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In 2014 the International Society of Urological Pathology (ISUP) supported to change the ISUP-2005 modified Gleason scoring system, as previously proposed by Pierorazio et al.[1,2] Besides decisions on terminology and scoring of specific morphological patterns, a renumbering of the existing scores was suggested.[3] In clinical practice this comprises a transformation from a 6-10 risk spectrum including 9 different Gleason scores (3+3=6, 3+4=7, 4+3=7, 3+5=8 4+4=8, 5+3=8, 4+5=9, 5+4=9, and 5+5=10) to a 1-5 score with 5 grade groups (1: ≤3+3, 2: 3+4, 3: 4+3, 4: Gleason scores 8, and 5: Gleason score 9-10). One of the reasons is that the lowest risk group is now more intuitively indicated '1' instead of the intermediate disease implied by '6', contributing to the acceptance of active surveillance for the cancers considered most indolent. Another substantiation for the novel classification system is that importantly different Gleason scores were often unfairly combined into one score (e.g. 7 including both 3+4 and 4+3). The novel 5-tier system was validated in >20.000 prostatectomy specimens and >16.000 needle biopsy specimens.[1]

Here, we evaluated the impact of introducing the novel ISUP-2014 grading system on biochemical recurrence (BCR) rates after radical prostatectomy (RP). The specific focus was on the potential differences in prognostic value of the ISUP-2005 Gleason scores, now combined into one grade group. BCR was defined as a post-RP PSA of >=0.2 ng/ml and rising. Separate analyses were performed for biopsy and prostatectomy Gleason score. Kaplan-Meier curves with Log-Rank test for comparisons between curves were used. Cox regression analysis was used to assess the impact of confounders on time dependent outcomes. P-values of <0.05 were considered statistically significant.

After combining the RP-databases of our two centers (Epworth, Melbourne, Australia and NKI, Amsterdam, The Netherlands), Gleason score information of 3,416 biopsies and 3,479 RP specimen were available (December 2003-September 2015; 8% <2005). ISUP guidelines were followed. In general, a 'first and worst' pattern principle was followed for needle biopsy grading. The grade for the case was based on the average (global) grade as if all the tumor sites from all cores were added together. For prostatectomy, the grading was based on the highest individual nodule. All RP specimen were reviewed by local specialist uro-pathologists.

Table 1 presents the biopsy and prostatectomy ISUP-2005 modified Gleason score and corresponding ISUP-2014 grade group distribution. Median follow-up to BCR or last visit was 1.7 years (25-75p 0.7-3.7). For the total group, the 5-year BCR rate was 30%.

The 5-year BCR rates for the grade groups 1-5 on biopsy were 19%, 23%, 44%, 52%, and 79% (Figure 1a). The 5-year BCR rates for the grade groups 1-5 based on RP were 14%, 19%, 45%, 51%, and 73% (Figure 1b). All biopsy and prostatectomy grade groups were statistically significantly different from each other ($p<0.05$).

Figure 2a presents the BCR rates after surgery per biopsy Gleason score. While Gleason scores 3+5 and 4+3 are considered as grade groups 3 and 4 respectively in the ISUP-2014 5-tier system, BCR showed considerable overlap ($p=0.738$). Conversely, Gleason scores 3+5 and 4+4 are both assigned to grade group 4 in the new system, but BCR showed a trend to more favorable in the 3+5=8 group ($p=0.065$). Whilst overlap of BCR were seen in additional ISUP-2005 Gleason score categories, these are likely due to limited patient numbers (BCR 4+3 similar to 5+3, $p=0.806$ and 5+3 similar to 5+5, $p=0.114$).

Figure 2b presents the BCR rates after surgery per prostatectomy specimen Gleason score. Again, BCR for 3+5 was not different from 4+3 ($p=0.756$) and BCR for 3+5 was significantly more favorable than 4+4 ($p=0.009$). More overlap between ISUP-2005 Gleason scores was found, again likely due to limited patient numbers (5+3 similar to 4+3, $p=0.535$; 4+4 similar to 5+5, $p=0.183$; 4+5 similar to 5+3, $p=0.109$; and 5+3 similar to 5+5, $p=0.175$).

For biopsy Gleason score, after correcting for margin status, pathological T and N stage, score 3+5 versus 4+4 no longer showed a statistically significant

difference in BCR in Cox regression analysis (p=0.793). The overlap in BCR between 3+5 and 4+3 however remained BCR (p=0.406).

For prostatectomy Gleason score, after correcting for margin status, pathological T and N stage, score 3+5 versus 4+4 remained to statistically significantly impact BCR (p=0.047). Score 3+5 versus 4+3 remained to show overlap (p=0.182).

Limitations of the current analysis include the lack of centralized pathological review, the use of the intermediate endpoint BCR, and limited patient numbers for some subgroups. The method of grading needle biopsies in the current study differs from how the grading was done in the initial and validation studies on grade groups [1-3] and could account for differences in the results. For example, there could be a core with a focus of 4+5=9 and many other cores with 3+4=7 which would have been graded as 4+5=9 in the initial and validation studies on grade groups [1-3], but would have been graded as 3+5=8 in the current study.

Huynh et al also reported on the heterogeneity within grade group 4.[4] Patients treated with brachytherapy with or without external-beam radiotherapy and/or androgen deprivation therapy with either biopsy 3+5 or 5+3 disease were combined and showed worse disease-specific (hazard ratio 2.77; p=0.026) and overall survival (hazard ratio 1.75; p=0.028) than 4+4. When we combined 3+5 and 5+3 disease and compared this group to 4+4, it on the contrary showed a trend to more favorable BCR for biopsy Gleason score (p=0.066) and again a significant advantage for prostatectomy Gleason score (p=0.013). Mahal et al analysed SEER data and found similar disease-specific death rates for patients with 3+5 and 4+4 disease, but a twofold increase for patients with 5+3 (hazard ratio 1.89; p<0.001) versus 4+4.[5] The validation of the novel 5-group grading system stated that Gleason scores 3+5 and 5+3 were not considered due to its low frequency.[1]

The quantitative grading of Gleason patterns 4 and 5 have been suggested to add important predictive value for BCR over the presence of the pattern only after analysis of 12,823 RP and 2,971 biopsy samples.[6] Furthermore, in clinical practice other RP parameters (margin status, extracapsular extension, or seminal vesicle invasion) are used in addition to improve risk stratification for BCR within Gleason 8-10 disease.[7]

Concluding, condensing 9 Gleason scores into the 5-tier system resulted in good risk stratification for BCR after surgery, both for biopsy and RP data. Some higher risk patients however may unjustifiably be combined into the same grade group. Specifically, the risk for the minority of patients with Gleason 3+5 patients (ISUP-2014 grade group 4) may be overestimated, as the BCR resembles that of Gleason 4+3 (grade group 3) patients rather than the remainder Gleason 8 tumors.

Conflicts of Interest: Authors have no conflict of interest to declare

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Table 1 – Biopsy and prostatectomy classic Gleason score and novel risk group distribution

Biopsy				Prostatectomy			
Classic score		Novel risk group		Classic score		Novel risk group	
3+3=6	1351 (38.8%)	1	1351 (38.8%)	3+3=6	731 (21.4%)	1	732 (21.4%)
3+4=7	1211 (34.8%)	2	1212 (34.8%)	3+4=7	1587 (46.5%)	2	1587 (46.5%)
4+3=7	441 (12.7%)	3	441 (12.7%)	4+3=7	648 (19.0%)	3	648 (19.0%)
3+5=8	50 (1.4%)	4	317 (9.1%)	3+5=8	62 (1.8%)	4	212 (6.2%)
4+4=8	252 (7.2%)			4+4=8	134 (3.9%)		
5+3=8	16 (0.5%)			5+3=8	15 (0.4%)		
4+5=9	124 (3.6%)	5	158 (4.5%)	4+5=9	186 (5.4%)	5	237 (6.9%)
5+4=9	23 (0.7%)			5+4=9	43 (1.3%)		
5+5=10	11 (0.3%)			5+5=10	8 (0.2%)		
	3479		3479		3416		3416

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Figure 1a – Biochemical recurrence rates after surgery per biopsy Gleason risk group ($p<0.05$ for all Log-Rank comparisons)

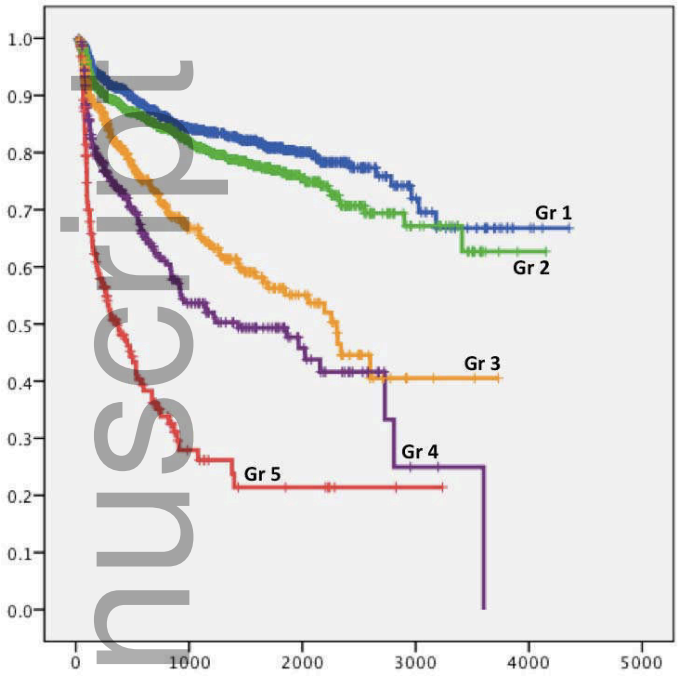

Figure 1b – Biochemical recurrence rates after surgery per prostatectomy Gleason risk group ($p<0.05$ for all Log-Rank comparisons)

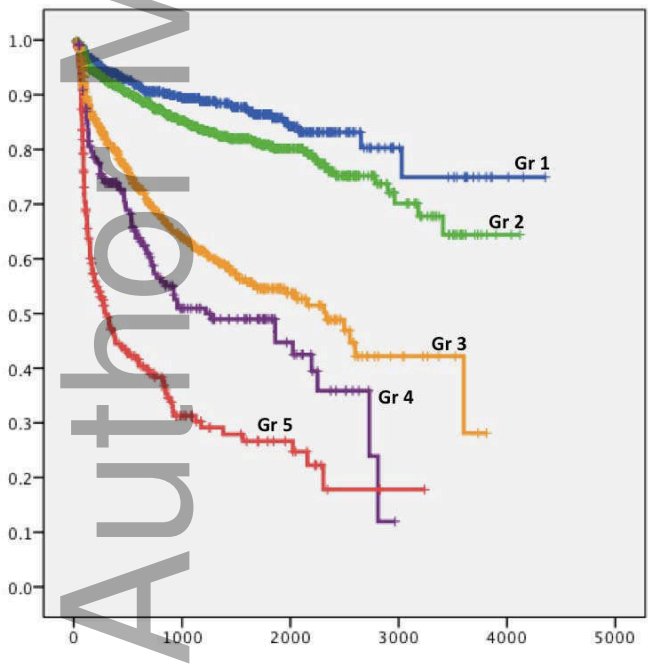

Figure 2a – Biochemical recurrence rates after surgery per biopsy Gleason score and risk group

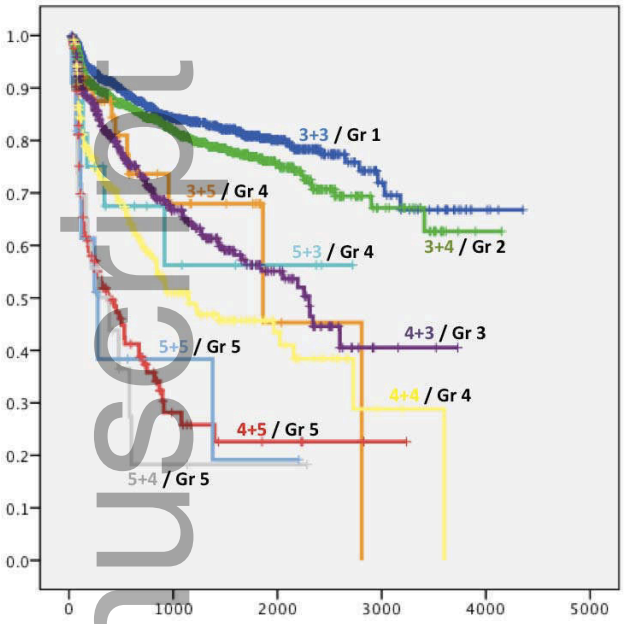

Figure 2b – Biochemical recurrence rates after surgery per prostatectomy Gleason score and risk group