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Pathologic Upgrading and Upstaging with Immediate Repeat Biopsy for Patients Eligible for Active Surveillance

Ryan K Berglund, Timothy A Masterson, Kinjal C Vora, Scott E Eggener, James A Eastham, and Bertrand D Guillonéau

Division of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

Purpose—AS is a treatment regimen used in patients with low-risk prostate cancer. Decision making is based on pre-treatment PSA, clinical stage, and prostate biopsy results. We review our experience with immediate repeat biopsy in patients eligible for AS.

Materials and Methods—A retrospective review of consecutive patients undergoing repeat biopsy within 3 months of a first positive biopsy from March 2002 until June 2007 was analyzed. Patients were considered eligible if they had a PSA < 10 ng/ml, clinical stage ≤ T2a, Gleason pattern ≤ 3, 3 or less cores positive, and no single core with ≥ 50% cancer involvement.

Results—A total of 104 patients met the eligibility criteria. Of the repeat biopsies performed, 27/104 (26%) were negative, 59/104 (57%) had Gleason score ≤ 6, 17/104 (16%) had Gleason score 7, one patient had Gleason score 9, 10/104 (10%) of patients had > 3 cores involved on repeat biopsy, and 12/104 (12%) had ≥ 50% involvement of at least one core. A total of 28/104 (27%) patients were upgraded and/or upstaged. Treated patients who were upgraded and/or upstaged were more likely to have higher pathologic stage ($p = 0.003$) and grade ($p = 0.001$) at RP than those who were not.

Conclusions—Immediate repeat biopsy for patients on AS resulted in 27% being upgraded or upstaged, and those were more likely to have higher grade and stage disease at RP. We recommend repeat biopsy as it improved our discrimination as to whom are the best candidates for AS.

Keywords

prostate cancer; surveillance; prostate biopsy

Introduction

Prostate cancer is the second leading cause of cancer deaths among men, with an estimated 27,050 deaths in 2007, yet most men who develop prostate cancer will not die from it. It is also the most common non-skin cancer in men, and the incidence-to-mortality ratio in 2007 is estimated to be approximately 8-to-1.¹ Given the known negative impact of treatment on health related quality of life, an approach is sought that reduces the number of patients treated to those in whom the disease will lead to an adverse outcome or death.^{2, 3}

Active surveillance (AS) is one approach that would seek to reduce the number of patients with indolent disease that are treated. In this approach, patients with characteristics of

indolent disease (low serum PSA value or density, localized disease on DRE, and biopsy pathology showing a small area of well-differentiated disease) are placed on an observation protocol. Frequent repeat evaluation with serum PSA level, DRE, and repeat biopsy are performed, and a recommendation of intervention is made with signs of progression. Eventually, many of the patients are treated, but this delays treatment and its negative impact on quality of life without impairing their chance for cure.^{4–6}

At a referral institution such as ours, many patients under consideration for AS present with an outside biopsy specimen suggestive of indolent disease. To confirm this situation, we recommend immediate repeat biopsy. In this study, we evaluate the diagnostic value of performing an immediate repeat biopsy in patients referred to our institution who are considering AS as a management option.

Materials and Methods

We identified all patients undergoing repeat biopsy at our institution from March 2002 to June 2007 with Institutional Review Board approval. All data were retrospectively analyzed from a central database. Inclusion criteria included an AJCC (1992) clinical stage $\leq$ T2a, PSA < 10 ng/ml, and low risk features on initial prostate biopsy. All patients included in this study had their initial biopsies performed at a referring institution, and all patients advised to enroll in AS were advised to undergo repeat biopsy at our institution. All outside specimens were reviewed with our central pathologists and patients were considered eligible for AS if they had three or less cores involved, no single core with $\geq 50\%$ maximum involvement of cancer, and no Gleason grade > 3 present in the specimen. An immediate repeat biopsy was performed at our institution within three months of the initial biopsy, with all patients undergoing an eMRI confirming no definitive radiologic evidence of extracapsular extension or extensive tumor involvement. A repeat biopsy was performed as a standard 12 core biopsy of the medial and lateral aspects of the base, middle, and apical portions of the prostate bilaterally. Two additional biopsies of the transition zone were performed, for a total of 14 cores. Additional cores were taken for any suspicious areas found on DRE, TRUS, or eMRI. Patients were considered upgraded if they had any elements of Gleason pattern 4 or 5 on repeat biopsy. Patients with greater than 3 cores positive or any single core with $\geq 50\%$ cancer were considered upstaged by biopsy.

Clinical and pathological features were compared including pathologic upstaging and upgrading, pathology at surgery, and recurrence (biochemical and metastatic). Patients were advised of the result of their repeat biopsy and all therapeutic options were discussed at that time. Statistical comparison of patients was performed using Fisher's exact test. Statistical analyses were conducted using Stata 9.2 (Stata Corp., College Station, TX).

Results

Between March 2002 and June 2007, 250 patients presented to our institution with a prostate biopsy from a referring institution and subsequently underwent a repeat biopsy at our institution. A total of 104 patients met our eligibility criteria. The median age of our patients at the time of initial biopsy was 62 (range 42 to 80), and the median PSA at the time of biopsy was 4.7 ng/ml (range 0.8 to 9.9). Prior to biopsy, most patients had multiple prior outside PSA values available (median 3, range 0 to 11). Prior negative biopsies were performed in 18 patients, with 15 having one prior negative biopsy, one patient had two, and two patients had three negative prior biopsies. Overall, 1% of patients had clinical stage T1b (1/104), 81% T1c (84/104), and 18% T2a (19/104).

The extent of initial outside biopsies varied, with a median of 10 cores sampled (range 2 to 27). With the repeat 14 core biopsies performed, 27/104 (26%) were negative. On 77 repeat biopsies that were positive for cancer, 59/77 (76.6%) had a Gleason score ≤ 6 , 17/77 (22%) had Gleason score 7, and one patient had a Gleason score 9 (1.3%). Among those with positive repeat biopsies, 10/77 (13%) of patients had > 3 cores and 12/77 (16%) had maximum involvement of at least one core of $\geq 50\%$. A total of 28/104 (27%) patients were upstaged or upgraded on repeat biopsy. A comparison of biopsy results on initial biopsy to repeat biopsy are listed in Table 1. Of note, 32% (9/28) of patients that were upstaged and/or upgraded had 2 – 3 positive cores on initial biopsy, while only 4% (1/27) of the negatives and 10% (5/49) of the positives with no upstaging and/or upgrading did. Overall, 92% (70/76) of all patients who were not upstaged and/or graded had only 1 core positive on initial biopsy, with 8% (6/76) having 2 cores positive. Of those patients who were upstaged and/or upgraded, 68% (19/28) had only 1 core positive on initial biopsy, while 18% (5/28) had 2 cores positive and 14% (4/28) had 3 cores positive. Every patient with 3 cores positive on initial biopsy were upstaged and/or upgraded.

Among patients who were not upstaged and/or upgraded, 86% (65/76) were clinical stage T1b or T1c, while 14% (11/76) were stage T2a. In the patients who were upstaged and/or upgraded, 71% (20/28) were stage T1c, while 29% (8/28) were stage T2a ($p = 0.2$).

eMRI was performed at our institution in 66/104 patients (63.5%). No patients were considered for AS who had definitive findings of ECE, seminal vesicle invasion, lymph node involvement, or other findings of advanced disease. In all, 48/66 (72.7%) of patients had findings consistent with organ confined disease, while 18/66 (27.2%) had findings suspicious for ECE. Among patients with findings of organ confined disease, none were upstaged or upgraded, while 7/18 (38.9%) of those with findings suspicious for ECE were upstaged or upgraded.

After a discussion of the results of the repeat biopsy with the patients, 21/28 (75%) of upstaged and/or upgraded patients went on to have surgery at a median 4.2 months (range 0.8 to 8.9 months), while 38/76 (50%) of the others went on to surgery at a median 3 months (range 1 to 16.4 months). Pathologic outcomes of surgery are listed in Table 2. Of those treated with surgery, more patients in the upstaged and/or upgraded group had a pathologic stage $\geq T3a$ (48% versus 11%, $p = 0.003$), and more in that group had Gleason score ≥ 7 (91% versus 42%, $p = 0.001$). All but one patient underwent bilateral pelvic lymph node dissection at the time of surgery, and all patients were pathologic N0. In the group of patients with no cancer on repeat biopsy, 8/28 (28.6%) went on to RP. All 8 patients had pathologic organ confined disease ($\leq pT2b$), and 3/8 (37.5%) had Gleason score 6, while 5/8 (62.5%) had Gleason score 7.

At a median follow up 13 months, one patient who underwent surgery in the non-upstaged/upgraded group developed distant metastatic disease 46 months after surgery, confirmed by bone scan. This patient was initially diagnosed with Gleason 6 (3 + 3) disease in 1/14 cores which was not upstaged and/or upgraded at repeat biopsy. His final pathology came back as Gleason 6 (3 + 3), pT2bN0 with negative margins.

Additionally, 10 patients went on to have primary radiation therapy; 4 with brachytherapy and 6 with external beam radiation. Of these, 2 were from the upstaged and upgraded group (2/28, 7.1%), and 8 were not (8/76, 10.5%). Eight patients show no evidence of disease with a median follow-up of 30 months (range 11 to 39 months), while 2 patients had a biochemical recurrence with an increasing PSA first noted at 31 and 34 months. One biochemical recurrence occurred in a patient upstaged with 4/14 cores positive on repeat biopsy who underwent brachytherapy and had a recurrence at 31 months. The other occurred

in a patient who was not upstaged or upgraded who underwent external beam radiation therapy and had a biochemical recurrence at 34 months. Neither patient had started second line therapy at last follow-up.

A total of 34 patients have remained on AS for a median 36 months. There have been no other biochemical failures in treated patients or metastatic failures in untreated patients.

Discussion

AS is an approach to low risk prostate cancer which can help avoid treatment with RP or radiation in some patients with indolent prostate cancer while delaying intervention in others. Although most patients diagnosed with prostate cancer will not ultimately die of their disease, treating patients for prostate cancer improves overall and cancer-specific survival compared to watchful waiting, as well as reducing the risk of developing metastatic disease.⁷ In fact, if a patient has a life expectancy of greater than 15 years, untreated prostate cancer eventually leads to an increasing risk of overall mortality.^{8–11}

Enrollment in an AS program is dependent on developing a method for selecting patients with a high likelihood of having an indolent cancer. One proposed method includes variations on the Epstein criteria, which use a cutoff value for PSA density of 0.1 ng/ml per gram of tissue, < 3 cores positive, and no core > 50% involved.^{4–6, 12} Using these criteria to select for insignificant disease has a positive predictive value of 95% and a negative predictive value of 66%. Another method uses a validated nomogram to predict indolent cancer defined as pathologically organ confined cancer 0.5 cc or less in volume and without poorly differentiated elements, which has good discrimination as a screening tool with area under the receiver operating characteristics curves of 0.64 to 0.79.^{13, 14}

In our study, we use a modified Epstein criteria of serum PSA < 10 ng/ml, positive biopsy cores ≤ 3, and maximum involvement of any single core ≤ 50%. The number of positive cores used in our study represents a percentage of positive cores of ≤ 21% on a 14 core biopsy, and the lower the percentage of cores involved, the lower the risk of ECE at RP and the lower the risk of disease recurrence after RP, which has been demonstrated in other series.^{15–17} In our series, only 4 patients had 3 positive cores, and all four of these patients were upstaged or upgraded at repeat biopsy. Patients with 3 positive cores are, not surprisingly, more likely to be upstaged or upgraded, and careful consideration should be used in including them in an AS protocol. eMRI added valuable information in that patients with findings of extracapsular or locally advanced disease were not offered AS. No patients with organ confined disease on eMRI were upstaged or upgraded, while 38.9% of those with suspicion of ECE were upstaged or upgraded.

We demonstrated that 26% of our patients had a negative repeat biopsy, which has previously been associated with a low likelihood of progression at 10 years.⁶ Not surprisingly, 96% of patients with a negative repeat biopsy had only one positive core on initial biopsy, while 32% with upstaging/upgrading on repeat biopsy had 2 – 3 cores positive on initial biopsy. The maximum percentage of cancer on a single core was evenly distributed among groups. We observed that 27% of patients were upstaged and/or upgraded on biopsy, and given the natural history of prostate cancer, this upstaging and/or upgrading was likely the result of sampling error from the initial biopsy and not from tumor growth.¹⁸ This compares to the series from Toronto in which patients enrolled in an AS program were rebiopsied at a mean 22 months (range 7 – 81 months). In that series of patients with Gleason score ≤ 7, 31% were unchanged, 35% were upgraded, and 32% were downgraded, where upgraded disease was Gleason score of ≥ 8.¹⁹ The Miami AS series enrolling low-risk patients with PSA ≤ 15, clinical stage ≤ T2, and Gleason score ≤ 6, found only 34% of

enrolled patients had cancer on repeat biopsy, with none of the patients have Gleason score ≥ 7 disease.²⁰

Interestingly, most patients in our series (69/104, 66.3%) went on to have definitive therapy, with 59/104 (56.7%) undergoing RP and 10/104 (9.6%) undergoing radiation therapy. This is in contrast to the Toronto series, where through 8 years of follow up, 65% of patients remain free from treatment.⁴ The high rate of treatment in our group by comparison likely represents differences between institutions in the preferences of patients referred to our institution as well as the recommendations of our treating physicians. Results from the ongoing START trial which began enrolling patients in 2006 should help to clarify which patients are best suited to AS versus definitive therapy. Its goal is to enroll 2,100 patients who will be randomized to AS versus their choice of definitive therapy. Until then, AS recommendations to low-risk patients among referral centers remain heterogeneous.

The majority of patients in both of our groups underwent RP, and the pathologic results show that the patients with upstaging/upgrading had less organ confined disease (53% versus 89%) and Gleason score ≤ 6 disease (10% versus 58%) than the patients whose biopsies showed no upstaging/upgrading. All patients were lymph node negative at RP, though, and the only metastatic recurrence in our limited follow up in this series occurred in a patient who was not upstaged or upgraded.

The limitations of this study include its retrospective nature and the limited follow up available on patients treated with surgery (median 13 months). The immediate repeat biopsy redistributed over half of our AS patients into different risk groups, with 26% entering the very low risk group of having a negative repeat biopsy, while 27% were upstaged and/or upgraded. These latter patients, as we expected, also had statistically significant higher stage and grade disease at RP than patients who were not, so the additional information from the immediate repeat biopsy prompted us to recommend earlier intervention for their disease. Longer-term follow up in a prospective setting is necessary to determine whether immediate repeat biopsy improves outcomes.

Conclusions

Immediate repeat biopsy in patients with prostate cancer being considered for AS resulted in more than one quarter being upgraded or upstaged, and those upgraded or upstaged were more likely to have higher grade and stage disease at RP than those who were not. Repeat biopsy improved our discrimination of candidates for AS, and we recommend immediate repeat biopsy in all patients being considered for AS. Eventually, the majority of patients in this low-risk group elected radical prostatectomy or radiation therapy.

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Abbreviations and Acronyms

AJCC	American Joint Committee on Cancer
AS	active surveillance with selective delayed intervention
DRE	digital rectal exam
ECE	extracapsular extension
eMRI	endorectal coil pelvic magnetic resonance imaging

PSA	prostate specific antigen
RP	radical prostatectomy
START	Surveillance Treatment Against Restricted Treatment
TRUS	transrectal ultrasound

Table 1

Pathologic results of repeat biopsy

Original Biopsy Result		Repeat Biopsy Result	
# cores positive	Negative (27)	Positive, No Upstaging/Upgrading (49)	Positive with Upstaging/Upgrading (28)
1 (n = 89)	26/27 (96%)	44/49 (90%)	19/28 (68%)
2 (n=11)	1/27 (4%)	5/49 (10%)	5/28 (18%)
3 (n=4)	0/27 (0%)	0/49 (0%)	4/28 (14%)
Max % Positive Core			
< 5% (n=52)	18/27 (67%)	20/49 (41%)	14/28 (50%)
5–20% (n=40)	7/27 (26%)	24/49 (49%)	9/28 (32%)
20–50% (n=12)	2/27 (7%)	5/49 (10%)	5/28 (8%)

Table 2

Pathologic results at surgery

Pathologic Stage [*]	No upstaging/upgrading (38)	Upstaged/Upgraded (20)
pT2a	15/38 (39%)	0/21 (0%)
pT2b	17/38 (45%)	9/21 (43%)
pT2c	2/38 (5%)	2/21 (10%)
pT3a	4/38 (11%)	9/21 (43%)
pT4	0/38 (0%)	1/21 (5%)
pN0	38/38 (100%)	21/21 (100%)
pN1	0/38 (0%)	0/21 (0%)
Pathologic Grade ^{**}		
Gleason score ≤ 6	22/38 (58%)	2/21 (10%)
Gleason score 7 (3 + 4)	14/38 (37%)	17/21 (81%)
Gleason score 7 (4 + 3)	2/38 (5%)	1/21 (5%)
Gleason score 8	0/38 (0%)	1/21 (5%)

* presence of ≥ p T3a in non-upstaged/upgraded vs those upstaged/upgraded (11% vs. 48%, p=0.003)

** presence of Gleason score ≥ 7 in non-upstaged/upgraded vs those upstaged/upgraded (42% vs. 91%, p=0.001)