Prostate cancer pathology audits: is central pathology review still warranted?

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Introduction: *Estimating the risk of extraprostatic extension and the probability of recurrence with different treatment modalities is common practice in cancer management. A strong predictor of recurrence and organ-confined disease is tumor grade. However, differences exist between genitourinary and non-specialist pathologists in grading prostate cancer. As such, the primary objective of this study was to assess the accuracy of non-specialist prostate cancer biopsies at our institution by analyzing the proportion of cases changing pathologic risk category upon expert review.*

Materials and methods: *Log books from 2003 where our genitourinary pathologists reviewed prostate needle-core biopsies were used to identify cases. A retrospective chart review was completed and descriptive statistics were used to summarize the results for the following synoptic variables: 10 and 20 Gleason Score, number of biopsy sites, overall % involvement, perineural invasion – PNI (present/absent), extracapsular extension - ECE (present/absent).*

Results: *A total of 151 patients were reviewed. Twenty eight percent of cases (42/151) had a change in risk category after expert review. Of the 98 low risk cases, 33% were upgraded in risk category. Of the 24 intermediate risk cases, 12% were upgraded to high risk and none were downgraded. Of the 29 high risk cases, 24% were downgraded in risk category.*

Conclusion: *All referred patients should continue to have their pathology centrally reviewed. This practice will help facilitate optimal prostate cancer management and improve quality of care. While these findings are dated given pathologic practice change, such changes do not necessarily equate with disparity elimination or reduction; conclusions can only be drawn with a more recent audit to see if such disparities still exist.*

Key Words: prostate cancer, Gleason grading, central pathology review, quality assurance

Introduction

Prostate cancer is the most common non-cutaneous cancer diagnosed in Canadian men. It is estimated that in 2010, over 24,000 men will be diagnosed with the disease and 4,300 will die from it.[1] Standard treatments for prostate cancer include surgery and radiotherapy and optimal management is individualized to the patient. Included in each individual's assessment is often an estimation of the risk of disease spreading beyond the prostate (non-organ confined or extraprostatic disease) and the probability of recurrence with different treatment modalities. These risks are well documented and are used in various nomogram predictive tools.[2-4] One of the strongest predictors of recurrence and organ-confined disease is the pathologic grade of the tumor (Gleason score). Consequently, grading of prostatic biopsies is of crucial importance, particularly for radiotherapy treatments where the use of brachytherapy or adjuvant androgen deprivation is driven by risk group. However, it has been recognized that interobserver differences exist among pathologists – especially between genitourinary pathologists (GUP) and non-specialist pathologists (NSP) in the grading of prostate cancer and extent to which key pathologic characteristics are reported.[5-10]

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TABLE 1. **Change in risk category**

Non-expert pathologic risk category	Expert pathologic risk category			
	Low GS 2-6 (% of row total)	**Intermediate GS 7 (% of row total)**	**High GS 8-10 (% of row total)**	**Column total**
Low, GS 2-6	66 (67%)	27 (28%)	5 (5%)	**98**
Intermediate, GS 7	0	21 (88%)	3 (12%)	**24**
High, GS 8-10	1 (3%)	6 (21%)	22 (76%)	**29**
Row total	**67**	**54**	**30**	**151**

GS = Gleason score

Given these discrepancies, this study focused on the accuracy and completeness of NSP prostate cancer biopsies compared to GUP at our institution. The primary objective was to determine the proportion of cases which changed pathologic risk category based on expert review and defined as follows: low risk – Gleason score 6; intermediate risk – Gleason score 7; high risk – Gleason score 8-10. The secondary objectives were to determine: the proportion of pathologic synoptic variables that were not reported in the NSP reviews; the proportion of cases which were determined not to have cancer; and the proportion of cases which were up or downgraded (by the above risk categories).

Materials and methods

Log books from 2003 where prostate needle-core biopsies were reviewed by GUP at Sunnybrook Health Sciences Centre were used to identify cases. A subsequent retrospective chart review was completed and the following variables for both GUP and NSP were abstracted: primary Gleason score; secondary Gleason score; number of sites; percentage of each core involved (%); perineural invasion (present/absent); and extracapsular extension (present/absent). We selected these pathologic data elements based on the most essential and commonly reported items by our GUP. In addition, current standards for synoptic reporting do exist; Cancer Care Ontario (CCO) has adopted the College of American Pathologist (CAP) cancer checklist for prostate cancer needle-biopsies, which includes histologic type, histologic grade (both primary and secondary), percent of prostatic tissue involved by tumor and/or total linear mm of carcinoma/length or core(s) and/or number of cores positive/total number of cores.[11] Our data abstraction follows the CAP/CCO synoptic reporting standards (save histologic type) and we were sure to capture Gleason score, which is the most clinically significant, requested and used when planning therapy.[12] Descriptive statistics were used to summarize the results.

Results

The charts of all 151 patients who had a GUP review of their prostate biopsies in 2003 were identified and abstracted. All patients reviewed were pathologically determined to have prostate cancer. A total of 42 of cases (28%) had a change in the pathologic risk category after GUP review Of the 42 cases, the following up and downgrade results were observed: 6 were downgraded one category; 1 was downgraded two categories; 30 were upgraded one category; and 5 were upgraded two categories. Table 1 summarizes the change in pathologic risk category after expert review. Other pathologic data elements were collected during the retrospective chart review. The particulars are summarized in Table 2.

TABLE 2. **Missing data elements - external reports**

Pathologic data element	# of cases where score not reported	% of cases where score not reported (n = 151)
Primary Gleason	0	0
Secondary Gleason	1	1
Number of biopsy sites	31	21
Overall (%) involvement	28	18
Perineural involvement	29	19
Extracapsular extension	35	23

Discussion

Before delving into the implications of these results, it is prudent to discuss the particulars that differentiate a GUP from a NSP. All GUP at our center are not only trained in GU pathology (i.e. residency, fellowship), but also have extensive experience in reviewing prostate biopsy cases. To give an idea of what "extensive" means, one of our GUP reviews approximately 2000 such cases annually and has been specializing in GU pathology for 29 years. Further, GUP, unlike NSP, have a practice that is generally restricted to GU specimens. In addition to in-house cases, they act as consultants to community pathologists and if they work in a hospital that has a cancer center, they also review most or all of the clinical cases. Further, GUP are also involved in the education of residents and practicing pathologists. With regards to quality assurance (QA) practices, weekly rounds are held involving GUP sharing cases for consensus diagnoses. Cases are regularly reviewed for tumor board and teaching, which also provides ongoing QA. GUP also set the standards for handling and reporting of specimens within our institution, which is parallel with best practices. Thus, the quality of samples and slides for prostate biopsies is fairly consistent. One key difference is in the handling of specimens; some hospitals put more than one biopsy core in one cassette, unlike the "gold standard" practiced at most teaching hospitals, where a single core is placed in one cassette. With multiple cores, it is difficult to assess the numbers of them involved. Such practices contribute to a significant challenge in GU pathology: interpretation of slides. While there is a "gold standard" for pathology reporting, the problem of interpretation exists which with practice improves. It is the extensive practice associated with GUP which enables better interpretation of slides relative to NSP and thus, greater consensus. In other words, the interobserver variability is narrower amongst GUP compared to NSP, and has been documented previously.[13,14]

With regards to the results from our review, significant implications for prostate cancer management arise if one were to solely rely on external pathology reports. For patients who are up or downgraded, even if only by one risk category, the management options and outcomes differ considerably. When looking at the non-expert pathology reports, 20% (on average) were missing the following data elements: number of sites, percentage of each core involved, PNI and ECE. As such, variation exists not only with up and downgrading of GS scores, but also with the reporting of key pathologic variables. This inconsistency diminishes the quality of pathology reports, which in turn can have implications for clinical decision making.

The clinical implications are well documented for various prostate cancer scenarios; patients have different management options available that are best suited to their risk category. A patient with low risk disease, for instance, may choose low dose rate (LDR) seed brachytherapy over radical prostatectomy or external beam radiotherapy (EBRT), given favorable side effects, excellent biochemical control and convenience.[15,16] However, if the patient actually has Gleason 7 disease (28% chance), the same choice of LDR would give inferior biochemical control rates compared to dose-escalated EBRT (5 y bDFS 92% versus 80%, MSKCC nomograms). Similarly, a patient actually having low or intermediate risk disease, but initially graded as high risk, may be managed with EBRT to the pelvis and prostate with 3 years of adjuvant hormonal therapy (i.e. androgen deprivation therapy - ADT).[17] Unnecessarily, this patient would be subjected to: the bothersome side effects associated with hypotestosteronemia; slow recovery, with a 10% chance of no recovery at all; increased risk of coronary artery disease, diabetes, sudden death, myocardial infarction and osteopenic fractures for every year of ADT exposure.[18-21]

Aside from the clinical implications of management, quality of life (QOL) is also affected. It is well known that a diagnosis of prostate cancer significantly and negatively impacts a patient's QOL and can affect them in such domains as vitality, social functioning and mental status.[22,23] In addition, varying degrees of anxiety are experienced by men depending on their risk category diagnosis, and is further exacerbated by and negatively affects other QOL domains when faced with different treatment options.[23-28] Patients are also affected post-treatment; decisional regret is known to occur when individuals think about potential outcomes that could have been realized if an alternative treatment was chosen.[29,30] This phenomenon has been observed in terms of treatment modality chosen over time (e.g. higher levels of regret with radical prostatectomy compared to EBRT) as well as the impact on sexual and urinary dysfunction and limitations on various personal activities.[31] Knowing that QOL is affected by and decisional regret is experienced when patients undergo prostate cancer treatment, it is all the more important to have an accurate pathological diagnosis up front to direct management.

Lastly, costs to the healthcare system vary according to the therapy pursued. ADT, for instance, is expensive, costing approximately $12,000-$15,000 for 3 years of treatment if it is added unnecessarily. In addition, if a less effective treatment was chosen based on belief that the Gleason score was a 6 instead of 7 then a greater number of patients would require lifetime ADT, an

extremely costly result. Furthermore, surgery versus EBRT versus seed brachytherapy all require different amounts of resources (e.g. personnel, time) and, like ADT, should only be selected where appropriate. Again, we believe an accurate pathological diagnosis is critical for the appropriate selection of the type and extent of treatment.

Limitations

We recognize that the data presented are from a time period predating the guidelines following the 2005 ISUP Consensus Conference.[32] As such, our study compared prostate pathology reporting practices using the original Gleason grading system and not those of the improved 2005 ISUP modification. This temporal factor of biopsy collection vis-à-vis prostate pathology practice improvement is a significant study limitation and thus warrants further investigation to assess the degree to which current pathologic grading disparities exist.

Nevertheless, the release of these guidelines does not necessarily equate to widespread pathologic practice improvement amongst NSP; the possibility remains that uptake may be slow or non-existent and thus, the value of mandatory secondary review is high seeing that oncologists making management decisions do not know which NSP are reviewing prostate specimens according ISUP guidelines. Such unfamiliarity is noted by Brimo et al, who also report a 14.7% inter-institutional disagreement resulting in risk category change and concur with the practice of routine pathology review in light of the potential to significantly affect therapy.[33] Potential contributors to differences in prostate pathology grading on the part of NSP could be attributed to lack of experience and expertise compared to GUP; educational efforts (e.g. systematic training using prostate tissue microarrays on a CD-ROM) to bridge this gap have been suggested in other studies as means for remediation.[5,13,34]

We also acknowledge that inter and intraobserver variability can play a role in accuracy and consistency of pathologic interpretation of grade and stage, even among experts (i.e. GUP). Gleason himself reported his own intraobserver variability at 50%, which increased to 85% within one histologic grade, while other studies have shown intraobserver variation in the range of 63% to 78% for both radical and transurethral resection specimens.[35-37] Though outside of the genitourinary community, good ($\kappa = 0.4$ to 0.74) to high ($\kappa > 0.75$) intra- and inter-observer variability has been documented in the breast cancer literature, there is interobserver variance between general and expert breast pathologists where borderline lesions are concerned.[38,39]

Similar contentious areas exist in the prostate pathology with regards to distinguishing high grade Gleason pattern 4 from Gleason pattern 3.[5] However, given the expertise of our GUP and the discussion of our GU pathology practice earlier, the degree of inter and intraobserver variability is likely small.

Conclusion

In light of the disparity between NSP and GUP, all referred patients should continue to have central pathology review. Paying due diligence to this practice will not only help facilitate optimal prostate cancer management, but also improve the quality of care by ensuring the right diagnosis is made at the earliest stages of management. To assess whether disparities still exist between NSP and GUP for prostate cases referred to our center and to ascertain what knowledge and practice gaps exist, a more recent audit post ISUP guideline publication should be completed. □

References

1. Canadian Cancer Society. Prostate Cancer Stats. http://www.cancer.ca/Canada-wide/About%20cancer/Cancer%20statistics/Stats%20at%20a%20glance/Prostate%20cancer.aspx?sc_lang=en. Last accessed November 8, 2010.
2. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol* 1999;17(5):1499-1507.
3. Stephenson AJ, Scardino PT, Eastham JA et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Clin Oncol* 2005; 23(28):7005-7012.
4. Walz J, Chun FK, Klein EA et al. Nomogram predicting the probability of early recurrence after radical prostatectomy for prostate cancer. *J Urol* 2009;181(2):601-607.
5. Fine SW, Epstein JI. A contemporary study correlating prostate needle biopsy and radical prostatectomy Gleason score. *J Urol* 2008;179(4):1335-1338.
6. King CR. Patterns of prostate cancer biopsy grading: trends and clinical implications. *Int J Cancer* 2000;90(6):305-311.
7. Lattouf JB, Saad F. Gleason score on biopsy: is it reliable for predicting the final grade on pathology? *BJU Int* 2002;90(7):694-698.
8. Paulson DF. Impact of radical prostatectomy in the management of clinically localized disease. *J Urol* 1994;152(5 Pt 2):1826-1830.
9. San Francisco IF, DeWolf WC, Rosen S et al. Extended prostate needle biopsy improves concordance of Gleason grading between prostate needle biopsy and radical prostatectomy. *J Urol* 2003;169(1):136-140.
10. Steinberg DM, Sauvageot J, Piantadosi S et al. Correlation of prostate needle biopsy and radical prostatectomy Gleason grade in academic and community settings. *Am J Surg Pathol* 1997;21(5): 566-576.

11. Cancer Care Ontario. Pathology Reporting Project Information for Professionals. http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=48158. Last accessed November 11, 2010.
12. Rubin M, Bismar T, Curtis S, Montie J. Prostate needle biopsy reporting: how are the surgical members of urologic oncology using pathology reports to guide treatment of prostate cancer patients? *Am J Surg Pathl* 2004;28(7):946-952.
13. Burchardt M, Engers R, Muller M, Burchart T et al. Interobserver reproducibility on Gleason grading: evaluation using prostate cancer tissue microarrays. *J Cancer Res Clin Oncol* 2008;134(10):1071-1078.
14. Bova GS, Parmigiani G, Epstein JI, Wheeler T, Mucci NR, Rubin MA. Web-based tissue microarray image data analysis: initial validation testing through prostate cancer Gleason grading. *Hum Pathol* 2001;32(4):417-427.
15. Chen RC, Clark JA, Talcott JA. Individualizing quality-of-life outcomes reporting: how localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel, and sexual function. *J Clin Oncol* 2009;27(24):3916-3922.
16. Pickles T, Keyes M, Morris WJ. Brachytherapy or conformal external radiotherapy for prostate cancer: a single-institution matched-pair analysis. *Int J Radiat Oncol Biol Phys* 2010;76(1):43-49.
17. Lukka H, Warde P, Pickles T, Morton G, Brundage M, Souhami L. Controversies in prostate cancer radiotherapy: consensus development. *Can J Urol* 2001;8(4):1314-1322.
18. Yoon FH, Gardner SL, Danjoux C, Morton G, Cheung P, Choo R. Testosterone recovery after prolonged androgen suppression in patients with prostate cancer. *J Clin Oncol* 2008;180(4):1438-1443.
19. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24(27):4448-4456.
20. Alibhai SMH, Duong-Hua M, Sutradhar R et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. *J Clin Oncol* 2009;27(21):3452-3458.
21. Shahinian VB, Kuo YF, Freeman JL, Orihuela E, Goodwin JS. Characteristics of urologists predict the use of androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2007; 25(34):5359-5365.
22. Love AW, Scealy M, Bloch S et al. Psychosocial adjustment in newly diagnosed prostate cancer. *Aust N Z J Psychiatry* 2008;42(5):423-429.
23. Rosenfeld B, Roth AJ, Gandhi S et al. Differences in health related quality of life of prostate cancer patients based on stage of cancer. *Psychooncology* 2004;13(11):800-807.
24. Bellizzi KM, Latini DM, Cowan JE et al. Fear of recurrence, symptom burden, and health-related quality of life in men with prostate cancer. *Urology* 2008;72(6):1269-1273.
25. Sanda MG, Dunn RL, Michalski J et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358(12):1250-1261.
26. Burnett AL, Aus G, Canby-Hagino ED et al. Erectile function outcome reporting after clinically localized prostate cancer treatment. *J Urol* 2007;178(2):597-601.
27. Hinz A, Krauss O, Stolzenburg JU et al. Anxiety and depression in patients with prostate cancer and other urogenital cancer: a longitudinal study. *Urol Oncol* 2009;27(4):367-372.
28. Bacon CG, Giovannucci E, Testa M et al. The association of treatment-related symptoms with quality-of-life outcomes for localized prostate carcinoma patients. *Cancer* 2002;94(3):862-871.
29. Hu J, Kwan L, Saigal CS, Litwin MS. Regret in men treated for localized prostate cancer. *J Urol* 2003;169(6):2279–2283.
30. Clark JA, Inui TS, Silliman RA et al. Patients' perceptions of quality of life after treatment for early prostate cancer. *J Clin Oncol* 2003;21(20):3777–3784.
31. Diefenbach MA, Mohamed NE. Regret of treatment decisions and its association with disease-specific quality of life following prostate cancer treatment. *Cancer Invest* 2007;25(6):449-457.
32. 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 Pathl* 2005;29(9):1228-1242.
33. Brimo F, Schultz L, Epstein JI. The value of mandatory second opinion pathology review of prostate needle biopsy interpretation before radical prostatectomy. *J Urol* 2010;184(1):126-130.
34. Kuroiwa K, Shiraishi, Ogawa O, Usami M. Discrepancy between local and central pathological review of radical prostatectomy specimens. *J Urol* 2010;183(3):952-957.
35. Gleason DF. Histologic grading of prostate cancer: a perspective. *Hum Pathol* 1992;23(3):273-279.
36. Ozdamar SO, Sarikaya S, Yildiz L, Atilla MK, Kandemir B, Yildiz S. Intraobserver and interobserver reproducibility of WHO and Gleason histologic grading systems in prostatic adenocarcinomas. *Int Urol Nephrol* 1996;28(1):73-77.
37. Cintra ML, Billis A. Histologic grading of prostatic adenocarcinoma: intraobserver reproducibility of the Mostofi, Gleason and Bocking grading systems. *Int Urol Nephrol* 1991;23(5):449-454.
38. Rakovitch E, Mihai A, Pignol JP et al. Is expert breast pathology assessment necessary for the management of ductal carcinoma in situ? *Breast Cancer Res Treat* 2004;87(3):265-272.
39. Verkooijen HM, Peterse JL, Schipper MEI et al. Interobserver variability between general and expert pathologists during the histological assessment of large-core needle and open biopsies of non-palpable breast lesions. *Eur J Cancer* 2003;39(15):2187-2191