Review Article

Percent Gleason pattern 4 in stratifying the prognosis of patients with intermediate-risk prostate cancer

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Abstract: The Gleason score remains the most reliable prognosticator in men with prostate cancer. One of the recent important modifications in the Gleason grading system recommended from the International Society of Urological Pathology consensus conference is recording the percentage of Gleason pattern 4 in the pathology reports of prostate needle biopsy and radical prostatectomy cases with Gleason score 7 prostatic adenocarcinoma. Limited data have indeed suggested that the percent Gleason pattern 4 contributes to stratifying the prognosis of patients who undergo radical prostatectomy. An additional obvious benefit of reporting percent pattern 4 includes providing critical information for treatment decisions. This review summarizes and discusses available studies assessing the utility of the percentage of Gleason pattern 4 in the management of prostate cancer patients.

Keywords: Gleason grading; prognosis; prostate biopsy; radical prostatectomy

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Introduction

A critical component in the management of prostate cancer patients includes proper risk stratification which guides treatment decisions. Only a subset of prostate cancer is lethal, and treating low-risk prostate cancer is often considered overtreatment (1). On the other hand, some of intermediate-risk prostate cancers may need to be treated aggressively. The goal is thus to provide the appropriate treatment for each patient.

The Gleason grading system, originated in 1966, is based solely on architectural patterns of prostatic adenocarcinoma, consisting of grades 1 to 5 (2-4). The Gleason score, which is derived by adding the most predominant and secondary patterns, has guided not only prostate cancer grading but also risk stratification and still represents the most reliable prognosticator. A number of changes have been made in the original Gleason system, including a recommendation from the International Society of Urological Pathology (ISUP) consensus published in 2005, that stated even a low volume (<5%) of a higher grade tumor should be incorporated into the score (5). Consequently, the Gleason score of a needle biopsy involved by cancer with >95% Gleason pattern 3 and <5% Gleason pattern 4 became 3+4=7, whereas that of a radical prostatectomy specimen involved by a tumor nodule with identical patterns was 3+3=6 with tertiary pattern 4. The issue of tertiary grade patterns was further updated in the ISUP 2014 consensus conference, and currently tertiary patterns are only recommended for radical prostatectomy specimens (6). Meanwhile, various studies have demonstrated significantly worse outcomes of patients with Gleason score 4+3=7 cancer, compared to those with Gleason score 3+4=7 cancer (7-13). Thus, the new grading system proposed in the ISUP 2014 consensus

Table 1 The relationship between the percentage of GP4 and the prognosis of prostate cancer patients undergoing RP

Study [author, year (reference)]	No. of patients	Specimen type	Separation method of GP4	Prognostic significance of RP %GP4
Cheng *et al*., 2007 (17)	504	RP	0%/1–20%/>20% (GP4, GP5, or both)	Independent predictor of CSS
Huang *et al*., 2014 (18)	256	Bx	≤5%/6–50%	Predictor of pT3 on RP
Choy *et al*., 2016 (19)	585	RP	1–5%/6–10%/11–20%/21–30%/31–40%/41–50%/51–60%/61–70%/71–80%/81–90%	Independent predictor of BCR
Cole *et al*., 2016 (20)	1,691	Bx	1–9.9%/10–19.9%/20–39.9%/40–59.9%/60–79.9%/80–100%	Independent predictor of BCR
Kir *et al*., 2016 (21)	372	Bx	<6%/6–25%/26/49%/≥50%	Independent predictor of BCR
Sauter *et al*., 2016 (22)	12,823	Bx and RP	(I) ≤25%/26–49%/50–74%/≥75%; (II) ≤5%/6–10%/11–20%/21–30%/31–49%/50–60%/61–80%/>80%	Predictor of BCR
Perlis *et al*., 2017 (23)	1,255	Bx	1–5%/6–10%/11–20%/21–49%	Predictor of pT3 on RP

GP4, Gleason pattern 4; RP, radical prostatectomy; Bx, prostate needle biopsy; CSS, cancer-specific survival; BCR, biochemical recurrence.

conference (6,14,15) has separated cancers with Gleason score 7 into grade group 2 (3+4=7) and grade group 3 (4+3=7) categories.

An additional major recommendation from the ISUP 2014 consensus conference was to report the percentage of Gleason pattern 4 in both needle biopsy and radical prostatectomy specimens (6). This is particularly important in Gleason score 3+4=7 disease detected in prostate biopsy. Some men with minimal Gleason pattern 4 cancer may still be eligible for active surveillance as a more favorable form of intermediate risk disease (16), while those with more extensive pattern 4 may be recommended for early definitive treatment with curative intent. Another advantage for recording the percent of pattern 4 involves biopsies that have tumor burden that is borderline between Gleason score 3+4=7 and 4+3=7. Reporting the percentage of pattern 4 helps clarify the aggressiveness of the tumor regardless of whether pathologists diagnose 3+4=7 with 40% pattern 4 or 4+3=7 with 60% pattern 4. Similarly, borderline cases between 4+3=7 (e.g., 90% pattern 4) and 4+4=8 would also be evident. This can have clinical implications as patients who undergo radiotherapy may have differing treatment protocols for Gleason scores 4+4=8 versus 4+3=7. In this article, we review available data indicating the benefits of recording the percentage of Gleason pattern 4 as well as its controversies, primarily in men with Gleason score 7 prostate cancer.

Methods

A PubMed search was conducted, using search terms of "prostate cancer", "Gleason", "pattern", and "percentage", and a total of 116 articles were identified. Abstracts were first reviewed, and if relevant, full texts were retrieved for more comprehensive review. Final decisions for inclusion were based on quality of evidence and relevance by mutual agreements by the authors.

Does percent Gleason pattern 4 stratify the prognosis of patients undergoing radical prostatectomy?

Table 1 summarizes the findings in previous studies assessing the impact of percent Gleason pattern 4 in prostate needle biopsy, radical prostatectomy, or both on stratifying patient outcomes.

Prior to the recommendation from the ISUP 2014 consensus conference, the relative proportion of high-grade carcinoma (the percent Gleason pattern 4, 5, or both) in radical prostatectomy specimens was reported to strongly associate with established prognostic factors, such as higher preoperative prostate-specific antigen (PSA) levels, positive surgical margins, extraprostatic extension, and lymph node metastasis. In a study by Cheng *et al.* involving 504 men who underwent radical prostatectomy for clinically localized

prostate cancer, the rates of 10-year cancer-specific survival were 100%, 85%, and 67% in those with 0% Gleason pattern 4/5, 1–20% Gleason pattern 4/5, and >20% Gleason pattern 4/5, respectively (17). Thus, in these 504 patients, the combined percent Gleason patterns 4 and 5 were found to be an independent predictor of cancer-specific survival.

More recent studies have assessed the utility of pattern 4 fractions in predicting biochemical (PSA) recurrence following radical prostatectomy in men with Gleason score 7 cancer (19-22). In a major German study involving 12,823 consecutive patients (22), the risks of biochemical recurrence were first compared in subgroups of 3+4=7 low (1–25% pattern 4) versus 3+4=7 high (26–49% pattern 4) as well as 4+3=7 low (50–74% pattern 4) versus 4+3=7 high (75–94% pattern 4) and were found to be significantly different for each (P<0.0001). Further divisions of subgroups (*i.e.*, ≤5%, 6–10%, 11–20%, 21–30%, 31–49%, 50–60%, 61–80%, and >80% pattern 4) resulted in an even finer distinction of the patient risk. Of note, patients with 4+3=7 cancer showing >80% pattern 4 versus 4+4=8 cancer had closely similar recurrence-free survivals. In addition, there was no significant difference in the Kaplan-Meier curves in those treated in 2005–2008 versus 2009–2014.

A similar distinction in biochemical recurrence (1–20%, 21–50%, 51–70%, *vs.* >70% Gleason pattern 4) was seen in 585 consecutive patients undergoing radical prostatectomy (19). Following the definition of further subgroups, 5-year recurrence-free survival rates were 87% (1–5% pattern 4), 79% (6–10% pattern 4), 87% (11–20% pattern 4), 74% (21–30% pattern 4), 84% (31–40% pattern 4), 58% (41–50% pattern 4), 60% (51–60% pattern 4), 73% (61–70% pattern 4), and 38% (71–80% pattern 4). The percentage of Gleason pattern 4 was also found to be an independent prognosticator [*e.g.*, 21–50% pattern 4: hazard ratio (HR)=2.21, 51–70% pattern 4: HR=2.59, >70% pattern 4: HR=6.57 *vs.* 1–20% pattern 4]. Additionally, in these patients, the presence of cribriform (HR=1.78, P=0.02) or glomeruloid (HR=0.43, P=0.03) architectures as Gleason grade 4 patterns was significantly associated with elevated or reduced risk of biochemical recurrence, respectively.

The percentage of Gleason pattern 4 in prostate biopsy was also shown to have prognostic significance (20). In 1,691 patients undergoing radical prostatectomy, the percentage of pattern 4, defined as tumor length containing pattern 4 divided by total tumor length, was correlated with pT3 or higher disease at prostatectomy as well as biochemical recurrence. The percentage of pattern 4 was also a strong prognosticator in a multivariate setting (HR=1.02, 95% confidence interval: 1.01–1.03, P=0.006), with better outcomes found in patients with 1–9.9% pattern 4 cancer compared with 3+3=6 cancer.

Another study compared biopsy Gleason score 7 cases for biochemical recurrence after radical prostatectomy (21). Overall, the percentage of Gleason pattern 4 could stratify the risk of biochemical recurrence. Compared with Gleason score 6 cancer, HRs of 6–25%, 26–49%, and ≥50% pattern 4 cancers in a multivariate setting were 2.381 (P=0.029), 7.612 (P=0.001), and 6.380 (P=0.001), respectively. However, some of the prognostic differences in subgroups of patients were not statistically significant (e.g., <6% *vs.* 6–25%, 26–49% *vs.* ≥50%).

Sauter *et al.* (24) subsequently assessed a system for integration of both Gleason patterns 4 and 5 into a continuous numerical scale or score [integrated quantitative (IQ)-Gleason score]. Based on their data from 13,261 prostatectomy specimens and 3,295 matched biopsies, the IQ-Gleason score appeared to represent an efficient approach for combining quantitative Gleason grading and tertiary patterns into a single prognostic variable.

Accuracy of estimated percent Gleason pattern 4

Correlation of percent pattern 4 between needle biopsy and radical prostatectomy specimens

Correlations between Gleason scores at needle biopsy and corresponding radical prostatectomy remain a major issue, although the modified Gleason grading system has contributed to achieving better concordance. For instance, a study involving 7,643 matched biopsies—prostatectomies published in 2012 revealed up-grading in 36.3%, 25.8%, and 30.6% of cases with biopsy Gleason scores 5–6, 3+4, and 4+3, and down-grading in 12.0% and 41.1% cases with biopsy with Gleason scores 3+4 and 4+3, respectively (25). To the best of our knowledge, only a few studies have assessed the concordance between the quantity of Gleason pattern 4 in prostate biopsy and prostatectomy findings.

In one study, a total of 256 biopsy cases with Gleason score 7 cancer divided into five groups, 1–20%, 21–40%, 41–60%, 61–80%, and 81–100%, according to the highest percentage of GP4 in the biopsy were correlated with histopathological findings of matched radical prostatectomy (18). Up-grading at prostatectomy was observed in 15.9% of biopsy Gleason score 3+4=7 cases and 11.5% of biopsy Gleason score 4+3=7 cases. Higher percentage of Gleason

pattern 4 in biopsy was significantly associated with not only higher incidence of Gleason score ≥7 but also larger tumor volume and higher pathologic stage (pT3) in prostatectomy specimens.

In a study by Sauter *et al.* (22), the utility of percentage pattern 4 in biopsy specimens for predicting Gleason score on radical prostatectomy was investigated. Categorization based on both the worst positive biopsy and average percentage resulted in finer distinction of Gleason score on prostatectomy specimen, and the latter showed a stronger predictive impact.

Interobserver reproducibility of percent pattern 4

It has been documented that interobserver reproducibility for the recognition of Gleason pattern 4 in prostate needle biopsies is not high. In particular, the rate of the agreement between an expert genitourinary pathologist and general pathologists was lower in cases where pattern 4 was scattered among pattern 3 than in those with discrete tumor foci (26). In a recent study (27), interobserver reproducibility of percent Gleason pattern 4 in prostate needle biopsy was also assessed in a prospective manner. In 422 biopsy cores received for a second opinion at their institution, 75% of cores were within ±10%, with 32% being a perfect match, between an expert genitourinary pathologist and 1 of 4 genitourinary pathology fellows nearing the end of their fellowship. However, in 88 cases with less than10% tumor involvement of the core, an agreement rate was lower (*i.e.*, 61% within ±10% and 30% perfect match). As a result, the authors did not recommend recording the percentage of pattern 4 in a small focus of Gleason score 7 cancer where grading only a few cancer glands might radically overestimate the amount of pattern 4 in the case.

Impact of percent Gleason pattern 4 on active surveillance

Active surveillance is now common practice for patients with clinically localized, low-volume Gleason score 3+3=6 prostate cancer (28). In addition, depending on age, comorbidity, PSA level, tumor extent, and patient desire, some Gleason score 3+4=7 tumors, with only focal, low-volume areas of pattern 4 disease, may be appropriate for active surveillance (16). Therefore, recording the percentage of pattern 4 in the pathology report is clinically relevant in such cases.

Indeed, previous studies described above have demonstrated that more than 90% of cases with Gleason score 3+4=7 with ≤5% pattern 4 in prostate biopsy had Gleason score 3+4=7 or less or organ-confined disease in radical prostatectomy (18,22). Similarly, the rates of biochemical recurrence following radical prostatectomy in patients with biopsy Gleason score 3+4=7 (with ≤5% pattern 4) cancer were comparable with those of biopsy Gleason score 3+3=6 cancer (21,22). Another recent study involving 1,255 patients with biopsy Gleason score 3+3=6 or 3+4=7 cancer showed that grouping percentage of pattern 4 by 1–5%, 6–10%, 11–20%, and 21–49% predicted extraprostatic extension at radical prostatectomy, and the HRs were 1.68, 1.86, 2.54, and 2.27, respectively, compared with 0% pattern 4, in a multivariate analysis (23). Importantly, in patients with biopsy Gleason score 3+4=7 with ≤10% pattern 4, age and preoperative PSA were found to associate with the risk of extraprostatic extension. Specifically, it was11.2% in men <60 years with a PSA level of ≤4 ng/mL and <15% positive cores versus 57.8% in men >60 years with a PSA level of >8 ng/mL and >30% positive cores (23). Moreover, a similar study (15) showed that the odds of adverse pathology at radical prostatectomy, such as Gleason score 4+3=7 or higher cancer and/or pT3 disease, were significantly higher when percent pattern 4 on biopsy reached 20–29.9% (HR=2.47), compared with 1–9.9% (HR=1) or 10–19.9% (HR=1.26) pattern 4.

Conclusions

Current evidence indicates that the benefits of recording percent Gleason pattern 4 include stratifying patient outcomes and providing critical information for the decision of patient management. However, the amount of data available on the utility of reporting percent Gleason pattern 4 is still limited. In particular, it appears that data in patients undergoing non-surgical definitive treatment, such as brachytherapy and external beam radiation therapy, is not yet available. A threshold of percent pattern 4 for initiating definitive treatment should also be determined. Thus, whether providing the percentage of pattern 4 can be translated into a relevant parameter for clinical practice remains to be determined. Further studies determining the role of percent pattern 4 in the management of prostate cancer patients are therefore required. In addition, a consensus needs to be reached in order to achieve unified reporting in pathology reports.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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