Patient-reported pain, discomfort, and anxiety during magnetic resonance imaging-targeted prostate biopsy

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Abstract

Introduction: The addition of targeted prostate biopsy to systemic biopsy impacts patient experience. We examined patient-reported pain, discomfort, anxiety, and tolerability among men undergoing magnetic resonance imaging (MRI)-targeted prostate biopsy in addition to transrectal ultrasound-guided systematic biopsy compared to those undergoing systematic biopsy alone.

Methods: All patients underwent transrectal systematic 14-core biopsies. Patients with regions of interest on MRI underwent additional targeted biopsies. All patients received equivalent periprostatic nerve block. Four single-item, standard, 11-point numerical rating scales evaluating pain, discomfort, anxiety, and tolerability were completed immediately after biopsy. Differences in means were compared using t-tests. Correlation between rated domains was tested using Spearman's correlation coefficient.

Results: Of 273 consecutive patients, 195 (71%) underwent targeted biopsy and 188 (69%) had undergone prior biopsy. In all men, the median score for pain and tolerability was 3, while the median score for discomfort and anxiety was 4. Pain was rated at 7 or above by 15% of patients. Moderate correlation between pain, discomfort, anxiety, and tolerability of repeat biopsy was observed (Spearman's ρ between 0.48 and 0.76). Compared to patients undergoing systematic biopsy alone, men who received both targeted and systematic biopsies reported higher anxiety scores (difference 1.2; 95% confidence interval [CI] 0.4–2.0; p=0.004) and discomfort (difference 1.0; 95% CI 0.3–1.7; p<0.001).

Conclusions: Patients undergoing targeted and systematic biopsies report more discomfort and anxiety than patients undergoing systematic biopsies alone. Absolute differences are small, and patients are willing to undergo repeat biopsy if advised. Interventions to reduce biopsy-related anxiety are needed.

Introduction

Transrectal ultrasound (TRUS)-guided prostate biopsy has long been considered the gold standard for diagnosing prostate cancer in men with an abnormal finding on digital rectal exam (DRE) or an elevated serum prostate-specific antigen (PSA) level.[1,2] Although generally regarded as a well-tolerated procedure that can be safely performed in an outpatient setting, prostate biopsy is associated with significant morbidity in <5% of men.[3,4] In a contemporary prospective cohort of 1147 British men undergoing prostate biopsy, approximately one-third experienced a moderate or major adverse event within 35 days after the procedure, with 1.4% requiring hospital admission.[5] Even among men who do not experience complications, anxiety related to the experience of undergoing a biopsy is common and leads to significant biopsy-related distress in 49% of men,[6,7] suggesting that the procedure itself also carries a significant psychological burden. Both the physical and psychological morbidity of serial prostate biopsies are barriers to active surveillance (AS) for men with low-risk prostate cancer.

Recently, magnetic resonance imaging (MRI) has transformed the diagnostic evaluation of suspected prostate cancer. MRI can identify tumors that may otherwise not be detected by a traditional systematic biopsy sampling scheme, especially in the anterior zone.[8] Software that co-registers ultrasound and MRI has allowed effective targeting of these lesions during biopsy and increased the detection of higher-grade cancer compared to standard biopsy.[9-11] Despite the increased detection rates seen on MRI-targeted prostate biopsies, the combination of targeted biopsy with systematic biopsy still offers the best detection rate for prostate cancer and many biopsy and surveillance protocols rely on both these types of biopsies.[12]

The few potential drawbacks of adding targeted biopsy to systematic biopsy in an outpatient setting include an increase in pain related to the greater number of cores collected and

longer procedural times. Furthermore, patients may experience greater anxiety due to the knowledge that there are imaged areas suspicious for cancer. While many studies have characterized pain, discomfort, and anxiety related to systematic prostate biopsy, the patient experience among men undergoing targeted biopsy in addition to systematic biopsy has not been adequately studied. We compared the experience of men undergoing MRI-targeted and TRUS-guided systematic biopsies with the experience of those undergoing TRUS-guided systematic biopsy alone at our institution. Secondary objectives were to determine how patient-reported anxiety regarding biopsy impacted pain and attitudes toward repeat biopsy and to compare the experience of patients undergoing first vs. repeat biopsy procedures.

Methods

The study was approved by Memorial Sloan Kettering Cancer Center's Institutional Review Board. A short, four-question quality-of-life tool was created to capture patients' experience of undergoing prostate biopsy. Patients were asked the following questions related to their biopsy: "*Overall, how much pain did you experience during the biopsy?*" (referred to as the pain scale); "*Overall, how much discomfort did you experience during the biopsy?*" (referred to as the discomfort scale); "*Overall, how anxious or tense were you during the biopsy?*" (referred to as the anxiety scale); and, "*Overall, how would you feel about having to repeat a biopsy?*" (referred to as the tolerability scale). Each patient rated their answer on a standard numerical rating scale from 0–10, with 0 representing no pain, discomfort, or anxiety, and 10 representing very severe pain, discomfort, or anxiety.[13] For the tolerability scale, a score of 0 corresponded to the patient being able to tolerate a repeat biopsy with "no problem" and 10 to the patient being unable to tolerate a repeat biopsy.

These questionnaires were prospectively provided to 273 consecutive patients receiving prostate biopsy at our institution between April and October of 2015. All biopsies were performed by a single urologist (BE) and informed consent was obtained. The questionnaire was integrated into post-procedural care and completed immediately after completion of the biopsy by all patients during the study period. The patients were consecutively enrolled, representing the mix of men undergoing biopsy at our institution at the time. All men received identical periprocedural care. Men were not randomized to either systematic plus targeted biopsy or systematic biopsy alone but were pragmatically evaluated based on the type of biopsy performed. Biopsy technique was chosen based on imaging and clinical indications prior to enrollment into the study. All men underwent pre-biopsy MRI and all men who had targetable lesions underwent targeted biopsy in addition to systematic biopsy.

All patients underwent a transrectal systematic 14-core prostate biopsy using TRUS guidance, taking cores from medial and lateral base, mid-prostate, and apex, as well as one from the transition zone on the left and right side. Patients in whom an abnormal lesion was identified on MRI also underwent two additional biopsies targeting the lesion. Typically, one targeted core was obtained with cognitive visual targeting and another attained using MRI-ultrasound fusion software (UroStation, Koelis, Grenoble, France), with optimum targeting technique based on surgeon preference to optimize detection of prostate cancer in the region of interest.[14] All biopsies were collected using an 18-gauge Tru-Cut needle. Indications for biopsy included elevated serum PSA levels, AS in patients with prostate cancer, or suspicious findings on MRI or DRE. Analgesia was administered prior to the biopsy in the form of a peripheral nerve blockade (PNB) using 2% plain lidocaine; 5 mL was injected on either side of the prostate lateral to the neurovascular bundle.[15] No patients received peri-procedural sedation or anxiolytics.

Statistics

We used t-tests to assess the significance of differences in mean pain, discomfort, and anxiety scores between patients who received systematic biopsy only and patients who received both systematic and targeted biopsy. To assess the monotonic relationship between each pair of scales, Spearman's correlation coefficient was applied. Locally weighted polynomial regression was used to examine relationships among the scales.

Results

Patient characteristics are summarized in Table 1. Of the 273 patients referred for prostate biopsy, 195 (71%) underwent systematic and targeted biopsy, and 188 (69%) had had a prior prostate biopsy. The most common indication for biopsy was AS in men with prostate cancer (40%), followed by elevated serum PSA (33%).

Fig.1 shows the score distribution of the four outcomes. The median score for the pain and tolerability scales was 3, and the median score for the discomfort and anxiety scales was 4. Pain levels of 7 or above were reported by 15% of patients, and anxiety levels of 7 or above by 24% of patients. Across all scales, 41% of patients reported a score of 7 or higher on at least one domain.

Patients who received both systematic and targeted biopsies were more anxious (difference of 1.2; 95% confidence interval [CI] 0.4, 2.0; p=0.004) and experienced more discomfort (difference of 1.0; 95% CI 0.3, 1.7; p=0.005) than those who received systematic biopsy only (Table 2). Patients undergoing systematic and targeted biopsies also reported higher pain levels, but the differences were not statistically

Table 1. Patient characteristics

	Systematic biopsy (n=78; 29%)	Fusion + systematic biopsy (n=195; 71%)
Age, years	64 (59, 71)	65 (59, 69)
Patient race (n=261)		
Asian	2 (2.8%)	7 (3.7%)
Black	8 (11%)	7 (3.7%)
Other	1 (1.4%)	2 (1.1%)
White	60 (85%)	174 (92%)
Prior prostate biopsy	64 (82%)	124 (64%)
Biopsy indication*		
Restaging biopsy	26 (33%)	84 (43%)
Elevated PSA	13 (17%)	76 (39%)
Active surveillance	23 (29%)	30 (15%)
Post-radiation	15 (19%)	2 (1.0%)
Prostate nodule/ abnormality	3 (3.8%)	4 (2.1%)
Abnormal MRI	0 (0%)	6 (3.1%)
Abnormal DRE	0 (0%)	5 (2.6%)
Pain scale	2 (2, 5)	3 (2, 5)
Discomfort scale	3 (2, 5)	5 (2, 7)
Anxiety scale	2 (1, 6)	4 (2, 7)
Tolerability scale	3 (1, 5)	3 (1, 5)
Pain scale 7–10	8 (10%)	34 (17%)
Discomfort scale 7–10	13 (17%)	48 (25%)
Anxiety scale 7–10	12 (15%)	54 (28%)
Tolerability scale 7–10	11 (14%)	29 (15%)
Any QoL scale 7-10	26 (33%)	86 (44%)

Data are presented as frequency (percent) or median (interquartile range [IQR]). *More than one biopsy indication may apply to each patient. DRE: digital rectal examination; MRI: magnetic resonance imaging; PSA: prostate specific antigen; QoL: quality of life.

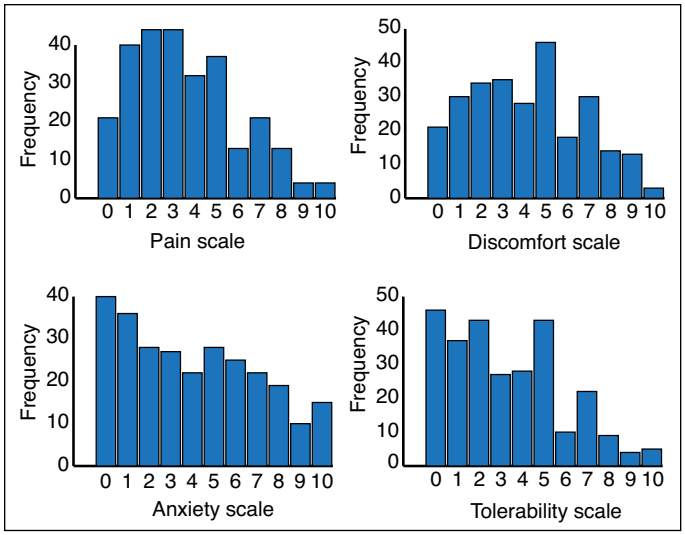

Fig. 1. Distributions of quality of life (QoL) scales. For each scale, patients rated their experience during biopsy, except for the tolerability scale, which refers to the patients' willingness to undergo a repeat biopsy.

significant (difference 0.6; 95% CI 0.0–1.2; p=0.067). We did not observe any significant differences in pain, discomfort, anxiety, or tolerability between patients who had or had not undergone a prior prostate biopsy (Table 3).

All four scales were significantly correlated with one another (Fig. 2). However, the levels of association were moderate, with Spearman correlation coefficients ranging from 0.48–0.76. The pain and tolerability scales showed the lowest correlation of any pair (Spearman's ρ=0.48), and pain and discomfort exhibited the highest correlation (ρ=0.76). All other correlations ranged from 0.53–0.60. Due to the modest pairwise correlations, excluding any one of the scales would substantively reduce information about a patient.

Discussion

MRI-targeted biopsy is increasingly used in prostate biopsies, particularly in the AS population.[16] Biopsy techniques that combine targeted biopsy with systematic biopsy have been shown to increase the detection of clinically significant prostate cancer. Compared with targeted biopsy alone, the addition of systematic biopsy to targeted biopsy avoids the risk of missing up to 15% of significant cancers.[17] As a moderate proportion of men undergoing AS experience disease-related anxiety,[18] evaluating the impact of anxiety on biopsy can aid in surveillance-related counselling and may improve AS compliance. We sought to compare biopsy-related pain, discomfort, and anxiety between patients undergoing systematic biopsy alone with patients undergoing both systematic and MRI-targeted biopsy.

Uniquely, our study evaluated the different impact biopsy technique had on these four patient-reported domains. The standard, 11-point numerical rating scale is established and has been validated in evaluation of pain and discomfort.[19-21] Similarly, the 11-point numerical rating scale has been used to evaluate perioperative anxiety and was shown to correlate with physiologic stress response in preoperative patients.[22,23] Numerical rating scale has also been used to evaluate willingness to undergo repeat procedures.[24] Our study is unique in combining all four domains in numerical rating scale evaluations immediately after prostate biopsy.

Notably, our data demonstrates that MRI-targeted biopsy is associated with increases in both patient discomfort and anxiety, and that these domains are moderately correlated to each other with a Spearman ρ=0.60. Though patients undergoing both MRI-targeted and systematic biopsies reported more discomfort, their tolerability of future biopsy did not differ from that of patients undergoing systematic biopsy alone. While pain was increased among the targeted biopsy with systemic biopsy cohort, the increase was smaller and not statistically significant. Importantly, we found that reporting of pain, anxiety, discomfort, and tolerability were separately and uniquely correlated; therefore, a survey of each

Table 2. Differences in quality of life scales by biopsy scheme (targeted and systematic vs. systematic only)

	Systematic biopsy (n=78)	Systematic and targeted biopsy (n=195)	Mean difference	95% CI	p
Pain scale	3.2 (2.3)	3.8 (2.4)	-0.6	-1.2, 0.0	0.067
Discomfort scale	3.5 (2.5)	4.5 (2.6)	-1.0	-1.7, -0.3	0.005
Anxiety scale	3.2 (2.9)	4.4 (3.1)	-1.2	-2.0, -0.4	0.004
Tolerability scale	3.2 (2.6)	3.4 (2.6)	-0.2	-0.8, 0.5	0.7

Scores presented as mean (standard deviation). CI: confidence interval.

item is important to understand the experience of patients during prostate biopsy.

TRUS-guided systematic prostate biopsy has been the established method of prostate biopsy detection for the past three decades. The procedure causes significant pain and discomfort, as evidenced by the extensive body of research, including over 100 randomized trials, into interventions aimed at decreasing biopsy-related pain.[25] The most effective of these, the PNB, renders prostate biopsy tolerable in most patients; studies employing PNB fairly consistently report mean pain scores between 2 and 4 on 11-point NRS.[26-30] Congruent with these findings, median pain, discomfort, and anxiety scores in our series of 273 patients were 3, 4, and 4, respectively. Nevertheless, 41% of men in our series reported severe (>7/10) pain, discomfort and/or anxiety, suggesting that prostate biopsy remains an uncomfortable and anxiety-inducing procedure despite PNB in a substantial proportion of men. Fifteen percent of men described severe (>7/10) pain associated with the procedure.

This is a novel finding that has been obscured in past studies by almost exclusive reporting of average pain scores and not the proportion of patients who report significant pain or discomfort. It also suggests the need to identify those men at highest risk of experiencing significant pain, such as those with high pre-biopsy anxiety,[31-33] so that they may receive additional interventions. Prior biopsy or AS status was not associated with a score of ≥7 on the measured domains of pain, discomfort, anxiety, or tolerance of procedure, indicating that further research is warranted to prospectively identify men at greatest risk for biopsy-related pain, anxiety, and discomfort.

Importantly, we found only moderate correlation between measures of pain, discomfort, anxiety, and tolerability, defined as the attitude toward repeat biopsy. Prior prostate biopsy series have reported tolerability rates exceeding 80%.[34-36] However, only three studies have assessed the correlation between the biopsy experience and willingness to undergo repeat biopsy. Robins et al showed no difference in patient-reported pain or discomfort when comparing systematic biopsy and targeted biopsy with systematic biopsy alone and that both groups were willing to repeat the biopsy, if advised.[24] In a study of 476 Australian men undergoing prostate biopsy with PNB, only 12 (2.5%) said that they would be unable to tolerate a repeat biopsy without sedation or a general anesthetic, and these 12 men reported significantly higher pain scores during probe insertion, PNB, and biopsy.[36] We attribute the moderate correlation between pain and discomfort and tolerability to the significant proportion of men in this study who had undergone prior biopsy and were thus prepared for the experience. This complements the findings of Carlsson et al that surveillance biopsy-related anxiety significantly decreased over time within the Gothenburg branch of the European Randomized Study of Screening for Prostate Cancer.[37] Based on our findings, we hypothesize that counselling biopsy-naive men on the experience of prostate biopsy and setting expectations using appropriate framing techniques will reduce anxiety and improve tolerability.

Although we report significantly greater discomfort and anxiety among men undergoing targeted and systematic biopsies compared with those undergoing systematic biopsy alone, the mean absolute difference was approximately one point on an 11-point numerical rating scale. The likelihood that this increase in discomfort and anxiety is clinically significant seems low, as it did not decrease tolerability of future repeat prostate biopsy. The minimal clinically important difference in pain scores as measured on an 11-point numerical rating scale has been variably defined in the anesthesia literature as either 1.3[38,39] or two points,[40,41] and it would seem

Table 3. Differences in quality of life scales by prior biopsy

	No prior biopsy (n=85)	Prior biopsy (n=188)	Mean difference	95% CI	p
Pain scale	3.5 (2.3)	3.6 (2.5)	-0.1	-0.7, 0.5	0.8
Discomfort scale	4.0 (2.3)	4.2 (2.7)	-0.2	-0.9, 0.5	0.6
Anxiety scale	4.4 (3.1)	3.9 (3.0)	0.5	-0.3, 1.3	0.2
Tolerability scale	3.4 (2.5)	3.3 (2.6)	0.2	-0.5, 0.8	0.6

Scores presented as mean (standard deviation). CI: confidence interval.

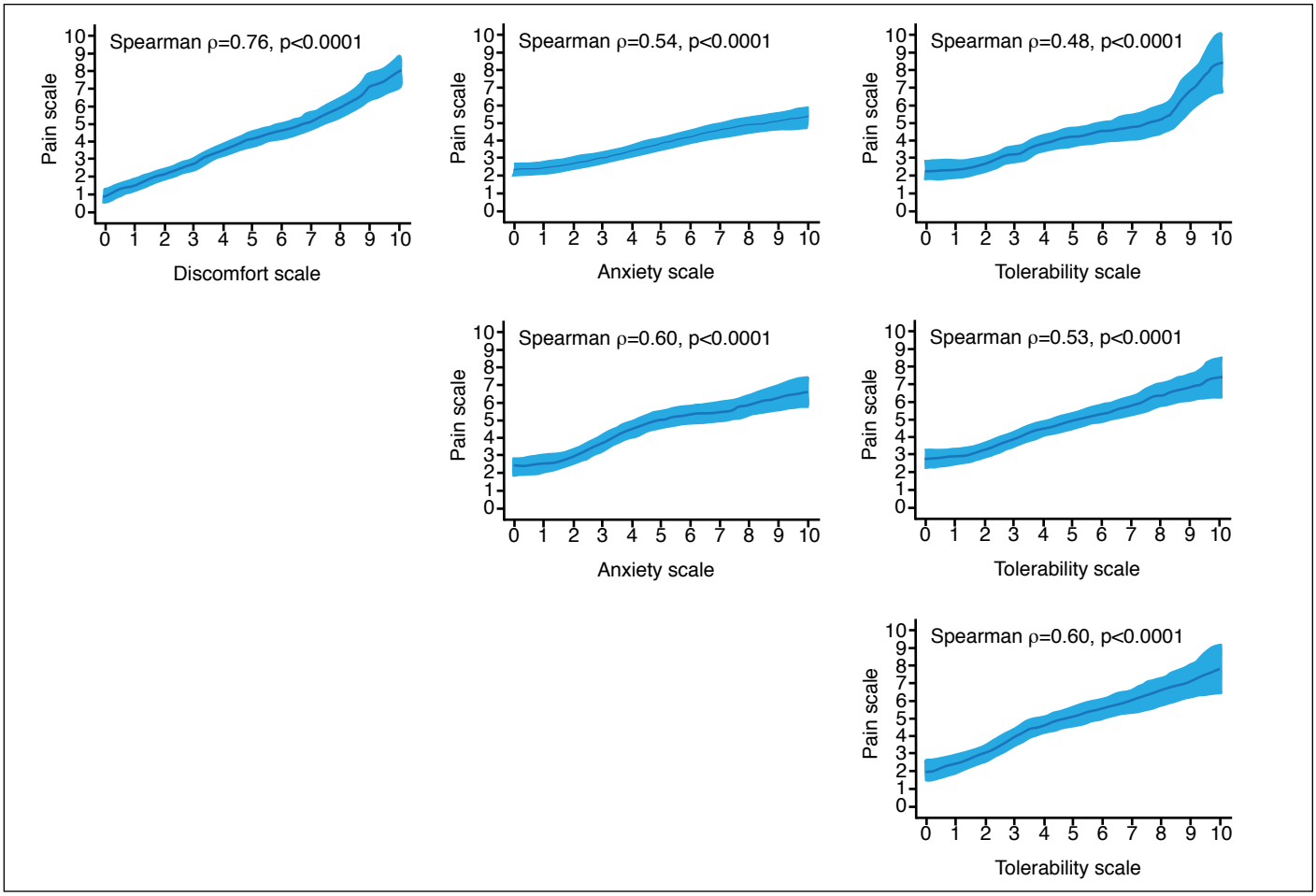

Fig. 2. Relationships among the quality of life (QoL) scales.

reasonable to extrapolate this minimal clinically important difference to our measures of pain and discomfort. Thus, the additional discomfort and anxiety conferred by adding targeted biopsy to a systematic biopsy scheme does not appear to outweigh the benefits of this approach, namely enhanced sensitivity of cancer detection.

The observed increases in discomfort and anxiety scores with the addition of targeted biopsy could be explained by the larger number of cores sampled and longer procedural duration. On average, 16 cores were sampled during targeted and systematic biopsy, compared to 14 cores during systematic biopsy only. As prior studies have shown that increasing the number of cores does not significantly increase pain or discomfort even in the absence of PNB,[42,43] this is unlikely to be the main contributing factor. An alternative explanation is that because targeted biopsies were performed only in patients who had a lesion documented on MRI, they may have thought of themselves as being more likely to have a positive biopsy, increasing their anxiety. It is likely that a combination of adding the additional targeted biopsy cores to the procedure and the patient's knowledge that a targetable lesion exists combine to increase the patient's experience of discomfort and anxiety at prostate biopsy. This suggests that techniques that manage patient expectations when evaluating a targetable lesion may offer the potential of improved patient experience at time of targeted biopsy.

Strengths of our study include measurement of multiple domains of the patient experience using a simple numerical rating scale that has been applied extensively in prior studies of prostate biopsy,[44] as well as having the questionnaire filled out by patients directly and confidentially, thus reducing bias. All evaluations were performed after biopsy by a single urologist experienced with image-guided prostate biopsy techniques, thus limiting variation in patient-provider counselling and overall biopsy experience. Though a single surgeon's bedside manner may not be generalizable to all settings, it can serve as a benchmark to evaluate patient-reported pain, discomfort, anxiety, and tolerability in future studies and ongoing evaluations of patient experiences. Another potential limitation is that we assessed tolerability immediately after biopsy, while prior studies have shown that willingness to undergo repeat biopsy may be affected by biopsy-related

symptoms that occur days and weeks after the procedure.[5,45] The generalizability of our findings may also be limited by the relatively small number of cores collected during MRI-targeted biopsy (two is our standard practice); this procedure could add significantly more pain and discomfort at other institutions. As our study included all consecutive men undergoing prostate biopsy for any reason at our institution, we did not randomize men to receive targeted plus systematic biopsy vs. systematic biopsy alone. As such, there may be differences in these cohorts that disproportionally impact patient-reported outcomes. Further evaluations within these groups are topics of ongoing research at our institution.

Conclusions

Men undergoing targeted and systematic prostate biopsies experience more discomfort and anxiety during the procedure than those undergoing systematic biopsy alone. However, the absolute difference is small and, therefore, its clinical significance is uncertain. As MRI-targeted biopsies become more widely adopted, interventions aimed at decreasing patient biopsy-related anxiety will become more important; this may result in less procedural discomfort and improved AS compliance.

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