BJU Int 2025 doi:10.1111/bju.70109

Original Article

BJUI
BJU International

Comparable recurrence risk for MRI-detected Gleason Grade Group (GG) 2 and systematic biopsy-detected GG1 prostate cancer

Abderrahim-Oussama Batouche[1,2,3†], Eugen Czeizler[1,3†], Timo-Pekka Lehto[1,3], Andrew Erickson[1,3,6], Tolou Shadbahr[1,3], Teemu D. Laajala[1], Joona Pohjonen[1,3], Tuomas Mirtti[1,3,4,7] and Antti S. Rannikko[1,3,5]

[1]*Research Program in Systems Oncology, Research Programs Unit, Faculty of Medicine,* [2]*Doctoral Program in Computer Science, University of Helsinki,* [3]*ICAN-Digital Precision Cancer Medicine Flagship,* [4]*Department of Pathology,* [5]*Department of Urology, Helsinki University Hospital, Helsinki, Finland,* [6]*Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, and* [7]*Department of Biomedical Engineering, Emory University, Atlanta, GA, USA*

†A.-O.B. and E.C. contributed equally.

Objective

To determine the likelihood of definitive treatment and risk of post-treatment recurrence for patients with Gleason Grade Group (GG) 2 cancer diagnosed using targeted biopsies relative to men with GG1 cancer diagnosed using systematic biopsies.

Materials and Methods

We performed a retrospective study using a large tertiary centre registry (the HUS Acamedic data lake) to retrieve data on prostate cancer (PCa) diagnosis, treatment, and cancer recurrence. We included patients with either GG1 PCa detected by systematic biopsies (n = 3317) or GG2 PCa detected with targeted biopsies (n = 554) between 1993 and 2019. We assessed the risk of curative treatment and recurrence after treatment. Kaplan–Meier curves were used to estimate treatment- and recurrence-free survival, and Cox proportional hazards regression was used to evaluate the risk of post-treatment recurrence.

Results

Patients with systematic biopsy-detected GG1 cancer had a significantly longer median time to treatment (31 months) than those with targeted biopsy-detected GG2 cancer (4 months; $P < 0.0001$). Risk of recurrence after curative treatment was similar in the two groups, with the upper bound of the 95% confidence interval (CI) excluding any significant difference (hazard ratio 1.04, 95% CI 0.75–1.43; $P = 0.83$).

Conclusion

Men diagnosed with GG2 PCa based on MRI-targeted biopsy had a similar risk of recurrence after treatment compared to men with GG1 disease diagnosed using systematic biopsy, although they were more likely to undergo curative treatment. These findings suggest that at least a portion of the apparent increase in GG2 diagnoses in the MRI era may reflect reclassification rather than more aggressive disease. Improved risk stratification is needed to identify which men with MRI-era GG2 cancer may be suitable for active surveillance.

Keywords

GG2, magnetic resonance imaging, neoplasm grading, recurrence, survival, watchful waiting

Introduction

Until the early 2010s, prostate cancer (PCa) was typically diagnosed using systematic TRUS-guided biopsy [1]. Recently, MRI-guided targeted biopsies have gained popularity [2]. MRI targeting has been purported to improve both the sensitivity and specificity of biopsy, avoiding biopsy in men at low risk of high-grade cancer, and thereby reducing the risk

of overdiagnosis and biopsy-related complications [3,4] and ensuring that the regions of the prostate most likely to harbour aggressive disease are sampled. Currently, clinical guidelines, including those of the American Urology Association and the European Association of Urology, support active surveillance (AS) for selected men with Gleason Grade Group (GG) 2 PCa [5,6].

There is compelling evidence that targeted biopsy has decreased the detection of low-grade cancers and increased the detection of higher-grade cancers compared to systematic biopsy [3,7–9]. For instance, in the PRECISION trial, men randomised to the MRI pathway had a 13% absolute decrease in GG1 cancers and a 12% increase in GG2 cancers [7]. However, it is plausible that this finding is attributable, at least in part, to the reclassification of GG1 cancers as GG2 cancers, in other words, grade inflation. Indirect evidence for grade inflation comes from the observation that MRI targeting finds many high-grade cancers in groups of men who are known to have a very low risk of PCa mortality, such as those with a negative systematic biopsy result [10]. However, there have been few direct comparisons of the relative recurrence risk of tumours identified using MRI targeted vs systematic biopsy [11,12].

In this study, we examine large-scale registry data to compare PCa risks according to method of cancer detection. Specifically, we compared the recurrence rates between systematic biopsy-detected GG1 PCa and MRI targeted biopsy-detected GG2 PCa as a direct evaluation of the grade inflation hypothesis.

Materials and Methods

We used the Finnprostate dataset, a large patient registry study combining Finnish national healthcare data with local hospital data (n = 700 000) from men suspected of having PCa (based on PSA measurement) or diagnosed with PCa (Fig. S1). From Finnprostate, we gathered a sub-cohort of men from the Hospital District of Helsinki and Uusimaa (HUS; n = 326 796) with comprehensive patient information regarding outpatient clinic and hospital visits, as well as data on laboratory tests, medication, radiological, pathological, and surgical reports, and comorbidities, for the period 1993 to 2019. Men with pathology data available at biopsy were further selected for the analysis. The above data are embedded within the regional HUS Acamedic data lake.

We identified patients with an initial diagnosis of GG1 PCa in systematic biopsies or GG2 PCa in MRI targeted biopsies. The groups in our study were defined based on the diagnostic evaluation decisions made by the treating urologists. Although the recommendation (since 2014) was to use multiparametric (mp)MRI as a triage test before prostate biopsy in all men with suspected PCa, the final decision on the diagnostic approach was at the discretion of the treating urologist. Patients with a positive mpMRI underwent MRI targeted biopsy using a TRUS-MRI fusion biopsy system (UroNav, Philips Healthcare), with two to four cores taken per lesion. To avoid overdiagnosis, concomitant systematic biopsies were not routinely performed.

Treatment type was missing for 6% of the patients. To mitigate the effect of any missing treatment information on treatments with curative intent, a PSA drop of at least 75% but not less than 3 ng/mL within 1 year or at least 50% but not less than 4 ng/mL within 1 year were considered an indication of treatment with curative intent. AS was defined as no curative treatment received or the period from diagnosis until the first curative treatment received. These criteria correctly detect 90% of our known first curative treatments [13]. Depending on the kinetics of the PSA drop, we classified a drop below 0.1 ng/mL as radical prostatectomy (RP); otherwise, it was classified as radiation therapy (RT) [13]. Sankey diagrams were generated to display the treatment trajectories (Fig. S3).

Patients were considered to have experienced clinical recurrence (CR) based on either biochemical recurrence or second-line treatment (Fig. S2). Thus, the CR definition considered the clinical reality that some men are being referred to second-line treatment before the official definition of biochemical recurrence has been reached. We defined biochemical recurrence after RP as a PSA increase over 0.2 ng/mL, as this has been used in our centre as a trigger for salvage treatments after RP. For biochemical recurrence after RT, the definition was a PSA increase of 2 ng/mL over the nadir [13].

Statistical Methods

Our null hypothesis was that there would be no significant difference in risk of recurrence after treatment between GG1 detected with systematic biopsy and GG2 detected with MRI targeted biopsy. Descriptive statistics were used to summarise and present baseline characteristics, while inferential statistics were used to assess the likelihood of definitive treatment and risk of post-treatment recurrence. Kaplan–Meier survival curves and log-rank tests were used to analyse treatment- and relapse-free survival models.

We performed a series of sensitivity analyses to assess the robustness of the conclusions. Relapse-free survival was analysed in patients treated with RP alone to mitigate the effect of androgen deprivation therapy, which may have been present those treated with RT.

Given the long study period (1993–2019) and the associated uncertainties and evolving recommendations, we analysed recurrence data across different International Society of

Urological Pathology (ISUP) diagnostic eras at our study centre: patients diagnosed before 2005, between 2005 and 2010, and after 2010.

Men who were eventually treated after a period of surveillance longer than 1 year were more likely to have experienced an evolution of their PCa since their initial GG diagnosis. Therefore, we separately analysed a cohort of patients treated within 1 year of diagnosis: those treated only with RP within 1 year of diagnosis, those treated only with RT within 1 year of diagnosis, and those diagnosed with GG1 and never upgraded in subsequent biopsies.

Based on these four sub-cohorts, we performed Cox proportional hazards regression analysis to assess the risk of post-treatment recurrence in 'GG1 NoMRI' and 'GG2 MRI' patients. Furthermore, these analyses were controlled for PSA levels and the number of positive cores.

All analyses were performed using R Statistical Software (v4.1.2; R Core Team 2021), including the 'survival' and 'survminer' packages in R software (version 4.1), while Python (version 3.10) was used for data preprocessing.

Results

We identified 8407 patients diagnosed with GG1 or GG2 PCa (with and without MRI). We excluded patients for whom we were unable to identify their first biopsy with a PCa diagnosis, as well as patients who were over 80 years of age at the time of their first biopsy (Fig. S1). The final study cohort consisted of 3317 patients with systematic biopsy who were diagnosed with GG1 cancer and 554 patients with targeted biopsy who were diagnosed with GG2 cancer (Table 1). Patients with GG1 MRI and GG2 NoMRI, although not the main focus of this study, were added for completeness of the analysis (Tables 1 and 2).

Treatment patterns were visualised by plotting treatment trajectories in Sankey diagrams for the two groups (Fig. S3). In Kaplan–Meier analysis, the likelihood of curative treatment was significantly lower for men with systematic biopsy-detected GG1 compared to men with targeted biopsy-detected GG2: hazard ratio (HR) 2.1 (95% CI 1.9–2.4; $P < 0.05$ [Fig. 1b]). This result was also confirmed when modelling the likelihood of any type of treatment (Fig. 1a). The risk of curative treatment within 1 year of diagnosis was 39% for GG1 and 72% for GG2.

Next, we compared the pathology at biopsy with that of prostatectomy in RP-treated men. In 75% of the 268 men who had targeted biopsy-detected GG2 PCa, the biopsy pathology was concordant with RP pathology. In 564 men with systematic biopsy-detected GG1 PCa, the concordance was only 33% ($P < 0.0001$). In addition, 67% and 16% of the 564 men with systematic biopsy-detected GG1 PCa and 99% and 24% of the 268 men with targeted biopsy-detected GG2 PCa, who underwent RP, had GG2–5 and GG3–5 PCa at final pathology, respectively.

Finally, we compared relapse (CR)-free survival between men diagnosed with GG1 cancer using systematic biopsy and men diagnosed with GG2 cancer using targeted biopsy. In the Kaplan–Meier analysis that modelled recurrence after curative treatment (Fig. 2a), the curves virtually overlapped, with no statistically significant difference in median survival (HR 1.04, 95% CI 0.75–1.43; $P = 0.83$). This was additionally confirmed when modelling the CR after RP (HR 0.94, 95% CI 0.6–1.5; $P = 0.78$ [Fig. 2b]) and after RT up to 3 years after the treatment (HR 1.34, 95% CI 0.85–2.09; $P = 0.21$ [Fig. 2c]). Further, Cox proportional hazard models comparing different pairs of groups across treatment settings showed that the GG1 NoMRI and GG2 MRI groups had stable and confirmed 'no significant difference', compared to other models (Fig. 2, Table 2), and that systematic biopsy-detected GG2 was associated with a higher risk of recurrence than targeted biopsy-detected GG1 (Fig. 2).

In the sensitivity analyses, there was no statistically significant difference in recurrence between systematic biopsy-detected GG1 and targeted biopsy-detected GG2 in men with RP within the first year after diagnosis or when upgrading was excluded after diagnosis of GG1. A statistically significant

Table 1 Demographics of the study cohorts.

	GG1 NoMRI	GG2 MRI	GG1 MRI	GG2 NoMRI
Number of patients	3317	554	335	2759
Median age at diagnosis, years (quartiles)	66 (61–72)	67 (62–72)	66 (60–71)	68 (62–73)
Median PSA at diagnosis, ng/mL (quartiles)	7.3 (5.1–10.5)	8.1 (5.7–12.7)	8.19 (5.51–11.6)	8.41 (5.9–12.5)
CR* events (CR in 5 years)	517 (336)	43 (43)	18 (6)	511 (304)
Treatments				
RP (RP in 5 years)	655 (631)	184 (184)	56 (56)	751 (748)
RT (RT in 5 years)	1228 (1067)	126 (125)	78 (76)	994 (940)
MT	283 (199)	120 (120)	24 (24)	428 (372)
All	2166 (1897)	430 (429)	158 (156)	2173 (2060)

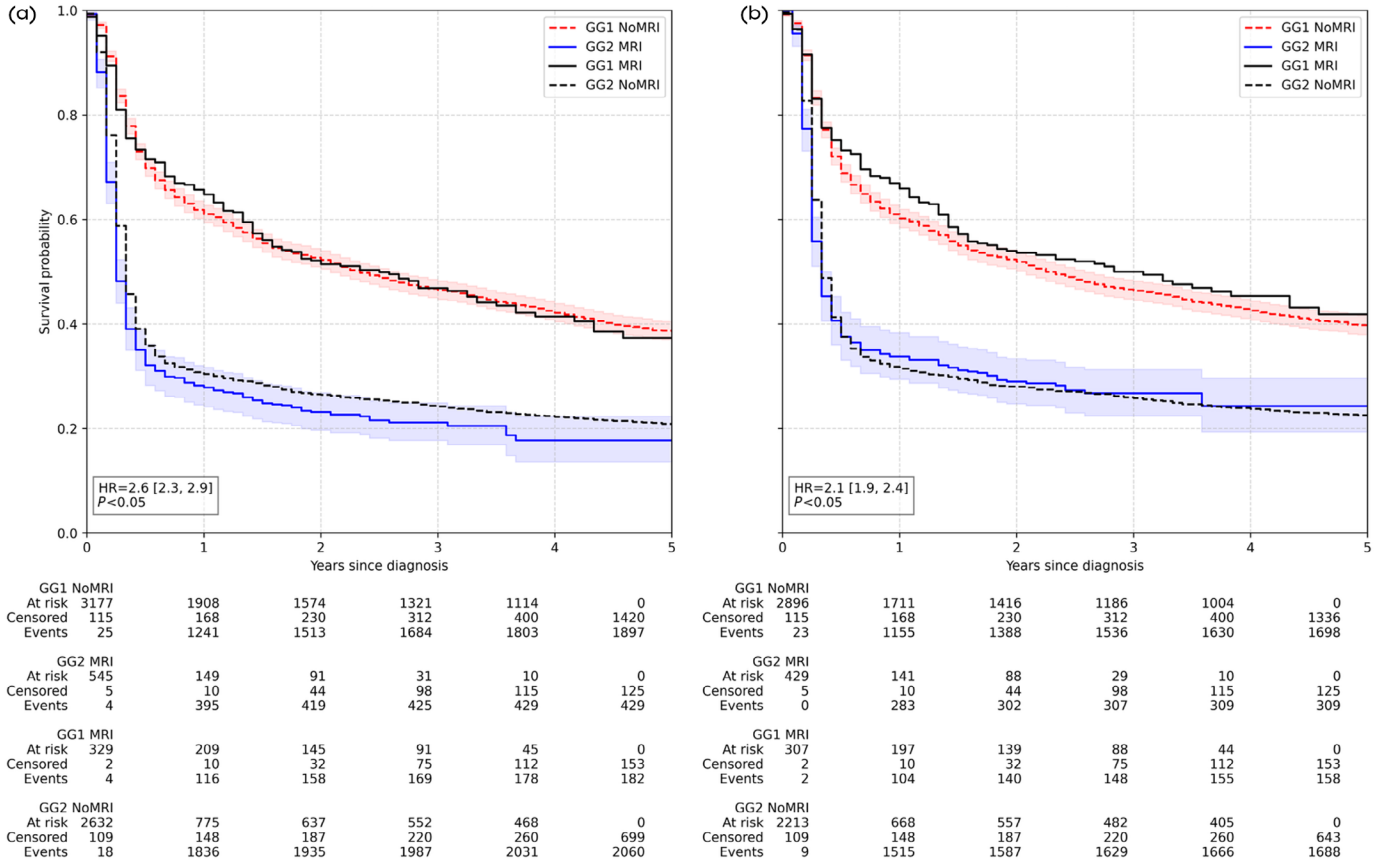
*CR, clinical recurrence; GG, Gleason Grade Group; MT, medication; RP, radical prostatectomy; RT, radiation therapy. *Biochemical recurrence event or a secondary treatment.*

Table 2 Summary of the relapse-free survival Cox proportional hazards models comparing different pairs of groups across treatment settings.

Pairs		After curative treatment				After radical prostatectomy				After radiation therapy			
		HR	CI lower	CI upper	*P*	HR	CI lower	CI upper	*P*	HR	CI lower	CI upper	*P*
GG1 NoMRI	GG1 MRI	2.90	1.29	6.51	*	3.69	0.91	14.94	0.07	2.36	0.88	6.34	0.09
GG2 MRI	GG1 MRI	2.99	1.27	7.02	*	3.36	0.79	14.30	0.10	3.22	1.10	9.40	*
GG2 NoMRI	GG1 MRI	2.64	1.18	5.94	*	5.01	1.24	20.20	*	1.52	0.56	4.12	0.41
GG2 MRI	**GG1 NoMRI**	**1.04**	**0.75**	**1.43**	**0.83**	**0.94**	**0.59**	**1.49**	**0.78**	**1.34**	**0.85**	**2.09**	**0.21**
GG2 NoMRI	GG1 NoMRI	0.96	0.82	1.12	0.61	1.39	1.09	1.77	*	0.72	0.59	0.89	*
GG2 NoMRI	GG2 MRI	0.87	0.63	1.20	0.41	1.43	0.92	2.24	0.12	0.47	0.30	0.76	*

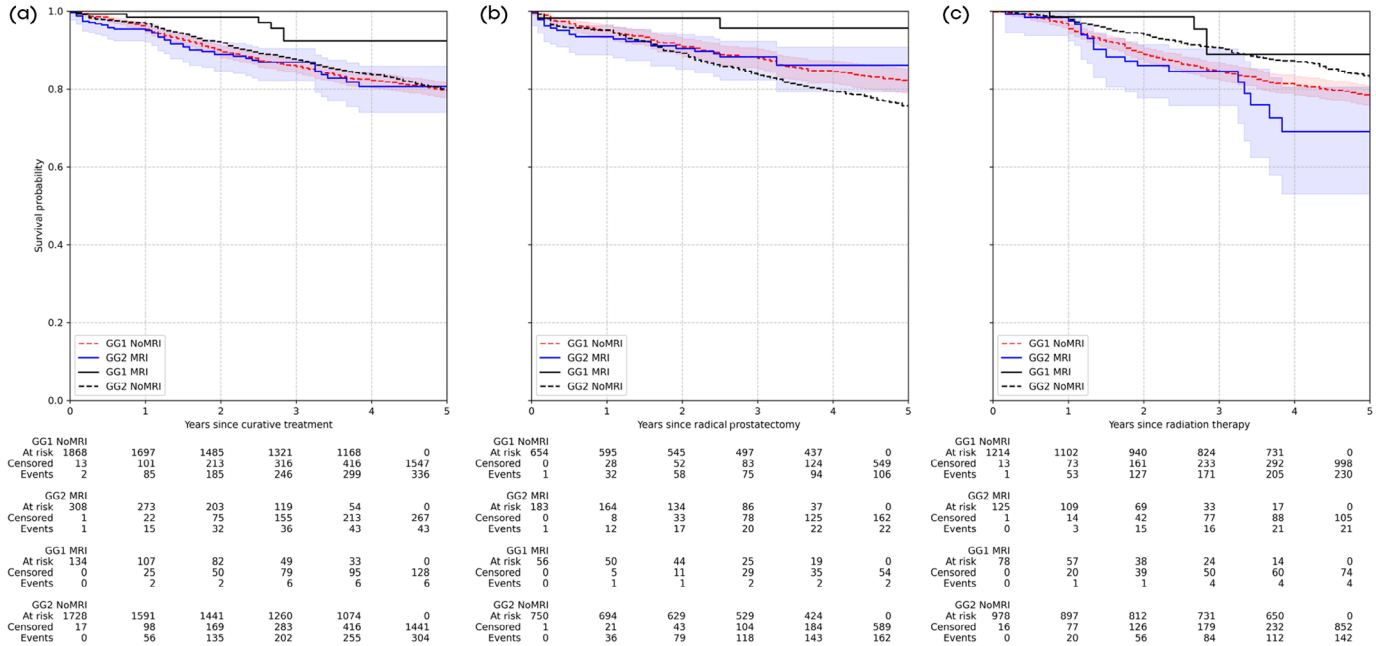
*GG, Gleason Grade Group; HR, hazard ratio. P values had a level of significance threshold α = 0.05. The only consistently nonsignificant comparison was GG2 MRI vs GG1 NoMRI, which is central to this study's hypothesis, and is shown in bold. *P < α.*

Fig. 1 Five-year treatment-free survival (Kaplan–Meier) for the Gleason Grade Group (GG) 1 NoMRI (red), GG2 MRI (blue), GG1 MRI and GG2 NoMRI (black) patient groups. (**a**) All types of treatment. (**b**) Only radical prostatectomy and radiation therapy. For our group of interest, the 95% CI is illustrated by corresponding colour lines. Hazard ratio (HR) and *P* values are included. The start time was defined as the date of diagnosis.



difference was found in men who received treatment within the first year of diagnosis across all curative treatments and in the RT subgroup (Fig. S4–S7 and Tables S1 and S2). After adjusting our analysis for different ISUP diagnostic eras, a higher risk of recurrence was observed in men treated with surgery before 2005. A similar trend was seen in those treated with RT, but no difference was found in the combined analysis (Fig. S8).

Fig. 2 Five-year relapse-free survival (Kaplan–Meier) for the Gleason Grade Group (GG) 1 NoMRI (red) and GG2 MRI (blue) patient groups, and the GG1 MRI and GG2 NoMRI (black) patient groups. (**a**) After any curative treatment (radical prostatectomy [RP] + radiation therapy [RT]). (**b**) After RP only. (**c**) After RT only. The 95% CI is illustrated with corresponding colour lines for the group of interest. Hazard ratios and *P* values are summarised in Table 2. The start time was defined as the date of treatment.



Discussion

The use of MRI targeted biopsies has led to a lower detection rate of GG1 PCa and an increased detection rate of GG2. Although this finding is generally attributed to the improved sensitivity and specificity of MRI for aggressive cancers, it might also be explained by grade inflation. We found direct evidence to support this hypothesis: GG2 cancers detected by MRI targeted biopsy showed no greater risk of recurrence than GG1 cancers detected by systematic biopsy. Not only were differences between groups nonsignificant, but the upper bound of the 95% CI also excluded a clinically relevant effect. In our main analysis, the upper bound of the HR between GG2 and GG1 was 1.43, and the highest upper bound found in the main sensitivity analyses was 2. Both values were far lower than those typically reported. For instance, in the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram, the HR for biochemical recurrence comparing GG2 to GG1 was approximately 3 [14]. Patients treated in the first year represent a clinically interesting group (Fig. S4), and the observed HR suggests a potential effect that prompted us to conduct further evaluation. When relapse-free survival was assessed within the first year after RP (Fig. S5) and RT (Fig. S6) separately, the difference in outcome seemed to be driven by men treated with RT only. This likely reflects selection of higher-risk cases for RT, but because there was no clinical staging information, we could not evaluate this further.

Limited use of MRI and known poor adherence to repeat biopsies in AS protocols during the systematic biopsy era may have hindered detection of occult higher-risk cancers, thereby influencing outcomes [15]. The present guideline recommendation is to use MRI at diagnosis and during AS to guide AS eligibility and treatment decisions [16]. In current practice, the major distinction is between GG1, which can be managed conservatively, and GG2 or higher, which generally requires treatment. However, a sub-cohort of low-volume pre-MRI era GG≤2 intermediate-risk PCa has been shown to have a similar prognosis to that of low-risk PCa in AS, according to a recent meta-analysis [17]. Furthermore, there are accumulating data on the extent of Gleason pattern 4, total cancer length, PSA density, and perineural invasion determining adverse findings in RP and worse prognosis during follow-up. However, these studies were conducted mainly in systematic biopsy cohorts, and differences between systematic biopsies and targeted biopsies indicate that they may predict recurrence risk differently [18]. Our observation of recurrence differences in the MRI era, despite comparable treatment rates between the groups regardless of MRI status, suggests that MRI targeting has led to more appropriate treatment selection rather than reflecting inherently more aggressive disease. Our results are further evidence to suggest that more men with MRI-era GG2 PCa could be monitored but a more precise risk stratification among targeted biopsy-detected cancers is warranted. Hence, before more long-term data accumulate from targeted biopsy studies,

treatment decisions should be based on individual risk assessments, not solely on the highest GG stratification and prediction nomograms that use systematic biopsy data [19].

The natural course of the disease is favourable, especially for low- and intermediate-risk PCa, as demonstrated in the recently updated ProtecT trial, which reported a PCa-specific mortality of only approximately 3% after a 15-year follow-up, irrespective of the treatment [20]. Thus, studies comparing PCa-specific mortality between patients diagnosed with systematic biopsy and those diagnosed with targeted biopsy are not expected at any time. We therefore considered it justified to use surrogates such as recurrence after curative treatment as outcomes, although we acknowledge that, over a longer follow-up, more events, and perhaps differences, might be observed.

The existing literature on targeted biopsy-induced grade inflation is mostly based on data available at diagnosis (pathology at biopsy and RP) and extrapolation to create cohorts with virtually no PCa mortality after benign or low-grade prostate cancer on systematic biopsy, even after an extended follow-up [10,21]. While our results and empirical evidence support grade inflation, they are also in line with both the expert opinion raised in the literature [22,23] and with the available literature findings [18,24–26].

Our results support the findings of two previous studies comparing the pathological concordance of systematic and targeted biopsies with RP specimens [24,25]. Downgrading to GG1 after RP was uncommon regardless of the biopsy method, while upgrading was significantly more common in men with GG1 on systematic biopsy. Thus, many men diagnosed with GG2 PCa on targeted biopsy would often be diagnosed with GG1 PCa on systematic biopsy and are candidates for AS. However, GG1 patients treated with RP likely represent a bias towards a more aggressive cohort of men than GG1 patients.

A clinical implication of our results, in the context of the existing literature, is that more men with MRI-era GG2 PCa could potentially be managed with AS. Ideally, AS protocols should be individualised based on known risk factors, and men should preferably be included in prospective AS trials such as PRIAS [27] or SPCG-17 [28].

Our study has some limitations. Many GG1 cancers were diagnosed before AS had become a guideline recommendation. This might have contributed to the relatively large proportion (60%) of GG1 cancers undergoing curatively intended treatments in 5 years. However, in the prospective PRIAS AS trial, 52% of the men had discontinued AS at 5 years [29]. To reduce overtreatment, triggers for treatment in PRIAS were later modified and, in the latest report, a 38% definitive treatment rate was reported [27]. It is also likely that the sub-cohort of men with curatively treated GG1 PCa would be those considered to harbour features of more aggressive disease, especially in the light of the 20% recurrence risk in our study. This risk is the same as that in patients from Helsinki enrolled in PRIAS (data not shown), suggesting that our GG1 cohort represents an AS cohort. Furthermore, a patient followed for GG1 PCa may progress to GG2 during follow-up and therefore would be expected to have a similar risk of progression as those with GG2 PCa at diagnosis. We therefore performed a series of sensitivity analyses in this study. First, we restricted the analyses to men treated in the first year only, to exclude most men who progressed. Next, we excluded men who had progressed on subsequent biopsies. Finally, we adjusted the risk of recurrence for PSA level and number of positive cores as covariates in the multivariable Cox regression model. These sensitivity analyses confirmed our original findings, with no statistically significant differences between groups, and the upper bound of all 95% CIs was far below published estimates of the HR for GG2 vs GG1 disease. As expected, systematic biopsy-detected GG2 was associated with a higher risk of recurrence than targeted biopsy-detected GG1.

Given the registry-based design of our study, some data were granular, some missing information was inferred (e.g., curative treatment was deduced from PSA trends), and other data were unavailable (e.g., clinical staging or imaging). The absence of clinical staging prevented the precise risk stratification of patients, potentially leading to inaccuracies in the results; however, based on a prior quality assessment of the data, this impact is expected to be limited [13]. Clinical indications for MRI and curative treatments were not recorded, and it is likely that these indications evolved during the study period, representing another limitation. Nevertheless, the extent to which this variability may have biased our findings remains uncertain. Additionally, shifts in Gleason grading criteria and treatment approaches during the study period likely led to risk inflation, particularly in patients included in the GG1 PCa cohort. This is supported by the analysis in which we adjusted for different ISUP diagnostic eras. This bias tends to favour the GG1 group, further reinforcing our results and interpretation.

The strengths of our study lie in the large sample size and the comprehensive clinical data available for each patient, from diagnosis to treatment and follow-up. Our registry included patients from the beginning of the MRI era, allowing a comparatively long follow-up period. This extended follow-up period provides us with valuable insights into the long-term effects of treatments or interventions and helps us better understand outcomes over time.

In conclusion, in this large registry-based study, men diagnosed with GG2 PCa based on MRI targeted biopsy had a similar risk of recurrence after treatment compared to men with GG1 disease diagnosed by systematic biopsy, despite

receiving more intensive treatment. These findings suggest that a portion of the increased detection of GG2 disease in the MRI era may reflect reclassification rather than biologically more aggressive cancer. To minimise overtreatment, improved methods are needed to identify which men with MRI-era GG2 cancers could be safely managed with AS.

Author Contributions

Conception and design: A.O.B., E.C., T.-P.L., A.E., T.S., T.D.L., J.P., T.M., A.S.R. Critical revision of the manuscript for scientific and factual content: A.O.B., E.C., T.-P.L., A.E., T.S., T.D.L., J.P., T.M., A.S.R. Data acquisition: A.O.B., E.C., A.E., T.S. Data analysis and interpretation: A.O.B., E.C., T.-P.L., A.E., T.S., T.D.L., J.P., T.M., A.S.R. Drafting the manuscript: A.O.B., E.C., A.S.R. Statistical analysis: A.O.B., E.C. Supervision: T.M., A.S.R.

Acknowledgement

Open access publishing facilitated by Helsingin yliopisto, as part of the Wiley - FinELib agreement.

Disclosure of Interests

A. Rannikko is a member of the board of the Ida Montin Foundation and Orion Research Foundation, an advisory board member for medical companies Bayer, Orion Pharma and Janssen, a clinical advisor for Aqsens company in which he has stock, and an investigator in clinical trials by Rho-Vac, Orion Pharma, Bayer, Astellas, Pfizer and Janssen. The other authors have no potential conflicts of interest to declare.

Funding

This work was supported by grants from the Cancer Society Finland (Tuomas Mirtti and Antti Rannikko), Academy of Finland (Tuomas Mirtti), Sigrid Jusélius Foundation (Tuomas Mirtti), Jane and Aatos Erkko Foundation (Antti Rannikko) and state funding for university-level health research (Tuomas Mirtti and Antti Rannikko). The funding sources did not play any role in the study design, execution, data analyses, writing of the report, or submission of the article for publication.

Ethics Statement

The use of registry data was approved by the Helsinki University Hospital (HUS) institutional board (HUS/333/2019). The research was conducted in compliance with the good research practice of the World Medical Association Declaration of Helsinki. The data were handled according to national laws and EU regulations. Since the study in question is a registry study, no explicit consent was required according to national legislation.

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Correspondence: Antti S. Rannikko, University of Helsinki, Haartmaninkatu 8, 00014, Helsinki, Finland.
e-mail: antti.rannikko@hus.fi

Abbreviations: AS, active surveillance; CR, clinical recurrence; GG, Gleason Grade Group; HR, hazard ratio; ISUP, International Society of Urological Pathology; mpMRI, multiparametric MRI; HUS, Hospital District of Helsinki and Uusimaa; mpMRI, multiparametric MRI; PCa, prostate cancer; RP, radical prostatectomy; RT, radiation therapy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Flow chart of the patient selection process.

Fig. S2. Clinical relapse (CR) definition. CR is defined as the earliest date of either biochemical recurrence or commencement of secondary therapies after primary treatment.

Fig. S3. Sankey diagrams depicting treatment trajectories in the two groups. No curative treatments given in blue, first curative treatment in red.

Fig. S4. Five-year relapse-free survival (Kaplan–Meier) for GG1 NoMRI (red line) and GG2 MRI (blue line) groups treated within the first year from diagnosis.

Fig. S5. Five-year relapse-free survival (Kaplan–Meier) for GG1 NoMRI (red line) and GG2 MRI (blue line) groups treated with RP within the first year from diagnosis.

Fig. S6. Five-year relapse-free survival (Kaplan–Meier) for GG1 NoMRI (red line) and GG2 MRI (blue line) groups treated with RT within the first year from diagnosis.

Fig. S7. Five-year relapse-free survival (Kaplan–Meier) for GG1 NoMRI not upgrading on subsequent biopsy (red line) and GG2 MRI (blue line) groups.

Fig. S8. Five-year relapse-free survival (Kaplan–Meier) for GG1 NoMRI and GG2 MRI groups in different diagnostic eras [before-2005 (<5), between 2005 and 2010 (5–10), after 2010 (>10)].

Table S1. Results of the relapse-free survival analysis including the sensitivity analysis.

Table S2. Results of the Cox model as a sensitivity analysis of the recurrence-free survival.

