Histologic upgrading in patients eligible for active surveillance on saturation biopsy

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Introduction: *We evaluated the risk of histologic upgrading and upstaging in patients who met strict active surveillance (AS) criteria on saturation biopsy and elected to undergo radical prostatectomy.*

Materials and methods: *A retrospective review was conducted of 362 consecutive, individual patients who underwent transrectal ultrasound guided saturation biopsy (32 cores) between 2006 and 2013. Thirty-one patients (9%) were eligible for AS based on Hopkins criteria for very low risk (VLR): stage T1c, prostate-specific antigen (PSA) density ≤ 0.15 ng/mL2, Gleason ≤ 6, ≤ 2 cores and ≤ 50% core. Twenty patients (64%) elected radical prostatectomy, 2 (7%) elected radiation treatment and 9 (29%) elected AS (n = 9, 29%). Radical prostatectomy results were used to evaluate for upgrading and upstaging.*

Results: *Patient and saturation biopsy characteristics were similar amongst radical prostatectomy, radiation and AS patients. Mean age was 63 years (range 50-75) and 27 patients (87%) had a prior negative biopsy. Median time to prostatectomy was 3 months (range 1-46). Upgrading (Gleason ≥ 7) was identified in 40% (n = 8) of patients: Gleason 3+4 (n = 7) and Gleason 4+3 (n = 1). Upstaging (≥ T3) was not identified. Mean follow up was 47 months (range 11-99) for all patients. No patient developed biochemical recurrence or required salvage treatment.*

Conclusions: *Despite increased prostate sampling, patients who met strict AS criteria on saturation biopsy were at high risk for Gleason upgrading, but fortunately at low risk for upstaging and biochemical recurrence. Patients contemplating AS based on saturation biopsy results should be counseled appropriately. MRI-TRUS fusion biopsy may be an alternative to saturation biopsy until proven otherwise.*

Key Words: active surveillance, image-guided biopsy, prostate cancer, watchful waiting, grade, stage

Introduction

The use of active surveillance (AS) is increasing in patients with low grade, stage and volume disease. AS relies on the presumption that the lead-time for low risk disease is long. This allows patients who develop signs of higher-risk disease to be treated with an opportunity for cure.[1,2] Approximately 81%-91% and 59%-75% of patients remain on AS after 2 and 5 years, respectively.[3,4] In one study, AS patients elected treatment due to Gleason upgrading (35%), higher volume of disease (≥ 3 positive cores or > 50% core involvement; 16%), change in patient preference (14%) and increased Prostate-specific antigen (PSA) without worsened biopsy features.[4] In an effort to better select patients for AS, an immediate confirmatory biopsy was recommended. Confirmatory standard biopsy identified underlying, high risk and AS ineligible cancer in 17%-32% of patients who were previously undersampled.[5,6] Increased sampling with saturation biopsy has also been proposed to improve cancer detection and patient selection for AS protocols.[7]

At our institution, we utilized saturation biopsy to 1) improve cancer detection in men with elevated PSAs and prior negative biopsies and 2) confirm cancer staging in men who met AS criteria on standard biopsy. Patients who meet AS criteria and elect AS may not know the true extent of their disease for many years. One method to assess the accuracy of saturation biopsy to adequately grade and stage prostate cancer is to correlate saturation biopsy results with prostatectomy specimens of patients who underwent both procedures. In this study, we evaluated the ability of saturation biopsy (using the highest number of cores reported) to accurately grade and stage patients who met Hopkins very low risk (VLR) AS criteria.

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Materials and methods

With Institution Review Board approval, a retrospective review was conducted of patients who underwent saturation biopsy at our institution between 2006 and 2013. This follows the modification of the Gleason score system conducted by the International Society of Urological Pathology in 2005.[8] Saturation biopsy was performed for patients to 1) improve cancer detection in men with elevated PSAs and prior negative biopsies and 2) confirm cancer staging in men who met AS criteria on standard biopsy. Transrectal ultrasound (TRUS) guided saturation biopsy was performed under conscious sedation as a day surgery procedure. Patients were treated with antibiotics according to the American Urologic Association (AUA) best practice policy.[9] Thirty-two cores were collected per patient using an end-fire probe. The biopsy template included four cores from eight sections of the peripheral zone (right and left base, middle 1, middle 2 and apex). The anterior and transitional zones were not targeted with this template.

Patients who met Hopkins criteria of VLR (stage T1c, PSA density ≤ 0.15 ng/mL^2, Gleason ≤ 6, ≤ 2 cores and ≤ 50% core) and had a minimum follow up of 10 months were included in the final analysis. Patients were counseled on all treatment options based on biopsy results. For the purpose of this study, patients were grouped by treatment status (radical prostatectomy, radiation or AS). Patient characteristics were compared between the three groups to decrease selection bias.

Patients who elected radical prostatectomy underwent laparoscopic or robotic-assisted laparoscopic prostatectomy. Pelvic lymph node dissection was performed at the discretion of the operating surgeon. Genitourinary pathologists conducted review of all biopsy and prostatectomy specimens at the time of management. Clinical, pathological and oncologic parameters were reviewed and compared between the three groups. Upgrading was defined as Gleason ≥ 7. Upstaging was defined as ≥ pT3. Biochemical recurrence was defined as a PSA ≥ 0.2 ng/mL at two separate time points for prostatectomy patients or a 2 ng/mL rise from nadir for patients treated with radiation.[10,11]

Statistical analyses were conducted using SPSS (IBM, Armonk, NY, USA). One-way ANOVA test was used to compare means. Pearson's chi-square test was used to compare categorical variables. All tests were 2-tailed and statistical significance was defined as p ≤ 0.05.

TABLE 1. **Patient and saturation biopsy parameters**

	Prostatectomy		Radiation		Active surveillance		p value
	#	%/range	#	%/range	#	%/range	
Patient characteristics							
Patients	20	64%	2	7%	9	29%	-
Mean age, years	63	(53-72)	60	(50-70)	63	(54-75)	0.84
Family history of prostate cancer	7	35%	0	0%	1	11%	0.27
African-American male	1	5%	0	0%	2	22%	0.31
Biopsy status							
Prior negative biopsy	19	95%	2	100%	6	67%	0.93
Prior positive biopsy on active surveillance	1	5%	0	0%	3	33%	
Clinical stage T1c	20	100%	2	100%	9	100%	-
Mean PSA, ng/mL	5.7	(2.0-15.2)	6.1	(5.0-7.2)	4.4	(1.9-6.1)	0.35
Mean PSA density	0.10	(0.05-0.14)	0.11	(0.10-0.13)	0.10	(0.06-0.15)	0.71
Saturation biopsy							
Mean cores	32	(32-32)	32	(32-32)	32	(32-32)	-
Mean cores with cancer	1.5	(1-2)	1.5	(1-2)	1.2	(1-2)	0.51
Mean highest % core with cancer	6%	(1-30)	10%	(5-15)	4%	(1-8)	0.46
Gleason 6	20	100%	2	100%	9	100%	-

TABLE 2. **Prostatectomy and follow up outcomes**

	Prostatectomy		Radiation		Active surveillance		p value
	#	%/range	#	%/range	#	%/range	
Prostatectomy			-	-	-	-	-
Median time to surgery, months	3.0	(1-46)	-	-	-	-	-
Gleason upgrading ≥ 7	8	40%	-	-	-	-	-
Gleason 3+4	7	35%	-	-	-	-	-
Gleason 4+3	1	5%	-	-	-	-	-
Stage ≥ T3	0	0%	-	-	-	-	-
Pelvic node dissection	8	40%	-	-	-	-	-
Node positive	0	0%	-	-	-	-	-
Metastasis positive	0	0%	-	-	-	-	-
Follow up							
Mean follow up, months	45	(11-99)	72	(71-73)	40	(12-92)	0.43
Biochemical recurrence	0	0%	0	0%	0	0%	-
Salvage treatment	0	0%	0	0%	0	0%	-
Androgen deprivation therapy	0	0%	0	0%	0	0%	-

Results

Prostate cancer was detected in 155 of 362 patients (43%) who underwent saturation biopsy. The final patient cohort included 31 patients who met VLR criteria on saturation biopsy and met study inclusion criteria, Table 1. Patients were divided into those who elected radical prostatectomy (n = 20, 64%), radiation (n = 2, 7%) and AS (n = 9, 29%). Age (p = 0.84), family history of prostate cancer (p = 0.27), African-American race (p = 0.31) and prior biopsy status (p = 0.93) were similar amongst the three groups. Mean age was 63 years (range 50-75) for all patients. Twenty-seven patients (87%) underwent saturation biopsy for elevated PSAs and prior negative biopsies. Four patients (13%) underwent saturation biopsy to confirm cancer staging in men who met AS criteria on standard biopsy. Positive core locations were evenly distributed between the apex, middle1, middle2 and base.

Median time to radical prostatectomy was 3 months (range 1-46), Table 2. Pelvic lymph node dissection was performed in 8 patients, all of whom had no nodal involvement on final pathology. Upgrading (Gleason ≥ 7) was identified in 40% (n = 8) of patients: Gleason 3+4 (n = 7) and Gleason 4+3 (n = 1). Upstaging (≥ T3) was not identified. One patient, initially on AS for 46 months, elected to undergo radical prostatectomy (final pathology was Gleason 3+4) due to personal preferences. Mean follow up was 47 months (range 11-99) for all patients. No patient developed biochemical recurrence or required salvage treatment.

Discussion

The goal of AS is to reduce the overtreatment of low risk disease and avoid adverse outcomes from primary therapy. Identifying patients best suited for AS remains a challenge due to undersampling with current biopsy techniques. Missing intermediate risk disease is not benign and may compromise outcomes. Abern et al identified that delays in radical prostatectomy for intermediate risk men, but not low risk men, were associated with biochemical recurrences and positive surgical margins.[12] At our institution, saturation biopsy was performed to help identify potentially missed Gleason ≥ 7 disease. Forty percent of patients who met VLR criteria on saturation biopsy were found to have clinically significant upgrading (Gleason ≥ 7) after prostatectomy. Fortunately, no patient was identified with non-organ confined disease. The median time to prostatectomy was 3 months, which is too short to account for disease progression and suggests that saturation biopsy is inadequate in identifying all Gleason ≥ 7 disease. It is disappointing that the true extent of disease was missed despite the use of 32 cores.

Linder et al reinforced our finding that increased sampling with saturation biopsy does not protect AS patients from upgrading. Standard 12-core and

saturation biopsy (median 27 cores) were performed in 218 patients eligible for AS based on University of California San Francisco criteria (stage T1 or T2a, PSA < 10, Gleason ≤ 6, ≤ 33% core).[13] Upgrading (Gleason ≥ 7) was similar between patients who underwent 12-core (14%) and saturation biopsy (15%). Upstaging (≥ pT3) was also similar between patients who underwent 12-core (1.6%) and saturation biopsy (0%). The higher rate of upgrading in our cohort (40% versus 15%) is not unexpected. Our cohort is a higher-risk cohort with a larger percentage of patients with prior negative (87% versus 45%) or positive biopsies (13% versus 0%). Furthermore, our 32-core template targeted the peripheral zone alone and did not specifically sample the transitional zone or anterior prostate.

A large Hopkins cohort of VLR patients underwent 12 or 14-core biopsy and radical prostatectomy.[3] Thirteen percent of VLR patients were upgraded (Gleason ≥ 7) and 9% had non-organ confined disease after radical prostatectomy. Although the Hopkins study had low rates of upgrading, this is not the case for all studies. A European study evaluated 626 patients meeting PRIAS criteria (Gleason < 7, PSA ≤ 10 ng/mL, density < 0.2 ng/mL, ≤ 2 positive cores, clinical stage T1c-T2) who underwent TRUS biopsy with a median of 15 cores (range 9-21).[14] Upgrading (Gleason ≥ 7) occurred in 44.9% of patients and upstaging (≥ T3) in 20.6%, which is closer to the results of our study. AS cohorts, whether based on PRIAS or Hopkins criteria, are indeed separate entities. Variations exist in the ability for AS protocols to predict pathologically insignificant cancer at radical prostatectomy.[15] These differences in protocols should be considered when evaluating patients for AS and comparing AS studies.

Use of saturation biopsy at our institution has decreased significantly due to the procurement of a MRI-TRUS fusion biopsy platform. We believe the role of saturation biopsy is limited due to the potential for undersampling and should not be used to confirm or follow AS patients. Although we have embraced MRI-TRUS fusion technology, the vast majority of urologists do not have access to this platform or prostate MRI. Rather than relying on saturation biopsy, urologists without MRI-TRUS fusion technology should consider referring challenging patients to tertiary care centers. If saturation biopsy is to be performed, it should include transitional and anterior zone biopsies and patients should be counseled for increased risk for infection and complications that may occur with increased sampling. Patients must also be counseled on the risk for undersampling that still exists despite the increased number of cores as exhibited in this study. Percent involvement of Gleason 4 should be considered in patients with Gleason 3+4 disease. Long term cancer progression for patients with a small percent of high grade disease may not be significantly different in patients who undergo AS versus surgery. Prostatectomy specimens from 6 of 7 patients with Gleason 3+4 disease from this study were reviewed. The relative mean contribution of Gleason 4 disease per patient was 8.8% (range 5%-20%).

This retrospective study with a small sample size has several limitations that warrant discussion. The majority of patients had an elevated PSA in the setting of prior negative biopsies and therefore do not represent the more general population that has VLR on initial biopsy. Pathological correlation of location of cancer on biopsy and prostatectomy specimen was not conducted, and could have provided further insight into areas of undersampling in our cohort.

AS criteria were designed for standard 12-core biopsy and may not directly apply to saturation biopsy. Despite these limitations, this study provided review of biopsy from one institution and evaluated a patient population eligible based on the highest number of biopsy cores reported.

Conclusions

Despite increased prostate sampling, patients who met strict AS criteria on saturation biopsy were at high risk for Gleason upgrading, but fortunately at low risk for upstaging and biochemical recurrence. Patients contemplating AS based on saturation biopsy results should be counseled appropriately. Due to the high risk for undersampling with saturation biopsy, MRI-TRUS fusion biopsy may be an alternative to saturation biopsy until proven otherwise. □

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