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Impact of immediate TRUS rebiopsy in a patient cohort considering active surveillance for favorable risk prostate cancer

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Abstract

Introduction and Objective—Active surveillance (AS) is an option for the management of favorable risk prostate cancer (CaP) in the PSA era. Published studies have reported variable inclusion criteria for cohort selection. Accurate assessment of individual patient risk in AS is dependent not only upon rigorous selection criteria, but also reliability of diagnosis at tissue biopsy. To date, the impact of immediate transrectal ultrasound (TRUS) rebiopsy in confirming candidates for AS has been incompletely defined.

Methods—From a total of over 567 men, 67 met criteria for AS (Gleason <7, PSA <10, PSAD <0.15, <3 cores with <50% involvement of any 1 core). Fifty-two men agreed to a 12-core TRUS rebiopsy within 6 months of first diagnosis performed in clinic. Statistical analysis was performed using Wilcoxon signed rank test and logistic regression to determine predictors of rebiopsy characteristics, histopathologic outcomes, and impact on treatment choice.

Results—Mean cohort age was 63.9 years (range 56–72 years), PSA 5.9 ng/ml (4.1–10), and PSA density 0.12 ng/ml/cc at initial biopsy. Tumor involved 1.1 cores and 3.2% (range 1%–5%) of the total tissue. Average time to rebiopsy was 2.7 months. Notably, 29 of 52 men (56%) demonstrated no evidence of CaP on repeat biopsy; 14 of 23 men with a positive repeat biopsy showed either an increase in cancer volume (2.8% mean increase) and 9 (18%) were upgraded to Gleason pattern 3+4 = 7. Rebiopsy demonstrated 9 (17%) patients exceeded AS criteria. Nine patients chose curative surgical intervention (radical prostatectomy) based on increased cancer volume or grade (4) or an elective desire for treatment (5). All had organ confined disease with negative margins on final pathologic analysis. Statistical review revealed that initial Gleason

score, PSA density, and number of positive cores at first biopsy were not predictive of men with higher volume/grade on re-biopsy.

Conclusions—Immediate TRUS repeat biopsy after diagnosis frequently fails to redemonstrate prostate cancer confirming the favorable-risk nature of disease burden in this group being considered for AS. A subset of patients are upgraded (17%) leading to reconsideration of AS. We conclude this clinic-based approach provides valuable additional information to discriminate appropriate AS candidates.

Keywords

Active surveillance; Prostate cancer; TRUS biopsy

1. Introduction

Prostate cancer remains the most commonly diagnosed malignancy amongst male patients in both the United States and Europe. The widespread use of PSA-based screening in the United States has resulted in favorable-risk cancer burden now constituting nearly 60% of new diagnoses. This has led to a considerable lead-time bias as tumors are diagnosed well before they would otherwise become clinically evident, ranging from 5 to 10 years [1,2]. With the natural history of many clinically significant prostate cancers extending nearly 15 years, not all cancers diagnosed in the modern era may need aggressive treatment.

Active surveillance (AS) has received considerable attention in recent years in regards to the expectant management of low volume, lower-grade prostate cancer. Klotz et al. have published extensively on long-term follow-up of AS cohorts. They found a cancer specific survival of 99% and an overall survival of 85% in 453 men with a stringent AS protocol followed for a median period of 7.2 years [3]. These protocols used patient preference, PSA kinetics, or histologic progression on repeat biopsy to trigger curative intervention. Together with other cohorts [4–6], these studies suggest AS is a viable option in selected patients to preserve therapeutic efficacy while reducing treatment-related morbidities.

A critical issue in AS has been defining reliable inclusion criteria for cohort selection. Enrollment criteria are largely based on the modified Epstein et al. criteria for low-risk disease [7]. Published surveillance protocols, including the National Comprehensive Cancer Network (NCCN) Practice Guidelines, have included favorable risk factors such as Gleason score of 6 or less (no pattern 4), PSA <10, PSA density <0.15 ng/ml/cc, and T1c-T2a stage. These entry criteria have varied slightly from institution to institution. Stricter entry criteria for AS candidates are associated with lower risks of Gleason upgrading and extracapsular extension on radical prostatectomy [8]. More stringent criteria also limit the number of men considered candidates for AS. A critical issue that remains undefined in the selection of patients for AS is the potential for diagnostic understaging and the extent of evaluation that is necessary for inclusion. Current imaging modalities have a limited ability to evaluate the extent of cancer in the prostate gland, especially in the context of microscopic disease [9]. To date, an initial diagnostic biopsy has been utilized in most studies to identify candidates for AS [3,4,8], yet the optimal timing of follow-up surveillance biopsy in AS remains unknown. One risk patients encounter when considering a surveillance approach for their

diagnosis of prostate cancer is that of understaging. Increased biopsy number has been correlated with a reduced risk of unrecognized cancer volume [10], however, the impact of repeat 12 core biopsy immediately after diagnosis has not been well defined in this population of cancer patients.

In this study, we evaluated a modern cohort of patients with favorable risk prostate cancer who were considering AS. To further assess cancer extent, repeat transrectal ultrasound (TRUS) and biopsy was performed within 6 months of initial diagnosis. With our current AS criteria, we find a large group of these men have no evidence of cancer on rebiopsy. A subpopulation was identified that did demonstrate upgrading on rebiopsy, however, on multivariate statistical analysis no clinicopathologic factors predict this finding. We conclude that immediate repeat biopsy impacts the recommendation for AS.

2. Materials and methods

Of 567 consecutive men undergoing evaluation for prostate cancer at the University of Wisconsin (2007–2011), we identified 67 men who met the published Epstein et al. criteria for AS [7]. These criteria included stage T1c, Gleason <7, PSA <10, <3 cores involved with cancer, PSAD <0.15, and no core involved more than 50%. Using these criteria all patients had <10% total tissue involvement. No age limitations were placed on patients being offered AS. All men were subjected to an initial biopsy scheme of 10–12 cores and all pathology was later reviewed internally by a fellowship-trained genitourinary pathologist to ensure uniformity of analysis. Institutional review board approval was obtained for the study.

Subsequently, 52 men agreed to a 12 core TRUS rebiopsy utilizing a standard biopsy template [4]. Time to rebiopsy was limited to a period of less than 6 months after initial biopsy and was performed in our clinics. Clinical evaluation including digital rectal exam, PSA and prostate volume were recorded; PSAD was calculated using the standard formula of serum PSA level divided by TRUS-derived prostate volume (ng/mL/cc).

Histopathologic outcomes of the second biopsy were compared to the original biopsies, and treatment options reviewed. For those men electing subsequent surgical intervention, whole mount specimens were analyzed for tumor grade, cancer volume, and stage. With the exception of routine TRUS during biopsy, additional radiologic evaluation was not performed given the low probability of extraprostatic disease in this cohort.

On the basis of initial cohort characteristics, PSA level, PSA density, Gleason score, and tumor core percentage were analyzed for their ability to predict the absence, presence, and extent of cancer on repeat biopsy. To test for differences between biopsies in percent cancerous tissue and number of positive cores, a Wilcoxon signed rank test was used. Multivariate logistic regression was used to model the probability of having a repeat biopsy Gleason score of at least 7 or total percentage cancer of at least 20% as a function of continuous variables (PSA, tissue percentage, first biopsy Gleason score). Fisher exact tests were used to test for association between having a repeat biopsy Gleason score of at least 7 or tissue percentage of greater or equal to 20% and categorical predictors (left lobe positive, right lobe positive, first biopsy Gleason 7 or higher). Two-sided *P* values were obtained with *P* < 0.05 used as the criterion for significance.

3. Results

Of patients found eligible for AS, 52 of 67 (78%) agreed to undergo a second diagnostic TRUS biopsy. Reasons cited for refusing or not pursuing a second biopsy included pain/discomfort with the biopsy procedure and a perceived lack of impact for confirmation of histopathologic diagnosis. At the time of initial biopsy diagnosis, the mean age of the cohort was 63.9 years. Table 1 shows clinical and pathologic characteristics associated with this cohort. PSA at diagnosis was 5.9 ng/ml (range 4.1–10), prostatic volume by TRUS 47.6 ml, and mean PSA density was 0.12 ng/ml/cc. Bilateral disease was found on biopsy in 5/52 (10%) patients. The mean number of cores containing cancer on initial biopsy was 1.1 with 3.2% of the total biopsy volume containing cancer. Mean time interval between initial and repeat biopsies was 2.7 months.

Of the 52 patients, 29 (56%) showed no evidence of adenocarcinoma on repeat 12 core biopsy (Table 2). Of the 23 patients with cancer redemonstrated by biopsy, 6 had no change in cancer volume or grade. The remaining 17 patients with a positive repeat biopsy showed an increase in cancer volume (14) and/or an increase in Gleason score to 3+4=7 (9). Comparing repeat biopsy characteristics to initial biopsy data, an increase in cancer volume and the extent of cores involved was seen, but was not statistically significant overall when these groups were compared (Table 3). One patient had a change in the laterality of the cancer focus, another decreased from bilateral to unilateral evidence of disease, and 4 patients changed from unilateral to bilateral cancer. Bilateral cancer foci did not always correlate with increased Gleason grade or significant change in the percentage of malignant cores discovered.

When assessing our criteria for AS in patients based on their second biopsy, we found 9 patients (17%) no longer met these characteristics and were offered immediate treatment. We analyzed 5 patient variables at initial biopsy that might predict an increase in grade (Gleason sum 6 to 7) or more extensive cancer (>2 cores, >10% total tissue involvement) at repeat biopsy. Logistic regression analysis was performed using multiple variables including the initial PSA, extent or percentage of cancer, age, and prior previous negative TRUS-biopsy. None of these variables proved statistically significant.

In follow-up, 4 of 9 men who no longer met the criteria for AS chose to undergo radical prostatectomy and 5 declined surgery. Final pathology confirmed organ-confined disease in all 4 cases with no extraprostatic extension and negative surgical margins (Table 4). Cancer volumes averaged 4.3 cc (range 0.5–11.7 cc) within the whole mount specimens. Five other AS patients who were not upgraded chose elective intervention due to heightened concern over continued cancer burden. Pathology in these patients demonstrated organ-confined adenocarcinoma as well (1.1 cc, range 0.4–2.5 cc) and was not significantly different from upgraded final prostate pathology specimens ($P = 0.2$). The remaining 43 men elected to continue on active surveillance with biannual total and free PSA serum evaluation, DRE, and annual surveillance biopsies.

3.1. Comment

Our cohort demographics appear similar to prior AS analyses at academic centers with 10% of overall institutional prostate cancer diagnoses choosing AS [11]. The criteria we utilized for the consideration of AS and TRUS rebiopsy were based on the broadly utilized Epstein et al. criteria and are more strict than several prior studies [5,8,12]. Specifically, we excluded stage T2 cancers, cancer in more than 2 cores, and biopsy tumor volume greater than 10%. Notably, absence of disease on repeat biopsy was found in 56% of our cohort. In patients rebiopsied at 1 year or more after diagnosis in other published AS cohorts, the number found to have no cancer detected ranged from 47% to 63% [13–15]. This finding underscores the low-volume disease within this cohort of men considering AS, yet also highlights the inherent sampling error of TRUS biopsy at tissue diagnosis.

Increases in Gleason grade or more extensive cancer (>10%) triggered a recommendation for curative intervention in our cohort. No high grade cancers (Gleason 8–10) were detected. Upstaging in our study occurred less frequently (17%) than that seen after rebiopsy in another modern AS series (27%), perhaps reflecting our slightly more stringent AS protocol [12]. Not all patients found to exceed criteria for AS (5/9) elected radical prostatectomy based upon rebiopsy results. In the 4 patients who did, final pathology demonstrated organ-confined disease and negative surgical margins although cancer volumes were higher in several patients (Table 4). In a subgroup of patients not upgraded who chose elective RRP, final cancer volumes were less although this was not statistically significant. These findings of more minimal cancer volumes in men undergoing elective RRP are reassuring that the criteria we currently use for AS generates a minimal chance of extensive unrecognized disease.

Based on these findings, it may also be argued that these men might have had their cancers observed for a longer period of time on active surveillance before treatment. Indeed, a number of studies have suggested no difference in adverse pathologic features or biochemical disease progression in men with low-risk prostate cancers who delay radical prostatectomy for 6 to 26 months after diagnosis [16,17]. However, a meta-analysis of studies examining radical prostatectomy specimens in low risk patients indicates that a subset may contain higher-risk features [18], including extra-prostatic extension (EPE) in 17% and positive margins found in 12%. In a recently published analysis of low risk patients from our institution, EPE was found in 5% and a positive margin in 11% [19]. These patients were not routinely subjected to repeat biopsy, nor were all candidates for AS. Defining the subset of patients with higher risk elements remains an important ongoing area of focus within AS protocols and may ultimately require the use of novel molecular markers.

Previously, biopsy core number was found to predict upgrading in a low risk population at radical prostatectomy [20]. Patients in that study having more than 18 cores in total (over several sets of biopsies) were at lower risk of understaging. With a repeat biopsy performed in the outpatient setting in the current study, our patients had a minimum of 20–24 cores sampled. Indeed, the repeat 12 core biopsy protocol presented here has several potential advantages over saturation biopsy. Saturation biopsy, especially with a greater than 20 core schema in a single procedure, can have high rates of bleeding (5%), sepsis (1%), and urinary retention (19%) in selected studies [20–23]. In addition, a general anesthetic is typically

required, especially if sampling of the prostatic apex or a perineal approach is utilized. Some institutions have reported performing 20 core biopsy schema in the clinic [24], but ultimately additional study is required to determine patient tolerability and other advantages of this approach. Regardless, any repeat biopsy protocol must include a thorough informed consent of attendant risks of post-procedural infection and urosepsis, especially in an era with rising rates of ciprofloxacin-resistant urinary and fecal colonization [25,26].

Limitations of our study include its single-institution, retrospective approach and an overall lower number of men with prostate cancer choosing AS. Additionally, this university-based practice may not be entirely generalizable to the entire prostate cancer population. The rebiopsy group does, however, reflect the majority (78%) of AS patients encountered at a tertiary referral institution over a 3-year period.

Overall, previously published data does indicate that men choosing AS with no evidence of cancer on surveillance biopsy are at lower risk of disease progression than those with a positive finding (11% vs. 40%) [15]. Our immediate rebiopsy protocol presented here may help in identifying men who may have been understaged with a single TRUS 12 core biopsy. These men with higher volume or grade prostate cancer may be selected at an earlier time point for curative intervention. Further confirmation of its benefits for AS candidates may ultimately require a prospective trial with long-term measures of efficacy and outcome.

4. Conclusions

In the absence of reliable radiographic imaging for microscopic disease or novel biologic markers that correlate with the malignant potential of low volume prostate cancer, TRUS prostate biopsy remains a useful but imperfect tool to evaluate tumor extent. The optimal timing of TRUS rebiopsy in AS patients remains unknown. By offering TRUS repeat biopsy immediately after initial diagnosis rather than in a delayed fashion, typically at 1 year, a subset of understaged men may be identified earlier. Within our cohort choosing AS, immediate rebiopsy highlights the limitations of a single 12 core template biopsy, verifying favorable-risk disease in a majority of men. It discriminates a significant subset of patients with Gleason upgrading or tumor volume increase who may be best served by considering early curative intervention.

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Table 1

Active surveillance cohort characteristics at diagnosis

No. AS patients	67/567 men
No. rebiopsied 6 months	52 men
Mean age	63.9 years (range 56–72)
Mean PSA	5.9 ng/ml (range 4.1–10)
Mean prostatic volume	47.6 cc (range 31–92)
Mean PSA density	0.12 ng/ml/cc
Gleason 6 disease	52
No. of positive cores	1.1
% Total pathologic tissue	3.2%

Table 2

Rebiopsy characteristics

No tumor	29/52 (56%)
Tumor present	23/52 (44%)
Volume or Gleason increase	17/23 [*]
-Increased Gleason grade	9/23
-Increased tumor volume	14/23
Exceeded criteria for AS on rebiopsy	9/52 (17%)
-Gleason grade 7	9/52
-Tumor volume increase, >2 cores	4/52

^{*} Six patients had an increase in grade and tumor volume.

Table 3

Rebiopsy characteristics compared to initial biopsy

	Initial biopsy	Repeat biopsy	<i>P</i> value
Positive cores (no.)	1.1 (1–2)	2.0 (1–4)	(<i>P</i> = 0.94)
Total tissue positive	3.2% (1–20)	6% (1–40)	(<i>P</i> = 0.26)
Unilateral lobe disease	47/52 (90%)	43/52 (83%)	(<i>P</i> = 0.19)
Bilateral lobe disease	5/52 (10%)	9/52 (17%)	(<i>P</i> = 0.42)

Table 4

Comparison of repeat biopsy and final RRP pathology

Repeat biopsy			Final prostate pathology*		
	Cores positive, Gleason score	% Cancer	Grade*	Cancer volume	Pathologic stage
Upgraded	2/12, 3+4	1%	3+4	0.5cc, 1%	pT2a
	2/12, 3+4	3%	3+3	2.9cc, 5%	pT2a
	4/12, 3+4	8%	3+4	11.7cc, 30%	pT2c
	3/12, 3+4	15%	3+4	2.2cc, 5%	pT2c
		Average (6.8%)		Average (4.3cc, 10.3%)	
Elective	1/12, 3+3	8%	3+3	0.4cc, 1%	pT2c
	2/12, 3+3	6%	3+4	2.5cc, 5%	pT2c
	1/12, 3+3	10%	3+3	0.9cc, 2%	PT2a
	1/12, 3+3	2%	3+4	1.1cc, 2%	pT2c
	1/12, 3+3	5%	3+3	0.8cc, 2%	pT2c
		Average (6.2%)		Average (1.1cc, 2.4%)	

* All margins negative at RRP; no significant difference in volume between upgraded and elective groups.