Pathology (February 2022) **54(1)**, pp. 49–54

ANATOMICAL PATHOLOGY

Percentage grade 4 tumour predicts outcome for prostate adenocarcinoma in needle biopsies from patients with advanced disease: 10-year data from the TROG 03.04 RADAR trial

B. Delahunt[1], A. Steigler[2], C. Atkinson[3], D. Christie[4], G. Duchesne[5], L. Egevad[6], D. Joseph[7], D. N. Kenwright[1], J. Matthews[8], J. D. Murray[1], C. Oldmeadow[9], H. Samaratunga[10], N. A. Spry[11], M. C. Thunders[1], H. Hondermarck[9,12], J. W. Denham[2]

[1]*Department of Pathology and Molecular Medicine and Health Sciences, University of Otago, and Southern Community Laboratory, Wellington, New Zealand;* [2]*School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia;* [3]*St Georges Cancer Care Centre, Christchurch, New Zealand;* [4]*Genesis Care, Tugun, Qld, Australia;* [5]*Peter MacCallum Cancer Centre and University of Melbourne, Vic, Australia;* [6]*Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden;* [7]*Sir Charles Gairdner Hospital, Perth, WA, Australia;* [8]*Auckland City Hospital, Auckland, New Zealand;* [9]*Hunter Medical Research Institute, Newcastle, NSW, Australia;* [10]*Aquesta Uropathology and University of Queensland, Brisbane, Qld, Australia;* [11]*Genesis Care, Perth, WA, Australia;* [12]*School of Biomedical Sciences and Pharmacy, University of Newcastle, NSW, Australia*

Summary

Previous reports have shown that quantification of high tumour grade is of prognostic significance for patients with prostate cancer. In particular, percent Gleason pattern 4 (GP4) has been shown to predict outcome in several studies, although conflicting results have also been reported. A major issue with these studies is that they rely on surrogate markers of outcome rather than patient survival. We have investigated the prognostic predictive value of quantifying GP4 in a series of prostatic biopsies containing Gleason score 3+4=7 and 4+3=7 tumours. It was found that the length of GP4 tumour determined from the measurement of all biopsy cores from a single patient, percent GP4 present and absolute GP4 were all significantly associated with distant progression of tumour, all-cause mortality and cancer-specific mortality over a 10-year follow-up period. Assessment of the relative prognostic significance showed that these parameters outperformed division of cases according to Gleason score (3+4=7 versus 4+3=7). International Society of Urological Pathology (ISUP) Grade Groups currently divide these tumours, according to Gleason grading guidelines, into grade 2 (3+4=7) and grade 3 (4+3=7). Our results indicate that this simple classification results in the loss of important prognostic information. In view of this we would recommend that ISUP Grade Groups 2 and 3 be amalgamated as grade 2 tumour with the percentage of GP4 carcinoma being appended to the final grade, e.g., 3+4=7 carcinoma with 40% pattern 4 tumour would be classified as ISUP Grade Group 2 (40%).

Key words: Prostate adenocarcinoma; modified Gleason grade; Gleason pattern 4; International Society of Urological Pathology Grade Group; prognosis.

Received 7 November, revised 29 November, accepted 1 December 2021
Available online 24 December 2021

INTRODUCTION

The clinical utility of prostate cancer grading has been confirmed in numerous studies and Gleason grading criteria remain the cornerstone of prognostic assessment. Gleason grading recognises the relative importance of both tumour architecture and cancer volume with Gleason scores, being a composite of morphology, expressed as a grade or pattern, and the relative volume of each grade present in the biopsy.[1]

Despite the obvious importance of the Gleason score as a prognostic parameter, it is evident that both Gleason grading and the assignment of International Society of Urological Pathology (ISUP) Grade Groups,[2] which are effectively Gleason grading by another name, lack the granularity to provide detailed outcome data.[3,4] In his various publications Gleason recognised that the volume of pattern 4 adenocarcinoma present in a tumour influences prognosis and introduced a cut-point in his grading classification according to the presence of more or less than 50% of pattern 4 tumour.[1] A major criticism of Gleason grading is that for tumours classified as Gleason score 7 (3+4=7 and 4+3=7 carcinoma), the component of high grade tumour may vary widely.[3,4] This can be partially corrected for by the subdivision of these scores into 7a and 7b, although these grading subdivisions remain relatively crude and may still include tumours that are likely to have highly differing outcomes. An assessment of the percentage of high grade cancer (Gleason patterns 4 and 5) present in a biopsy was initially proposed by McNeal *et al.* in 1990[5] and since then a number of studies have shown this to have prognostic significance for patients treated either

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: https://doi.org/10.1016/j.pathol.2021.11.004

conservatively with watchful waiting/active surveillance or by radical prostatectomy.[6–9]

The presence of any of pattern 4 tumour, or the presence of more than a small volume of pattern 4 tumour in biopsies, is considered a feature that precludes active surveillance in current protocols.[10] This reinforces the suggestion that an assessment of the relative volume of pattern 4 tumour in a biopsy provides prognostic information additional to Gleason grading.

In this study we have investigated the prognostic predictive utility of dividing Gleason 3+4=7 and 4+3=7 acinar carcinomas according to the percentage of Gleason pattern 4 tumour (%GP4) present. The cases in this series were derived from a clinical trial which investigated various treatment modalities in a large cohort of patients, whose tissues underwent central pathological review, with close patient follow-up for a period of 10 years or until death.

MATERIALS AND METHODS

The cases in this study were accessed as the histological component of the Trans-Tasman Radiation Oncology Group TROG 03.04 RADAR (Randomised Androgen Deprivation and Radiotherapy). This is a phase 3 trial coordinated between Australia and New Zealand with 1071 subjects recruited from 23 treatment centres between October 2003 and August 2007.[11,12] The TROG 03.04 Trial is registered with the National Institutes of Health Clinical Trials Registry, number NCT00193856, and has approval from Hunter New England Human Research Ethics Committee (Trial ID 03/06/11/3.02).

Eligibility criteria for enrolment in the trial were men $\geq$18 years of age with histologically confirmed acinar adenocarcinoma of the prostate. They had no evidence of systemic metastases or lymph node involvement, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and absence of concurrent disease that was likely to limit life expectancy to <5 years. Tumours were of clinical staging category cT2b to cT4, of any ISUP grade and baseline serum prostate-specific antigen (PSA) level, or clinical staging category cT2a with ISUP grade >1 and baseline PSA of $\geq$10 ng/mL.

Subjects were randomised to one of four groups in a 2×2 factorial study design: Group 1, a control group of 6 months androgen suppression (AS) prior to radiotherapy (designated standard treatment, 6AS); Group 2, standard treatment plus 12 months zoledronic acid therapy (6AS+Z); Group 3, standard treatment plus 12 months androgen suppression after radiotherapy (18AS); and Group 4, standard treatment plus 12 months androgen suppression after radiotherapy, and 18 months zoledronic acid therapy (18AS+Z). Radiotherapy to the prostate and seminal vesicles was administered according to an embedded dose escalation program.[11,12]

Diagnostic thin core biopsies had been taken randomly. The biopsies were retrieved for all cases and reviewed blind by the trial pathologist (BD) in the post-randomisation phase of the trial, during the period 2010–2015. The tumours were graded according to the recommendations of the ISUP consensus conference and a Gleason grade was assigned to each case, with grading of tumours reassessed according to 2014 ISUP criteria.[2,4,13] All cores and levels containing tumour were graded and in accordance with the recommendations of ISUP, the grade of any intraductal carcinoma of the prostate was included in the final grade of the core.[14,15] The length of the tumour present in each core was measured in mm. The total length of each core was also measured in mm and the volume percentage of malignant tissue for each case was derived as a percentage of the cumulative length of all cores. Three metrics were derived for the volume of GP4 in each case: (1) total length of GP4 in all cores, (2) the case %GP4, defined as the percentage of cancer that was GP4 (total length GP4/total length malignant tissue), and (3) the absolute %GP4 defined as the percentage of biopsied tissue that was GP4 (%GP4 multiplied by % biopsied tissue positive for tumour divided by 100).[16]

Participants were routinely followed up at 3 monthly intervals to 30 months, then 6 monthly to 60 months, then annually with PSA measures and clinical examinations. Investigations such as biopsy, computed tomography (CT) scan, chest x-ray and bone scintigraphy were performed at the treating clinician's discretion. Ten-year follow-up data from the time of randomisation were available for each case and were utilised in the time to event analysis. In our 10-year main endpoints report, global testing for interactions found no significant differences between the four treatment arms,[11] hence arms could be collapsed to compare treatment factors separately.

Outcomes

The primary endpoints for this study were time to the development of distant progression (defined as bone or soft tissue metastases), prostate cancer-specific mortality and all-cause mortality. Investigations to diagnose metastases, including CT scans of the abdomen and pelvis, chest x-ray and isotopic whole-body bone scintigraphy, were mandated if symptoms suggested a need or if the PSA levels reached 20 ng/mL. Death was attributed to prostate cancer if it occurred in the context of progressive metastatic disease or recurrent primary cancer causing urinary obstruction, without reasonable alternative unrelated causes. All endpoint imaging reports and causes of death were monitored at source and reviewed centrally by a group of senior clinician investigators, blinded to patient and treatment identity. Time-to-event endpoints were measured from randomisation.

Statistical methods

Descriptive statistics were used to compare baseline clinicopathological factors between the ISUP modified Gleason score (3+4 and 4+3) groups. Continuous and categorical variables were summarised using medians (interquartile ranges) and frequencies (percentages). Associations between clinicopathological variables and Gleason groups were assessed using chi-square for categorical variables, and Wilcoxon rank sum tests for continuous variables. Univariable and multivariable Cox regression analyses were performed to measure the prognostic impact of the %GP4 metric as a continuous variable on each outcome. In these models, competing risks were accounted for using the method of Fine and Gray.[17] Competing risks were defined as death due to any cause for the endpoint distant progression, and death from other cause for prostate cancer-specific mortality. Multivariable models were adjusted for patient age at randomisation, baseline PSA (log-transformed continuous), tumour stage (cT2 vs cT3/cT4), duration of androgen suppression (6AS vs 18AS), use of 18 months of zoledronic acid (no vs yes), and radiotherapy dose [low (66 Gy or 70 Gy) vs high (74 Gy or high dose rate brachytherapy)].

The relative prognostic significance of the GP4 metrics for each outcome were compared by calculating the Harrell's concordance C-index[18] and the Akaike Information Criteria (AIC).[19,20] The C-index is a measure of predictive discrimination and is defined as the proportion of subjects' pairs in which predictions and outcomes are concordant. A higher C-index indicates better discriminative ability and C-index of $\leq$0.5 indicates no predictive accuracy. Bootstrapping using the bias-corrected and accelerated method was used to generate 95% confidence intervals for C-index for each model. Statistical testing of the difference in C-indices, which is known to be insensitive, was not undertaken. The AIC, a much more sensitive testing method than C-index, assigns a score to each model based on its log-likelihood and number of parameters, with the best model determined by the lowest AIC value. An AIC difference of 4 or greater between models is strong evidence that the model with the minimum AIC provides a superior fit.

Analyses were performed on an intention-to-treat basis and a two-sided p value of <0.05 was considered statistically significant for all tests. Statistical analyses were programmed using Stata/IC Version 15.1 (StataCorp, USA) and R version 4.0.5 software (The R Foundation for Statistical Computing).

RESULTS

Histological material was available for review from 976/1071 cases enrolled into the trial. Of these cases, 588 patients had both Gleason pattern 3 and pattern 4 tumour, as well as complete pathological and treatment data available for analysis. The median age of this cohort was 68.5 years [interquartile range (IQR) 63.3–72.9]. The median number of cores available for review from each case was 10 (IQR 8–12). In 229 cases (38.9%) the Gleason score was 3+4=7, while in 359 cases (61.1%) the Gleason score was 4+3=7. A summary of clinico-pathological characteristics according to Gleason score (3+4=7 and 4+3=7) is shown in Table 1.

Table 1 Clinicopathological characteristics of patients according to ISUP modified Gleason score

Characteristic	Total (*n*=588)	ISUP 2 (Gleason 3+4) (*n*=229)	ISUP 3 (Gleason 4+3) (*n*=359)	*p* value
Age, median (IQR), years	68.5 (63.3–72.9)	67.9 (62.7–72.6)	68.7 (63.8–72.9)	0.31
PSA, median (IQR), ng/mL	14.0 (9.2–22.9)	12.0 (8.1–17.4)	15.8 (9.9–25.0)	0.0001
<10	170 (28.9)	80 (34.9)	90 (25.1)	0.002
10–20	248 (42.2)	100 (43.7)	148 (41.2)	
>20	170 (28.9)	49 (21.4)	121 (33.7)	
Clinical T-stage category				0.027
T2	392 (66.7)	165 (72.1)	227 (63.2)	
T3	196 (33.3)	64 (27.9)	132 (36.8)	
NCCN risk group				0.0003
Intermediate	294 (50.0)	136 (59.4)	158 (44.0)	
High	294 (50.0)	93 (40.6)	309 (56.0)	
Treatment arm				0.76
6 months AS	150 (25.5)	55 (24.0)	95 (26.5)	
6 months AS+Z	141 (24.0)	60 (26.2)	81 (22.6)	
18 months AS	152 (25.8)	59 (25.8)	93 (25.9)	
18 months AS+Z	145 (24.7)	55 (24.0)	90 (25.1)	
Radiation dose				0.11
66 Gy	70 (11.9)	26 (11.3)	44 (12.3)	
70 Gy	252 (42.9)	111 (48.5)	141 (39.3)	
74 Gy	139 (23.6)	52 (22.7)	87 (24.2)	
HDRB	127 (21.6)	40 (17.5)	87 (24.2)	
Biopsy cores, median (IQR)				
Number taken	10 (8–12)	10 (7–12)	10 (8–12)	0.15
Percent positive	58 (42–82)	56 (41–79)	60 (42–83)	0.13

Data are *n* (%) unless otherwise stated.
Percentages may not total 100 due to rounding.
AS, androgen suppression; Gy, Gray; HDRB, high dose rate brachytherapy; IQR, interquartile range; ISUP, International Society of Urological Pathology; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; Z, zoledronic acid.

The extent of prostate cancer and measures of GP4 according to Gleason score are presented in Table 2. The distribution of cases according to cT staging category is shown in Table 3. The frequency distributions of case and absolute percentage of GP4 cancer in all cases in the series are shown in Fig. 1.

Median follow-up was 10.8 years (IQR 9.0 to 11.9). During the follow-up period distant progression of tumour occurred in 137 patients. The total number of deaths was 180, with 52 (29%) attributable to prostate cancer. The association between each GP4 parameter and time-to-event outcome is summarised in Table 4. Each of the GP4 measures as continuous variables (total length of GP4, case %GP4, and absolute %GP4) were predictors of distant progression, prostate cancer-specific mortality and all-cause mortality in both uni- and multivariable models. ISUP Grade Group (Gleason score 4+3 vs 3+4) was also predictive of all outcomes but did not retain statistical significance in the adjusted model for all-cause mortality.

A comparison of the relative prognostic significance of the GP4 parameters according to the AIC and Harrell's C-index for each outcome is presented in Table 5. The absolute %GP4 had the lowest AIC and highest C-index for every outcome, providing evidence that it was prognostically superior to total length and case %GP4 as well as the ISUP modification of Gleason grading (3+4 vs 4+3). This is further supported by the AIC model differences between each GP4 parameter and absolute %GP4 which exceeded 4 for every outcome, the only exception being prostate cancer-specific mortality where the case GP4 percentage model provided an equally good fit (AIC difference 3.3).

Table 2 Extent of prostate cancer and measures of GP4 according to ISUP modified Gleason score

	ISUP modified Gleason score	
	3+4=7 (*n*=229)	4+3=7 (*n*=359)
Length of biopsied tissue, mm	112 (86–143)	122 (93–153)
Length of PCa, mm	26.8 (15.3–44.7)	35.0 (19.7–57.0)
Percentage of biopsy tissue positive for PCa, %	25 (13–39)	31 (18–47)
Length of GP4, mm	5.8 (2.6–13.6)	26.1 (14.4–42.6)
Case percentage of GP4, %[a]	30 (15–38)	78 (65–90)
Absolute percentage of GP4, %[b]	5.4 (2.5–11.5)	22.6 (13.3–36.3)

Measurements presented are medians and interquartile ranges.
GP4, Gleason pattern 4; ISUP, International Society of Urological Pathology; PCa, prostate cancer.
[a] Percentage of GP4 in tumour.
[b] Percentage of GP4 in biopsy tissue.

DISCUSSION

The concept that quantification of the volume of higher grade tumour present in a prostate biopsy is of prognostic significance was first proposed by McNeil who showed that percentage pattern 4+5 tumour was associated with tumour volume in a series of radical prostatectomies, and later that this was also associated with PSA biochemical failure.[5–7] More recently it has been demonstrated that stratification of percent pattern 4/5 correlated with cancer-specific survival.[8,9]

It is clear that of all Gleason patterns, pattern 5 has the poorest prognosis and attention turned to assessing whether or not pattern 4 tumour volume on its own provided additional prognostic information. In several studies, based on intermediate grade cancers (3+4=7 and 4+3=7), the percentage of pattern 4 tumour in biopsies was correlated with

Table 3 Distribution of cT staging categories according to ISUP modified Gleason score

cT stage category	ISUP modified Gleason score			
	3+4=7 (*n*=229)		4+3=7 (*n*=359)	
T2a	21	(9.2)	27	(7.5)
T2b	74	(32.3)	102	(28.4)
T2c	70	(30.6)	98	(27.3)
T3	64	(27.9)	132	(36.8)

Data are *n* (%).
Percentages may not total 100 due to rounding.
ISUP, International Society of Urological Pathology.

histological features associated with adverse prognosis and with PSA biochemical failure in patients treated by radical prostatectomy.[4,21–28] In 2016 Cole *et al.* investigated the prognostic significance of volume %GP4 carcinoma in 3+4=7 and 4+3=7 tumours from biopsies of patients who subsequently underwent radical prostatectomy.[21] They showed that, in cases divided at 1–<10%, 10–<20% and then at 20% intervals of %GP4, the overall %GP4 tumour predicted adverse pathology and PSA biochemical failure, and that this parameter was superior to the assessment of maximum %GP4 within a tumour. Similar results were obtained from a separate study published in 2016,[22] although

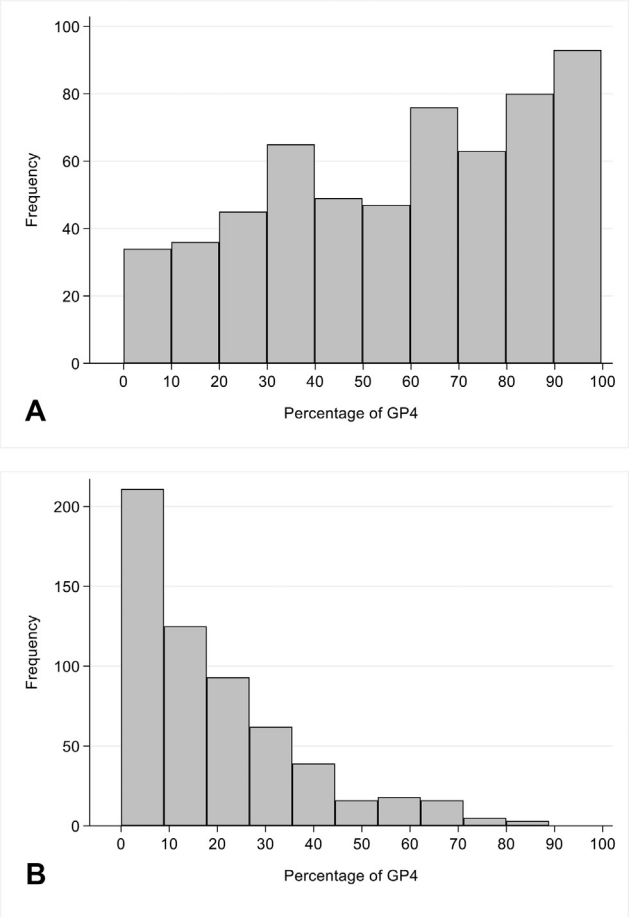

Fig. 1 Frequency distributions of percentage of GP4 (*n*=588). (A) Percentage of tumour with GP4 (case %GP4). (B) Percentage of biopsy with GP4 (absolute %GP4).

the difference in time to PSA biochemical failure was not statistically significant between some of the groupings of % GP4. Grouping of %GP4 at 1–5%, 6–10% and then at 10% intervals was also shown to stratify PSA recurrence-free outcomes in a separate series that investigated prognostic factors in patients who had undergone radical prostatectomy for prostate cancer.[23]

In a large series of cases, with results based upon both prostate biopsies and radical prostatectomy specimens, stratification of cases by %GP4 at intervals of 25% correlated with PSA biochemical failure. It was also shown that if the % GP4 was further refined to intervals of 1–5%, 6–10% and then at 10% intervals, the risk of PSA biochemical failure could be more accurately predicted.[24] These results reflected those of Cole's earlier study,[21] by demonstrating that average %GP4 was superior to highest biopsy score in predicting PSA biochemical failure. In a detailed study utilising differing methodologies for the calculation of GP4 volume, it was shown that stratification of %GP4 by three methods in patients treated by radical prostatectomy, all correlated with the detection of adverse pathological features in the subsequent radical prostatectomy specimen.[25] Of the three methods of quantifying volume of GP4, it was shown that the total length of GP4 in all cores was superior to both the overall %GP4 (length of GP4/length of all cancer in all cores) and maximum %GP4 present in a single core in predicting outcome. However, it was noted in an editorial comment on the study, that determination of length of GP4 present in cores may vary between institutions depending on the number of cores taken as targeted biopsies.[26] Perlis *et al.* investigated parameters that were predictive of extraprostatic extension of tumour in a series of Gleason score 3+3=6 and 3+4=7 tumours.[27] It was shown that for each percentage increase in pattern 4 tumour present in a biopsy, there was a 2% increase in the likelihood of having disease that was not organ-confined; however, this was influenced by PSA levels at diagnosis, patient age and tumour volume. In a separate study investigating multiple prognostic parameters for prostate cancer, %GP4 was not shown to be significantly associated with PSA biochemical recurrence on univariable analysis, with independent predictors of outcome being confined to lymph node metastases, Gleason score and length of positive surgical margins.[28]

The reliance on surrogate markers of outcome, rather than definitive survival studies, limits the value of many of the previous investigations relating to the prognostic significance of %GP4. This issue was partially overcome in the study of Martell *et al.*[16] who included interval to the development of metastatic disease, in addition to interval to either the development of PSA biochemical failure or to androgen usage to treat biochemical failure, in their outcome analysis. They showed that absolute %GP4 but not %GP4 was correlated with these outcome parameters. Specifically, it was found that division of cases at an absolute %GP4 of 3.3% predicted PSA biochemical failure, while division at 6.6% correlated with the initiation of androgen deprivation and 17.5% predicted the presence of metastatic disease.

Our study, based on patients with advanced disease, involved a variety of both %GP4 parameters and outcome measures including cancer-specific and all-cause mortality, with follow-up for a period of 10 years or until death. On multivariable analysis, total length of GP4 in mm, %GP4 per case and absolute %GP4, as previously defined,[16] were significantly associated with all measured outcome

Table 4 Prognostic significance of measures of GP4 on distant progression and mortality endpoints

Endpoint	Univariable			Multivariable[a]		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Distant progression[b]						
Gleason 4+3 vs 3+4	2.55	(1.71–3.78)	<0.0001	2.38	(1.59–3.54)	<0.0001
Length of GP4, mm, continuous	1.02	(1.01–1.02)	<0.0001	1.02	(1.01–1.02)	<0.0001
Case %GP4, continuous	1.02	(1.01–1.03)	<0.0001	1.02	(1.02–1.03)	<0.0001
Absolute %GP4, continuous	1.03	(1.02–1.04)	<0.0001	1.03	(1.02–1.04)	<0.0001
Prostate cancer-specific mortality[b]						
Gleason 4+3 vs 3+4	2.90	(146–5.76)	0.002	2.68	(1.32–5.44)	0.006
Length of GP4, mm, continuous	1.02	(1.01–1.02)	<0.0001	1.01	(1.01–1.02)	<0.0001
Case %GP4, continuous	1.02	(1.01–1.04)	<0.0001	1.02	(1.01–1.04)	0.0003
Absolute %GP4, continuous	1.03	(1.02–1.05)	<0.0001	1.03	(1.02–1.04)	<0.0001
All-cause mortality						
Gleason 4+3 vs 3+4	131	(0.96–1.79)	<0.0001	1.23	(0.90–1.68)	0.19
Length of GP4, mm, continuous	1.01	(1.00–1.01)	0.006	1.01	(1.00–1.02)	0.002
Case %GP4, continuous	1.01	(1.00–1.01)	0.011	1.01	(1.00–1.01)	0.018
Absolute %GP4, continuous	1.02	(1.01–1.02)	<0.0001	1.02	(1.01–1.03)	<0.0001

CI, confidence interval; HR, hazard ratio.
[a] Multivariable models adjusted for patient age at randomisation (years), baseline PSA (log-transformed continuous, ng/mL), tumour stage (T2 vs T3/T4), duration of androgen suppression (6AS vs 18AS), use of 18 months of zoledronic acid (no vs yes); and radiotherapy dose (66 Gy vs 70 Gy vs 74 Gy vs high dose rate brachytherapy).
[b] Sub-hazard ratios presented from Fine and Gray models.

Table 5 Relative prognostic significance of GP4 parameters according to Akaike Information Criteria (AIC) and Harrell's concordance index (HCI)

Endpoints	GP4 metric	AIC	HCI (95% CI)
Distant progression	3+4=7 vs 4+3=7	1630.7	0.708 (0.646–0.734)
	Length of GP4, mm	1621.0	0.719 (0.661–0.745)
	Case %GP4	1621.4	0.717 (0.655–0.740)
	Absolute %GP4	1609.4	0.733 (0.679–0.757)
Prostate cancer-specific mortality	3+4=7 vs 4+3=7	623.1	0.733 (0.624–0.768)
	Length of GP4, mm	623.3	0.736 (0.647–0.773)
	Case %GP4	615.6	0.746 (0.635–0.770)
	Absolute %GP4	612.3	0.765 (0.685–0.796)
All cause mortality	3+4=7 vs 4+3=7	2145.7	0.642 (0.576–0.661)
	Length of GP4, mm	2138.6	0.645 (0.579–0.664)
	Case %GP4	2141.7	0.644 (0.578–0.664)
	Absolute %GP4	2130.1	0.656 (0.593–0.677)

GP4, Gleason pattern 4.

parameters. Assessment of the relative prognostic value of these parameters showed absolute %GP4 to be of the greatest utility in predicting outcome. These results reinforce our previous comments questioning the current recommendations that the overall Gleason score for a tumour should be based upon the core with the highest score.[3,29] These recommendations do not accord with our finding that, however measured, %GP4 provides additional prognostic information.

This study and those of others have shown that quantification of GP4 is of prognostic significance for patients with localised disease and for those undergoing treatment for advanced disease. In view of this, the current division of ISUP Grade Groups 2 and 3, where tumours consisting of Gleason patterns 3 and 4 are divided at a cut-point of 50% (i.e., 3+4=7 vs 4+3=7), results in loss of considerable prognostic information as %GP4 stratifies outcome as a continuous variable. For these reasons we would recommend that ISUP grades 2 and 3 (Gleason score 3+4=7 and 4+3=7) tumours be amalgamated into a single grade and that this be designated ISUP Grade Group 2. The grade of these tumours could be further stratified with the percentage of GP4 carcinoma being appended to the final grade, e.g., 3+4=7 with 40% pattern 4 carcinoma would be classified as ISUP Grade Group 2 (40%). This would clearly identify Gleason score 3+4=7 tumours with a low proportion of pattern 4 tumour, where active surveillance may be appropriate. It would also permit more accurate assessment of outcome, which would be informed by the percentage of GP4 tumour present in the biopsy.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

Address for correspondence: Prof Brett Delahunt, Department of Pathology and Molecular Medicine, University of Otago, PO Box 7343, Wellington South, New Zealand. E-mail: brett.delahunt@otago.ac.nz

References

1. Gleason DF. Classification of prostate carcinomas. *Cancer Chemother Rep* 1966; 50: 125–8.
2. Epstein JI, Egevad L, Amin MB, *et al*. The 2014 International Society of Urological Pathology (ISUP) consensus conference of Gleason

grading of prostatic carcinoma. Definition of grading pattern and proposal for a new grading system. *Am J Surg Pathol* 2016; 40: 244–52.
3. Srigley JR, Delahunt B, Samaratunga H, *et al*. Controversial issues in Gleason and International Society of Urological Pathology (ISUP) prostate cancer grading: proposed recommendations for international implementation. *Pathology* 2019; 51: 463–73.
4. Delahunt B, Egevad L, Srigley JR, *et al*. Validation of International Society of Urological Pathology (ISUP) grading for prostatic adenocarcinoma in thin core biopsies using TROG 03.04 'RADAR' trial clinical data. *Pathology* 2015; 47: 520–5.
5. McNeal JE, Villers AA, Redwine EA, Freiha FS, Stamey TA. Histologic differentiation, cancer volume, and pelvic lymph node metastases in adenocarcinoma of the prostate. *Cancer* 1990; 66: 1225–33.
6. Stamey TA, McNeal JE, Yemoto CM, Sigal BM, Johnstone IM. Biological determinants of cancer progression in men with prostate cancer. *JAMA* 1999; 281: 1395–400.
7. Stamey TA, Yemoto CM, McNeal JE, *et al*. Prostate cancer is highly predictable: a prognostic equation based on all morphological variables in radical prostatectomy specimens. *J Urol* 2000; 163: 1155–60.
8. Egevad L, Granfors T, Karlberg L, Bergh A, Stattin P. Percent Gleason grade 4/5 as prognostic factor in prostate cancer diagnosed at transurethral resection. *J Urol* 2002; 168: 509–13.
9. Cheng L, Davidson DD, Lin H, *et al*. Percentage of Gleason pattern 4 and 5 predicts survival after radical prostatectomy. *Cancer* 2007; 110: 1967–72.
10. Amin MB, Lin DW, Gore JL, *et al*. The critical role of the pathologist in determining eligibility for active surveillance as a management option in patients with prostate cancer. Consensus statement with recommendations supported by the College of American Pathologists, International Society of Urological Pathology, Association of Directors of Anatomic and Surgical Pathology, the New Zealand Society of Pathologists, and the Prostate Cancer Foundation. *Arch Pathol Lab Med* 2014; 138: 1387–405.
11. Denham JW, Joseph D, Lamb DS, *et al*. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): 10-year results from a randomised, phase 3, factorial trial. *Lancet Oncol* 2019; 20: 267–81.
12. Joseph D, Denham JW, Steigler A, *et al*. Radiation dose escalation or longer androgen suppression to prevent distant progression in men with locally advanced prostate cancer: 10-year data from the TROG 03.04 RADAR Trial. *Int J Radiat Oncol Biol Phys* 2020; 106: 693–702.
13. Delahunt B, Egevad L, Samaratunga H, *et al*. Gleason and Fuhrman no longer make the grade. *Histopathology* 2016; 68: 475–81.
14. Samaratunga H, Delahunt B, Egevad L, *et al*. Intraductal carcinoma of the prostate is an aggressive form of invasive carcinoma and should be graded. *Pathology* 2020; 52: 192–6.
15. van Leenders GJLH, van der Kwast T, Grignon DJ, *et al*. The 2019 International Society of Urological Pathology (ISUP) consensus conference on grading of prostate cancer. *Am J Surg Pathol* 2020; 44: e87–99.
16. Martell K, Mendez LC, Chung H, *et al*. Absolute percent of biopsied tissue positive for Gleason pattern 4 disease (APP4) appears predictive of disease control after high dose rate brachytherapy and external beam radiotherapy in intermediate risk prostate cancer. *Radiother Oncol* 2019; 135: 170–7.
17. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496–509.
18. Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; 15 (4): 361–87.
19. Akaike H. A new look at the statistical model identification. *IEEE Trans Autom Control* 1974; 19: 716–23.
20. Burnham KP, Anderson DR. Multimodel inference: understanding AIC and BIC in model selection. *Sociological Methods Res* 2004; 33: 261.
21. Cole AI, Morgan TM, Spratt DE, *et al*. Prognostic value of percent Gleason grade 4 at prostate biopsy in predicting prostatectomy pathology and recurrence. *J Urol* 2016; 196: 405–11.
22. Kir G, Seneldir H, Gumus E. Outcomes of Gleason score 3+4=7 prostate cancer with minimal amounts (<6%) vs ≥6% of Gleason pattern 4 tissue in needle biopsy specimens. *Ann Diagn Pathol* 2016; 20: 48–51.
23. Choy B, Pearce SM, Anderson BB, *et al*. Prognostic significance of percentage and architectural types of contemporary Gleason pattern 4 prostate cancer in radical prostatectomy. *Am J Surg Pathol* 2016; 40: 1400–6.
24. Sauter G, Steurer S, Clauditz TS, *et al*. Clinical utility of quantitative Gleason grading in prostate biopsies and prostatectomy specimens. *Eur Urol* 2016; 69: 592–8.
25. Dean LW, Assel M, Sjoberg DD, *et al*. Clinical usefulness of total length of Gleason pattern 4 on biopsy in men with grade group 2 prostate cancer. *J Urol* 2019; 201: 77–82.
26. Perlis N. Editorial comment on Dean LW, Assel M, Sjoberg DD et al. Clinical usefulness of total length of Gleason pattern 4 on biopsy in men with grade group 2 prostate cancer. *J Urol* 2019; 201: 82.
27. Perlis N, Sayyid R, Evans A, *et al*. Limitations in predicting organ confined prostate cancer in patients with Gleason pattern 4 on biopsy: implications for active surveillance. *J Urol* 2017; 197: 75–81.
28. Hollemans E, Verhoef EI, Bangma CH, *et al*. Prostate carcinoma grade and length but not cribriform architecture at positive surgical margins are predictive for biochemical recurrence after radical prostatectomy. *Am J Surg Pathol* 2020; 44: 191–7.
29. Delahunt B, Egevad L, Grignon DJ, Srigley JR, Samaratunga H. Prostate cancer grading: recent developments and future directions. *BJU Int* 2016; 117 (Suppl. 4): 7–8.