Recutting prostate needle core biopsies with high grade prostatic intraepithelial neoplasia increases detection of adenocarcinoma

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RAPP DE, MSEZANE LP, REYNOLDS WS, LOTAN TL, OBARA P, O'CONNOR RC, TAXY JB, GERBER GS, ZAGAJA GP. Recutting prostate needle core biopsies with high grade prostatic intraepithelial neoplasia increases detection of adenocarcinoma. The Canadian Journal of Urology. 2009;16(1):4484-4489.

Objectives: *We sought to evaluate the ability of biopsy core recutting to increase cancer detection in patients with high grade prostatic intraepithelial neoplasia (HGPIN).*

Methods: *This prospective study encompasses all patients undergoing 12 core TRUS guided prostate biopsy between February 2004 and January 2007. In patients with HGPIN on initial biopsy, the paraffin blocks were resampled for cancer by additional deeper levels per core. Additional analysis was performed in the patients with HGPIN in order to detect whether significant differences in prebiopsy variables were associated with patients subsequently found to have benign versus carcinoma on recutting. Last, the costs associated with this procedure were studied.*

Results: *Forty of 584 (6.8%) patients undergoing prostate biopsy were found to have HGPIN in the absence of prostatic adenocarcinoma on initial histopathology. Following recutting, 12.5% (5/40) of these patients were found to have prostatic adenocarcinoma not previously detected. Of the remaining 35 patients, 18 underwent repeat biopsy. Of these, five patients were found to have adenocarcinoma and three were found to have persistent HGPIN. The PSA, PSA density (PSAD), and PSA velocity (PSAV) prior to initial biopsy were not statistically different when comparing patients found to have benign tissue versus carcinoma on recutting. In patients with HGPIN, at our institution, recutting the biopsy would yield a cost savings of $436/patient as opposed to universal rebiopsy.*

Conclusions: *Our data suggest that prostate biopsy recutting may increase cancer detection in patients initially found to have HGPIN. Additionally, a significant cost savings is associated with the recutting protocol.*

Key Words: prostatic intraepithelial neoplasia, cancer, histology

Introduction

High grade prostatic intraepithelial neoplasia (HGPIN) is identified in 2%-17% of prostate needle biopsies and is recognized by both urologists and pathologists as a significant risk factor in the subsequent development of invasive prostatic carcinoma.[1] HGPIN is characterized by cells of a luminal phenotype that display a variety of atypical cytological features. Evidence demonstrates a spectrum of similarities with invasive prostate cancer, including phenotypical and morphometrical abnormalities, increased apoptosis, similar genetic alterations, basal cell disruption, and increased neovascularity.[1] Accordingly, HGPIN may represent a premalignant stage in the development of invasive acinar carcinoma.[2]

Accepted for publication September 2008

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Historically, HGPIN has been associated with a significant risk for the subsequent detection of prostate cancer. Cancer detection rates in patients with HGPIN vary from 5% to as high as 100%, however, more recent series have demonstrated a trend towards lower detection rates ranging between 20% and 35%.[3-5] Nonetheless, HGPIN on sextant biopsy is associated with a risk ratio of approximately 15 and is found to be a stronger predictor than other independent risk factors such as patient age and PSA threshold of 4 ng/ml.[3] Based on this risk, aggressive follow-up entailing repeat prostate biopsy and serial PSA testing has been commonly recommended following the identification of HGPIN.

Concurrently, the optimal sampling practice for histologic analysis of prostate needle biopsies in patients with HGPIN remains ill defined. Despite data suggesting that a minimum of three levels per core may increase sensitivity of cancer detection in routine prostate biopsy analysis, similar data is not reported in patients with HGPIN.[6-8] As a method of increasing cancer detection, recutting biopsy tissue blocks has been examined in limited study. Accordingly, although routine recuts have not been shown to increase cancer detection in patients with otherwise benign tissue, some reports have demonstrated increased detection rates following recutting of cores with atypical foci suspicious but not diagnostic of malignancy.[9-10] A specific study of cancer detection rates following recutting prostate cores with HGPIN is not reported.

We sought to determine if recutting the biopsy cores at additional deeper levels beyond that which is routinely employed increases the detection of carcinoma in patients initially diagnosed with HGPIN, thereby avoiding the need for repeat biopsy. Additionally, we assessed for the presence of significant differences in prebiopsy variables as potentially predictive of cancer on recuts. Finally, a cost analysis addressed a possible advantage associated with this procedure.

Material and methods

Study protocol

A prospective investigation was performed on all patients undergoing transrectal ultrasound (TRUS) guided prostate biopsy between February 2004 and January 2007. A standard 12 core TRUS guided prostate biopsy was performed on all patients. Biopsies were performed at the University of Chicago by one of two surgeons. Standard pathological evaluation of each core was performed by the University of Chicago Department of Pathology in all cases. Cases in question were reviewed at the daily conference session with input obtained by all department physicians. In patients diagnosed with HGPIN on initial biopsy, the paraffin blocks were recut to examine additional cuts per core for potential foci of cancer. A complete description of the histology protocol is described below. In the absence of cancer detection, a discussion of HGPIN was held with each patient. Repeat biopsy was recommended to all patients in accordance with standard practice. However, mandatory repeat biopsy was not included as part of study protocol.

An outcomes analysis was performed to assess for the potential ability of biopsy core recutting to increase the detection of carcinoma. In addition, a comparison was undertaken to detect significant differences in prebiopsy variables as potentially predictive of cancer on recutting or subsequent biopsy. Finally, cost analysis was performed to determine if an advantage was associated with biopsy recutting. Fiscal officers at the University of Chicago provided data on physician fees, hospital fees, and processing charges. Univariate statistical analysis was performed utilizing Student's T-test and Fischer's exact test ($p < 0.05$ considered to be statistically significant).

The study protocol was approved by the University of Chicago Hospitals Institutional Review Board. Informed consent was obtained from each patient after a detailed discussion of the study protocol. Following a diagnosis of HGPIN, patient notification was deferred until the additional recuts were obtained and a final pathological diagnosis issued.

Histology

Histological processing and examination of prostate needle core biopsies was carried out per institutional practice. Briefly, after 3-6 hours fixation in 10% neutral buffered formalin, an average of 12 prostate needle core biopsies for each case were stretched between sponges in 4-6 histology cassettes and processed by standard tissue processing methods. The tissue was then embedded in paraffin blocks (2-3 needle cores/block). Ten serial 4 um histological sections were cut from each block and the first, fifth and tenth levels were stained with hematoxylin and eosin for microscopic examination, while the intervening unstained levels were saved for potential immunohistochemical examination. In patients found to have HGPIN, all blocks were again recut as above and the eleventh, fifteenth and twentieth levels were stained with hematoxylin and eosin and examined microscopically. In cases where cancer or atypical foci were identified on stained slides, immunohistochemistry (IHC) techniques (HMWK, p63, and/or p504s) were used to evaluate intervening unstained slides to aid in diagnosis.

Results

A total of 584 patients underwent TRUS guided prostate biopsy during the investigation period, with a mean follow-up of 21 months. Forty patients (6.8%) were found to have HGPIN in the absence of invasive prostatic carcinoma or atypia on histopathological examination. Following deeper cuts, 12.5% (5/40) of these patients were found to have a focus of prostatic adenocarcinoma that had not been detected initially. IHC was used in conjunction with 21/40 recuts and felt to aid in the diagnosis or exclusion of cancer in 13 cases.

Of the remaining 35 patients, 18 underwent subsequent repeat biopsy. Of these, four patients were found to have adenocarcinoma and three were found to have persistent HGPIN. Mean interval between initial and subsequent biopsy in these patients was 3.7 months. One additional patient was found to have adenocarcinoma on a third biopsy at 14 months following initial biopsy. The overall cancer detection rate in these patients with initially diagnosed HGPIN to date is 25% (10/40).

Carcinoma identification comprised a single microscopic focus in 3/5 recutting patients, as compared to 0/5 patients in the subsequent biopsy cohort. Meaningful comparison of cancer grade in these cohorts was not possible. In analysis of whole prostate tissue in patients found to have carcinoma of recut, three patients underwent radical prostatectomy at our institution. Two patients initially diagnosed with a single focus of carcinoma had pathologic T2a and T2c, GG 3 + 3 = 6, 1% and 15% core involvement, respectively. The final patient with 1% core involvement on recut was found to have T2c, GG 3 + 3 = 6 carcinoma with 15% core involvement. The remaining two patients underwent XRT.

Preoperative variables in HGPIN patients were then analyzed to determine whether significant differences were present in those HGPIN patients found to have carcinoma versus benign tissue on recut or rebiopsy. Patient age, PSA, PSA density (PSAD), and PSA velocity (PSAV) prior to initial biopsy were not statistically different when comparing these cohorts, Table 1. A separate analysis of the remaining cohort of patients not found to have isolated HGPIN on initial biopsy (n = 544) was also performed, Table 2. In this analysis, patient age, PSA and PSAD were significantly higher when comparing patients found to have benign (n = 250) versus carcinoma (n = 294) on biopsy. PSAV data was not available on a significant percentage of these patients and, therefore, comparison was not possible. Finally, a comparison of the subset of patients in the general cohort with benign findings (n = 250) and those patients with isolated HGPIN on final pathology (n = 30) was performed, and revealed no statistically significant differences in patient age, PSA, and PSAD.

A cost analysis of prostate biopsy recutting was next performed. The overall patient cost for biopsy and histologic analysis was $3971. Given a study cohort of 40 patients, the overall cost for initial biopsy and histologic analysis totaled $158,840. Assuming all patients with HGPIN undergo repeat biopsy, the recutting protocol reduces the total cost of second

TABLE 1. **HGPIN patient demographics and characteristics**

Variable	HGPIN (n = 30)	Adenocarcinoma (resection) (n = 5)	Adenocarcinoma (subsequent biopsy) (n = 5)	p value*
Age	61	62	61	.84/1.0
PSA (ng/ml)	7.1	6.4	9.8	.85/.14
Prostate V (cc)	52	53	64	.89/.41
PSA density (ng/ml/cc)	0.15	0.12	0.21	.49/.08
PSA velocity (ng/ml/yr)	1.7	1.3	1.4	.47/.58
Gleason grade	NA			NA
9-10		0	0	
8		0	2	
7		0	0	
6		2	3	
2-5		0	0	
Microscopic focus		3	0	

*First value indicates comparison of HGPIN and resection groups
Second value indicates comparison of HGPIN and subsequent biopsy groups

TABLE 2. **Patient demographics and characteristics**

Variable	Overall (n = 544)	Adenocarcinoma (n = 294)	Benign (n = 250)	HGPIN (n = 30)
Mean age (years) (range)	64 (30-91)	65 (30-91)	62* (41-82)	61** (30-85)
Mean PSA (ng/ml) (range)	37.6 (0.3-5831)	62.7 (0.6-5831)	7.5* (0.3-79)	7.1** (2.9-20)
Median PSA (ng/ml)	6.2	6.9	5.6	
Mean prostate V (cc) (range)	52 (14-245)	45 (14-245)	59* (14-196)	52** (18-140)
Mean PSAD (ng/ml/cc) (range)	0.8 (0.01-108)	1.3 (0.01-108)	0.15* (0.02-2.0)	0.15** (0.08-0.31)

*Value indicates comparison of adenocarcinoma and benign groups, $p < 0.05$ in all analyses
**Indicates comparison of HGPIN and benign groups, p not statistically significant (> 0.05) in all analyses

biopsy to $138,985 by excluding the five patients found to have cancer on recutting. Accounting for the additional costs of resectioning ($2400, $60/patient), a cost savings of $436/patient is observed using a recutting protocol in cases of HGPIN.

Discussion

Currently, there is no standard for histological sampling of prostate biopsies. This problem is compounded in biopsies with an atypical finding, such as HGPIN. Multiple reports have suggested that histological review of three levels per core is necessary to detect pathological features during routine histological analysis of prostate tissue.[6-8] Brat and colleagues found that review of only two levels would result in misdiagnosis in approximately 5% of cores reviewed.[7] Similar reports are seen using sampling at only one level.[7-8] Data is even more limited for sampling practices in patients with HGPIN. While Aydin et al found that the probability of detecting prostate carcinoma and PIN in prostate specimens was directly related to the extent of sampling, specific protocols for histological sampling in HGPIN patients are not published.[11]

The first of our study aims sought to evaluate the ability of recutting needle cores to detect carcinoma. Isolated literature has evaluated the effect of additional sectioning in nonmalignant biopsy specimens. Green et al found that, in patients with atypia, the analysis of intervening, previously unstained slides helped to establish a diagnosis of cancer in 23 (31%) of case.[10] Our investigation suggests that recutting biopsy cores may also increase carcinoma detection in HGPIN patients and warrants consideration in the formulation of optimal histological protocols in these patients. We would acknowledge, however, that the finding of missed cancer on biopsy following recutting suggests that close surveillance must be continued in these patients.

Although HGPIN does not elevate serum PSA, limited evidence is reported to define whether PSA/PSA derivatives (e.g. PSAV, PSAD) are useful in identifying HGPIN patients at increased risk of subsequent cancer development or of missed cancer on initial biopsy. Clinical variables generally demonstrate a poor predictive value for subsequent cancer in patients with HGPIN, although isolated study has demonstrated an increased PSAV in HGPIN patients subsequently developing cancer.[12-14] Concurrently, other investigation indirectly suggests that PSA/PSA derivatives may be helpful in identifying patients with missed cancer on initial biopsy.[3] If demonstrated, this risk stratification would allow for additional attention (e.g. additional sections, immunohistochemistry) to the histologic evaluation of these patients.

Given these data, the second study aim was to identify potential differences in prebiopsy clinical variables between HGPIN patients ultimately found to have benign versus malignant tissue on further examination (recutting or rebiopsy). Our primary analysis identified no differences in comparing HGPIN patients found to have benign versus cancerous tissue on recutting. We acknowledge that this subset analysis is significantly limited by low patient numbers and would caution the readers accordingly. Nonetheless, our data may suggest that not only PSAV, but also PSA and PSAD are not able to distinguish patients at risk for missed cancer. As expected, the subset of patients in the remaining general cohort found the have cancer on initial biopsy demonstrated a characteristic elevation in these variables. In contrast, data comparison of patients with benign tissue on initial biopsy and patients with isolated HGPIN demonstrated no differences. This finding again suggests that PSA levels/kinetics are similar in HGPIN and benign cohorts and that these variables are poor predictors of which HGPIN patients are at increased risk for cancer detection.

Similarly, no differences were found between HGPIN patients found to have benign versus cancerous tissue on subsequent biopsy. Given the extremely short interval between initial and subsequent biopsy in our patients, we believe this finding only confirms that PSA derivatives may not be predictive of patients with cancer missed on initial biopsy. We would feel that the finding of cancer on a third biopsy also represents a similar finding, although conclusions cannot be reached given only a single case. Other directed investigation is needed to determine whether such assays are useful in identifying HGPIN patients at risk for subsequent development of cancer.

Finally, the third study aim sought to assess for a cost benefit that may be associated with the recutting protocol. Prostate cancer screening and treatment represents an enormous expense, with a large proportion of this cost owing to prostate biopsy.[15-16] For this reason, revised screening plans have been proposed as a more effective and less expensive approach.[17] Given these costs, pathological protocols designed to maximize not only cancer detection, but also cost efficiency, are needed. Our analysis suggested a significant cost advantage to the recutting protocol that parallels the cancer detection benefit. Our cost calculations are based on the assumption that all patients will undergo repeat biopsy, a scenario not likely to occur in actuality. Nonetheless, with the dramatic savings calculated, we believe that a significant cost savings would remain even given a lower rate of repeat biopsy. In related discussion, we would forward that the prevention of repeat biopsy via recutting is valuable even given the limitations of its sensitivity. Prostate biopsy may be associated with pain, infection, and anxiety, in addition to well known potential morbidity. Given the sheer quantity of prostate biopsies performed annually, the ability to avoid the potential impact that biopsy can have on a patient is attractive.

Several issues related to this investigation deserve discussion. First, the authors acknowledge that recent investigation questions the need for rebiopsy in patients with HGPIN, based on evidence suggesting similar rates of cancer detection following rebiopsy of patients with benign tissue.[18] Indeed, contemporary literature suggests that comprehensive sampling techniques (extended and saturation biopsy), as well as modern advances in prostate imaging (contrast enhanced Doppler ultrasound), may serve as effective methods of increasing cancer detection.[19-20] While believe these data to be meaningful, we feel that, until definitive research is presented, the practice of offering repeat biopsy to patients with HGPIN will remain common. Underscoring this fact is contemporary literature forwarding a more aggressive approach comprising repeat biopsy every 3 or 6 months for 2 years and yearly thereafter.[3] Above all, our investigation provides a practical value in that prostate core recutting may be a useful addition to histological protocols until formal practice guidelines are forwarded.

Second, the lack of control population may limit our conclusions. Accordingly, it may be possible that recutting normal samples would, as well, yield increased cancer detection rates. However, unlike HGPIN, study assessing recutting of normal biopsy samples is published and fails to demonstrate a benefit. For this reason, recutting of normal samples was not a focus of our investigation. Third, we acknowledge that the finding of a significant number of cancer microfoci on recut may raise concern regarding unnecessary detection of "insignificant" cancer. Nonetheless, in 2/3 patients undergoing subsequent radical prostatectomy, final pathology revealed, in our opinion, significant tumor burden. Further study would be needed to address this concern. Finally, it is possible that our embedding protocol (3 cores/block in certain cases) may results in potential loss of core length during preparation. However, as described, we utilize a published protocol designed to optimize tissue processing and avoid tissue length lost for examination, even when using 3 cores/block.[21] While the technique for biopsy processing is not nationally standardized, we believe that the literature and our experience demonstrate our protocol to be both internally consistency, as well as within the mainstay of processing techniques described to date.

Conclusions

The present study has demonstrated that recutting prostate biopsy cores detects additional foci of cancer in patients with HGPIN. No significant differences are found when comparing prebiopsy PSA derivatives in those patients ultimately found to have benign versus cancerous tissue. Further, a significant cost savings and avoidance of potential morbidity is associated with a recutting protocol in the patient cohort. These data suggest that a recutting protocol in HGPIN patients may be of benefit. □

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