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Original Article: Clinical Investigation

Standard and saturation transrectal prostate biopsy techniques are equally accurate among prostate cancer active surveillance candidates

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Abbreviations & Acronyms
BCF = biochemical failure
BFS = biochemical-free survival
IQR = interquartile range
PSA = prostate-specific antigen
RP = radical prostatectomy

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Objectives: To examine the ability of standard and saturation transrectal prostate biopsy techniques to predict appropriate candidates for active surveillance.

Methods: Between 2005 and 2007, 500 consecutive patients underwent transrectal ultrasound-guided biopsy by a standard template (12 cores) or saturation template (≥18 cores, median 27 cores), with subsequent radical prostatectomy. Using the criteria of Gleason score ≤6, clinical stage T1 or T2a, prostate-specific antigen <10 and ≤33% of cores involved, 218 patients were potential candidates for active surveillance. Pathology results from the prostatectomy specimens were used to determine the accuracy of each biopsy technique. Biochemical failure after prostatectomy was evaluated using logistic and Cox proportional hazards regression.

Results: A standard biopsy was carried out for 124 patients and saturation biopsy for 94 patients. There was no statistically significant difference between the groups in terms of median age ($P = 0.14$), preoperative prostate-specific antigen ($P = 0.52$) and clinical stage ($P = 0.23$). Similar rates of Gleason score ≥7 at the time of radical prostatectomy were found, with 14% for standard biopsy and 15% for saturation biopsy ($P = 0.70$). Upstaging was shown in two standard biopsy patients (1.6%) and no saturation biopsy patients ($P = 0.62$). A multivariate analysis adjusting for prior prostate biopsy, preoperative prostate-specific antigen and clinical stage showed no difference in the rate of upgrading based on biopsy technique ($P = 0.26$). During follow up, 5-year biochemical failure-free survival estimates were not significantly different ($P = 0.11$).

Conclusions: In men with prostate cancer, standard and saturation transrectal prostate biopsies techniques are equally predictive of candidates for active surveillance.

Key words: active surveillance, prostate biopsy, prostate cancer, saturation biopsy.

Introduction

The use of PSA screening has substantially increased the proportion of patients diagnosed with low-grade, organ-confined prostate cancer.[1] In light of these indolent tumors, active surveillance has been increasingly utilized as a treatment approach for these men. Several protocols outlining selection criteria for active surveillance candidates have been proposed. In addition to Gleason score 6, PSA <10 and clinical stage T1c or T2a, more specific criteria regarding the number of positive biopsy cores, percentage of core involvement or length of tumor seen on biopsy are included in most models.[2–5] While we await clinically applicable and accurate molecular biomarkers, we are dependent on these protocols to help stratify indolent tumors from more aggressive, life-threatening cancers. Because of concern of underdiagnosis on the initial biopsy, some authors recommend immediate rebiopsy in the form of standard or saturation templates for active surveillance patients.[6] We evaluated the differences in diagnostic accuracy between our departmental standard 12-core biopsy and an extended saturation biopsy in patients who underwent RP, but would have been candidates for active surveillance.

Table 1 Clinical parameters for those diagnosed with standard (12 core) and saturation (≥18 cores) biopsy techniques

	Standard biopsy (n = 124)	Saturation biopsy (n = 94)	P-value
Median age (years)	61.4	60.6	0.14
Median preoperative PSA	4.7	4.5	0.52
PSA density	0.1	0.1	0.67
Clinical stage			0.23
T1c	92 (75.4%)	74 (82.2%)	
T2a	30 (24.6%)	16 (17.4%)	
Previous negative biopsy†	20 (16.1%)	42 (44.7%)	<0.0001
Median no. cores	12	27	<0.0001

†Patients with a prior negative biopsy were less likely to be upgraded, 4/62 (6.6%) versus 27/156 (17.3%), P = 0.042.

Methods

After Institutional Review Board approval, we evaluated 500 consecutive patients, between 2005 and 2007, that underwent both transrectal ultrasound-guided prostate biopsy and subsequent radical prostatectomy at the Mayo Clinic in Rochester, Minnesota, USA, to determine the predictive accuracy of biopsy techniques in candidates for active surveillance. Using previously determined active surveillance criteria by Dall'Era *et al*.[3] of a Gleason score ≤6 with no pattern 4 or 5, clinical stage T1 or T2a, PSA <10 and involvement of ≤33% of biopsy cores, 218 patients were identified as active surveillance candidates.

The prostate biopsy technique (probe type [B&K 8808 side-fire or B&K 8805 end-fire probe; B&K Medical Headquarters, Herlev, Denmark]) and number of cores were determined by the treating physician after history and physical exam. Patients were divided into two groups based on biopsy technique before radical prostatectomy: (i) our departmental standard 12-core biopsy (probe type [B&K 8808 side-fire; B&K Medical Headquarters]); or (ii) saturation ≥18 core saturation biopsy (probe type [B&K 8805 end-fire probe; B&K Medical Headquarters]). Saturation biopsies were carried out in an outpatient operating center with conscious sedation, and consisted of biopsies targeting the lateral and mid peripheral zones, the transitional zone and the anterior-apical horn of the prostate, to ensure thorough sampling. The number of cores taken was adjusted by individual practitioners according to gland size and ultrasonographic abnormalities. Our departmental standard 12-core biopsy follows a similar template; however, fewer cores are obtained and the transitional zone is not typically sampled. Biopsies were carried out by 17 senior residents and 11 attending physicians over the timeframe of the study. The accuracy of each biopsy technique was compared with final pathology of the prostatectomy specimen.

Preoperative PSA, PSA density, clinical and pathological Gleason score, clinical and pathological stage, lymph node status, surgical margins, and estimated tumor volume were prospectively collected in our prostatectomy database. PSA density was calculated using the preoperative PSA and prostate volume as estimated from the surgical specimen. Pathological staging of specimens was based on the 2002 tumor–nodes–metastasis staging system. Biopsy characteristics were obtained with retrospective review.

The institutional routine partial sampling protocol for preparing and reporting serially-sectioned whole mount prostates has been previously reported.[7] All sections were separately examined by routine formalin-fixed paraffin-embedded sections the next day.

Postoperative assessments, including physical examinations and serum PSA measurement, were carried out quarterly for the initial 2 years, semi-annually for an additional 2 years, and annually thereafter. For patients followed elsewhere, the prostatectomy registry at our institution monitors outcomes annually by correspondence. BCF was defined as PSA 0.4 ng/mL or greater.[8]

A Pearson's χ^2-test was used to test differences in categorical variables. A Wilcoxon rank test was used for continuous and ordinal variables. Event-free survival rates were estimated utilizing the Kaplan–Meier method, and compared with the log–rank test. All tests were two sided, with a P-value ≤0.05 considered significant. Statistical analyses were carried out using SAS version 9.1.3 statistical software (SAS Institute, Cary, NC, USA).

Results

From the 500 consecutive patients that underwent prostate biopsy, we identified 218 candidates for active surveillance, 124 patients that underwent a standard biopsy with 12 cores, while 94 had a saturation biopsy with ≥18 cores. The median number of cores in the saturation biopsy group was 27. Clinical parameters for each cohort can be seen in Table 1. Patients undergoing a saturation biopsy technique were more likely to have previously undergone a negative prostate biopsy (P < 0.0001). In terms of complications, there were rare cases of transient urinary retention in both

Table 2 Discordance rates of pathological variables after RP by prostate biopsy type

	Standard biopsy ($n = 124$)	Saturation biopsy ($n = 94$)	*P*-value
Upgrading, Gleason ≥7	17 (13.8%)	14 (14.9%)	0.71
pT3	2 (1.6%)	0 (0%)	0.62
Positive surgical margins	8 (7%)	6 (6%)	0.95
Nodal invasion	0	0	1
Estimated tumor volume, cc (IQR)	0.3 (0.1, 0.8)	0.2 (0.1, 0.7)	0.38
5-year biochemical-free recurrence	97%	95%	0.11

Table 3 Multivariate analysis of factors associated with Gleason upgrading at RP

	OR	95% CI	*P*-value
Prior prostate biopsy	0.24	0.07, 0.08	0.02
Preoperative PSA	1.58	0.90, 2.78	0.11
Clinical stage T2	1.78	0.71, 4.48	0.22
Biopsy technique (saturation *vs* office)	1.61	0.70, 3.74	0.26

cohorts, no episodes of sepsis and no subsequent hospital admissions secondary to a biopsy complication.

Comparisons between the biopsy findings and final pathology are presented by biopsy technique in Table 2. No significant differences in the rate of Gleason score upgrading was found, with upgrading to Gleason 7 in 17 (13.8%) of standard biopsy patients, and upgrading to Gleason 7 in 13 (13.8%) and Gleason 8 in one (1.1%) of saturation biopsy patients ($P = 0.71$). Furthermore, pT3 disease was noted in two standard biopsy patients (1.6%) and 0 saturation biopsy patients ($P = 0.62$). Additionally, there were no significant pathological differences between the cohorts, including tumor size ($P = 0.38$). On multivariate analysis adjusting for performance of a previous prostate biopsy, preoperative PSA and clinical stage, the biopsy technique utilized was not a predictor of upgrading ($P = 0.26$). Table 3 includes the results of this multivariate analysis.

Analysis of BFS rates showed no difference between the two cohorts ($P = 0.11$), with 5-year BFS of 97% and 95% for standard biopsy and saturation biopsy, respectively (Fig. 1). Additionally, no patients had evidence of clinical or systemic progression.

Discussion

The present study showed the ability of a standard (12 core) office biopsy to predict appropriate candidates for active surveillance when compared with a saturation (≥18 cores) biopsy technique, even when accounting for performance of prior biopsies. This is the first report to our knowledge to show similar concordance rates with surgical pathology between these techniques. In addition, we found no significant difference between the cohorts in terms of BFS.

Previous studies have reported an upgrading rate ranging from 28.6–65.9% in patients considered candidates for active surveillance based on a 12-core biopsy.[9–11] By comparison, we showed a 13.8% rate of upgrading in a cohort of patients with a 12-core biopsy. It is difficult to identify why the rate of upgrading in the present 12-core biopsy cohort was lower than those reported previously. Contributing factors might include that 16% of these patients had a prior negative biopsy, and the fact that all patients underwent prostate biopsy and prostatectomy at our institution, which might provide consistency in pathological interpretation. Furthermore, reports have shown an upgrading rate of 11–17.6% when utilizing a saturation biopsy technique.[9,12] This is similar to the 14.9% rate of upgrading in those that had an extended sampling with ≥18 cores seen in the present study.

Several different study designs have been used to evaluate the necessary extent of a prostate biopsy due to the potential issue of upgrading in active surveillance candidates. As a baseline for comparison, Beauval *et al*. evaluated the RP specimens from 919 men that met restrictive criteria for active surveillance preoperatively on 12-core biopsy (clinical T1c, PSA <10 ng/mL, a single positive biopsy, tumor length <3 mm and Gleason score <7) and found that the Gleason score was upgraded in 34% of patients, with 12.5% being upstaged (including 11.1% pT3 and 1.4% pT4).[11] Notably, all patients in their series had a 12-core biopsy preoperatively, and no central pathological review of the specimens was carried out. No comparison group with more extensive sampling was included in that study.[11]

The largest comparative study previously published on the extent of biopsying was by Ploussard *et al*., in which 297 patients that had undergone prostate biopsies using a 6-, 12- and 21-core template were used as their own control, to evaluate which scheme would have a lower risk of unfavorable pathology (Gleason ≥8 and/or pT3 to pT4) on prostatectomy specimen.[9] Their results showed a higher rate of unfavorable disease in patients who fulfilled active surveillance criteria on only a 12-core biopsy (28.6–35.9%, depending on criteria), when compared with patients that fulfilled the same criteria on both the 12- and 21-core

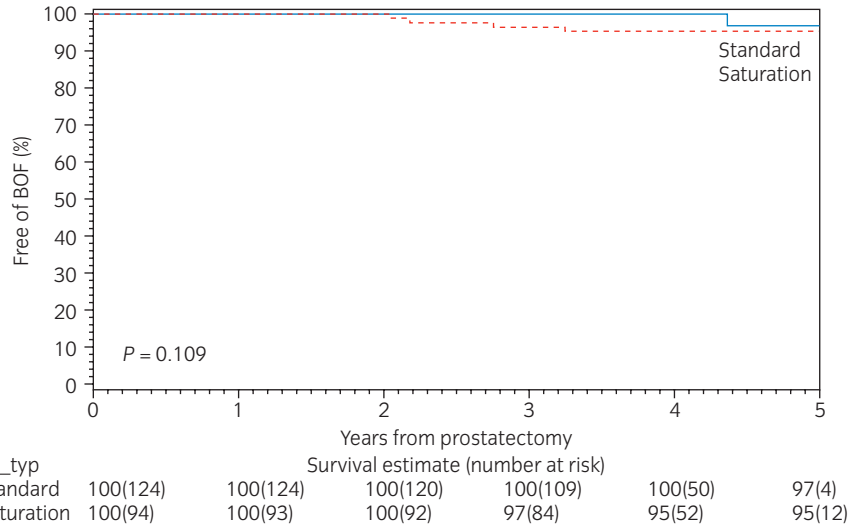

Fig. 1 Biochemical-free recurrence rates by biopsy technique.

schemes (14–17.6%). This grouping left few patients in the 12-core biopsy cohort ($n = 21$–39, depending on cohort) compared with patients meeting criteria in both a 12- and 21-core scheme ($n = 107$–142, depending on cohort). In addition, this grouping might increase the percentage of patients with upgrading in the 12-core group, because some candidates that might have been appropriate for active surveillance would only be reported with the cohort of patients that met the criteria using both the 12- and 21-core biopsies. Furthermore, it is possible that the spacing of the biopsy cores might have been different than those typically obtained in a 12-core sample, when the provider is not accounting for the additional biopsies to be taken for the study.

A retrospective study of 52 patients by Abouassaly *et al*. showed significant upgrading on repeat 20-core staging biopsy after an initial diagnostic biopsy with a variable number of cores (median 12, range 6–28).[12] In their study, upstaging was present in 38% of patients. When evaluating for factors that were predictive of upstaging, they found that of the 19 patients that had greater than 20 cores at diagnosis, just two (11%) were upstaged. This was compared with the 18 of 33 patients (55%) that were upstaged using a traditional 12-core technique. Of note, the patients that had more extensive biopsies carried out had a significantly lower disease burden than patients diagnosed with a 12-core biopsy scheme in that study.

A study with similar design to ours, including evaluation of candidates for active surveillance by comparison of biopsy results with the surgical pathology from RP, was reported by Capitanio *et al*.[10] Their study showed a significantly lower amount of Gleason sum upgrading (increase to Gleason score ≥7) with more extensive biopsying. When analyzing the cases with Gleason sum upgrading, 47.9% were from patients with 10–12 cores and 23.5% from those with >18 cores were taken ($P < 0.001$). Though not directly reported, it can be shown that if 47.9% of the 96 patients that underwent clinically significant upgrading had 10–12-core biopsies, 46 of the 71 patients (65.9%) with 10–12-core biopsies must have been upgraded. This is a higher rate of upgrading than seen in the other studies.

A recent study carried out by Villa *et al*. highlights an important feature in defining active surveillance criteria. They evaluated 233 men with a single microfocus of prostate cancer (Gleason 6, <5% core involvement or ≤0.5 mm in length) and compared the rate of unfavorable prostate cancer or pathologically insignificant prostate cancer in the prostatectomy specimen based on the extent of the diagnostic biopsy (cohorts of ≤12 biopsy cores, 13–18 cores and ≥19 cores). Of note, the cohort of patients with ≤12 cores included nine of the 52 (17%) with <10 cores and the number with 10 cores is unknown. Interestingly, similar to the present results, the rate of unfavorable disease (Gleason 7 or greater, pT3 disease or N+) on multivariate analysis did not show the number of cores being associated with the rate of unfavorable disease. Additionally, among the three cohorts, no difference in the rate of Gleason score upgrading at prostatectomy was seen ($P = 0.2$). However, on multivariate analysis, the number of biopsy cores was associated with the rate of finding pathologically insignificant prostate cancer at prostatectomy ($P < 0.001$). This difference is likely to be the result of the added size criteria of pathologically insignificant cancers being ≤0.5 mL, and the study only including patients with a single positive core rather than the percentage of total cores that are positive. In our cohort, there was no significant difference in the size of the lesion on prostatectomy between those diagnosed with a standard or saturation biopsy ($P = 0.38$). Determining which endpoint constitutes a candidate for active surveillance is crucial, as highly restrictive criteria might over limit the applicability of active surveillance. For instance, even with the highly selective criteria (minute focus in one core) in the

study by Villa *et al*., just 39% of patients diagnosed on saturation biopsy had pathologically insignificant cancer.[13]

We recognize that the present study was limited by its retrospective nature. In addition, there was a significant difference in the number of prior negative biopsies between the cohorts. However, on multivariate analysis controlling for this factor, we found no difference in the rate of upgrading based on biopsy technique. In addition, it is worth noting that there was no significant difference in estimated tumor volume and median PSA density between the cohorts. An additional confounding variable might be the discrepancy in the type of biopsy probe utilized in each group, as the saturation biopsies were carried out with an end-fire probe and the 12-core biopsies by side-fire probe. Last, the prostate biopsies were carried out by multiple urologists at our institution over the time period of our study. Thus, the outcomes might have been impacted by urologist technique and experience. However, this biopsy and subsequent prostatectomy series represents consecutive cases, and during this period there was no change in protocols and biopsies were equally distributed among the staff.

Our data show that overall, approximately one in six patients that were eligible for an active surveillance protocol underwent upgrading at the time of prostatectomy. In terms of predicting appropriate candidates for active surveillance, standard and saturation transrectal prostate biopsies techniques were equally effective.

Conflict of interest

None declared.

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Editorial Comment

Editorial Comment to Standard and saturation transrectal prostate biopsy techniques are equally accurate among prostate cancer active surveillance candidates

Active surveillance is a clear option in the management of clinically insignificant prostate cancer, potentially delaying the morbidity of active treatment. The authors attempt to identify the optimal cores taken on biopsy in correlation to the final pathology on prostatectomy, with implications to identify appropriate candidates for active surveillance.[1] The study included 218 consecutive patients meeting the University of California San Francisco criteria for active surveillance after transrectal ultrasound guided prostate biopsy by either standard (12 cores) or saturation template (>18 cores). There was no difference in upgrading, tumor size or upstaging between the two groups. Consistent with the literature, meeting active surveillance criteria on biopsy predicts a high rate of cure after radical prostatectomy.[2]