Asian Journal of Urology (2019) 6, 321–329

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajur

Original Article

Extent and predictors of grade upgrading and downgrading in an Australian cohort according to the new prostate cancer grade groupings

Kerri Beckmann [a,b,*], Michael O'Callaghan [c,d], Andrew Vincent [d], Penelope Cohen [e], Martin Borg [f], David Roder [a], Sue Evans [g], Jeremy Millar [g], Kim Moretti [a,d]

[a] *Cancer Research Institute, School of Health Sciences, University of South Australia, Adelaide, Australia*
[b] *School of Cancer and Pharmaceutical Sciences, King's College London, London, UK*
[c] *Flinders Medical Centre, Urology Unit, Adelaide, Australia*
[d] *School of Medicine, University of Adelaide, Adelaide, Australia*
[e] *SA Pathology, Health SA, Adelaide, South Australia, Australia*
[f] *Genesis Care, University of Adelaide, Adelaide, Australia*
[g] *Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia*

Received 2 May 2018; received in revised form 6 August 2018; accepted 12 February 2019
Available online 7 March 2019

KEYWORDS
Prostate cancer;
Grade misclassification;
Biopsy;
Radical prostatectomy;
Pathology

Abstract *Object:* To determine the extent and impact of upgrading and downgrading among men who underwent radical prostatectomy (RP) according to new grade groupings and to identify predictors of upgrading from biopsy grade Group I and II, and downgrading to grade Group I, in a community setting.
Methods: Study participants included 2279 men with non-metastatic prostate cancer diagnosed 2006–2015 who underwent prostatectomy, from the multi-institutional South Australia Prostate Cancer Clinical Outcomes Collaborative registry. Extent of up- or down-grading was assessed by comparing biopsy and prostatectomy grade groupings. Risk of biochemical recurrence (BCR) with upgrading was assessed using multivariable competing risk regression. Binomial logistic regression was used to identify pre-treatment predictors of upgrading from grade Groups I and II, and risk group reclassification among men with low risk disease.
Results: Upgrading occurred in 35% of cases, while downgrading occurred in 13% of cases. Sixty percent with grade Group I disease were upgraded following prostatectomy. Upgrading from

* Corresponding author. Cancer Research Institute, School of Health Sciences, University of South Australia, Adelaide, Australia.
E-mail address: kerri.beckmann@unisa.edu.au (K. Beckmann).
Peer review under responsibility of Second Military Medical University.

https://doi.org/10.1016/j.ajur.2019.03.001

grade Group I was associated with greater risk of BCR compared with concordant grading (Hazard ratio: 3.1, 95% confidence interval: 1.7—6.0). Older age, higher prostate-specific antigen levels (PSA), fewer biopsy cores, higher number of positive cores and more recent diagnosis predicted upgrading from grade Group I, while higher PSA and clinical stage predicted upgrading from grade Group II. No clinical risk factors for reclassification were identified.
Conclusion: Biopsy sampling errors may play an important role in upgrading from grade Group I. Improved clinical assessment of grade is needed to encourage greater uptake of active surveillance.

1. Introduction

Grade is an important prognostic indicator for prostate cancer (PCa) and is used extensively in defining risk categories for disease progression to guide treatment decisions [1—3]. Recently, a new "patient friendly" grading system for classification PCa grade was endorsed [4] which classifies grade as: Grade Group I (Gleason score $\leq 3+3$); grade Group II (Gleason score $3+4=7$); grade Group III (Gleason score $4+3=7$); grade Group IV (total Gleason score $=8$) and grade Group V (total Gleason score $=9$—10).

Evidence consistently shows that grade Group I (Gleason score $\leq$6) has very low potential to metastasise [5,6]. Given the indolent nature of low grade PCa and the high morbidity associated with radical treatments, active surveillance (AS) is the preferred treatment option for grade I tumours with no other adverse clinical characteristics [6]. Some AS protocols also include grade Group II in selected circumstances [7]. However, both clinicians and patients may be reluctant to undergo AS due to the risk under-grading at biopsy [8]. Studies comparing biopsy-assessed grade to pathological findings after radical prostatectomy (RP) indicate substantial grade reclassification, most involving upgrading [9,10]. Twelve to fourteen ultrasound-guided trans-rectal (TRUS) core needle biopsy, currently the most common biopsy method, is associated with high rates of grade upgrading [11]. While a number of new diagnostic methods (saturation biopsy, trans-perineal template biopsy, image-guided) promise more accurate assessment of grade and ability to distinguish indolent from progressive cases, not all men have access to these newer technologies.

The aims of this study were to 1) measure the extent of upgrading and downgrading for needle biopsy results compared with pathological findings following RP; 2) determine whether upgrading from lower grade categories is associated with greater risk of biochemical recurrence (BCR), and 3) identify clinical characteristics, known prior to surgery, that are predictive of upgrading from grade Group I and grade Group II, and downgrading to grade Group I, given major clinical implications regarding treatment choices for men with low or intermediate grade disease.

Importantly, our study examines these grade shifts within a community setting, whereas range of biopsy approaches apply and where reporting of grade is not centralised and may involve non-specialist uro-pathologists.

2. Patients and methods

2.1. Data source and subjects

The South Australian Prostate Cancer Clinical Outcomes Collaborative (SA-PCCOC) database is a long running prospective multi-institutional clinical cancer registry which collects clinical, treatment and outcome data for men with PCa across both the public and private sectors in South Australia [12]. The registry recruits from all public hospitals and radiotherapy centres, and from approximately 50% of urologists in private practice, including most high-volume surgeons. Participation rates for men invited are around 90%. The study sample included participants with non-metastatic PCa diagnosis between 2006 and 2013 who underwent RP within 1 year of diagnosis as their primary treatment who had biopsy Gleason grade patterns recorded.

Diagnoses before 2006 were excluded to limit cases to those graded after International Society for Urologic Pathology (ISUPs) revision of the grading system in 2005 [13]. Those receiving prior androgen deprivation therapy or radiotherapy were also excluded due to potential for these treatments to interfere with pathological interpretation, as well as men who were diagnosed through a trans-urethral resection of the prostate. The majority of eligible men (95%) had undergone TRUS biopsy procedures (across public and private sectors), with the remainder having trans-perineal biopsies, predominantly in the private sector. Across the cohort, grade assignment involved multiple pathology services, both at biopsy and post-surgery. The final eligible cohort consisted of 2279 men.

2.2. Measures

Data on patient characteristics, clinical features, treatment modalities, and dates of BCR and death were extracted from SA-PCCOC for eligible cases. Death data were obtained via the South Australian Births Deaths and Marriages registry and National Death Index.

Grade groups at biopsy and post-surgically were classified according to new five-tier grade groups, based on primary and secondary Gleason grade patterns [4]. Upgrading was defined as a shift from diagnostic biopsy grade group to any higher grade grouping on RP specimen, while

downgrading was defined as a shift to any lower grade group based on surgical pathology. BCR was defined as two consecutive prostate-specific antigen (PSA) values of >0.2 ng/mL [14]. BCR-free durations were calculated from the date of operation to the first evidence of BCR, with death considered a competing risk and individuals censored at June 30, 2016 (latest update of recurrence data) if no event had occurred.

2.3. Analysis

Descriptive analyses of demographic, clinical and treatment characteristics according to grade groups were undertaken, with extended Wilcoxon rank-sum tests used to assess trends across ordered groups. Cross tabulations were used to compare grade groups based on biopsy results (biopsy grade) with grade based on histopathology following surgery (prostatectomy grade) and the proportion of cases upgraded and downgraded for each biopsy grade group is reported.

To examine whether upgrading has an impact on clinical outcomes we compared risk of BCR over time after surgery by plotting cumulative incidence functions for upgraded and concordant grade groups. We further examined the impact of upgrading on risk of BCR using multivariable competing risk regression according to Fine and Gray's methodology [15], for upgrading from grade Groups I and II, compared with concordant grade groupings. Covariates included age, year of diagnosis, stage and initial biopsy grade. This analysis was restricted to men diagnosed between 2006 and 2013 who had ≥2 PSA measures recorded following their prostatectomy ($n = 1552$).

Risk factors associated with upgrading were identified via multivariable binomial logistic regression. Separate models were run for upgrading from grade Group I (to any higher grade group) and from grade Group II (to any higher grade group). These models specifically examined clinical factors known prior to treatment and included pre-treatment PSA levels, clinical T-stage, peri-neural invasion (PNI), biopsy method, number of cores sampled and number of positive cores, along with age and year of diagnosis.

Further multivariable logistic regression analysis was undertaken in the subset of men who were defined at biopsy as having low or favourable intermediate risk disease (PSA <10 ng/mL, T2a or less, grade Group I or II and <3 positive cores or <30% positive cores if more than 10 cores were taken). The outcome in this model was upgrading that would lead to reclassification to intermediate or high risk disease (*i.e.* grade Group III or higher).

Statistical analyses used Stata v 12.1 [16]. Ninety-five percent confidence intervals (CI) are reported throughout. Ethics approval was obtained from Southern Adelaide Clinical and University of South Australia Human Research Ethics Committees (protocols 307.14 and 3746).

3. Results

3.1. Clinical characteristics

Characteristics of the eligible 2272 men are shown in Table 1. Two thirds were classified with Grade I or II on biopsy. The mean age at diagnosis increased with increasing grade. Median PSA concentrations at diagnosis also varied across grade groups but a clear trend was not evident. The number of biopsy cores (median = 12) or proportion managed in the public sector was similar across grade groups. PCa specific death and BCR increased across biopsy grade groups. The median follow-up time (Kaplan–Meier method) was 73 months (95% CI: 70–76 months).

Table 1 Cohort characteristics by biopsy grade (new grade groupings).

Characteristic	Biopsy grade grouping					*p*-Value[a]
	Grade I	Grade II	Grade III	Grade IV	Grade V	
Gleason pattern	3 + 3	3 + 4	4 + 3	8	9–10	
N = 2272						
Total, *n* (%)	762 (34)	821 (36)	417 (18)	193 (9)	79 (3)	
Clinical characteristics						
Age, year (mean ± SD)	61 ± 7	63 ± 6	64 ± 7	65 ± 5	66 ± 5	<0.001
PSA, ng/mL (IQR)	7 (5–9)	7 (5–10)	8 (6–10)	7 (6–11)	8 (6–13)	<0.001
Public patient, *n* (%)	264 (35)	243 (30)	100 (24)	62 (32)	27 (34)	0.06
No. biopsy core (mean ± SD)	13 ± 6	13 ± 6	14 ± 5	14 ± 7	14 ± 7	0.08
Re-biopsy[b] rate, *n* (%)	123 (16)	73 (9)	37 (9)	23 (12)	4 (5)	<0.001
Outcomes						
PCa deaths[c], *n* (%)	3 (0.5)	4 (0.7)	3 (1.1)	6 (4.3)	4 (9.5)	<0.001
Other deaths[c], *n* (%)	17 (3)	18 (3)	9 (3)	10 (7)	2 (5)	0.05
Biochemical recurrence[d], *n* (%)	59 (10)	105 (19)	89 (38)	54 (43)	22 (56)	<0.001

IQR, interquartile range; PCa, prostate cancer; PSA, prostate-specific antigen; SD, standard deviation.
[a] *p*-Values from extended Wilcoxon rank-sum tests for trend across ordered groups.
[b] Any time prior to surgery (within 1 year of diagnosis).
[c] Total number of PCa/other deaths for men diagnosed in 2006–2013 ($n = 1763$).
[d] Total number of biochemical recurrences during the follow-up period among men diagnosed in 2006–2013 who had PSA follow-up data ($n = 1552$).

3.2. Extent of upgrading and downgrading

The number and proportions of concordant, upgraded or downgraded cases, based on histopathology following RP, are presented in Table 2. Overall, we saw concordance in 52% of cases. Upgrading occurred in 35% of cases, while downgrading was indicated in 13% of cases. Among men classified as grade Group I at biopsy, 60% of cases were upgraded on the basis of RP specimen pathology. Only 74 men in higher grade groups assigned at biopsy were downgraded to grade Group I in their final pathology.

3.3. Risk of biochemical recurrence

Fig. 1 presents the crude cumulative incidence of BCR following prostatectomy for men classified who were subsequently upgraded or downgraded in final surgical pathology, compared with those with concordant surgical grade groupings, without adjustment for other factors. Incidence function curves are similar for men who were upgraded from grade Group I and men with concordant grade Group II classification. Likewise, the curves indicate that men upgraded from grade Group II have similar risk of BCR to those with concordant grade Group III.

Multivariable competing risk regression (Table 3) confirmed that men upgraded from grade Group I had a higher risk of BCR to concordant classification as grade Group I (sub-distribution hazard ratio [SHR] = 3.1, 95% CI: 1.7–6.0), after adjusting for age, stage, pre-treatment PSA levels and year of diagnosis. There was no difference in risk of BCR among those upgraded from grade Group I and those within the concordant grade Group II (SHR = 0.9, 95% CI: 0.6–1.3). Similarly the risk of BCR among those who were upgraded from grade Group II was similar to those with concordant grade Group III disease (SHR = 0.8, 95% CI: 0.5–1.2).

3.4. Factors associated with upgrading

Table 4 presents results of binomial logistic regression to determine clinical factors, known prior to treatment, for risk of upgrading among men within biopsy grade Group I, and also separately for grade Group II. Upgrading from grade Group I was associated with older age (*e.g.* odds ratio [OR] = 2.0; 95% CI: 1.0–3.7 for men aged 70+ years *vs.* <60–64 years), pre-treatment PSA concentration (OR = 1.6; 95% CI: 1.0–2.6 for 10–19.9 ng/mL *vs.* <10 ng/mL), higher number of positive cores (OR = 1.6; 95% CI: 1.1–2.4 for 3–4 *vs.* 1–2 cores), fewer biopsy cores (OR = 0.3; 95% CI: 0.1–0.7 for ≥19 cores *vs.* ≤6 cores) and more recent diagnosis (OR = 1.2; 95% CI: 1.1–1.3). No statistically significant associations were detected for clinically evident PNI, clinical stage or biopsy method. Among men with biopsy as grade Group II, upgrading was associated with intermediate and high pre-treatment PSA concentration (*e.g.* OR = 1.6; 95% CI: 1.1–2.1 for PSA 10–19.9 *vs.* <10 ng/mL) and more extensive clinical stage (OR = 5.1; 95% CI: 2.0–12.9 for cT3 *vs.* ≤T2a). No associations were evident in relation to age, PNI, number of cores sampled, number of positive cores, biopsy method or year of diagnosis. The area under the receiver operating curve (AUC) was 0.68 and 0.63 for the models predicting upgrading from grade Group I and grade Group II, respectively.

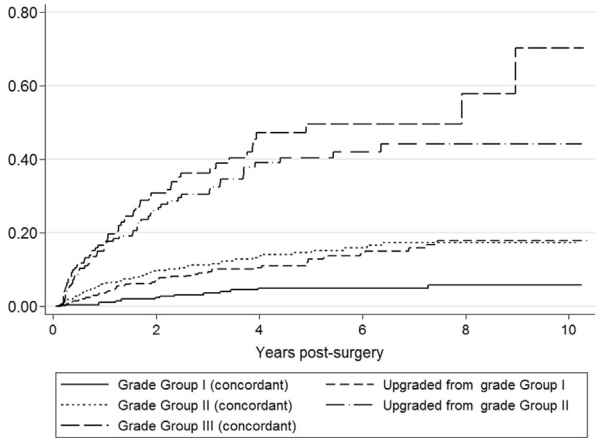

Figure 1 The crude cumulative incidence of biochemical recurrence following prostatectomy for men classified who were subsequently upgraded or downgraded in final surgical pathology.

Table 2 Upgrading/downgrading of grade groupings among men who underwent radical prostatectomy, *n* (%).

Primary RP cases, *n*=2272	Biopsy grade grouping					
	Grade I (3+3)	Grade II (3+4)	Grade III (4+3)	Grade IV (8)	Grade V (9–10)	Total
	n = 762	*n* = 821	*n* = 417	*n* = 193	*n* = 79	
Grade I (3+3)	306 (40)	68 (8)	4 (1)	2 (1)	0	
Grade II (3+4)	386 (51)	522 (64)	113 (27)	22 (11)	4 (5)	
Grade III (4+3)	58 (8)	198 (24)	227 (54)	74 (38)	8 (10)	
Grade IV (8)	8 (1)	18 (2)	41 (10)	60 (31)	10 (13)	
Grade V (9–10)	4 (1)	15 (2)	32 (8)	35 (18)	57 (72)	
Total upgraded	456 (60)	231 (28)	73 (18)	35 (18)	0 (0)	795 (35)
Total downgraded	0 (0)	68 (8)	117 (28)	98 (51)	22 (28)	305 (13)

RP, radical prostatectomy.

Table 3 Risk of biochemical recurrence upgraded cases relative to concordant grade Group I.

Grade category	SHR	95% CI	*p*-Value
Concordant BX- and RP-grade Group I	1.0	—	—
Upgraded from BX-grade Group I	3.1	1.7—6.0	<0.001
Concordant BX- and RP-grade Group II	3.6	1.9—6.9	<0.001
Upgraded from BX-grade Group II	9.4	5.0—17.9	<0.001
Concordant BX- and RP-grade Group III	11.8	6.1—22.6	<0.001

BX, biopsy; CI, confidence interval; RP, radical prostatectomy; SHR, sub-distribution hazard ratio; —, not applicable.
Adjusted sub-hazard ratio for biochemical recurrence from multivariable competing risk regression adjusted for age, year of diagnosis, clinical stage and pre-treatment prostate-specific antigen.
SHR = 0.9 (95% CI: 0.6—1.3, $p = 0.49$) for upgrade from grade group I *vs.* concordant grade group II.
SHR = 0.8 (95% CI: 0.5—1.2, $p = 0.25$) for upgrade from grade group II *vs.* concordant grade group III.

Table 5 shows the results of our analyses of upgrading which would lead to risk group reclassification in men originally classified as having low risk disease likelihood of reclassification was higher among those with biopsy grade Group II (OR = 2.9; 95% CI: 1.6—5.4) compared with biopsy grade Group I. ORs were elevated with respect to percentage of positive cores from 15% to <20% and 20% to <25% compared with <10%, but were not statistically significant. No other associations were evident.

4. Discussion

Our findings indicate that a substantial proportion of men were upgraded following pathological review of their prostatectomy specimen, while a much smaller proportion was downgraded. Being reclassified to a higher grade group was strongly associated with greater risk of BCR, equivalent to that of their "true" grade grouping.

Our finding of 35% upgrading and 13% downgrading is similar to findings reported by Epstein et al. [9] (33% and 10%) who also classified grade according to the new grade groupings and those presented by the SEARCH study Group (27% upgrading and 11% downgrading) where grade classification differed (*i.e.* ≤6, 3 + 4 and ≥4 + 3) [17]. Further, our findings are consistent with results reported from another Australian jurisdiction indicating 31% upgrading and 14% downgrading [18]. Each of these studies indicates greater likelihood of upgrading in lower grade groups, as was the case in our study (60% upgraded from grade Group I and 28% from grade Group II). The proportion of upgrading reported in other studies involving predominantly low risk or low grade cases ranges from 25% to 65% depending on inclusion criteria and grade categories [10,17,19—25].

Overall, most upgrading was from grade Group I to II, which has major implications for treatment decisions. High risk of upgrading among those with supposedly insignificant PCa is likely to be a key factor deterring clinicians and patients from opting for surveillance [26]. Our findings underscore the need for careful consideration in selecting men for AS, especially younger fit men with long life expectancy. They also highlighted the importance of repeat biopsy or further diagnostic evaluation to exclude significant disease due to under-grading errors at initial diagnosis [7].

Upgrading from the lowest grade group was more likely with older age, higher pre-treatment PSA levels, fewer cores at biopsy and more positive cores, which is consistent with others recent studies [9,17,23,25,27—29]. These findings suggested inadequate sampling in men with greater tumour burden [27]. The reason for the observed increased risk of upgrading in more recent years is unclear but this finding is consistent with results from the SEARCH study team who also noted increasing risk with more recent surgery [17].

Interestingly, findings for upgrading from grade Group II indicate greater risk with higher pre-surgical PSA concentration and higher clinical stage, but not higher number of cores sampled or positive cores. The lack of association with number of positive cores is consistent with the findings of Corcoran et al. [30] who specifically examined upgrading from Gleason 3 + 4. While upgrading from grade Group II may be clinically significant for decisions about AS, higher risk in this grade group was more likely in men with PSA >10 ng/mL and those with clinical T stage ≥2b/c, which would likely preclude them from consideration for AS.

Our analysis in men with potential candidates for AS failed to identify any factors that were predictive of upgrading to a higher risk category, with the exception of biopsy grade score (3 + 4). While percentage positive cores is potentially useful in determining risk of progression, it did not independently predict upgrading which would result in reclassification of risk category, and hence, suitability for AS according to current protocols [31]. Number of cores taken was similarly unhelpful, which underscores the need for more accurate methods of determining disease grade at diagnosis.

The AUCs for each of our models predicting upgrading were relatively low (0.68 for grade Group I and 0.63 for grade Group II). Hence it is likely that additional factors may also influence the accuracy of biopsy and likelihood of upgrading. For example, increased body mass index (BMI) [32] and increased serum testosterone levels [33,34] have been found to be independent predictors of upgrading at biopsy in men with low risk or intermediate risk PCa. Likewise, de Cobelli et al. [35] have shown that PiRADs scores from magnetic resonance imaging (MRI) 6—8 weeks after TRUS biopsy independently predicted the likelihood of upgrading and worse prognosis in men with low risk disease, indicating the potential value of MRI in the selection of men for AS. Such findings indicated the need for more refined predictive models for risk stratification to improve selection of men for AS.

The relatively low level of downgrading suggests that decisions to pursue definitive treatment where biopsy indicates intermediate (*i.e.* grade Group II or III) or high grade disease (grade Group IV and V) is not leading to high levels of overtreatment, based on current criteria.

Table 4 Factors predicting risk of upgrading from biopsy grade Group I and grade Group II.

Factors	Grade Group I (n = 735)				Grade Group II (n = 797)			
	No. of upgraded/total	Adj. OR[a]	95% CI	p-Value	No. of upgraded/total	Adj. OR[a]	95% CI	p-Value
Age at diagnosis (year)								
<55	80/139	1.2	0.7–1.9	0.45	22/91	0.8	0.4–1.4	0.35
55–59	93/166	1.1	0.7–1.8	0.58	34/126	0.9	0.6–1.6	0.76
60–64	104/195	1.0	–	–	56/209	1.0	–	–
65–69	109/162	1.7	1.1–2.7	0.03	60/232	0.9	0.6–1.4	0.58
70+	52/73	2.0	1.1–3.7	0.02	50/139	1.5	0.9–2.4	0.10
Pre-treatment PSA ng/mL								
<10	328/570	1.0	–	–	135/538	1.0	–	–
10–19.9	73/107	1.6	1.0–2.6	0.04	46/134	1.6	1.1–2.1	0.02
≥20	12/20	1.5	0.6–4.0	0.41	13/29	2.5	1.2–6.6	0.02
Not reported	38/58	1.1	0.5–2.1	0.87	28/96	1.4	0.8–2.3	0.22
Clinical T stage								
≤T2a	179/318	1.0	–	–	60/247	1.0	–	–
T2b/c	144/225	1.0	0.7–1.5	0.99	97/324	1.4	1.0–2.9	0.08
T3	–	–	–	–	13/23	5.1	2.0–12.9	0.001
Not reported	115/192	1.0	0.7–1.6	0.81	52/203	1.1	0.7–1.7	0.74
Peri-neural invasion								
No evidence	302/503	1.0	–	–	128/483	1.0	–	–
Yes	48/79	1.0	0.6–1.7	0.94	71/248	1.2	0.8–1.6	0.51
Not reported	96/153	1.4	0.9–2.1	0.11	23/66	1.7	0.9–3.0	0.09
Biopsy procedure								
TRUS	425/707	1.0	–	–	211/247	1.0	–	–
Trans-perineal	13/28	0.8	0.5–1.4	0.40	11/32	1.2	0.7–1.9	0.52
No. of biopsy cores								
≤6	59/97	1.0	–	–	16/55	1.0	–	–
7–11	110/204	0.7	0.4–1.3	0.24	66/225	1.2	0.6–2.3	0.68
12–14	174/270	0.8	0.4–1.3	0.30	82/304	1.0	0.5–2.1	0.95
15–18	62/99	0.5	0.3–1.0	0.06	31/122	1.0	0.4–2.2	0.95
≥19	33/65	0.3	0.1–0.6	0.005	27/91	1.1	0.4–2.7	0.91
No. of positive cores								
≤2	163/309	1.0	–	–	35/136	1.0	–	–
3–4	125/201	1.6	1.1–2.4	0.02	65/230	1.1	0.7–1.8	0.71
5–7	106/168	1.5	1.0–2.3	0.07	77/267	1.1	0.7–1.8	0.69
≥8	44/59	2.3	1.2–4.7	0.02	24/164	0.9	0.5–1.6	0.68
Diagnosis year (continuous)	–	1.2	1.1–1.3	0.001	–	1.0	0.9–1.0	0.43

Adj. OR, adjusted odds ratio; CI, confidence interval; PSA, prostate-specific antigen; TRUS, transrectal ultrasound guided.
[a] Multi-variable logistic regression, adjusted for all factors simultaneously; –, not applicable.

Furthermore, only 25% of those downgraded would be eligible for AS (*i.e.* shifted to grade Group I) since most downgrading involved reclassification from grade Group III to II or IV to III.

The consistently high level of upgrading indicates a clear need for more accurate assessment of grade through improved diagnostic biopsy methods. While there has been a shift from 6 to 12–14 core needle biopsies and an increasing use of saturation biopsy (>20 cores) in recent years, accuracy of grade remains uncertain due to the non-targeted nature of sampling in TRUS guided biopsy methods [11]. Template perineal and image-guided fusion biopsy approaches may provide more accurate assessment of grading. One promising development is the use of multi-parametric magnetic resonance image (mp-MRI) targeted biopsy, whereby lesions identified as intermediate or high grade (*i.e.* Gleason score 4 or 5) can be targeted during biopsy. Multiple studies reported higher detection rates for significant PCa compared with standard TRUS biopsy methods which are not targeted [36,37]. While the role of mp-MRI in determining suitability for AS is still being evaluated, and no clinical guidelines are available, the combination of MRI rating and grading on biopsy may be a future standard for consideration for AS [38,39]. Similarly, trans-perineal biopsy, which better samples the anterior zone, may offer more accurate assignment of grade at diagnosis [40]. While we included trans-perineal versus TRUS biopsy in our modelling, no difference in risk of upgrading was observed, which may be due to small numbers in our cohort who underwent trans-perineal biopsy (~5%). While MRI-guided and trans-perineal approaches are increasingly being used in the diagnostic setting, higher costs and inefficiencies in throughput may limit widespread implementation [26]. In the absence of access to these newer

Table 5 Factors associated with upgrading leading to reclassification of risk category among men with low risk prostate cancer at biopsy.

Factors (Low risk disease only $n = 409$)	No. reclassified/ total	Adj. OR[a]	95% CI	*p*-Value
Age at diagnosis (cont.)	60/409	1.0	1.0—1.1	0.80
Year diagnosis (cont.)	—	1.0	0.9—1.1	0.54
Pre-treatment PSA ng/mL (cont.)	—	1.1	1.0—1.3	0.11
Grade Group				
- I	25/260	1.0	—	—
- II	35/149	2.9	1.6—5.3	
Clinical stage				
- T1c	18/156	1.0	—	—
- T2	42/253	1.5	0.8—2.9	0.22
No. cores taken (cont)	—	1.0	1.0—1.1	0.58
Percent positive cores				
- <10	8/91	1.0	—	—
- 10 to <15	13/81	1.7	0.7—4.6	0.26
- 15 to <20	22/100	2.1	1.0—5.2	0.11
- 20 to <25	12/64	1.8	0.6—4.8	0.27
- 25 or more	5/73	0.5	0.1—1.5	0.20

Adj. OR, adjusted odds ratio; CI, confidence interval; PSA, prostate-specific antigen; —, not applicable.

[a] Multivariable logistic regression, adjusted for all factors simultaneously.

technologies, consideration should be given to the idea of a mandatory second pathological opinion on all biopsy specimens, as advocated by Brimo et al. [41].

In undertaking this study we did not commission a review the original grade assignment but rather reclassified groupings based on recorded primary and secondary Gleason patterns. In addition, data on several clinical factors which are known to predict upgrading were unavailable or were inconsistently collected within our cohort so could not be included in our models (*e.g.* prostate size, tumour volume, PSA density, BMI, testosterone levels, MRI findings). Despite these limitations we can conclude upgrading of biopsy grade occurs frequently among men diagnosed who undergo RP, most often involving upgrading from lower grade groups.

5. Conclusion

The high proportion of discordant grading at biopsy has major consequences for adopting conservative management for men with supposed low risk PCa. The high risk of undergrading at biopsy is likely to deter some clinicians from recommending AS and discourage some men from opting for AS to manage their PCa. Current research suggests that trans-perineal and MRI guided biopsy approaches are likely to improve accuracy of grading at diagnosis. Where resources and logistics limit access to these emerging techniques, early repeat saturation biopsy or second pathology review, particularly for men classified as grade Group I or II on initial biopsy who are considering AS, is recommended.

Author contributions

Study design: Kerri Beckmann, David Roder, Kim Moretti.
Data acquisition: Michael O'Callaghan, Kim Moretti.
Data analysis: Kerri Beckmann, Andrew Vincent.
Drafting of manuscript: Kerri Beckmann.
Critical revision of the manuscript: Kerri Beckmann, Michael O'Callaghan, Andrew Vincent, Penelope Cohen, Martin Borg, David Roder, Sue Evans, Jeremy Millar, Kim Moretti.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

The authors wish to thank Ms. Tina Kopsaftis (SA-PCCOC Clinical Data Coordinator) and Mr. Scott Walsh (SA-PCCOC Data Manager) for their technical support in managing and compiling data. We also wish to thank collaborating clinicians for their ongoing contributions to the database and the men who participated in the registry. This project was funded by the Movember Foundation as part of their Australian and New Zealand prostate cancer outcomes registry initiative (PCOR-ANZ) which aims to develop a binational clinical registry for outcomes monitoring and research to inform practice and improve outcomes for men with prostate cancer. Dr. Beckmann is supported by an NHMRC Early Career Researcher Fellowship.

References

[1] National Comprehensive Cancer Network. NCCN clinical proactice guidelines in oncology: prostate cancer. Washington, DC, USA: NCCN; 2015 [Accessed May 12, 2018]. https://www.nccn.org/patients/guidelines/prostate/58/index.html.

[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. J Am Med Assoc 1998;280:969—74.

[3] Cooperberg MR, Pasta DJ, Elkin EP, Litwin MS, Latini DM, Du Chane J, et al. The University of California, San Francisco Cancer of the prostate risk assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol 2005;173:1938—42.

[4] 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.

[5] Eggener SE, Badani K, Barocas DA, Barrisford GW, Cheng JS, Chin AI, et al. Gleason 6 prostate cancer: translating biology into population health. J Urol 2015;194:626—34.

[6] Ross HM, Kryvenko ON, Cowan JE, Simko JP, Wheeler TM, Epstein JI. Do adenocarcinomas of the prostate with Gleason score (GS) ≤6 have the potential to metastasize to lymph nodes? Am J Surg Pathol 2012;36:1346—52.
[7] Bruinsma SM, Bangma CH, Carroll PR, Leapman MS, Rannikko A, Petrides N, et al. Active surveillance for prostate cancer: a narrative review of clinical guidelines. Nat Rev Urol 2016;13:151—67.
[8] Sandhu GS, Andriole GL. Active surveillance for prostate cancer: barriers to widespread adoption. Eur Urol 2012;62: 984—5.
[9] Epstein JI, Feng Z, Trock BJ, Pierorazio PM. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol 2012;61:1019—24.
[10] Schreiber D, Wong AT, Rineer J, Weedon J, Schwartz D. Prostate biopsy concordance in a large population-based sample: a surveillance, epidemiology and end results study. J Clin Pathol 2015;68:453—7.
[11] Scattoni V, Maccagnano C, Capitanio U, Gallina A, Briganti A, Montorsi F. Random biopsy: when, how many and where to take the cores? World J Urol 2014;32:859—69.
[12] Beckmann K, Pinnock C, Tamblyn DJ, Kopsaftis T, Stapleton AM, Roder DM. Clinical and socio-demographic profile of an Australian multi-institutional prostate cancer cohort. Asia Pac J Clin Oncol 2009;5:247—56.
[13] Epstein JI, Allsbrook WC, Amin MB, Egevad LL, Committee IG. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005;29:1228—42.
[14] Stephenson AJ, Kattan MW, Eastham JA, Dotan ZA, Bianco FJ, Lilja H, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. J Clin Oncol 2006;24:3973—8.
[15] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94: 496—509.
[16] StataCorp. Stata statistical software: release 12. College Station, TX: StatCorp LP; 2010.
[17] Freedland SJ, Kane CJ, Amling CL, Aronson WJ, Terris MK, Presti JC, et al. Upgrading and downgrading of prostate needle biopsy specimens: risk factors and clinical implications. Urology 2007;69:495—9.
[18] Evans SM, Patabendi BV, Kronborg C, Earnest A, Millar J, Clouston D. Gleason group concordance between biopsy and radical prostatectomy specimens: a cohort study from prostate cancer outcome registry—victoria. Prostate Int 2016;4: 145—51.
[19] Moussa AS, Kattan MW, Berglund R, Yu C, Fareed K, Jones JS. A nomogram for predicting upgrading in patients with low- and intermediate-grade prostate cancer in the era of extended prostate sampling. BJU Int 2010;105:352—8.
[20] Moussa AS, Li J, Soriano M, Klein EA, Dong F, Jones JS. Prostate biopsy clinical and pathological variables that predict significant grading changes in patients with intermediate and high grade prostate cancer. BJU Int 2009;103:43—8.
[21] Corcoran NM, Casey RG, Hong MK, Pedersen J, Connolly S, Peters J, et al. The ability of prostate-specific antigen (PSA) density to predict an upgrade in Gleason score between initial prostate biopsy and prostatectomy diminishes with increasing tumour grade due to reduced PSA secretion per unit tumour volume. BJU Int 2012;110:36—42.
[22] Athanazio D, Gotto G, Shea-Budgell M, Yilmaz A, Trpkov K. Global Gleason grade groups in prostate cancer: concordance of biopsy and radical prostatectomy grades and predictors of upgrade and downgrade. Histopathology 2017;70:1098—106.
[23] Marra G, Eldred-Evans D, Challacombe B, Van Hemelrijck M, Polson A, Pomplun S, et al. Pathological concordance between prostate biopsies and radical prostatectomy using transperineal sector mapping biopsies: validation and comparison with transrectal biopsies. Urol Int 2017;99:168—76.
[24] Quintana L, Ward A, Gerrin SJ, Genega EM, Rosen S, Sanda MG, et al. Gleason misclassification rate is independent of number of biopsy cores in systematic biopsy. Urology 2016;91:143—9.
[25] Yang CW, Lin TP, Huang YH, Chung HJ, Kuo JY, Huang WJ, et al. Does extended prostate needle biopsy improve the concordance of Gleason scores between biopsy and prostatectomy in the Taiwanese population? J Chin Med Assoc 2012; 75:97—101.
[26] Rosenkrantz AB, Taneja SS. Prostate MRI can reduce overdiagnosis and overtreatment of prostate cancer. Acad Radiol 2015;22:1000—6.
[27] Mizuno K, Inoue T, Kinoshita H, Yano T, Kawanishi H, Kanda H, et al. Evaluation of predictors of unfavorable pathological features in men eligible for active surveillance using radical prostatectomy specimens: a multi-institutional study. Jpn J Clin Oncol 2016;46:1156—61.
[28] Porcaro AB, Siracusano S, de Luyk N, Corsi P, Sebben M, Tafuri A, et al. Clinical factors stratifying the risk of tumor upgrading to high-grade disease in low-risk prostate cancer. Tumori 2018;104:111—5.
[29] Vora A, Large T, Aronica J, Haynes S, Harbin A, Marchalik D, et al. Predictors of Gleason score upgrading in a large African-American population. Int Urol Nephrol 2013;45:1257—62.
[30] Corcoran NM, Hong MK, Casey RG, Hurtado-Coll A, Peters J, Harewood L, et al. Upgrade in Gleason score between prostate biopsies and pathology following radical prostatectomy significantly impacts upon the risk of biochemical recurrence. BJU Int 2011;108:e202—10.
[31] Kinsella N, Helleman J, Bruinsma S, Carlsson S, Cahill D, Brown C, et al. Active surveillance for prostate cancer: a systematic review of contemporary worldwide practices. Transl Androl Urol 2018;7:83—97.
[32] de Cobelli O, Terracciano D, Tagliabue E, Raimondi S, Galasso G, Cioffi A, et al. Body mass index was associated with upstaging and upgrading in patients with low-risk prostate cancer who met the inclusion criteria for active surveillance. Urol Oncol 2015;33:e1—8.
[33] Porcaro AB, De Luyk N, Corsi P, Sebben M, Tafuri A, Cacciamani G, et al. Preoperative plasma levels of total testosterone associated with high grade pathology-detected prostate cancer: preliminary results of a prospective study in a contemporary cohort of patients. Curr Urol 2017;10:72—80.
[34] Ferro M, Lucarelli G, Bruzzese D, Di Lorenzo G, Perdona S, Autorino R, et al. Low serum total testosterone level as a predictor of upstaging and upgrading in low-risk prostate cancer patients meeting the inclusion criteria for active surveillance. Oncotarget 2017;8:18424—34.
[35] de Cobelli O, Terracciano D, Tagliabue E, Raimondi S, Bottero D, Cioffi A, et al. Predicting pathological features at radical prostatectomy in patients with prostate cancer eligible for active surveillance by multiparametric magnetic resonance imaging. PLoS One 2015;10:e0139696. https://doi.org/10.1371/journal.pone.0139696.
[36] Futterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, Kirkham A, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. Eur Urol 2015;68:1045—53.
[37] Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MG. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-

guided biopsy: a systematic review and meta-analysis. Eur Urol 2015;68:438—50.
[38] Barrett T, Haider MA. The emerging role of MRI in prostate cancer active surveillance and ongoing challenges. AJR Am J Roentgenol 2017;208:131—9.
[39] Tay KJ, Gupta RT, Holtz J, Silverman RK, Tsivian E, Schulman A, et al. Does mpMRI improve clinical criteria in selecting men with prostate cancer for active surveillance? Prostate Cancer Prostatic Dis 2017;20:323—7.
[40] Scott S, Samaratunga H, Chabert C, Breckenridge M, Gianduzzo T. Is transperineal prostate biopsy more accurate than transrectal biopsy in determining final Gleason score and clinical risk category? A comparative analysis. BJU Int 2015; 116:26—30.
[41] Brimo F, Schultz L, Epstein JI. The value of mandatory second opinion pathology review of prostate needle biopsy interpretation before radical prostatectomy. J Urol 2010;184: 126—30.