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Original Article

The value of second-opinion pathology diagnoses on prostate biopsies from patients referred for management of prostate cancer

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Abstract: Gleason score (GS) (sum of primary plus secondary grades) is used to predict patients' clinical outcome and to customize treatment strategies for prostate cancer (PC). However, due in part to pathologist misreading, there is significant discrepancy of GS between needle-core biopsies (NCB) and radical prostatectomy specimens. We assessed the requirement for re-evaluating NCB diagnosed by outside pathologists in patients referred to our institution for management of PC. In 100 patients, we reviewed both their original "outside" and second-opinion ("in-house") diagnoses of the same NCB specimens, and compared them with the diagnoses of the whole-mount radical prostatectomy (WMRP) specimens (gold standard for analysis). We found that both outside and in-house biopsy GS vary significantly from the WMRP diagnoses, with GS undergrading substantially predominating above overgrading. Statistical analysis demonstrated that the main diagnostic discrepancy was in the differentiation between primary and secondary Gleason grades (mainly 3 and 4) and that outside NCB GS was significantly less accurate with respect to the WMRP specimens than the in-house NCB GS. In addition, in a different cohort of 65 NCB cases, we found that in 5 out of 11 patients, outside pathologists failed to report the presence of extraprostatic extension, an important feature for diagnosis of a higher pathology stage (pT3a). Since histopathological evaluation is a critical factor for appropriate treatment selection, we recommend that a re-evaluation by in-house urologic pathologists should be performed in all outside NCB specimens before patients are admitted for treatment in any given institution.

Keywords: Prostate cancer, Second-opinion, Gleason Score, Gleason Grade, Needle-core Biopsy, Whole Mount Radical Prostatectomy

Introduction

Gleason score (GS) (sum of primary plus secondary grades) is currently the most practical evaluation tool to predict patients' clinical outcomes and to customize the most adequate treatment strategy for patients with prostate cancer (PC). However, the published data show a significant discrepancy of the GS accuracy between needle-core biopsy (NCB) specimens and radical prostatectomy specimens, varying from 28% to 76% [1, 2] (**Table 1**); and up to a quarter of grading errors could have significant clinical impact. These errors may result from multiple factors, such as the number and length of cores obtained; and at least 17% of them could be due to pathologist misreading [3].

Inconsistencies in Gleason grade diagnosis are more striking when given by general pathologists as compared to specialized urologic pathologists [4, 5]. Several studies have shown that review of NCB specimens by urologic pathologists would have changed the GS in a significant number of previously diagnosed specimens, with a subsequent change in patients' therapeutic management [5-7].

At our institution, many patients referred for treatment usually come for consultation with pathology diagnoses performed by outside general pathologists. As a basic policy, all outside specimens are reviewed by our in-house urologic pathologists before further clinical management is performed. We report here the re-

Table 1. Previous reports on Gleason score (GS) accuracy in NCB specimens

Source	Year	Accuracy	Undergraded	Overgraded
Mills SE et al [14]	1986	45 %	50 %	5 %
Bostwick DG [15]	1994	54 %	NA	NA
Johnstone PA et al [16]	1995	71 %	23 %	6 %
Kojima M et al. [17]	1995	48 %	47 %	5 %
Thickman D et al [1]	1996	28 %	57 %	15 %
Steinberg DM et al [4]	1997	58 %	36 %	6 %
Cookson MS et al [18]	1997	31 %	54 %	15 %
Djavan B et al [19]	1998	37 %	50.1 %	12.7 %
Carlson GD et al [20]	1998	68 %	24.5 %	7.5 %
Ruijter E. et al [3]	2000	75 %	21 %	4 %
King CR [21]	2000	41 %	42 %	17 %
King CR et al [22]	2000	57 %	35 %	8 %
Prost J et al [23]	2001	37 %	47.6 %	15.4 %
Fukagai T et al [24]	2001	46 %	47 %	7 %
S. Francisco IF et al [25]	2003	67 %	22 %	11 %
Hsieh TF at al [26]	2005	31 %	40 %	29 %
Stav K et al [27]	2007	51 %	41 %	8 %
Freedland SJ et al [28]	2007	62 %	27 %	11 %
Ooi K et al [29]	2007	43 %	46 %	11 %
Fine SW et al [2]	2008	76 %	17.6 %	6.5 %
Average		51.4 %	38 %	11 %

sults of our observations on the value of these second-opinion diagnoses before patients are considered for PC treatment.

Material and methods

For the purpose of the analysis of patient data, we obtained approval from the Colorado Multiple Institutional Review Board (COMIRB # 05-0045). We reviewed 136 consecutive medical records at our institution, from July 2001 to June 2003, from patients undergoing radical prostatectomy for clinically localized PC. In the whole cohort, 124 had complete in-house clinical records but only 100 fit the requirements for this study, namely (a) an original "outside" NCB pathology evaluation, (b) an "in-house" second-opinion evaluation of the same specimen, and (c) the pathology diagnosis of the whole-mount radical prostatectomy (WMRP) specimen. Patients excluded were 23 missing outside data, 10 missing whole-mount data, 2 missing in-house second-opinion evaluation, and 1 with an error in the transcription of the Gleason grading (Gleason 7 + 7). The general clinical characteristics of our selected patients are shown in **Table 2**, who showed an average age of 55.5 ± 6.3 years.

The median pretreatment PSA value was 7.1 ng/mL (range 0.0 – 43.0). The clinical stages were 49 cases with stage T1, 18 cases with stage T2 and 1 case with stage T3; 32 cases had no documented clinical stage. The pathologic stages were 75 cases at stage T2 and 25 cases at stage T3.

All outside NCB specimens were obtained through conventional transrectal, ultrasound guided procedure and stained with hematoxylin and eosin. Prostatectomy specimens were formalin fixed, sectioned at 4mm intervals from apex to base, paraffin embedded, and stained with hematoxylin and eosin as previously described [8, 9]. GS was assigned to each individual PC lesion, both in NCB and WMRP specimens, based on the sum of their primary and secondary tumor patterns. The examination of the NCB by the in-house pathologists was performed before the WMRP specimens were studied. WMRP evaluations were performed with no knowledge of the previous NCB results and no change in NCB diagnosis was done retroactively. Nevertheless, we consider a potential bias in this study that the in-house urologic pathologists performed the GS in both the NCB specimens and in the WMRP specimens.

GS in each NCB case, from outside and in-house diagnoses, were compared to the GS of in-house WMRP specimens. For patients with more than one positive biopsy, the highest GS was used. Neither specific count of the number of cores studied nor their topographic location

Table 2. General clinical characteristics of the selected patients (Total 100 cases)

Age (years): Mean (Range)	55.5 ± 6.3 (40 - 70)
PSA (ng/ml): median (Range)	7.1 ± 5.43 (0.0 – 43.0)
Outside NCB GS: median (Range)	6 (2 – 8)
In-house NCB GS: median (Range)	6 (2 – 9)
Whole-mount GS: median (Range)	7 (4 – 9)
Clinical stage T1	49
Clinical stage T2	18
Clinical stage T3	1
Clinical stage not available	32
Pathologic stage T2	75
Pathologic stage T3	25

Table 3. Gleason Scores (Gleason grade sums) NCB (outside and in-house) versus WMRP (Total 100 cases)

Gleason Score	Biopsies		WMRP
	Outside	In-House	
2*	1%	2%	0%
3*	1%	0%	0%
4*	3%	1%	4%
5	6%	5%	7%
6	62%	60%	30%
7	24%	27%	50%
8	3%	3%	4%
9	0%	2%	5%
10	0%	0%	0%

* Some NCB cases were diagnosed with primary and secondary Gleason grades <3, both by outside and in-house pathologists. These cases were evaluated before the new recommendation was in effect to use at least one Gleason grade 3 in NCB specimens [10].

was included for this study. The GS from each WMRP was used as the gold standard for this analysis. Some NCB cases were diagnosed with primary and secondary Gleason grades of less than 3, both by outside and in-house pathologists. These cases were evaluated before the new recommendation went into effect of using at least one Gleason grade 3 in biopsy specimens [10].

In a separate cohort of 65 consecutive outside NCB cases submitted for second-opinion evaluation, we compared the diagnoses of extraprostatic extension only.

Among the group of outside pathologists, we were not able to differentiate whether they were general pathologists or specialized urologic pathologists; thus, more specific comparisons were not possible.

Results

As shown in **Table 2**, the median GS was 6 for both outside and in-house NCB specimens (ranges of 2-8 and 2-9 respectively), whereas the median GS in WMRP specimens was 7 (range 4-9). **Table 3** shows the overall GS of the WMRP specimens diagnosed by our in-house pathologists. These values, used as the gold standard, are compared side by side with the GS frequency obtained from NCB specimens diagnosed by outside general pathologists and by our in-house urologic pathologists.

As shown in **Table 4**, we found agreement in GS between needle biopsies and WMRP specimens in 41 outside pathology diagnoses, and 52 of in-house pathology diagnoses. There was agreement in both primary and secondary grades between needle biopsies and whole-mount specimens in 35 outside and 45 in-house pathology diagnoses. McNemar's test demonstrated significant disagreement between outside and in-house primary and secondary grades (McNemar statistic 6.250, p=0.012). For Gleason sum not equal to 7, there was agreement in both primary and secondary grades between needle biopsies and whole-mount specimens in 60% in-house and 46%

Table 4. Gleason Score Undergrading and Overgrading of Needle-core Biopsies as Compared with Whole Mount Radical Prostatectomy Specimens (Total 100 cases)

	GS Difference	Outside Biopsies	In-house Biopsies
Over - Graded	+ 2	6	6
	+ 1	7	4
Agree*	0*	41	52
Under - Graded	- 1	32	31
	- 2	10	4
	- 3	3	2
	- 4	-	-
	- 5	1	1

*Whole-mount grading and NCB grading agree. 9 cases scored outside as <7 were upgraded to GS ≥7 by in-house pathologists. When compared with WMP specimens, 38 cases scored outside as <7 were upgraded to GS ≥7 and 31 cases scored in-house as <7 were upgraded to GS ≥7. Statistical analysis demonstrated that the in-house NCB Gleason scoring was significantly more accurate with respect to the whole-mount specimens than the outside scoring (McNemar statistic 6.368, p=0.012).

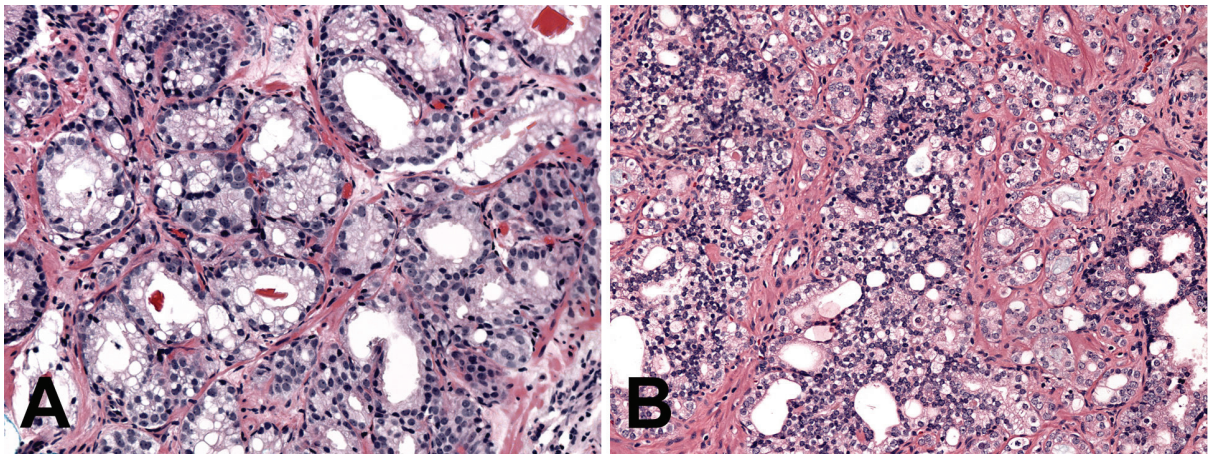

Figure 1. Two examples of PC Gleason grade 3+4 (score=7) diagnosed by outside pathologists as Gleason 3+3 (score=6). The differentiation between Gleason patterns 3 and 4 is an important reason for this discrepancy. (A, 40x) (B, 20x).

outside pathology diagnoses. McNemar's test neared significance for disagreement between outside and in-house primary and secondary grades (statistic 3.769, p=0.052). When compared to the whole-mount specimens, Gleason undergrading occurred in 46% outside and 38% in-house NCB diagnoses. As demonstrated by McNemar's test, there was a significant difference in undergrading between outside and in-house grading (statistic 4.571, p=0.032). For NCB diagnoses resulting in overgrading, there were 13% outside and 10% in-house diagnoses that were overgraded. A McNemar test did not reveal a difference in the proportions overgrading between outside and in-house diagnoses (statistic 1.00, p=0.317). Finally, 9 cases scored outside as <7 were upgraded to GS ≥7 by in-house pathologists. When compared with WMP specimens, 38 cases scored outside as <7 were upgraded to GS ≥7 and 31 cases scored in-house as <7 were upgraded to GS ≥7. **Figure 1** shows two NCB cases with PC Gleason grade 3+4 (score = 7) diagnosed by outside pathologists as Gleason 3 + 3 (score =6).

The in-house diagnoses of NCB specimens were consistently closer to the GS of WMRP specimens. Of the 59 NCB diagnoses with GS undergrading (1 grade or less), 41 (69.5%) cases corresponded to outside pathologists, when compared with their corresponding WMRP specimens. In contrast, undergrading corresponded to only 35 (59.3%) cases in the in-house pathologists. Of the 41 NCB diagnoses with GS overgrading (1 grade or more), 13 (31.7%) cases corresponded to outside pathologists, when compared with their corresponding WMRP specimens. In contrast, overgrading corre-

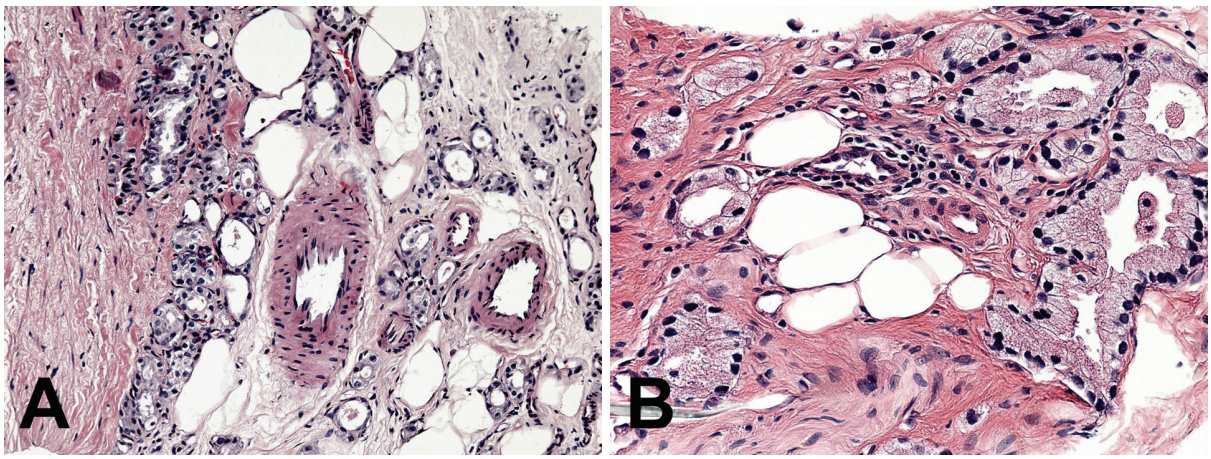

Figure 2. The invasion of adipose tissue by PC shown here is consistent with extraprostatic extension, which implies a higher pathology stage (AJCC T3a). This feature was often not reported by outside pathologists. (A, 20x) (B, 40x)

sponded to only 8 (19.5%) cases in the in-house pathologists. The difference between the outside and in-house GS undergrading was statistically significant (McNemar statistic 4.50, p=0.034), while the difference in overgrading did not reach statistical significance (McNemar statistic 3.57, p=0.059). There were no significant differences in age or PSA levels determined by t-tests between the correctly graded and incorrectly graded groups for either outside Gleason grading (age p=0.66; PSA p=0.34), or in-house Gleason grading (age p=0.64; PSA p=0.79).

In addition to Gleason grading discrepancies, our in-house pathologists have been able to identify some critical histopathologic features in prostate biopsies that are not usually reported by outside pathologists. An important diagnostic feature frequently not reported by outside pathologists is the presence of adipose tissue invasion, usually at one of the ends of a biopsy core, which strongly correlates with extraprostatic extension and an increased incidence (approximately 14 times) of metastatic disease [11, 12]. Even though the presence of suspected extraprostatic extension is not a common finding in NCB specimens, in a separate cohort of 65 consecutive cases, we observed that almost half of the specimens containing this lesion (5 out of 11) were not reported by the outside pathologists. **Figure 2** shows two NCB cases with PC invasion into adipose tissue, consistent with extraprostatic extension, which were not reported by outside pathologists.

Discussion

Our study reveals a significantly higher accuracy rate on diagnosing histopathologic features in NCB specimens by in-house urologic pathologists, as compared with outside pathologists (**Tables 3** and **4** and **Figures 1** and **2**). The accuracy of GS was 41% for outside pathologists and 52% for our in-house pathologists when matched with their corresponding WMRP specimens. These results are in agreement with previous data that show a higher GS accuracy in diagnosing NCB specimens among pathologists with special interest in uropathology when compared with general pathologists [4, 13]. A recent report by Truesdale MD et al [5] also correlates with our observation, in which they find that in-house second-opinions of biopsies predicted prostatectomy GS better than did original community NCB reports.

Previous reports on GS accuracy in NCB specimens reveal a substantial undergrading drift of NCB diagnoses compared to overgrading [1, 2, 4, 14 – 29] (**Table 1**). Our overall results, correlate with this observation in which both in-house and outside NCB GS vary significantly from the WMRP assessments, with GS undergrading substantially predominating above overgrading: 46% of outside and 38% of in-house specimens are undergraded, when compared with the WMRP specimens. This significant out-

side undergrading was mainly in diagnosing GS 6 as opposed to GS 7 found in WMRP specimens. Thus, the differentiation between Gleason grades 3 and 4 is interpreted as the sole reason for this discrepancy.

GS has been shown to be the most important independent risk factor for PSA recurrence-free survival, and strongly influences the treatment strategies for PC. Thus, the importance of making an accurate diagnosis of GS in NCB is a crucial element in the management of patients with PC. However, regardless of the fact that the Gleason grading system has been widely used for more than 40 years, since Dr. Gleason's first publication in 1966 [30, 31], GS accuracy of NCB specimens is still a challenge for pathologists.

Two major potential factors have been described affecting the GS interpretation in NCB specimens: sampling error and interpretation bias [4, 22]. One of the main intricacies is the multifocal and heterogeneous character of PC which makes it difficult to sample the prostate gland adequately. In addition, a significant statistical sampling variation occurs with the use of a standard number of biopsy cores in prostate glands that fluctuate in volume (i.e. it is easier to find a PC lesion with 12 cores in a 40 mL gland as compared with a 100 mL gland) . Thus, increasing the number of biopsy cores significantly improves PC sampling and by consequence the accuracy in the assessment of overall GS [22, 25, 28, 29, 37, 38]. On the other hand, interpretation bias on GS accuracy was shown to decrease by using a consensus diagnosis among two or more pathologists and by improving tumor sampling as well [20]. Ruijter E et al [3] found that at least 17% of overgrading GS in NCB specimens was due to misreading by the pathologist only, as compared with prostatectomy specimens. In contrast, most clinically significant GS discrepancies were due to undergrading and inversely proportional to the lengths of the biopsy cores obtained.

GS being a descriptive method fully based on architectural patterns of the prostatic tumors has an inherent degree of subjectivity. Inter-observer and intra-observer variability does exist [30, 31], and are found to be higher among general pathologists as compared with urologic pathologists [34, 35, 36]. Several studies suggest that the accuracy of GS in NCB specimens depends on experience and degree of interest in uropathology, as well as depending on the pathologist's workload. According to Arellano L et al [39], the GS accuracy in NCB interpretation significantly increased with gaining experience, with more accurate diagnoses observed in the second half of a 10-year study period when compared with the first half. Pathologists signing out more than 5000 cases per year showed a better agreement with consensus GS than those with fewer than 1000 cases per year, 78.8% and 48.9% respectively [40]. NCB GS by in-house urologic pathologists showed better correlation with WMRP specimens and tumor pathologic stage [4].

Intra-observer bias might also have a significant influence on GS accuracy due to intrinsic variability. Gleason himself in 1992 [41], after reviewing for a second time the same specimens he used for his original classification, reported exact GS agreement in only 50% of the cases. Nevertheless, the observed higher concordance between our in-house NCB diagnoses and WMRP GS could be due to an intrinsic bias as well. This bias is difficult to overcome, and in most studies the interpretation and diagnoses of NCB and radical prostatectomy specimens were done by the same pathologists. In our study, the diagnoses of NCB specimens were performed before the WMRP specimens were obtained and no retrospective change in the diagnosis of NCB specimens was done. However, we could not determine the impact of this intrinsic bias and intra-observer variability on GS accuracy. As discussed above, the addition of more NCB to the standard sextant scheme should reduce both sampling error and interpretation bias by detecting the higher Gleason grade PC foci.

Regarding histopathologic findings, other than GS, but important for patient clinical evaluation and prognosis, our in-house pathologists also detected significant features not reported by some of the outside pathologists. For example, the presence of adipose tissue invasion (**Figure 2**), which is consistent with extraprostatic extension by tumor, is often not reported by outside pathologists. Nevertheless, caution must be applied in the interpretation of this fat invasion since up to 4% of prostates may show intraprostatic adipose tissue [12]. Thus, it is recommended to report the term "consistent with extraprostatic extension" in these cases. Accord-

ing to the American Joint Committee on Cancer Classification [42], the presence of extraprostatic extension is correlated with an increased risk for developing distant metastases and corresponds to a higher pathology stage pT3a. Among men who underwent radical prostatectomy, those with extraprostatic tumor growth had 14 times the risk of PC death as those without it [11-12].

Based on the data reported here, the diagnosis of lower GS tumors and the omission of important histological lesions such as extraprostatic extension can significantly change the treatment strategy for PC in our patients. Therefore, we strongly recommend that a re-evaluation by in-house urologic pathologists should be performed on all outside NCB specimens before patients are admitted for treatment in any institution.

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