Over half of contemporary clinical Gleason 8 on prostate biopsy are downgraded at radical prostatectomy

Robert Qi, MD,[1,3] Wen-chi Foo, MD,[2] Michael N. Ferrandino, MD,[1]
Leah G. Davis, MS,[1] Sitharthan Sekar, BS,[3] Thomas A. Longo, MD,[1]
Ghalib Jibara, MD,[1] Tracy Han, MBA,[3] Ilhan Gokhan, BSE,[4] Judd W. Moul, MD[1]

[1]Division of Urology, Department of Surgery and Duke Cancer Institute, Duke University Medical Center, Durham, North Carolina, USA
[2]Department of Pathology, Duke University Medical Center, Durham, North Carolina, USA
[3]School of Medicine, Duke University Medical Center, Durham, North Carolina, USA
[4]Pratt School of Engineering, Duke University, Durham, North Carolina, USA

QI R, FOO W-C, FERRANDINO MN, DAVIS LG, SEKAR S, LONGO TA, JIBARA G, HAN T, GOKHAN I, MOUL JW. Over half of contemporary clinical Gleason 8 on prostate biopsy are downgraded at radical prostatectomy. *Can J Urol* 2017;24(5):8982-8989.

Introduction: *Contemporary clinical guidelines utilize the highest Gleason sum (HGS) in any one core on prostate biopsy to determine prostate cancer treatment. Here, we present a large discrepancy between prostate cancer risk stratified as high risk on biopsy and their pathology after radical prostatectomy.*

Materials and methods: *We retrospectively reviewed 1424 men who underwent either open or robotic-assisted prostatectomy between 2004 and 2015. We analyzed 148 men who were diagnosed with HGS 8 on prostate biopsy. Biopsy and prostatectomy pathology were compared in aggregate and over 1 year time intervals. Chi-squared test, Fisher's exact test, Student's t-test, and Wilcoxon Rank-Sum test were used for statistical analysis.*

Results: *A total of 61.5% (91/148) of clinical HGS 8 diagnoses were downgraded on prostatectomy, with 58.8% (87/148) downgraded to Gleason 7 (Gleason 4 + 3 n = 59; Gleason 3 + 4 n = 28). Factors associated with downgrading include lower prostate-specific antigen (PSA) at biopsy (median 6.8 ng/mL versus 9.1 ng/mL, $p < 0.001$), number of Gleason 8 biopsy cores (median 1 versus 2, $p < 0.02$), presence of Gleason pattern 3 on biopsy cores (67.9% versus 44.8%, $p < 0.03$), pT2 staging (72.4% versus 55.1%, $p < 0.04$), positive margins (53.9% versus 69.1%, $p < 0.04$), extracapsular extension (53.4% versus 74.1%, $p < 0.02$), and smaller percent tumor (median 10% versus 15%, $p < 0.004$).*

Conclusion: *The large percentage of pathology downgrading of biopsy-diagnosed HGS 8 suggests suboptimal risk-stratification that may lead to suboptimal treatment strategies and much patient distress. Our study adds great urgency to the efforts refining prostate cancer clinical assessment.*

Key Words: prostate cancer, prostate biopsy, Gleason score, prostatectomy

Introduction

Prostate cancer is the most common cancer in men and the third-leading cause of cancer-specific mortality in the United States.[1] Risk-stratification is essential for the proper management of prostate cancer, with popular criteria including National Comprehensive Cancer Network (NCCN) guidelines, D'Amico criteria, and American Urological Association (AUA) and European Association of Urology (EAU) guidelines that stratify patients into low, intermediate, and high risk groups, as well as very low and high risk groups from the NCCN.[2-5] Gleason scoring of biopsy specimens is essential for proper patient risk-stratification, thereby determining prognosis and management. In all guidelines, the final Gleason score used to risk-stratify patients is the biopsy core with the combined highest Gleason score (HGS). For example, a patient with one core of Gleason 4 + 4 = 8 and three cores of Gleason 4 + 3 = 7 would be diagnosed

Accepted for publication April 2017

Acknowledgement
Work for this manuscript was supported by the Duke Department of Surgery – Division of Urology and the Duke Department of Pathology

Address correspondence to Dr. Judd W. Moul, Department of Surgery, Duke University Medical Center, DUMC 3707, Duke South, Room 1562, Durham, NC 27710 USA

with clinical high risk disease instead of intermediate risk disease under current guidelines.

A HGS ≥ 8 on prostate biopsy automatically classifies a patient with high risk or very high risk disease in all guidelines. Current literature supports aggressive treatment of high risk prostate cancer. Neoadjuvant androgen deprivation therapy (ADT) is generally recommended in conjunction with primary radiotherapy,[6] with long term neoadjuvant ADT and radiation therapy providing superior survival for locally advanced prostate cancer compared with short term neoadjuvant ADT and radiotherapy.[7] While the AUA does not recommend the extent of lymph node dissection, both the NCCN and EAU guidelines recommend extended pelvic lymph node dissection (PLND) at radical prostatectomy (RP) for patients with high risk of metastasis to improve diagnostic accuracy and possibly survival.[8]

Unfortunately, ADT presents significant side effects including increased risk of cardiovascular disease, thromboembolism, osteopenia, diabetes as well as hot flashes, loss of libido, and weight gain that decrease quality of life.[9] Morbidities occur up to three times more frequently with extended PLND than standard PLND,[10] and can include neurovascular and ureteral injury, thromboembolisms, and lymphoceles.[11] As such, the interpretation of prostate biopsy results should ensure men are not incorrectly classified with clinical high risk prostate cancer, over-treated with neoadjuvant ADT or extended PLND, and thereby subjected to unnecessary comorbidities.

In this study, we report that a very high percentage of men with biopsy-diagnosed HGS 8 disease have Gleason 7 or 6 on final prostatectomy. Consequently, many men diagnosed with HGS 8 prostate cancer on biopsy could be over-treated with neoadjuvant ADT and extended PLND and are being exposed to unnecessary morbidity risks. Clinically diagnosing high risk prostate cancer based on biopsy HGS thus may not be optimal.

Materials and methods

We retrospectively reviewed clinicopathologic data from a total of 1424 men who underwent prostatectomy at our institution between 2004 and 2015. We reviewed 1034 men who underwent open retropubic RP (RRP) by a single surgeon at our institution between 2004 and 2015 for primary analysis. Secondary analysis was performed by retrospectively reviewing clinicopathologic data from 390 men who underwent robotic-assisted laparoscopic prostatectomy (RALP) by a second surgeon at our institution between 2010 and 2015. Patients whose biopsy cores had Gleason 8 as the highest or only Gleason score were termed "biopsy-diagnosed HGS 8 pathology" and were selected for this study. Patients whose RPs (either open RRP or RALP) were aborted and whose surgical pathology did not report Gleason scoring were excluded from final analysis. Research was approved by our institutional review board and compliant with the Health Insurance Portability and Accountability Act.

Prostate biopsy specimens were taken both at our institution and from outside institutions. Majority of biopsies taken at outside institutions for patients who eventually underwent open RRP were re-analyzed by pathologists at our institution specializing in genitourinary pathology; if there was a discrepancy, then the score from pathologists at our institution was utilized. Biopsies taken after 2005 were read in accordance with 2005 International Society of Urological Pathology (ISUP) modified Gleason guidelines.[12]

All RP specimens were taken at our institution and analyzed by pathologists at our institution who specialize in genitourinary pathology. RP specimen were weighed, inked, and sectioned at 3 mm intervals according to our institutional protocol. Gleason scoring and adverse pathologies were assessed after evaluating the entire prostate.

Downgrading was defined as either a) decrease in the Gleason score between biopsy HGS and the final overall Gleason score on prostatectomy specimen or b) decrease in order of primary and secondary grading toward lower grade (i.e. Gleason 5 + 3 to Gleason 3 + 5) between biopsy HGS and the final overall Gleason score on prostatectomy specimen. Downgrading was analyzed both in the aggregate and separated into 1 year cohorts based on year of RP.

Preoperative clinical and pathological variables chosen for this study included patient age, race, clinical staging, prostate-specific antigen (PSA) at biopsy, the HGS on biopsy cores, "pure" or "heterogeneous" Gleason 8 on biopsy, the number and percent positive biopsy cores, and the number and percent of positive high risk biopsy cores. Specimen classified as "pure" Gleason 8 reported only Gleason 8 cores on biopsy. Specimen classified as "heterogeneous" Gleason 8 reported biopsy cores of Gleason 6 or 7 in addition to Gleason 8. Percent positive biopsy cores was defined as number of biopsy cores positive for cancer (all Gleason scores) divided by the total number of biopsy cores taken. Percent positive high risk biopsy cores was defined as number of biopsy cores with combined Gleason 8 pathology divided by the total number of biopsy cores taken.

Surgical pathology included Gleason scoring, prostate size, percent of prostate that was tumor, positive margins, extracapsular extension, seminal vesicle invasion, and lymph node invasion. Presence of tertiary Gleason pattern 5 was included for specimen with Gleason ≤ 8.

Continuous variable were compared with the Wilcoxon Rank-Sum test if not normally distributed and with Student's t-test if normally distributed between the downgraded and not downgraded pathologies. Categorical variables compared between the downgraded and not downgraded pathologies, as well as downgrading over time, were analyzed with Chi-squared test and Fisher's exact test. Statistical significance was set at $p < 0.05$. Statistics were analyzed using JMP Pro 12.

Results

Patient population

In total, we retrospectively reviewed 1424 men who underwent either open RRP or RALP between October 2004 and August 2015. We investigated the 148 men with biopsy-diagnosed HGS 8 pathology (105 Caucasian, 34 African American, 9 of other races) who met our inclusion criteria.

A total of 1034 men underwent open RRP by a single surgeon between October 2004 and August 2015. One hundred and twelve men were diagnosed with HGS 8 pathology on prostate biopsy. We excluded 5 patients whose RPs were aborted and 4 whose neoadjuvant treatments prevented proper Gleason scoring on surgical pathology. As such, 103 patients (78 Caucasian, 21 African American, and 4 of other races) were included for analysis. Only 1 patient underwent prostatectomy in 2004.

A total of 390 men underwent RALP by a single surgeon between February 2010 and September 2015. Forty-five men were diagnosed with HGS 8 pathology on prostate biopsy. All patients were analyzed (27 Caucasian, 13 African-American, 5 of other races).

Gleason score on biopsy and prostatectomy pathology

Overall, 95.3% (141/148) of patients had HGS 4 + 4 = 8 on biopsy, Table 1. A total of 61.5% (91/148) were downgraded on final prostatectomy. A single biopsy was listed as HGS 8 without primary or secondary Gleason patterns, and had Gleason 3 + 4 = 7 on final prostatectomy pathology. The most common downgrading was HGS 8 to Gleason 7 (58.8%, n = 87), with 39.9% (n = 59) diagnosed as Gleason 4 + 3 and 18.9% (n = 28) diagnosed as Gleason 3 + 4.

Biopsy-diagnosed Gleason 8 downgrading on prostatectomy pathology by year

Biopsy-diagnosed HGS 8 pathologies were classified as being downgraded or not downgraded on RP, and then

TABLE 1. **Gleason score on biopsy and surgical pathology**

Biopsy Gleason 8 scoring	**Number (%) Open RRP (n = 103)***	**RALP (n = 45)**	**All RP (n = 148)**
3 + 5	3 (2.9%)	2 (4.4%)	5 (3.4%)
4 + 4	99 (96.1%)	42 (93.3%)	141 (95.3%)
5 + 3	0	1 (2.2%)	1 (0.7%)
Surgical specimen Gleason score			
< 6	0	0	0
6	3 (2.9%)	1 (2.2%)	4 (2.7%)
7	60 (58.3%)	27 (60.0%)	87 (58.8%)
3 + 4	21 (20.4%)	7 (15.6%)	28 (18.9%)
4 + 3	39 (37.9%)	20 (44.4%)	59 (39.9%)
8	13 (12.6%)	12 (26.7%)	25 (16.9%)
9	27 (26.2%)	5 (11.1%)	32 (21.6%)
10	0	0	0

*1 biopsy was listed as combined Gleason 8 without primary or secondary Gleason patterns. This biopsy was listed as Gleason 3 + 4 = 7 on surgical pathology.
RRP = retropubic radical prostatectomy; RALP = robotic-assisted laparoscopic prostatectomy; RP = radical prostatectomy

TABLE 2. **Downgrading of biopsy-diagnosed Gleason 8 on surgical pathology by year for all radical prostatectomies**

Year	No. biopsy Gleason 8 total	No. biopsy Gleason 8 downgraded	% biopsy Gleason 8 downgraded
2004	1	1	100%
2005	8	4	50%
2006	9	2	22.2%
2007	6	1	16.7%
2008	9	6	66.7%
2009	12	7	58.3%
2010	15	8	53.3%
2011	18	12	66.7%
2012	20	15	75%
2013	24	17	70.8%
2014	18	12	66.7%
2015	7	6	85.7%

$p < 0.09$ (overall in-group statistical difference among the yearly, individual % biopsy Gleason 8 downgraded)

subsequently separated into 1 year cohorts. Combined results from both open RRP and RALP cohorts yielded borderline in-group differences among the 1 year cohorts ($p < 0.09$), Table 2, with a general trend of increasing downgrading over time. Pathological downgrading increased from 53.3% (8/15) to 75.0% (15/20) from 2010 to 2012, while 72.5% (50/69) of biopsy-diagnosed HGS 8 were downgraded on RP between 2012 and 2015.

Preoperative clinicopathological characteristics

Biopsy-diagnosed HGS 8 patients that were downgraded on RP had significantly lower median PSA (6.8 versus 9.1, $p < 0.007$), Table 3, than those that were not downgraded. Downgraded patients also had significantly less median percent-positive high risk cores on biopsy (8.7% versus 16.7%, $p < 0.0007$) and fewer median biopsy cores-positive for Gleason 8 pattern (median 1 versus 2, $p < 0.02$).

Pure biopsy-diagnosed HGS 8 patients were less likely to be downgraded than heterogeneous biopsy-diagnosed HGS 8 (44.8% versus 67.9%, $p < 0.03$). The 132 biopsy samples that were internally reviewed by our institutional before prostatectomy had higher rates of downgrading than 16 samples that were not (64.4% versus 37.5%, $p < 0.04$). Biopsy specimen that were not internally reviewed had higher numbers of positive biopsy cores than those that were reviewed, with significant in-group differences among the number of HGS 8 biopsy cores ($p < 0.03$) and borderline significant in-group differences among the number of total positive biopsy cores ($p < 0.07$) (data not shown).

There were no statistically significant differences in race, age, or clinical staging between patients whose pathologies were downgraded and those whose pathologies remained the same.

Prostatectomy pathology characteristics

Analyzing the pathology of patients who underwent open RRP and RALP together yielded several statistically significant parameters. Only 55.1% of pathological stage T3 were downgraded while pathological stage T2 had 72.4% chance of downgrading ($p < 0.04$), Table 4. 53.9% of specimens with positive margins were downgraded compared with 69.1% of specimen with negative margins ($p < 0.04$). Specimens with extracapsular extension were downgraded in 53.4% of samples compared with 74.1% of specimen without extracapsular extension ($p < 0.02$).

Specimens with less percent tumor (median 10% versus 15%, $p < 0.004$) were more likely to be downgraded. Seminal vesicle invasion had a lower chance of downgrading compared with specimen that did not, although this was borderline significant (42.9% versus 65.1%, $p < 0.06$).

Of downgraded specimen, 27.5% (25/91) had tertiary Gleason pattern 5 noted. 34.8% (8/23) Gleason 8 RP specimen had tertiary Gleason pattern 5.

Downgrading representation

We stratified the percentage of downgraded biopsy-diagnosed HGS 8 by PSA at biopsy and the number of biopsy cores that were Gleason 8, Table 5. In general, a higher PSA and a greater number of biopsy cores

TABLE 3. **Preoperative clinicopathological characteristics for all radical prostatectomies (n = 148)**

Characteristic	Downgraded	Not downgraded	p value
Race			p < 0.86
Caucasian	62.9% (n = 66)	37.1% (n = 39)	
African-American	58.2% (n = 20)	41.2% (n = 14)	
Other	55.6% (n = 5)	44.4% (n = 4)	
Age (mean years)	61.9	63.4	p < 0.10
Median PSA at biopsy (ng/mL)	6.8	9.1	p < 0.007
Median % positive cores at biopsy[1]	41.7%	43.8%	p < 0.22
Median % positive high risk cores at biopsy[2]	9.1%	18.8%	p < 0.0002
Median # positive cores at biopsy[3]	4	4	p < 0.52
Median # positive high risk cores at biopsy[4]	1	2	p < 0.02
Pure biopsy Gleason 8[5]			p < 0.03
Yes	44.8% (n = 13)	55.2% (n = 16)	
No	67.9% (n = 76)	32.1% (n = 36)	
Internal biopsy review			p < 0.04
Yes	64.4% (n = 85)	35.6% (n = 47)	
No	37.5% (n = 6)	62.5% (n = 10)	
Clinical stage[6]			p < 0.94
T1x	61.4% (n = 35)	38.6% (n = 22)	
T2x	58.1% (n = 36)	41.9% (n = 26)	
T3x	66.7% (n = 2)	33.3% (n = 1)	

[1]missing n = 31; [2]missing n= 47; [3]missing n = 4; [4]missing n = 5; [5]missing n = 7; [6]missing n = 26

TABLE 4. **Surgical pathology characteristics in all radical prostatectomies (n = 148)**

Characteristic	Downgraded	Not downgraded	p value
Pathological stage[1]			p < 0.04
T2x	72.4% (n = 42)	27.6% (n = 16)	
T3x	55.1% (n = 49)	44.9% (n = 40)	
Margins[1]			p < 0.04
Positive	53.9% (n = 35)	46.2% (n = 30)	
Negative	69.1% (n = 56)	30.9% (n = 25)	
Extracapsular extension[2]			p < 0.02
Positive	53.4% (n = 47)	46.6% (n = 41)	
Negative	74.1% (n = 43)	25.9% (n = 15)	
Seminal vesicle invasion			p < 0.06
Yes	42.9% (n = 9)	57.14% (n = 12)	
No	65.1% (n = 82)	34.9% (n = 44)	
Mean prostate weight (g)	37	41	p < 0.34
Median % tumor	10	15	p < 0.004

[1]missing n = 2; [2]equivocal n = 1

TABLE 5. **Downgrade stratification predictor table**

(#downgrade/#total) (% downgrade)	1 core positive with Gleason 8	2 cores positive with Gleason 8	3 cores positive with Gleason 8	4+ cores positive with Gleason 8	All cores positive with Gleason 8
PSA < 10 ng/mL	46/60 76.7%	16/20 80%	2/8 25%	4/8 50%	68/96 70.8%
PSA 10-20 ng/mL	6/9 66.7%	4/7 57.1%	2/3 66.7%	1/3 33.3%	13/22 59.1%
PSA > 20 ng/mL	3/8 37.5%	3/4 75%	2/5 40%	0/2 0%	8/19 42.1%
All PSA	55/77 71.4%	23/31 74.2%	6/16 37.5%	5/13 38.5%	89/137 65%

*missing n = 11; PSA = prostate-specific antigen

positive for Gleason 8 are correlated with decreased chance of downgrading. Nonetheless, there is a substantial chance of downgrading regardless of the number of biopsy cores or PSA.

Discussion

In this study, we show that over half of all prostate cancer patients with HGS 8 between 2004 and 2015 are downgraded at surgical prostatectomy. Lower median PSA at biopsy, fewer median number and percentage of biopsy cores positive for Gleason 8 cancer, and samples with heterogeneous HGS 8 were significantly associated with downgrading. Prostatectomy specimens with stage T2, negative margins, without extracapsular extension, and lower median percent tumor are significantly more likely to have been downgraded.

Contemporary NCCN, AUA, and EAU guidelines for prostate cancer utilize the HGS on prostate biopsy as the final Gleason score to risk-stratify patients. However, our results indicate that over half of patients classified as HGS 8 high-risk disease under current guidelines are downgraded based on prostatectomy specimen while presenting with significantly less severe adverse outcomes on surgical pathology. This raises the possibility that utilizing the biopsy HGS may over-estimate the risk classification of a substantial percentage of patients clinically diagnosed with final Gleason 8 prostate cancer, potentially leading to substantial risks to health and quality of life with ADT and extended PLND. This possibility of overtreatment could be especially relevant to patients who choose radiation therapy, cryotherapy, high intensity focused ultrasound, and other treatment options where the prostate is not removed and which the Gleason score for risk-stratification and adjunctive therapies depends solely on biopsy results.

Moreover, patients diagnosed with high risk disease are more likely to receive bone scans and abdominal imaging to investigate potential metastasis.[2] Because many biopsy-diagnosed Gleason 8 disease are downgraded to intermediate risk where such scans are not indicated, many patients may not necessarily require such imaging. In addition to radiation exposure, inconvenience to patients and additional imaging costs could thus be incurred.

It is notable that 21% of biopsy-diagnosed Gleason 8 patients are upgraded to Gleason 9 disease. Under the 2016 updated Gleason scoring system, they would be moved from Gleason Group 4 (Gleason 8 disease) to Gleason Group 5 (Gleason 9-10 disease).[13] However, such a change would not alter the management of prostate cancer under current guidelines, whereas a diagnostic change from Gleason 8 to Gleason ≤ 7 potentially would. Nonetheless, there is a large need for better clinical risk assessment.

In 2003, Kunz and Epstein recommended that if multiple biopsy cores contain prostate cancer with differing Gleason scores, each core should be reported separately rather than assigning an overall score. Therefore, patients with Gleason pattern 4 + 4 = 8 on 1 core but Gleason pattern grade 3 on other cores should be given a final biopsy Gleason score of 4 + 4 = 8 on that core instead of an overall score of 4 + 3 = 7.[14] Their results showed that compared to patients with biopsy cores of purely Gleason 4 + 3 = 7, patients with biopsy cores of 4 + 4 = 8 on at least 1 core with 1 or more cores also containing Gleason pattern 3 had higher percentage of seminal vesicle invasion (43% versus

15%, no p value) and higher Gleason grade on RP (RP 4 + 4 = 8 29% versus 10%, no p value; RP 4 + 5 or 5 + 4 = 9 27% versus 3%, no p value). The authors also asserted that the pathological results are comparable to those from patients diagnosed with only Gleason 4 + 4 = 8 cores on biopsy, although no explicit comparison was written in the methodology and results. This study significantly influenced the 2005 ISUP consensus guidelines on reporting of needle core biopsy results.[12]

The current study has several differences compared to the study by Kunz and Epstein. Kunz and Epstein compared 40 men with pure Gleason 4 + 3 on biopsy with 35 men who had at least 1 Gleason 4 + 4 = 8 biopsy core from 127 total subjects, while we utilized 148 men HGS 8 from 1424 total subjects. Kunz and Epstein combined Gleason 4 + 4 = 8 with pattern 3 on other cores at biopsy as one cohort regardless of prostatectomy Gleason score, while we explicitly compared clinical and pathological data between biopsy-diagnosed HGS 8 pathologies that were downgraded or not on prostatectomy. Our study has different pathological Gleason scorings compared with Kunz and Epstein (61% versus 44% Gleason 6 or 7; 16.9% versus 29% Gleason 8; 21.6% versus 27% Gleason 9). Of note, this study identified a marked increase in the pathologic downgrading after 2008. This cohort is years after the cohort of pathologies studied by Kunz and Epstein (1996-2000).

Our results contribute to a growing body of literature that suggests utilizing biopsy-diagnosed HGS ≥ 8 may not be optimal for clinical risk stratification. Between 48% and 67% of biopsy-diagnosed HGS 8 have been reported as downgraded on RP since 2009, primarily to Gleason 7.[15-19] We agree with Brimo et al that downgraded prostatectomy specimen had fewer HGS 8 on biopsy cores compared with non-downgraded prostatectomy specimen,[19] while Pierorazio et al reported that more HGS 8 biopsy cores was associated with seminal vesicle or lymph node invasion.[18] Moreover, we also described that the presence of Gleason pattern 3 on biopsies with HGS 8 was associated with downgrading under current guidelines, while we examined the pathology results for potential clinical implications.

Given the ongoing development of biopsy Gleason scoring and the concern about the practicality of advanced technology for general use outside of academic medical centers,[20] we have created a stratifying table predicting the likelihood of biopsy-diagnosed HGS 8 downgrading that is both easily accessible for the patient and convenient for the typical clinical practice to counsel patients and help determine patient-centric management courses. We believe this model of delineating the likelihood of downgrading can be further refined and used for other clinical diagnoses given the discordance among clinical and pathological Gleason scores.[21-23]

Our study has several strengths. Patients who underwent both open RRP and RALP were both included in our cohort to limit potential surgical biases. The overwhelming majority of our biopsies was either performed at our institution or was re-reviewed by our institution's pathologists if performed at an outside institution. We presented a decade of recent data; indeed, the majority of our patients underwent procedures after 2005 and as such their pathologies were subjected to the 2005 ISUP guidelines.

Our institution's pathologists provided Gleason grading for analysis. While there may be discrepancies among our institution's pathologists, our practice reflects real-world experience. In a typical practice, Gleason scores are not re-reviewed by a single pathologist before being used to determine management, while there are numerous genitourinary pathologists reading prostate specimen in a healthcare system. Our results thus may be more generalizable and applicable to the practicing physician.

Potential limitations include that our study comprises patients from two surgeons at one institution. Unfortunately, we did not have the total number of biopsy cores taken for many patients, given that many patients were initially diagnosed at outside institutions. Patients who choose radiation therapy or other modalities may have different tumor characteristics than ones undergoing RP. Finally, future directions should investigate potential differences between the RP pathology from pure and heterogeneous HGS 8 on biopsy.

Conclusion

Our investigation reveals a very high percentage of biopsy-diagnosed HGS 8 prostate cancer is downgraded on prostatectomy, and such downgrading could be increasing in recent years. Treatment planning and patient consultation may thus be suboptimal for biopsy-diagnosed HGS 8 prostate cancer. Our study adds great urgency to the efforts refining prostate cancer clinical assessment. □

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin* 2017;67(1):7-30.
2. Mohler J, Bahnson RR, Boston B et al. NCCN clinical practice guidelines in oncology: prostate cancer. *J Natl Compr Canc Netw* 2010;8(2):162-200.

3. D'Amico AV, Whittington R, Malkowicz SB et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280(11):969-974.
4. Thompson I, Thrasher JB, Aus G et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol* 2007;177(6):2106-2131.
5. Heidenreich A, Bastian PJ, Bellmunt J et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent – update 2013. *Eur Urol* 2014;65(1):124-137.
6. Payne H, Mason M. Androgen deprivation therapy as adjuvant/neoadjuvant to radiotherapy for high-risk localized and locally advanced prostate cancer: recent developments. *Br J Cancer* 2011;105(11):1628-1634.
7. Bolla M, de Reijke TM, van Tienhoven G et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009;360(24):2516-2527.
8. Briganti A, Blute ML, Eastham JH et al. Pelvic lymph node dissection in prostate cancer. *Eur Urol* 2009;55(6):1251-1265.
9. Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. *Urology* 2003;61(2 Suppl 1):32-38.
10. Clark T, Parekh DJ, Cookson MS, et al. Randomized prospective evaluation of extended versus limited lymph node dissection in patients with clinically localized prostate cancer. *J Urol* 2003;169(1):145-147.
11. Loeb S, Partin AW, Schaeffer EM. Complications of pelvic lymphadenectomy: do the risks outweigh the benefits? *Rev Urol* 2010;12(1):20-24.
12. Epstein JI, Allsbrook WC, Amin MD et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol* 2005;29(9):1228-1242.
13. Epstein JI, Zelefsky MJ, Sjoberg DD et al. A contemporary prostate cancer grading system: a Validated alternative to the Gleason score. *Eur Urol* 2016;69(3):428-435.
14. Kunz GM, Epstein JI. Should each core with prostate cancer be assigned a separate Gleason score? *Hum Pathol* 2003;34(9):911-914.
15. Moussa AS, Li J, Klein EA. Prostate biopsy clinical and pathological variables that predict significant grading changes in patients with intermediate and high grade prostate cancer. *BJU Int* 2009;103(1):43-48.
16. Epstein JI, Feng Z, Trock BJ et al. 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(5):1019-1024.
17. Imamoto T, Suzuki H, Takanobu U et al. External validation of a nomogram predicting the probability of prostate cancer Gleason sum upgrading between biopsy and radical prostatectomy pathology among Japanese patients. *Urology* 2010;76(2):404-410.
18. Pierorazio PM, Ross AE, Lin BM et al. Preoperative characteristics of high-Gleason disease predictive of favourable pathological and clinical outcomes at radical prostatectomy. *BJU Int* 2012;110(8):1122-1128.
19. Brimo F, Xu B, Scarlata E et al. Biopsy characteristics in men with a preoperative diagnosis of prostatic adenocarcinoma with high Gleason score (8-10) predict pathologic outcome in radical prostatectomy. *Hum Pathol* 2014;45(10):2006-2013.
20. Whitson JM, Porten SP, Cowan JE et al. Factors associated with downgrading in patients with high grade prostate cancer. *Urol Oncol* 2013;31(4):442-447.
21. Filippou P, Welty CJ, Cowan JE et al. Immediate versus delayed radical prostatectomy: updated outcomes following active surveillance of prostate cancer. *Eur Urol* 2015;68(3):458-463.
22. Jin BS, Kang SH, Kim DY et al. Pathological upgrading in prostate cancer patients eligible for active surveillance: Does prostate-specific antigen density matter? *Korean J Urol* 2015;56(9):624-629.
23. ElShafei A, Nyame Y, Kara O et al. More favorable pathological outcomes in men with low-risk prostate cancer diagnosed on repeat versus initial transrectal ultrasound-guided prostate biopsy. *J Urol* 2015;195(6):1767-1772.