pT3 or higher	1.43	(1.10–1.86)	1.95	(1.41–2.70)	1.46	(0.88–2.42)	3.42	(1.69–6.93)
Surgical margins								
Negative	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
Positive	3.91	(2.93–5.22)	1.88	(1.33–2.66)	3.16	(1.90–5.26)	2.36	(1.17–4.73)
Indeterminate	4.12	(3.06–5.56)	1.88	(1.27–2.79)	3.00	(1.64–5.49)	1.86	(0.72–4.82)

Multivariable Cox regression with hazard ratios (HR) and 95% confidence intervals (CI). PSA at date of diagnosis was also included in the models. GGG = Gleason Grading Groups. PSA = Prostate-specific antigen.

Table V

Risk of biochemical recurrence after prostatectomy for men with modified GGG 2 compared to men with original GGG 1, using preoperative characteristics

	cT1		cT2	
	PSA <10	PSA 10–20	PSA <10	PSA 10–20
Ratio of positive cores	HR (95%)	HR (95%)	HR (95%)	HR (95%)
33%	2.33 (1.32–4.13)	1.00 (0.30–3.41)	0.80 (0.29–2.19)	0.83 (0.18–3.73)
34–50%	0.94 (0.40–2.18)	1.50 (0.38–5.91)	1.29 (0.53–3.15)	1.16 (0.34–3.98)
>50%	0.99 (0.34–2.84)	1.06 (0.31–3.65)	1.18 (0.43–3.27)	5.05 (1.04–24.49)

Multivariable Cox regression with hazard ratios (HR) and 95% confidence intervals (CI).

GGG = Gleason Grading Group, PSA = Prostate-specific antigen

Table VI

Risk of biochemical recurrence after prostatectomy for men with modified GGG 2 compared to men with original GGG 1, using postoperative characteristics

	pT2		pT3 or higher	
	PSA <10	PSA 10–20	PSA <10	PSA 10–20
Surgical margins	HR (95%)	HR (95%)	HR (95%)	HR (95%)
Negative	2.08 (1.17–3.69)	0.73 (0.17–3.25)	1.22 (0.51–2.90)	5.12 (0.28–94.41)
Positive	1.51 (0.55–4.13)	0.67 (0.17–2.58)	0.97 (0.43–2.20)	1.75 (0.77–3.94)
Indeterminate	0.90 (0.34–2.40)	0.25 (0.03–2.24)	0.56 (0.08–3.92)	1.69 (0.27–10.42)

Multivariable Cox regression with hazard ratios (HR) and 95% confidence intervals (CI).

GGG = Gleason Grading Group, PSA = Prostate-specific antigen