The Value of Mandatory Second Opinion Pathology Review of Prostate Needle Biopsy Interpretation Before Radical Prostatectomy

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Abbreviations and Acronyms

GS = Gleason score

PCa = prostatic adenocarcinoma

PNI = perineural invasion

RP = radical prostatectomy

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Purpose: We determined the value of mandatory second opinion pathology review to interpret prostate needle biopsy before radical prostatectomy.

Materials and Methods: In all cases referred to our institution for radical prostatectomy in 1 year we compared pathological parameters in original and reviewed pathology reports, including benign, atypical or malignant diagnosis, final Gleason score, positive core number, core highest cancer percent and perineural invasion or extraprostatic extension. A major Gleason score discrepancy was defined as a change to a different risk category (6, 7 and 8–10). We defined a significant difference in the highest percent of cancer in a core as 30% or greater.

Results: Of the 855 cases originally diagnosed as prostatic adenocarcinoma cancer was confirmed in 844 (98.8%) by needle biopsy and prostatectomy, of which 9 (1%) were atypical and 2 (0.2%) were benign upon review. A major discrepancy in Gleason score was present in 124 cases (14.7%), of which 57 (46.0%) were upgraded and 67 (54%) were downgraded. Of cases with a final Gleason score of 6, 8.4% were originally diagnosed as 7 (7.8%) or 8–10 (0.6%), 21% with a final score of 7 had an original score of 6 (13.2%) or 8–10 (7.8%) and 21 of 61 (34%) with a score of 8–10 were originally diagnosed as 7 or less. There were 80 cases (64.5%) of disagreement between scores 6 and 7. Of the 777 cases with the positive core number in each report 71 (9.1%) had discrepancies. After review the positive core number was higher in 45 cases (63.4%) and lower in 26 (36.6%). We noted a significant difference in the highest cancer percent in a core in 76 of 844 evaluable cases (9%) in which cancer was originally underestimated. In 60 of 76 cases (78.9%) cancer discontinuously involved the core on review. Review revealed perineural invasion in 138 of 844 cases (16.3%) that was not originally reported in 37 of 138 (26.8%). In 4 cases review showed extraprostatic extension on needle biopsy.

Conclusions: Compared to a smaller study more than 10 years ago at our institution the rate of unconfirmed cancer was identical (1.2%). To our knowledge this is the first study to analyze concordance upon review of the number of positive cores and maximum percent positive in a core (each discrepancy 9%). In a few cases mandatory second opinion on prostate needle biopsy results in significant differences that may affect therapy.

Key Words: prostate, adenocarcinoma, pathology, diagnosis, biopsy

MANDATORY second opinion pathology review is the practice in which pathology reports and slides prepared at an initial institution are routinely reviewed at a second institution before treatment at the latter. Reviews im-

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prove care in a small percent of cases, resulting in a significant change in the original diagnosis that may alter management.[1–5] In 1993 the Association of Directors of Anatomical and Surgical Pathology recommended the adoption of mandatory second opinion review as institutional policy when patients are referred elsewhere but to date no national guidelines exist.[5,6] As part of a mandatory review program at our hospital, all pathology slides and reports of patients initially diagnosed elsewhere and undergoing significant therapy are reviewed before treatment.

More than a decade ago we addressed this issue in men diagnosed with prostate cancer elsewhere who were referred to our hospital for RP. However, we noted improved pathologist accuracy for diagnosing limited PCa in this period. Thus, in the current study we determined whether mandatory second review is still valid for interpreting prostate needle biopsy.[7]

MATERIALS AND METHODS

We reviewed all prostate needle biopsy surgical pathology reports on patients referred to our hospital from January 1 to December 31, 2008 for a second opinion before RP. Slides from elsewhere were reviewed by 1 of 7 general surgical pathologists with extensive experience with prostate pathology. In most cases original slides were available. When there were significant discrepancies in diagnosis and the case was exceptional and consisted of recut, original slides were requested for review. In cases in which a discrepant diagnostic category, cancer grade or PNI status was present in the original report, the case was shown in consultation with 1 of 2 urological pathology experts.

We compared pathological parameters between original and reviewed pathology reports, including benign, atypical or malignant diagnostic category, final cancer GS, number of positive cores, highest percent of cancer in a single core and PNI presence/absence. A major GS discrepancy was defined as a change that directly impacted treatment by placing the patient in a different risk stratification category. The 3 GS prognostic categories considered were 6, 7 and 8–10. A significant difference in reporting the highest percent of cancer in a single core was defined as a 30% or greater difference between the 2 pathology reports.

RESULTS

Of the 1,027 RPs done at our institution in 2008 we included 855 in which the full original reports could be reviewed. All 855 cases had an original diagnosis of PCa, including 844 (98.8%) in which PCa was confirmed on needle biopsy and subsequent RP. Nine cases (1%) were diagnosed as atypical and 2 (0.2%) were diagnosed as benign upon review. Nine of the 11 cases with discrepant diagnoses had repeat biopsies showing a diagnosis of PCa in 4, atypical in 2, high grade prostatic intraepithelial neoplasia in 1 and benign in 2. The 2 cases not rebiopsied had an atypical diagnosis after review.

Of the 844 cases with a concordant PCa diagnosis a major discrepancy in GS between original and reviewed reports was present in 124 (14.7%), of which 57 (46.0%) were upgraded and 67 (54%) were downgraded upon review (see table). Of 512 cases with an original GS of 6, 36 (7%) were upgraded to GS 7. Of 269 cases originally graded as GS 7, 44 (16.4%) were downgraded to 6 and 27 (7.8%) were upgraded to 8–10. Of 63 GS 8–10 cases diagnosed elsewhere 21 (33.3%) were downgraded to 7 and 2 (3.2%) were downgraded to 6. Of the cases with discrepancies 80 (64.5%) were between GS 6 and 7. Interinstitutional agreement was highest for GS 6 (476 of 512 cases or 93%) and lowest for GS 8–10 (40 of 63 or 63.5%). Cancer grade (3 + 4 or 4 + 3) was unchanged in 179 of the 204 (88%) with an original and revised GS of 7 while GS was changed in 13 from 3 + 4 to 4 + 3 and in 12 from 4 + 3 to 3 + 4.

Information on the number of cores involved by cancer was available after review in 784 of 855 original (91.7%) and 805 of 844 final (95.4%) pathology reports. In some final reports the number of cores could not be determined due to fragmented cores. In 60 original reports lacking this information and confirmed to contain cancer we determined the number of positive cores in 36 cases after review. Of the 777 cases in which the number of positive cores was available in each report 71 (9.1%) discrepancies were present, in which the difference was 1 core in 53 (75%). The number of positive cores was higher in 45 of 71 cases (63.4%) and lower in 26 of 71 (36.6%) after review.

The highest percent of cancer in a single core was reported in 780 of 855 original (91.2%) and 820 of 844 review (97.1%) reports. In original reports without this parameter cancer extent was reported as an overall percent of the submitted biopsy specimen or as a cancer measurement in mm. A significant difference in this variable between the 2 institutions was present in 76 of 844 cases (9%), in which cancer extent was underestimated in the original report. In 60 of 76 cases (78.9%) cancer involved the core discontinuously on review.

Original and revised GS

	No. Revised GS (%)			
Original GS	6	7	8–10	Total No.
6	476 (93)	36 (7)	0	512
7	44 (16.4)	204 (75.8)	21 (7.8)	269
8–10	2 (3.2)	21 (33.3)	40 (63.5)	63
Totals	522	261	61	844

PNI noted in 138 of 844 cases (16.3%) upon review was not originally reported in 37 of 138 (26.8%). In 4 cases extraprostatic extension was noted on needle biopsy only upon review.

DISCUSSION

Although numerous publications show the clinical and economic benefits of implementing a pathology second review program when patients are referred for treatment to a different institution than where the diagnosis was rendered, and despite the recommendations of the Association of Directors of Anatomical and Surgical Pathology in adopting such a program in 1993, it is not a nationally mandatory practice.[2–5] When 126 hospitals were surveyed, as many as 50% did not require a second pathology review before surgery.[2] The main reasons are the resistance of some surgeons concerned about delayed treatment or increased patient cost and the reticence of some pathologists concerned about an increased work load or the remuneration status of consultations, which may be considered only a form of a nonremunerated quality control measure.[1–4] Also, the institutional administration may resist implementing and maintaining such a new, large-scale program in times of economic and budgetary constraints.[4–5,8–10] The few large studies of the subject involving all body sites showed a mean of 3.5% (range 1.5% to 5.8%) significant diagnostic discordances that had a direct impact on treatment when pathology material was reviewed before treatment.[3–5–11,12] Diagnostic disagreement was higher for certain body sites, including ovary, endometrium, soft tissue, lymphoma, serosa, cervical cytology, testis and prostate.[3–11,13–20]

To date few groups have specifically addressed the value of pathology second review when interpreting prostate needle biopsy. In 1996 we reported that 7 of 535 men (1.3%) referred in 1 year to our hospital with a PCa diagnosis had a change in diagnosis to benign upon review.[1] In the current study in which similar methods were used the rate of diagnostic discrepancy 13 years after the initial study remained virtually unchanged at 1.2%. Seven of the 9 patients in whom the original diagnosis of cancer was changed to atypical after review underwent rebiopsy, in which cancer was diagnosed in 4 (57%). Detecting cancer on repeat biopsy in this context does not necessarily indicate cancer under diagnosis in the initial biopsy after review but rather reflects the caution that we apply when diagnosing small foci of cancer on needle biopsy in general.

Our data show that, in addition to uncommon situations leading to a complete change in diagnosis, mandatory second review also brings changes to the cancer grade on which major therapeutic decisions are based. In the contemporary era any GS change that places the patient in a different risk stratification category is considered a major change. The 3 categories used at most institutions are GS 6, 7 and 8–10. In the current study we noted significant interinstitutional disagreement in GS in 14.7% of cases, which is a nonnegligible percent in view of the potential change in treatment modality that could ensue. In contrast, Wayment et al reviewed 117 prostate biopsies preoperatively and reported a 10% disagreement rate but only 10 cases had major discrepancies.[21] The other 2 studies documenting the interobserver reproducibility of Gleason grade among institutions in a real-life practice setting included men with prostate cancer referred for radiation therapy.[20–22] Those referred for radiation or hormonal therapy generally have higher grade, more extensive cancer than those treated surgically and the issue of diagnosing small cancer foci is usually not noted in the former group. Thus, we refrain from comparing our results with those of the 2 mentioned studies due to different patient populations and cancer characteristics.

In the current study interinstitutional agreement on GS was the highest for GS 6 (93%) and about two-thirds of discrepancies were between GS 6 and 7. Part of the cause of reproducibility problems when diagnosing Gleason pattern 4 may be that not all pathologists are familiar with the changes recently brought to Gleason grading after the International Society of Urological Pathology consensus conference in 2005 and subsequent confirmatory studies.[23] A major change that emerged from this meeting was the inclusion of poorly defined glands with poorly formed lumina as Gleason pattern 4 and the other was that most if not all cases that in the past were called cribriform cancer pattern 3 should currently be diagnosed as cribriform pattern 4.[23–25]

In addition to Gleason grade, cancer quantification on needle biopsy is an important predictor of stage at RP that is recorded by pathologists in different ways, of which the 2 most common are the number of cores with cancer and the percent of core involved by cancer.[26,27] At our institution we use these 2 parameters to determine whether patients are candidates for active surveillance. Biopsy criteria to consider active surveillance include 1) GS 6 or less, 2) 2 or fewer cores involved by cancer and 3) cancer involving 50% or less of a single core.[8] In the current study 60 of 844 original reports (7.1%) lacked precise information on the number of positive cores, of which we determined the number of positive cores in 36 cases (60%) after review. The only occasions on which we do not report the number of cores with cancer is when the urologist places multiple cores in a specimen container and specimen fragmentation precludes assessment of the total

number of cores with cancer. In these cases we report the overall percent of cancer in the fragmented specimen in that container. Of the 844 study cases severe fragmentation was present in 24 (2.8%). We recently noted that biopsy fragmentation is related to multiple factors, including GS, the number of cores involved with cancer and the number submitted per container.[26] Thus, we recommend limiting the number of cores submitted per container to 1 or 2.

Upon review we reported the maximum percent of the core involved by cancer in 40 of 64 cases (62.5%) originally lacking this information. In the original reports without this parameter cancer extent was reported as an overall percent of the specimen per container when there were more than 1 core, or as a cancer measurement in mm. When the urologist places more than 1 core per specimen container, it is controversial among genitourinary pathologists whether the individual involved cores should be individually assessed for GS and tumor quantification or overall grade and quantification should be assigned for the specimen container.[23] Although cancer measurements in mm on needle biopsy is comparable to reporting the percent of the core involved by tumor, we prefer the latter since it is less time consuming and equally prognostic.[27,28]

Another observation in this study was that in all cases with a significant interinstitutional difference in the reporting of the maximum percent of core involved by cancer it was underestimated in the original report. In 78.9% of these cases cancer was reported to involve the core discontinuously upon review. These discrepancies are due in major part to the different methods used to calculate the cancer extent when more than 1 cancer focus separated by benign intervening stroma is present in a single core. Although there is no consensus among genitourinary pathologists on the best method to record tumor extent in those cases, we believe that it is highly unlikely for these foci to represent multiple separate cancer nodules on RP. Thus, we consider discontinuous cancer foci in a single core as a single tumor that should be recorded by measuring the cancer from 1 end to the other, including the amount of benign intervening stroma in the cancer measurement. A note is usually added to the report to indicate the discontinuous nature of cancer to explain the difference in measurement compared to that in the original report.

Our study also reveals that PNI is still under diagnosed by pathologists. Of 138 cases in which PNI was reported after review 37 (26.8%) lacked this information in the original reports. PNI on needle biopsy correlates with extraprostatic extension on RP.[29] Pathologists must be aware that this information is important to clinicians and should be routinely commented on in needle biopsy reports.

CONCLUSIONS

Mandatory second pathology review of prostate needle biopsies before RP can result in significantly different reports that may affect therapy. Thus, it should become routine practice.

REFERENCES

1. Epstein JI, Walsh PC and Sanfilippo F: Clinical and cost impact of second-opinion pathology. Review of prostate biopsies prior to radical prostatectomy. Am J Surg Pathol 1996; **20:** 851.
2. Gupta D and Layfield LJ: Prevalence of interinstitutional anatomic pathology slide review: a survey of current practice. Am J Surg Pathol 2000; **24:** 280.
3. Kronz JD, Westra WH and Epstein JI: Mandatory second opinion surgical pathology at a large referral hospital. Cancer 1999; **86:** 2426.
4. Rosen PP: Review of 'outside' pathology before treatment should be mandatory. Am J Surg Pathol 2002; **26:** 1235.
5. Weir MM, Jan E and Colgan TJ: Interinstitutional pathology consultations. A reassessment. Am J Clin Pathol 2003; **120:** 405.
6. Silverberg SG: The institutional pathology consultation. Documentation of its importance in patient management. Arch Pathol Lab Med 1995; **119:** 493.
7. Magi-Galluzzi C and Epstein JI: Threshold for diagnosing prostate cancer over time. Hum Pathol 2003; **34:** 1116.
8. Epstein JI, Chan DW, Sokoll LJ et al: Nonpalpable stage T1c prostate cancer: prediction of insignificant disease using free/total prostate specific antigen levels and needle biopsy findings. J Urol 1998; **160:** 2407.
9. Eisenberg JM: Economics. JAMA 1995; **273:** 1670.
10. Monaco GP and Goldschmidt P: What is proper cancer care in the era of managed care? Oncology (Williston Park) 1997; **11:** 65.
11. Abt AB, Abt LG and Olt GJ: The effect of interinstitution anatomic pathology consultation on patient care. Arch Pathol Lab Med 1995; **119:** 514.
12. Wetherington RW, Cooper HS, Al-Saleem T et al: Clinical significance of performing immunohistochemistry on cases with a previous diagnosis of cancer coming to a national comprehensive cancer center for treatment or second opinion. Am J Surg Pathol 2002; **26:** 1222.
13. Chafe S, Honore L, Pearcey R et al: An analysis of the impact of pathology review in gynecologic cancer. Int J Radiat Oncol Biol Phys 2000; **48:** 1433.
14. Jacques SM, Qureshi F, Munkarah A et al: Interinstitutional surgical pathology review in gynecologic oncology: II. Endometrial cancer in hysterectomy specimens. Int J Gynecol Pathol 1998; **17:** 42.
15. Harris M, Hartley AL, Blair V et al: Sarcomas in north west England: I. Histopathological peer review. Br J Cancer 1991; **64:** 315.
16. Prescott RJ, Wells S, Bisset DL et al: Audit of tumour histopathology reviewed by a regional oncology centre. J Clin Pathol 1995; **48:** 245.
17. Kim H, Zelman RJ, Fox MA et al: Pathology Panel for Lymphoma Clinical Studies: a comprehensive analysis of cases accumulated since its inception. J Natl Cancer Inst 1982; **68:** 43.

18. Segelov E, Cox KM, Raghavan D et al: The impact of histological review on clinical management of testicular cancer. Br J Urol 1993; **71:** 736.

19. Selman AE, Niemann TH, Fowler JM et al: Quality assurance of second opinion pathology in gynecologic oncology. Obstet Gynecol 1999; **94:** 302.

20. Wurzer JC, Al-Saleem TI, Hanlon AL et al: Histopathologic review of prostate biopsies from patients referred to a comprehensive cancer center: correlation of pathologic findings, analysis of cost, and impact on treatment. Cancer 1998; **83:** 753.

21. Wayment RO, Bourne A, Kay P et al: Second opinion pathology in tertiary care of patients with urologic malignancies. Urol Oncol 2009; Epub ahead of print.

22. Thomas CW, Bainbridge TC, Thomson TA et al: Clinical impact of second pathology opinion: a longitudinal study of central genitourinary pathology review before prostate brachytherapy. Brachytherapy 2007; **6:** 135.

23. Epstein JI, Allsbrook WC Jr, Amin MB et al: The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005; **29:** 1228.

24. Latour M, Amin MB, Billis A et al: Grading of invasive cribriform carcinoma on prostate needle biopsy: an interobserver study among experts in genitourinary pathology. Am J Surg Pathol 2008; **32:** 1532.

25. Qian J, Jenkins RB and Bostwick DG: Detection of chromosomal anomalies and c-myc gene amplification in the cribriform pattern of prostatic intraepithelial neoplasia and carcinoma by fluorescence in situ hybridization. Mod Pathol 1997; **10:** 1113.

26. Fajardo DA and Epstein JI: Fragmentation of prostatic needle biopsy cores containing adenocarcinoma: the role of specimen submission. BJU Int 2009; **105:** 172.

27. Brimo F, Vollmer RT, Corcos J et al: Prognostic value of various morphometric measurements of tumour extent in prostate needle core tissue. Histopathology 2008; **53:** 177.

28. Bismar TA, Lewis JS Jr, Vollmer RT et al: Multiple measures of carcinoma extent versus perineural invasion in prostate needle biopsy tissue in prediction of pathologic stage in a screening population. Am J Surg Pathol 2003; **27:** 432.

29. Bastacky SI, Walsh PC and Epstein JI: Relationship between perineural tumor invasion on needle biopsy and radical prostatectomy capsular penetration in clinical stage B adenocarcinoma of the prostate. Am J Surg Pathol 1993; **17:** 336.