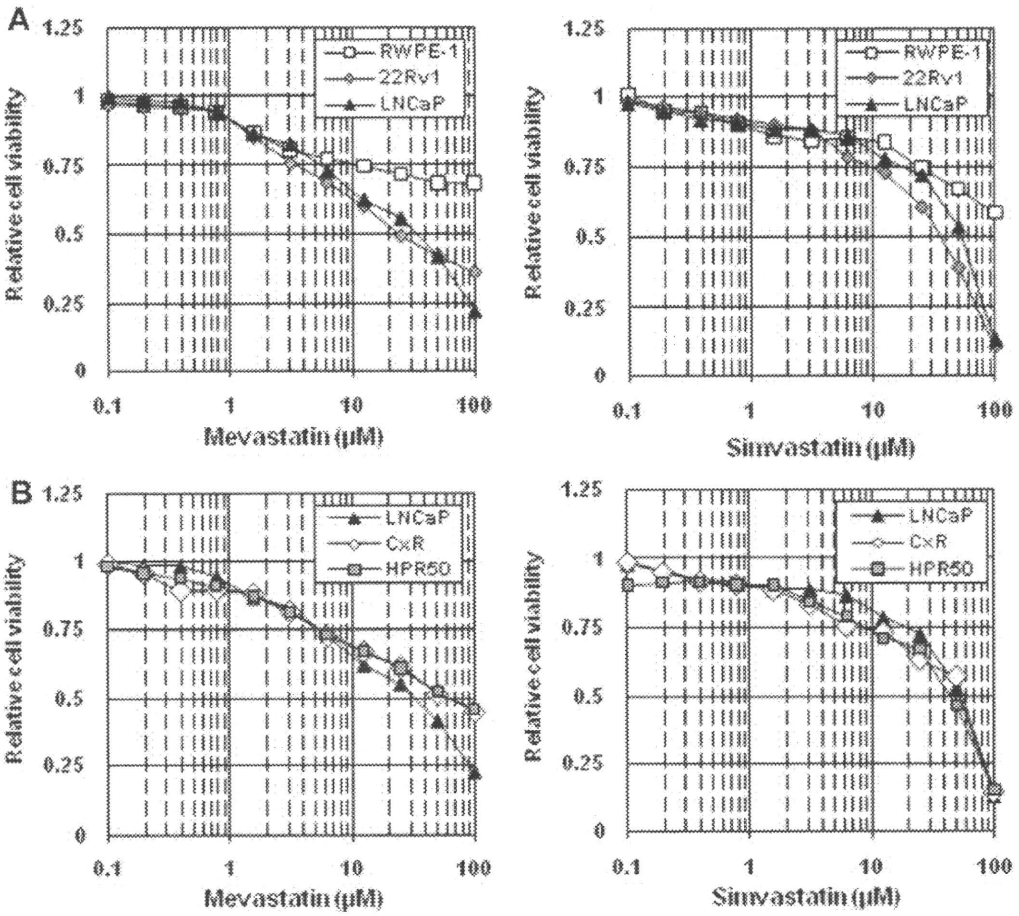

Fig. 4. The growth inhibitory effect of statins on AR negative (RWPE-1) and positive (LNCaP and 22Rv1) cell lines. RWPE-1, 22Rv1, and LNCaP cells (**A**) were seeded into 96-well plates. On the following day, various concentrations of mevastatin or simvastatin were added. After 72 hr the cell survival rates were evaluated using cytotoxicity analyses. Cell survival in the absence of mevastatin or simvastatin was set as 1. All values are representative of at least three independent experiments. Data represent mean value of LNCaP, CxR, and HPR50 cells (**B**) were subjected to cytotoxicity analyses as described in (A).

Finally, the influence of statins on androgen sensitivity was investigated as shown in Figure 5. LNCaP cell proliferation was increased in a dose dependent manner up to 10 nM of DHT, but cell growth of LNCap became saturated at concentrations of DHT exceeding 10 nM (Fig. 5). However, this growth saturation disappeared when 10 μM of mevastatin and simvastatin was added, suggesting that statins decreased androgen sensitivity in LNCaP cells (Fig. 5).

DISCUSSION

Our in vitro experiments clearly showed that statins decreased the level of AR protein by proteolysis, which resulted in a reduction in androgen sensitivity and cell proliferation in AR positive prostate cancer cells. These observations could support epidemiological evidence that indicated that PSA levels declined significantly after the initiation of statin treatment in a cohort of 1214 men in the Durham Veterans Affairs Medical Center 5 study and a cohort of 962 men in the University of Rochester Medical Center study [12].

Several molecular mechanisms had been investigated in relation to the correlation between statin exposure and prostate cancer cell proliferation. Sekine et al. [13] reported that simvastatin suppressed proliferation and induced apoptosis in PC-3 cells, and that the expression of insulin-like growth factor 1 receptor (IGF-1R) was suppressed by simvastatin. This IGF-1R pathway might be important in the inhibitory effect of simvastatin on prostate cancer cell proliferation, especially AR negative prostate cancer cells such as PC-3 cells [13]. Unfortunately, Sekine et al. failed to examine the correlation between statins and AR. As has previously been reported, PC-3 cells are AR-negative cells [14]. In addition, Hong et al. [15] reported that lovastatin inhibited AR-positive LNCaP cell proliferation. Their study focused on Chinese red yeast rice that contains a mixture of eight different monacolins, and monacolin K was identical to lovastatin. They found

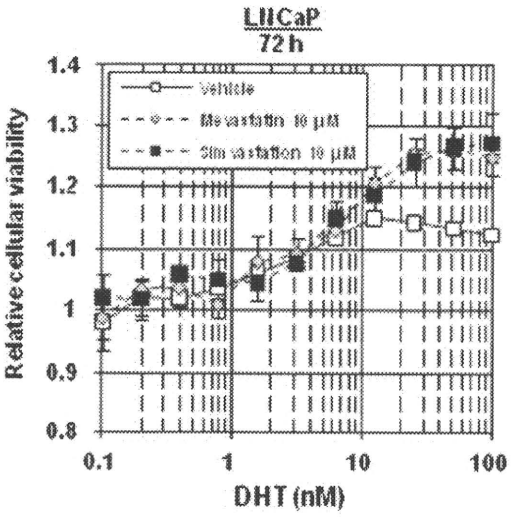

Fig. 5. Decreased androgen sensitivity by mevastatin and simvastatin. LNCaP cells were seeded into 96-well plates with vehicle, 10 μM of mevastatin or simvastatin. On the following day various concentrations of DHT were added. After 72 hr the cell survival rates were analyzed by cytotoxicity analyses. Cell survival in the absence of DHT was set as 1. All values are representative of at least three independent experiments. Data represent means ± SD.

that Chinese red yeast rice inhibited cholesterogenesis and had an inhibitory effect on LNCaP cells. They observed a similar statin induced growth inhibitory effect on LNCaP cells to that observed in the present study, but they failed to examine the precise molecular mechanism involved.

On the other hand, statins may influence prostate cancer cell growth by changing steroid sex hormone biosynthesis. Statins could alter the balance of steroid hormones by two methods. They could reduce the levels of cholesterol, a required intermediate in steroid synthesis, by affecting cytochrome P450 which is an enzyme complex involved in steroid-hormone metabolism [16]. Circulating androgen levels have been reported to be unchanged in statin users [17,18]. However, it has been suggested by Carruba that intraprostatic hormone levels are more important than circulating levels of hormone in prostate carcinogenesis [19]. As of yet, no published research has addressed the effects of statins on either intraprostatic sex-steroid levels or on circulating estrogen levels in men [20].

AR proteins undergo systematic protein degradation via the ubiquitin-proteasome pathway (UPP) [21]. Degradation via the UPP involves two discrete and successive steps. The first is a covalent attachment of multiple ubiquitin molecules to the AR protein to form a polyubiquitin chain and the second is degradation of the tagged protein by the 26S proteasome or, in certain cases, by lysosomes/vacuoles [21]. The precise molecular mechanism related to how statins affect the UPP are still unknown and further investigations are needed to elucidate the correlations between the UPP and downregulation of AR by statins.

CONCLUSIONS

This is the first report that has demonstrated that statins can downregulate AR protein in AR positive prostate cancer cells by proteolysis, resulting in a reduction in androgen sensitivity and cell proliferation.

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Gleason Score Correlation Between Biopsy and Prostatectomy Specimens and Prediction of High-grade Gleason Patterns: Significance of Central Pathologic Review

Kentaro Kuroiwa, Taizo Shiraishi, and Seiji Naito, for the Clinicopathological Research Group for Localized Prostate Cancer Investigators

OBJECTIVES To investigate the significance of dedicated central pathologic review for Gleason score (GS) correlation between the biopsy and radical prostatectomy (RP) specimens and the prediction of high-grade Gleason patterns. A discrepancy in the GS between the biopsy and RP specimens has been reported.

METHODS The Clinicopathological Research Group for Localized Prostate Cancer disease registry collated the data from 1629 patients who had undergone RP from 1997 to 2005. All biopsy and RP specimens were retrospectively re-evaluated by 2 central uropathologists according to the International Society of Urological Pathology consensus. The GS correlation between the biopsy and RP specimens and the presence of high-grade Gleason patterns (4 or 5) were recorded. The GS was categorized into 5 groups (2-4, 5-6, 3 + 4, 4 + 3, and 8-10).

RESULTS Central review significantly increased the exact concordance rate and decreased the undergrading and overgrading rates between the biopsy and RP specimens compared with local review ($P < .05$ for all). In each GS or prostate-specific antigen group, the central review biopsy GS had a significantly greater exact concordance rate with the RP specimen GS compared with the local review biopsy GS ($P < .05$ for all). Regarding high-grade Gleason patterns in the RP specimens, central review showed significantly greater sensitivity, positive predictive value, and negative predictive value than local review ($P < .05$ for all).

CONCLUSIONS We have demonstrated that central review using the International Society of Urological Pathology consensus improves the GS correlation and better predicts high-grade Gleason patterns compared with local review. We recommend central pathologic review by dedicated uropathologists for multi-institutional studies using data from prostate biopsy and RP specimens. UROLOGY 77: 407–411, 2011. © 2011 Elsevier Inc.

The Gleason grading system, proposed by Gleason[1] and represented as the Gleason score (GS) for each case, is the most widely used histologic grading system for prostate cancer. The GS in both biopsy and radical prostatectomy (RP) specimens is a powerful prognostic factor.[2,3] Accurate GS correlation between the biopsy and RP specimens is mandatory for preoperative estimation of the disease and for the planning treatment of each patient. However, the biopsy GS has been reported to have been undergraded in 18%-60% and overgraded in 6%-25% of specimens compared with the RP specimen GS.[4-11] Investigator error is one important factor for the discrepancy; thus, pathologic assessment by dedicated uropathologists might improve the GS correlation between the biopsy and RP specimens. Modern GS assessment according to the 2005 International Society of Urological Pathology (ISUP) consensus, reflecting contemporary changes regarding prostate cancer and the Gleason grading system, has shown better GS correlation than the previous assessment.[12] Pathologic assessment by dedicated uropathologists in a single academic institution has also shown better GS correlation than outside assessment.[6,11] However, the usefulness of pathologic assessment by dedicated uropathologists using the ISUP consensus for a large RP series from multiple institutions has not yet been studied.

Although high-grade Gleason patterns (4 or 5) in RP specimens, either a primary/secondary pattern or a ter-

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tiary pattern, have been reported to be related to a poor outcome, it remains unclear how effectively the biopsy GS determined by pathologic assessment by dedicated uropathologists will predict for high-grade Gleason patterns in the RP specimens.[13-15]

In the present, large-scale, multicenter study, we used the pathologic assessment by dedicated uropathologists according to the ISUP consensus for the biopsy and RP specimens from a large RP series with high-grade biopsy GSs using data from the Clinicopathological Research for Localized Prostate Cancer (CRPC) disease registry. The CRPC collates data from patients with clinically localized prostate cancer accrued from 108 academic and community practices throughout Japan. From 1997 to 2005, approximately 5000 patients with clinically localized prostate cancer who had undergone RP were consecutively enrolled into the CRPC registry after obtaining institutional review board approval from each institution.

MATERIAL AND METHODS

Patient Population

According to the CRPC data, the pathologic slides of the biopsy and RP specimens were available for 1650 patients with Stage cT1c-T3 disease and no preoperative therapy at 48 institutions that agreed to send the pathologic slides for central review. After excluding 21 patients (1.3%) without cancer cells in the biopsy specimens by central review, 1629 patients constituted the final cohort for the present study. In all patients, the diagnosis was made by systemic biopsy (≥6 cores). A total of 365 patients (22.4%) had only 6 cores taken at biopsy; 760 patients (46.7%) had ≥10 cores on taken at biopsy. The median number of biopsy cores taken was 8 (range 6-33). All RP specimens were processed using the whole mount technique at each institution. Preoperative information, including the serum prostate-specific antigen levels, and the original pathologic reports were available for all patients. The clinical stage was determined from the digital rectal examination findings and assigned according to the 2002 American Joint Committee on Cancer staging system.

Pathologic Analysis

The biopsy GS of each patient's original pathologic report was recorded as the local review biopsy GS. All pathologic slides and the biopsy and RP specimens were sent to, and reviewed by, 2 dedicated uropathologists (K.K. and T.S.) who were unaware of the original pathologic reports of each patient. In addition, the 2 uropathologists were unaware of the results from the biopsy specimens of each patient when reviewing the matching RP specimens, because the review of the RP specimens was separated from the review of the biopsy specimens. The Gleason pattern was assigned as the central review biopsy and RP GS according to the modified Gleason grading system using the ISUP consensus.[16] The GS was categorized into 5 groups (2-4, 5-6, 3 + 4, 4 + 3, and 8-10). For the biopsy specimens with multiple positive cores, a global GS was recorded, because the GS of each core was not available in most (>95%) of the original pathologic reports. For central review, the reporting rules for a secondary pattern occupying <5% and a tertiary pattern conformed to the ISUP consensus.[16] For the RP specimens, the global GS considering the entire tumor within the prostate as 1 lesion was recorded. A tertiary Gleason pattern in the RP specimens was not reflected as a primary or secondary pattern on the final RP GS. The presence of high-grade Gleason patterns (4 or 5), including tertiary patterns, in the RP specimens was recorded.

Statistical Analysis

Spearman's rank correlation coefficients for the GS in the biopsy and RP specimens were generated. The chi-square test was used for the comparison of the exact GS concordance rate between the local and central pathologic review and for the sensitivity, specificity, positive predictive value, and negative predictive value for the depiction of high-grade Gleason patterns. Two-sided P values were calculated; the significance level was set at 5%. All statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0 (SPSS, Chicago, IL).

RESULTS

Clinical Characteristics

For the 1629 patients whose CRPC data were analyzed, the median age was 65 years (range 44-84), and the median prostate-specific antigen level 8.0 ng/mL (range 0.5-85.9). Of the 1629, patients, 1058 (64.9%) had Stage cT1c disease.

GS in Biopsy and RP Specimens

By central review, no patient (0%) had GS 2-4 disease in the biopsy specimens compared with 107 patients (6.6%) who had GS 2-4 by local review. Of the 107 patients with local review biopsy GS of 2-4, central review found a biopsy GS of 5-6, 3 + 4, 4 + 3, and 8-10 in 66 (61.7%), 35 (32.7%), 4 (3.7%), and 2 (1.9%), respectively. In the other GS groups, the distribution of the central biopsy GS was 5-6 in 545 (33.5%), 3 + 4 in 602 (37.0%), 4 + 3 in 257 (15.8%), and 8-10 in 225 (13.8%). The corresponding distribution by local review for the biopsy GS was 687 (42.2%), 379 (23.3%), 192 (11.8%), and 264 (16.2%; Table 1). Of the patients with a biopsy GS of 5-6, 3 (0.6%) of 545 by central review and 138 (20.1%) of 602 by local review had GS 5. Exact concordance between the local and central biopsy GS was observed for 841 patients (51.6%). The undergrading and overgrading rate for local review was 32.6% and 15.8%, respectively. Spearman's rank correlation coefficient for local biopsy GS and central biopsy GS was 0.607. The central review RP GS distribution for GS 5-6, 3 + 4, 4 + 3, and 8-10 was 423 (26.0%), 675 (41.4%), 363 (22.3%), and 168 (10.3%), respectively.

GS Correlation Between Biopsy and RP Specimens

Table 2 lists the correlation between the local review biopsy GS and central review RP GS. The exact concordance rate and the concordance rate within ±1 GS group was 41.3% (672 of 1629) and 81.7% (1331 of 1629), respectively. The undergrading and overgrading rate for

Table 1. Biopsy Gleason score correlation between local review and central review

Local Review Biopsy GS	Central Review Biopsy GS (n)					Exact Concordance Rate (%)	Local Review	
	2-4	5-6	3 + 4	4 + 3	8-10		Undergrading Rate (%)	Overgrading Rate (%)
2-4 (n = 107)	0	66	35	4	2	0.0	100.0	0.0
5-6 (n = 687)	0	388	233	50	16	56.5	43.5	0.0
3 + 4 (n = 379)	0	64	225	62	28	59.4	23.7	16.9
4 + 3 (n = 192)	0	13	60	84	35	43.8	18.2	38.0
8-10 (n = 264)	0	14	49	57	144	54.5	0	45.5
Total (n = 1629)	0	545	602	257	225	51.6	32.6	15.8

GS, Gleason score.

Table 2. Gleason score correlation between local review biopsy and central review prostatectomy specimens

Local Review Biopsy GS	Central Review RP GS (n)					Exact Concordance Rate (%)	Undergrading Rate in Biopsy (%)	Overgrading Rate in Biopsy (%)
	2-4	5-6	3 + 4	4 + 3	8-10			
2-4 (n = 107)	0	42	48	14	3	0.0	100.0	0.0
5-6 (n = 687)	0	282	286	97	22	41.0	59.0	0.0
3 + 4 (n = 379)	0	73	204	86	16	53.8	26.9	19.3
4 + 3 (n = 192)	0	16	65	85	26	44.3	13.5	42.2
8-10 (n = 264)	0	10	72	81	101	38.3	0.0	61.7
Total (n = 1629)	0	423	675	363	168	41.3	39.3	19.5

RP, radical prostatectomy; GS, Gleason score.

Table 3. Gleason score correlation between central review biopsy and prostatectomy specimens

Central Review Biopsy GS	Central Review RP GS (n)					Exact Concordance Rate (%)	Undergrading Rate in Biopsy (%)	Overgrading Rate in Biopsy (%)
	2-4	5-6	3 + 4	4 + 3	8-10			
2-4 (n = 107)	0	0	0	0	0	—	—	—
5-6 (n = 687)	0	335	173	27	10	61.5	38.5	0.0
3 + 4 (n = 379)	0	83	391	113	15	65.0	21.3	13.8
4 + 3 (n = 192)	0	2	76	160	19	62.3	7.4	30.4
8-10 (n = 264)	0	3	35	63	124	55.1	0.0	44.9
Total (n = 1629)	0	423	675	363	168	62.0	21.9	16.1

Abbreviations as in Table 2.

the biopsy specimens was 39.3% and 19.5%, respectively. Of the 107 patients with a biopsy GS of 2-4, all had an RP GS of ≥5-6, including 65 patients (60.1%) with a RP GS of ≥7. Spearman's rank correlation coefficient for the local biopsy GS and central RP GS was 0.459.

Table 3 lists the correlation between the central biopsy GS and the central RP GS. The exact concordance rate and the concordance rate within ±1 GS group was 62.0% (1010 of 1629) and 94.4% (1537 of 1629), respectively. The undergrading and overgrading rate for the biopsy specimens was 21.9% and 16.1%, respectively. Central review had a significantly greater exact concordance and lower undergrading and overgrading rates than did the local review ($P < .05$ for all). Spearman's rank correlation coefficient for central biopsy GS and central RP GS was 0.687. In each GS group, the central review biopsy GS (GS 5-6, 61.5%; 3 + 4, 65.0%; 4 + 3, 62.3%; and 8-10, 65.1%) had a significantly greater exact concordance rate than did the local review biopsy GS (GS 5-6, 41.0%; 3 + 4, 53.8%; 4 + 3, 44.3%; and 8-10, 38.3%; $P < .05$ for all). In each prostate-specific antigen group, the central review biopsy GS (<4.0 ng/mL, 56.6%; 4.1-10 ng/mL, 64.1%; 10.1-20 ng/mL, 60.7%; and >20 ng/mL, 56.4%) had a significantly greater exact concordance rate than the local review biopsy GS (<4.0 ng/mL, 56.6%; 4.1-10 ng/mL, 64.1%; 10.1-20 ng/mL, 60.7%; and >20 ng/mL, 56.4%; $P < .05$ for all).

High-Grade Gleason Patterns (4 or 5)

The number of patients with Gleason pattern 4 or 5 in the biopsy GS as a primary or secondary pattern was 846 (51.9%) in the local review and 1084 (66.6%) in the central review.

Overall, 1371 patients (84.2%) had Gleason pattern 4 or 5 on RP specimens on the central pathology review of the RP specimens. Of these, 1206 (88.0%) had Gleason pattern 4 or 5 as the primary or secondary pattern. The remaining 165 (12.0%) with RP GS 3 + 3 had a high-grade Gleason pattern of <5% on the RP specimens.

Table 4 lists the correlation of high-grade Gleason patterns between the biopsy GS and RP specimens. The central review GS had significantly greater sensitivity and a significantly greater positive and negative predictive values ($P < .05$ for all).

Table 4. High-grade Gleason patterns (4 or 5) in biopsy Gleason score and prostatectomy specimens

Review	High-Grade GP in Biopsy GS	High-Grade GP in RP Specimens (n)		Sensitivity	Specificity	PPV	NPV
		Positive	Negative				
Local	Positive	797	49	0.581	0.810	0.942	0.140
	Negative	574	206				
Central	Positive	1052	32	0.767	0.876	0.970	0.415
	Negative	319	226				
P value				<.001	.053	.003	<.001

GP, Gleason pattern; NPV, negative predictive value; PPV, positive predictive value; other abbreviations as in Table 2.

COMMENT

In the pretreatment setting for prostate cancer in which clinicians can only use the biopsy information for histologic grade, a more accurate GS correlation between the biopsy and RP specimens must result in more precise evaluation of the disease, regardless of the treatment type planned. However, studies investigating the GS correlation between the biopsy and RP specimens have shown considerable discrepancy—especially of undergrading in biopsy specimens.[4-11] Although the number of patients involved in these studies has varied from 28 to 1455, very few men had high-grade biopsy GSs.[8-10] The present study included the largest number of patients with high-grade biopsy GS (local review 264, central review 168) for investigating the correlation of the GS between the biopsy and RP specimens. Pathology error and sampling error are thought to be the main reasons for the discrepancy.

Steinberg et al[11] previously reported that pathologists at an academic center had a better GS correlation than those at community sites. According to their recent study of 1455 patients, Fine and Epstein[6] reported that the exact GS concordance rate was improved in both community sites (from 34% to 70%) and an academic center (multiple pathologists; from 58% to 76%) compared with the rate in their older study. The effects of education and pathologists' efforts in the United States might have contributed to this improvement.

The present study had some differences from that conducted by Fine and Epstein.[6] First, each Gleason pattern was assigned according to the ISUP consensus, which was published in 2005 after their study period (2002-2003). Second, we used the global GS, considering the entire tumor within the prostate as 1 lesion for both the biopsy and the RP specimens because the GS of each core was not available in most (>95%) of the original pathologic reports. The use of the global GS should be considered a weakness of the present study. In the study by Fine and Epstein,[6] the RP GS was recorded from the dominant tumor or highest grade tumor. However, it was not clearly reported whether the global or highest core GS had been used for the biopsy specimens. Although almost all preoperative nomograms have used the highest core grade of the given case when multiple cores with different GSs are present, and urologists have tended to use the greatest GS to determine their treatment plan, some clinicians might use the global GS. ISUP did not actually specify that the highest core GS should be used for the biopsy GS in each case.[2,16,17] Third, the present study included significantly more patients with greater biopsy and RP specimens than the previous study. In the present study, 67% of the biopsy and 74% of the RP specimens had a GS of ≥7 compared with the previous 26% and 23%, respectively.[6,11] This might have resulted from patient selection bias and ethnic differences in the patients with prostate cancer, because the present cohort of patients underwent RP at academic or community institutions in Japan.[18] In addition to the differences in the distribution of GS, the division of GS 7 into 3 + 4 and 4 + 3 might explain the relatively low exact concordance rate in our study. When GS 3 + 4 and 4 + 3 were combined as 1 entity, the exact concordance rate was high (73.6%) in the present study. However, a GS of 3 + 4 and that of 4 + 3 have different biologic behavior and should not be combined into 1 category.[19]

Reflecting contemporary changes regarding prostate cancer and the Gleason grading system, the ISUP proposed a modified Gleason grading system in 2005.[16] The ISUP consensus has been reported to minimize biopsy undergrading and improve the GS correlation compared with the previous system.[12] In the present study, including patients who underwent RP from 1997 to 2005, biopsy GS 2-4 was originally diagnosed at each institution in 14.6% of all patients compared with 1.6% in another study.[6] ISUP recommended that a GS 2-4 should rarely, if ever, be considered, because of the poor correlation with the RP GS. Most expert uropathologists would not have assigned a GS of 2-4 even before the ISUP consensus.[20] In our study, all locally reviewed biopsy GS 2-4 specimens were upgraded by the central review and 61% actually had a RP GS of ≥7, including 3 patients with a RP specimen GS of 8-10. In addition, no RP specimens in the present study was graded with a GS of 2-4. For the GS categories other than 2-4, we also showed that central review using the ISUP consensus gave a more accurate GS correlation than local review, including biopsy GS 8-10. However, the exact concordance rate was far from perfect (100%) and was less satisfactory even when a central review using the ISUP consensus was done. The actual GS of each patient can be apparent only after RP has been performed. We believe this is an advantage for RP compared with other

treatment modalities that offer patient surveillance and adjuvant treatment according to the biopsy GS only.

High-grade Gleason patterns, either a primary/secondary pattern or a tertiary pattern, in RP specimens have been related to a poor outcome.[13-15] We have demonstrated that the central review biopsy GS using the ISUP consensus is superior to the local review biopsy GS in terms of predicting high-grade Gleason patterns in the RP specimens. It has been reported that the highest core GS has the largest effect on a significant upward shift of the biopsy GS among the reporting rules of the ISUP consensus.[21] Because we used a global biopsy GS for the central review, the difference in the interpretation of each Gleason pattern between the local review and central review might explain our results for high-grade Gleason patterns.

CONCLUSIONS

This is the first study to investigate the significance of dedicated pathologic reassessment using the ISUP consensus for biopsy and RP specimens from academic and community practices. Central pathologic review resulted in a more accurate GS correlation and prediction of high-grade Gleason patterns. We believe that more educational effort is needed for both pathology and urology communities to disseminate the ISUP consensus. We recommend central pathology review by dedicated uropathologists for a study of prostate biopsy and RP specimens from patients at multiple institutions, although the central review will cost more and is time-consuming. We should carefully interpret multicenter study data that have not included a central review. In addition, the exact concordance rate was far from perfect (100%) and was not satisfactory even when a central review using the ISUP consensus was done. Also, the actual GS of each patient can be apparent only when RP has been performed.

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