Second opinion pathologic review in the management of prostate cancer

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CHEN B, TALWAR R, SCHWARTZ LE, TERLECKI RP, GUZZO TJ, KOVELL RC. Second opinion pathologic review in the management of prostate cancer. *Can J Urol* 2021;28(1):10530-10535.

Introduction: *Inter-institutional re-review of prostate needle biopsy (PNBx) material is required at many institutions before definitive treatment, but adds time and cost and may not significantly alter urologic management. We aim to determine the utility of universal PNBx re-review on influencing the decision to recommend definitive local therapy for patients with prostate cancer.*
Materials and methods: *From 2017-2020, 590 prostate biopsy specimens from outside institutions were re-reviewed at our center for patients considering prostatectomy. Clinical and pathologic characteristics from initial and secondary review were analyzed. Potential for change in treatment candidacy (CTC) was determined by re-diagnosis to non-malignant tissue or change in candidacy for active surveillance (AS) versus definitive treatment (i.e. prostatectomy or radiation therapy). Thus, the following scenarios were considered CTC: downgrading to non-malignant tissue, downgrading ISUP Grade Group (GG) ≥ 2 to GG1, and upgrading GG1 to GG ≥ 2. Any changes between GG2 to GG5 were not considered CTC, as definitive treatment would be offered to all groups.*
Results: *Overall, 55 patients (9.3%) had potential for CTC based on secondary review, all of whom had initial pathologic GG (iGG) ≤ 2. Of the 152 patients with iGG1, 8 were downgraded to no malignancy and 41 were upgraded to GG2 or GG3. Of the 185 patients with iGG2, 6 were downgraded to GG1. No patients with iGG ≥ 3 qualified for a CTC. Features associated with CTC included iGG, number of positive cores, and highest core percentage. Upon multivariable analysis, only iGG1 diagnosis was predictive of CTC (OR 23.66, $p < 0.001$).*
Conclusion: *Second review may be helpful in determining need for definitive treatment in patients with GG1 and GG2 prostate cancer, i.e. those considering AS. This process appears unnecessary in GG3+ patients, as management for patients considering surgery would not change. This may allow for judicious redirection of hospital resources.*

Key Words: prostate cancer, prostate biopsy, secondary review, second opinion, quality improvement

Introduction

Inter-institutional pathology review is a common practice in health institutions across the United States.[1] Several studies spanning various medical specialties have found that second opinion pathologic review is a mechanism that may reduce medical error.[2-9] Currently, our institutional policy requires re-review of outside pathology prior to extirpative surgery for urologic malignancies. However, this requires additional upfront cost, time, and effort from all parties involved.[10]

Secondary review of prostate needle biopsy (PNBx) specimens has been studied previously and shown to improve Gleason diagnosis accuracy, but contemporary data on the generalizability of these conclusions are lacking.[11,12] Universal re-review may not be clinically useful for all ISUP Grade Groups (GG), especially patients in which the planned treatment is very unlikely to change. For patients considering definitive treatment such as radical prostatectomy to treat their localized prostate cancer, secondary

Accepted for publication December 2020

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review results may not always translate to clinical management changes for particular groups of patients. Furthermore, improvements in PNBx technique and specialized uropathology laboratories in both community and academic practice suggest a higher accuracy of outside pathology reports.

Given the time-consuming and costly routine of shipping biopsy slides and often waiting several additional weeks for an updated result, we sought to evaluate the utility of the re-review process in the management of prostate cancer. Our primary outcomes of interest are any change in pathologic grading between initial and secondary report and the likelihood that this would change eventual candidacy for definitive treatment. We hypothesize that secondary reviews may not always result in histologic revisions that would alter candidacy for definitive surgical management, and a more targeted selection of reviews by GG may allow for more efficient usage of hospital resources.

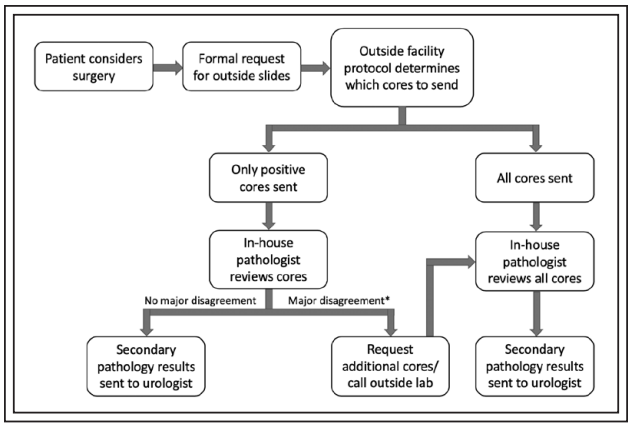

Figure 1. Process of pathology slide acquisition for secondary review.
*Major disagreement includes change from cancer to no cancer, change in underlying cancer cell origin, or change in lymph node staging. Changes in Gleason grade do not qualify as a major disagreement.

Materials and methods

The study deemed as a quality improvement endeavor was reviewed by the Quality Improvement Institutional Review Board at the University of Pennsylvania. We retrospectively reviewed data from 590 consecutive patients seen for urologic consultation who had an outside PNBx re-reviewed at our institution between January 1, 2017 and January 1, 2020. This pool of potential surgical candidates was referred to our urology clinic for consideration of extirpative surgery for prostate cancer. We excluded patients solely presenting to medical or radiation oncology clinic, those with non-cancerous outside pathology, as well as former biopsy results that were not from patients' immediate PNBx prior to presentation. Patients initially presenting to urology and then subsequently referred to radiation oncology were included. The process of pathology slide acquisition for secondary review is shown in Figure 1. All biopsy slides were reviewed by a fellowship-trained attending pathologist with clinical expertise in the genitourinary tract. Demographic variables, PSA, and the duration of time from clinic visit to secondary review were recorded. We then compared pathologic characteristics from both initial and secondary review, including diagnosis of cancer, Gleason score, GG, number of positive cores, highest core invasion percentage, and presence of perineural invasion (PNI).

A discordance between the initial and secondary review was labeled a change in treatment candidacy (CTC) if the change in pathology had potential to alter decision-making regarding definitive management. Examples of this include a change from malignant to non-malignant tissue, or a change in candidacy for definitive treatment versus active surveillance (AS). Examples of definitive treatment include prostatectomy or radiation therapy +/- hormonal therapy. At our institution, patients with GG1 disease are offered both AS/observation and definitive treatment with a shared decision-making model, while patients with GG ≥ 2 disease are offered definitive treatment, Figure 2. Patients with non-malignant disease require neither and are managed expectantly. Thus, CTC was classified

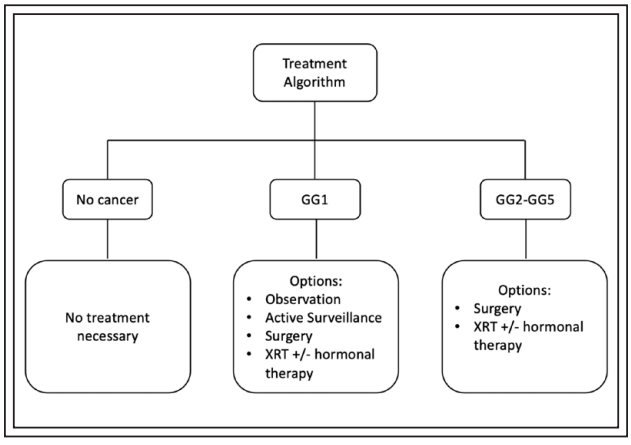

Figure 2. Treatment algorithm for patients presenting to urology clinic stratified by disease severity.

TABLE 1. **Initial versus secondary pathologic grading**

	No cancer	**Re-read GG 1**	**Re-read GG 2**	**Re-read GG 3**	**Re-read GG 4**	**Re-read GG 5**
Initial GG 1	**8**	103	**40**	**1**	0	0
Initial GG 2	0	**6**	159	17	3	0
Initial GG 3	0	0	22	77	6	11
Initial GG 4	0	0	4	11	39	18
Initial GG 5	0	0	2	1	2	60

GG = Grade Group
Clinically significant treatment change in **bold**

for the following three scenarios: downgrading from malignant to non-malignant diagnosis, downgrading from GG ≥ 2 to GG1, and upgrading from GG1 to GG ≥ 2. Any change in GG within GG2 to GG5 were not considered CTC, as these patients would all be offered definitive treatment, although there may have been implications for patient counseling, surgical planning, or length of hormonal therapy based on a re-read. We determined associations between clinicopathologic variables and CTC, with univariable and multivariable analyses identifying independent predictors of treatment change.

TABLE 2. **Clinicopathological features of change in treatment candidacy**

Change in treatment candidacy	**No**	**Yes**	**p value**
Defined by GG1 → 0, GG1 → ≥ 2, GG ≥ 2 → 1	**n = 535**	**n = 55**	
Race, n (%)			0.71
White	436 (81.5%)	41 (74.5%)	
Asian	11 (2.1%)	1 (1.8%)	
Black/African American	73 (13.6%)	11 (20.0%)	
Hawaiian/Pacific Islander	1 (0.2%)	0 (0.0%)	
Unknown	14 (2.6%)	2 (3.6%)	
Age, median (IQR)	65 (59-70)	65 (58-68)	0.30
PSA, median (IQR)	5.8 (4.5-8.1)	5.4 (4.6-8.8)	0.95
ISUP Grade Group, n (%)			< 0.001
1	103 (19.3%)	49 (89.1%)	
2	179 (33.5%)	6 (10.9%)	
3	116 (21.7%)	0 (0.0%)	
4	72 (13.4%)	0 (0.0%)	
5	65 (12.1%)	0 (0.0%)	
Positive cores in initial biopsy, median (IQR)	4 (2-6)	3 (2-5)	0.015
Highest core % in initial biopsy, median (IQR)	53 (25-80)	33 (13-52)	< 0.001
Perineural invasion in initial biopsy, n (%)			0.18
No	336 (62.8%)	40 (72.7%)	
Yes	199 (37.2%)	15 (27.3%)	
Time in days from clinic visit to 2nd read, median (IQR)	14 (6-32)	13 (2-38)	0.69

p values derived from Pearson's Chi Square or Fisher's Exact Test (for small cell values) tests between categorical variables and Kruskal-Wallis tests between continuous variables to identify nonrandom associations

Statistical analysis

Categorical variables are presented as absolute frequency with percentage, while continuous variables are presented as median with interquartile range. Baseline comparisons were performed using Pearson's Chi-square, Fisher's exact, or Kruskal-Wallis tests as appropriate. Univariable and multivariable analyses were conducted with logistic regression. All tests were two-sided, and significance was set at $p < 0.05$. Analyses were performed with STATA 16.1.

Results

Of all 1,052 outside institution PNBx specimens re-reviewed between 2017 and 2020, we included 590 consecutive biopsies that were initially read as consistent with prostatic malignancy and prompted urologic consultation for consideration of definitive management. The median age of our patient cohort was 65 years (IQR 59-70) with a median PSA of 5.75 (IQR 4.5-8.14). Based on the initial outside report, 152 patients (25.8%) were in GG1, 185 (31.3%) were in GG2, and 253 (42.9%) were in GG3 or above. The median number of positive cores was 4 (IQR 2-6) with a median highest core percentage of 50% (IQR 25-80%). PNI was present in 214 patients (36.3%). The median duration of time between the clinic visit at our institution and the completion of PNBx re-review was 14 days (IQR 5-32).

Although any discrepancy in Gleason score between the initial and secondary read occurred in 152 cases (25.8%), only 55 patients (9.3%) had a CTC after secondary pathology review, Table 1. CTC only applied to select patients with iGG1 and iGG2. Of the 152 patients with iGG1, 8 (5.3%) were downgraded to no malignancy, 40 (26.3%) were upgraded to GG2, and 1 (0.7%) was upgraded to GG3. Of the 185 patients with iGG2, 6 (3.2%) were downgraded to GG1. There was no CTC for patients with an initial diagnosis of GG ≥ 3.

On univariable analysis, initial variables of ISUP GG, number of positive cores, and highest core invasion percentage were significantly associated with CTC, Table 2. As mentioned, only iGG1 and iGG2 cohorts contained patients that had a CTC after re-review ($p < 0.001$). Patients with CTC had lower number of positive cores (3 versus 4, $p = 0.015$) as well as lower core invasion percentage (33% versus 53%, $p < 0.001$). Upon multivariable analysis of these same factors, only iGG1 was predictive of treatment change (OR 23.66, $p < 0.001$).

Discussion

In this single-institutional analysis of patients presenting for urologic consultation of prostate cancer, we found limited utility of performing universal second opinion PNBx reviews. No patients with iGG > 2 disease demonstrated a change in treatment candidacy, which was defined as a change in diagnosis or GG that would potentially alter clinical management options between active surveillance and definitive management options. Thus, these findings suggest secondary pathology review of PNBx may be appropriately reserved for GG1 and GG2 patients considering surgical options where a change in pathologic findings would alter their specific management course, as opposed to mandated reviews of all PNBx specimens prior to surgery, as is the case at our institution.

Several previous studies have looked into the clinical efficacy of instituting second opinion pathology reviews.[13,14] Specifically, within the field of urology, it has been shown that performing a re-review of biopsy slides can lead to more accurate diagnoses, but only a few studies have investigated the clinical utility of secondary pathology review for PNBx.[7-9,11,12] The first study on this topic by Epstein et al in 1996 showed that 1.3% of prostate cancer cases were reclassified as benign.[13] Wayment et al then found a 10% discordance rate in their prostate cancer cases, with 8.5% defined as "major disagreement" based on a change in D'Amico risk stratification.[12] The most recent investigation in 2010 by Brimo et al showed that 15.9% of cases demonstrated a "major discrepancy" between primary and secondary pathology read, also defined by change in D'Amico risk stratification.[11] All of these studies concluded that second opinion reviews should be performed to reduce diagnostic error.

However, there are several reasons why the results from the above studies may not reflect accurate changes in clinical management and may not be fully applicable to current practice. For one, the studies either did not sub-analyze the patients by Gleason score or used the D'Amico risk stratification to determine major disagreements.[15] Under the D'Amico system, patients with Gleason 7 are labeled intermediate risk while patients with Gleason 8+ and labeled high risk. Changes between these two risk categories were deemed a major change even though both groups would have offered definitive treatment in most cases based on current guidelines. On the contrary, our current study did not deem changes between GG2 (Gleason 3+4=7) and GG5 (Gleason 9+) to be a CTC as these patients would be managed definitively at most institutions. While counseling and approach to treatment would likely be affected, the decision to pursue definitive therapy would not. Using our contemporary definition of CTC, the discordance rate

from Wayment et al and Brimo et al would decrease from 10% to 1% and 15.9% to 9.7%, respectively. We certainly acknowledge that other aspects of non-surgical management or treatment decisions could be altered based on these changes from GG2-GG5. For example, patients in higher risk strata, in part defined by GG, may require longer durations of concurrent androgen deprivation therapy with radiation therapy or may be counseled from the beginning about a higher likelihood of requiring multi-modal therapy. If this would affect management, the provider may wish to consider pathologic re-review in these selected cases.

Furthermore, there have been significant recent changes in the workup and management of prostate cancer. The widespread adoption of multiparametric MRI-guided PNBx in practices across the country has improved the sensitivity and specificity of prostate cancer detection.[16,17] According to the 2019 AUA census, approximately 40% of all practicing urologists received fellowship training, suggesting community practices may now employ a growing number of subspecialists experienced in precise PNBx.[18] Also, around 90% of all graduating pathology residents pursue at least one fellowship, with the most popular choice of surgical pathology, suggesting increased national expertise in PNBx interpretation.[19,20] In addition, an increasing number of community practices send their biopsy specimens to be read at specialty uropathology facilities. In our data set, one private laboratory performed one-sixth of the initial outside reads. Such specialty centers are experienced in providing anatomic pathology services and have been shown to have high concordance rates of PNBx and RP specimen histology.[21] Thus, modern improvements in imaging technology and subspecialized pathology facilities suggest a movement toward more accurate initial prostate cancer diagnoses that may not necessarily require a central re-review at academic institutions.

Importantly, we would also like to acknowledge the lack of standardization in the process of PNBx secondary review. Across institutions, there are a variety of different methods for transferring biopsy slides, preparing specimens, and assuring quality standards.[22,23] For example, outside pathology facilities have independent protocols for the number of PNBx cores to send; some send all 12 standard cores, while others only send cores positive for cancer. In our data, approximately one-fourth of patients had less than 12 cores sent, suggesting a "partial re-review" in this cohort. We recognize that the lack of agreement seen in partial re-review could potentially be seen across the remainder of the specimen if subjected to similar scrutiny. These inconsistencies may cast doubt on the reliability and reproducibility of pathology reporting for prostatic malignancies.

We also acknowledge that many urologists may assume that the in-house secondary pathology review is the "final word." However, this is not necessarily the case. Elmore et al showed that there was still a 25% disagreement among three pathologists viewing just a single biopsy slide, suggesting pathology interpretations may be more subjective than realized.[24] Thus, rather than automatically assuming the secondary report to be the final word, urologists should use their clinical judgment to review the case when there is a pathologic discordance. One may also argue that specimens referred from another tertiary institution had already been subjected to a similarly expert degree of pathologic review. In our study, 12% of re-reviews that came from a tertiary institution had a CTC. The fact that there are still discrepancies among tertiary institutions suggests that secondary review can still be useful for at least some patients. Finally, we recognize that although any change between GG2-GG5 was not considered a CTC in our study, such changes can affect patient counseling, management options, and logistics of delivering care.

Several limitations of the study should be acknowledged, primarily the retrospective, single-institution design that may not be fully representative of other practices. There may be geographic differences in the rates of re-review discordance due to the use of different regional pathology facilities. Also, laboratories may have varying PNBx interpretations if specimens include a tertiary component (third-most common Gleason score pattern seen) that is simultaneously the highest grade among the biopsy cores.[25] In other words, some pathologists may include the tertiary component into their GG determination while others may instead just use the primary and secondary components; this may contribute to systematic inconsistencies in histologic determination. In addition, we did not have the data to perform a cost savings analysis. However, at our institution shipping pathology slides has, at times, even exceeded $500 per patient, so we suspect there is room for cost savings by limiting secondary reviews. Lastly, there may be a small subset of patients diagnosed with GG2 disease who have a limited life expectancy for whom urologists may offer AS. However, the majority of GG2 patients are still recommended prostatectomy due to intermediate- or high-risk cancer, so we determined this cohort to warrant receiving definitive treatment. Future directions include performing a multi-institutional analysis and extending our investigation to other urologic malignancies.

Conclusion

In summary, second opinion pathology review may be helpful in patients with GG1 and select patients with GG2 prostate cancer. However, re-review does not seem to alter decisions regarding definitive urologic management options and may be unnecessary in GG3+ patients. These updated findings on the utility of secondary pathology review for PNBx may allow for prudent redirection of hospital resources without compromising standards of care. □

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