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Upgrading on Per Protocol versus For Cause surveillance prostate biopsies: An opportunity to decreasing the burden of active surveillance

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Abstract

Background: Most prostate cancer (PC) active surveillance (AS) protocols recommend "Per Protocol" surveillance biopsy (PPSBx) every 1–3 years, even if clinical and imaging parameters remained stable. Herein, we compared the incidence of upgrading on biopsies that met criteria for "For Cause" surveillance biopsy (FCSBx) versus PPSBx.

Methods: We retrospectively reviewed men with GG1 PC on AS in the Michigan Urological Surgery Improvement Collaborative (MUSIC) registry. Surveillance prostate biopsies obtained 1 year after diagnosis were classified as either PPSBx or FCSBx. Biopsies were retrospectively deemed FCSBx if any of these criteria were met: PSA velocity > 0.75 ng/mL/year; rise in PSA > 3 ng from baseline; surveillance magnetic resonance imaging (MRI) (sMRI) with a PIRADS ≥ 4; change in DRE. Biopsies were classified PPSBx if none of these criteria were met. The primary outcome was upgrading to ≥GG2 or ≥GG3 on surveillance biopsy. The secondary objective was to assess for the association of reassuring (PIRADS ≤ 3) confirmatory or surveillance MRI findings and upgrading for patients undergoing PPSBx. Proportions were compared with the chi-squared test.

Results: We identified 1773 men with GG1 PC in MUSIC who underwent a surveillance biopsy. Men meeting criteria for FCSBx had more upgrading to ≥GG2 (45%) and ≥GG3 (12%) compared with those meeting criteria for PPSBx (26% and 4.9%, respectively, $p < 0.001$ and $p < 0.001$). Men with a reassuring confirmatory or surveillance MRI undergoing PPSBx had less upgrading to ≥GG2 (17% and 17%, respectively) and ≥GG3 (2.9% and 1.8%, respectively) disease compared with men without an MRI (31% and 7.4%, respectively).

Conclusions: Patients undergoing PPSBx had significantly less upgrading compared with men undergoing FCSBx. Confirmatory and surveillance MRI seem to be valuable tools to stratify the intensity of surveillance biopsies for men on AS. These data may help inform the development of a risk-stratified, data driven AS protocol.

KEYWORDS

active surveillance, genomic classifier, MRI, prostate biopsy, prostate cancer

1 | INTRODUCTION

Prostate cancer is the most common solid tumor diagnosed in men in America.[1] The vast majority of men with newly-diagnosed localized prostate cancer have a low probability of future distant metastasis and cancer-specific mortality, with or without treatment.[2] As a result, active surveillance (AS) has emerged to balance the risk of metastasis and death from prostate cancer in selected men while mitigating overtreatment and minimizing the morbidity of definitive treatment.[3–5]

Adequately characterizing prostate cancer is difficult due to its multifocality, heterogeneity, and the nonspecific nature of a prostate biopsy.[6] While there is no universally agreed upon AS protocol, most AS regimens involve a combination of PSA monitoring, digital rectal exams (DRE), magnetic resonance imaging, and surveillance prostate biopsy.[3,4,7–9] Due to the limitations of current imaging and biomarker technology aiding in the diagnosis and subsequent monitoring of men with favorable risk prostate cancer on AS, surveillance prostate biopsy remains a cornerstone of AS to diagnose disease reclassification and trigger intervention. AS protocols often utilize "For Cause" surveillance biopsy (FCSBx), in which a change or concern in surveillance parameters (i.e., rise in PSA, alarming PSA velocity, change in DRE, or concerning magnetic resonance imaging (MRI) findings) prompt a biopsy. Additionally, most AS protocols advocate for the use of "Per Protocol" surveillance biopsy (PPSBx) in which a surveillance biopsy is performed at some interval, even in the presence of stable clinical and imaging parameters.

While approximately one-fourth of men will be upgraded on their first surveillance biopsy, the other three-fourth will not.[10,11] Furthermore, with the emerging role of AS for select men with low volume GG2 disease, some men will continue on AS despite grade reclassification, further questioning the value of a majority of surveillance biopsies if this invasive procedure will not result in a change in management. Although necessary at times, surveillance biopsies have measurable morbidity with substantial patient discomfort, risk of urinary tract infections, sepsis, and hospitalization, further placing additional financial strain on the healthcare system.[12] While AS has slowly become more accepted among providers and patients, regularly scheduled prostate biopsies remain a barrier to broader AS implementation.[13,14] Thus, we have begun to wonder whether PPSBx are worthwhile in men with otherwise stable parameters. Herein, we examined the proportion of men with upgrading when meeting criteria for FCSBx versus PPSBx. We hypothesized that the proportion of men upgraded, which may be associated with the discontinuation of AS, will be higher among men meeting criteria for FCSBx compared with PPSBx.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a retrospective review of the MUSIC registry of men with GG1 prostate cancer undergoing a surveillance biopsy on AS. MUSIC is a consortium of over 260 urologists across 46 diverse practices in the state of Michigan.[15] All practices obtained approval or exemption from their local IRB to participate in MUSIC. This study was deemed exempt from review by the Wayne State University IRB. The study was performed in accordance with the Declaration of Helsinki.

2.2 | Study sample

We reviewed the MUSIC registry for men with GG1 prostate cancer diagnosed from 2016 to 2020 managed with AS. Men with any previous prostate cancer treatment (including monotherapy ADT) were excluded. *The Roadmap for Favorable Risk Prostate Cancer* is integral to the understanding of how MUSIC approaches AS.[16] The *Roadmap* conceptualizes AS into two phases: (1) the consideration phase, a period following diagnosis in which early confirmatory testing is encouraged and shared decision making is pursued and (2) the surveillance phase which follows the confirmatory phase where longitudinal disease monitoring ensues. AS is defined as the affirmative selection of active surveillance in the medical record and the absence of treatment within the first year of diagnosis. All patients included in the study underwent at least one surveillance biopsy, defined as a biopsy >12 months after the initial diagnostic biopsy. For the purposes of this study, biopsies obtained during the first 12 months of diagnosis were not considered surveillance biopsy and were considered confirmatory biopsies.

Additionally, the *Roadmap* encourages the uses of an early confirmatory test during the consideration phase in effort to aid in the medical decision-making process. Confirmatory tests can be (1) prostate MRI, (2) prostate biopsy with or without an MRI prior (confirmatory biopsy), and (3) a commercially available genomic classifier (GC). GC included in the registry are the Prolaris cell cycle progression score (Myriad Genetics), Decipher genomic classifier (GenomeDx Biosciences), and OncotypeDx genomic prostate score (Genomic Health). Confirmatory test results are classified as "reassuring" or "non-reassuring" based on previously defined criteria.[16] Non-reassuring confirmatory tests, which should promote additional shared decision-making, were defined as follows:

- MRI: PIRADS ≥ 4
- Genomics: (1) Prolaris: >3% probability of prostate cancer mortality; (2) OncoType Dx: <80% freedom from primary Gleason 4; (3) Decipher Score: >0.45.
- Confirmatory biopsy (with or without MRI prior): ≥GG2 disease.

2.3 | Study objectives

The primary objective was to estimate the proportion of men with GG1 prostate cancer who met either of two definitions of upgrading, which are often associated with the discontinuation of AS, on the first surveillance biopsy: (1) ≥GG2 disease and (2) ≥GG3 disease.[16,17] The primary independent variable was the type of surveillance biopsy: Per Protocol (PPSBx) versus For Cause (FCSBx). A surveillance biopsy

was considered a FCSBx if any of the follow criteria were met: PSA velocity >0.75 ng/mL/year; rise in PSA > 3 ng/dL from baseline; surveillance MRI with a PIRADS ≥ 4, or change in DRE. Surveillance biopsy was classified as PPSBx if no FCSBx criteria were met.

Secondary objectives were to assess for the association of confirmatory test outcomes (reassuring vs. non-reassuring) and upgrading by surveillance biopsy type, and to identify clinical scenarios in which PPSBx could potentially be omitted. Lastly, an additional category of upgrading was considered—patients who were upgraded from GG1 to high volume (>3 cores) of GG2 or any volumes ≥GG3 disease. This category was defined in the original MUSIC appropriateness criteria for active surveillance as high volume GG2 disease.[18] These results were included to reflect the clinical scenario in which some men are upgraded to low volume GG2 disease but may continue on AS. The results of this additional upgrading definition are detailed in the Supporting Information but excluded from the main manuscript text for brevity.

2.4 | Statistical analysis

Clinical, demographic, and oncological patient characteristics were summarized as medians with interquartile ranges for continuous variables and counts with proportions for categorical parameters. The proportion of patients upgraded in each clinical scenario was compared using Chi-squared test or Fishers exact test as appropriate. Continuous measures were compared with the Wilcoxon rank-sum test. Statistical analysis was performed with SAS 9.4 with a two-tailed p value of less than 0.05 considered statistically significant.

3 | RESULTS

3.1 | Demographics

We identified 1773 men with GG1 prostate cancer who were managed on AS and had a surveillance biopsy, of which 719 men (41%) met criteria for FCSBx and 1054 (59%) met criteria for PPSBx (Table 1). Men who met criteria for FCSBx tended to have a slightly higher PSA at diagnosis and more cores positive for cancer on the diagnostic biopsy compared with men who met criteria for PPSBx (5.6 vs. 5.1 ng/mL and 2 vs. 1 cores, respectively). The median time from diagnosis to surveillance biopsy for the FCSBx and PPSBx groups were 21.6 months (interquartile range [IQR]: 16.2–29.9) and 16.3 (IQR: 13.5–22.7) months, respectively.

TABLE 1 Clinical, demographic, and oncological parameters of patients with GG1 prostate cancer on AS undergoing a surveillance biopsy in MUSIC from 2016 to 2020.

	All patients	For Cause bx	Per Protocol bx	p
No. of patients	1773	719	1054	
Race				
White	1367 (77%)	573 (80%)	794 (75%)	0.038
African American	209 (12%)	82 (11%)	127 (12%)	
Other/unknown	197 (11%)	64 (8.9%)	133 (13%)	
Charlson Comorbidity Index				
CCI = 0	1325 (75%)	528 (73%)	797 (76%)	0.56
CCI = 1	257 (15%)	111 (15%)	146 (14%)	
CCI ≥ 2	191 (11%)	80 (11%)	111 (11%)	
Family history of PC				
Yes	538 (30%)	237 (33%)	301 (29%)	0.098
No	1173 (66%)	461 (64%)	712 (68%)	
Unknown	62 (3.5%)	21 (2.9%)	41 (3.9%)	
Clinical T stage				
T1	1637 (92%)	676 (94%)	961 (91%)	0.027
T2	136 (7.7%)	43 (6.0%)	93 (8.8%)	
Age	64.0 (59–69)	65.0 (60–70)	64.0 (59–68)	0.009
PSA at diagnosis	5.3 (4.3–6.9)	5.6 (4.5–7.4)	5.1 (4.1–6.6)	<0.001
No. of positive cores	1 (1–2)	2 (1–3)	1 (1–2)	<0.001

Abbreviations: AS, active surveillance; MUSIC, Michigan Urological Surgery Improvement Collaborative.

3.2 | Primary objective

Overall, 34% of men undergoing a surveillance biopsy were upgraded to ≥GG2 disease and 7.7% to ≥GG3 disease. Men who met criteria for PPSBx had significantly less upgrading to ≥GG2 disease (26%) and ≥GG3 disease (4.9%) compared with men who met criteria FCSBx (45% and 12%, respectively, $p < 0.001$ for each comparison, Figure 1).

3.3 | Secondary objectives

Next, we examined the influence of confirmatory tests on surveillance biopsy upgrading. Among men who met criteria for PPSBx, men with reassuring confirmatory tests (defined as testing within 12 months of diagnosis) had less upgrading (by both upgrading definitions) compared with men without confirmatory tests or men with non-reassuring confirmatory tests (Figure 2A). Interestingly, among men who met criteria for FCSBx, results of the confirmatory tests (reassuring vs. non-reassuring vs. no confirmatory test) were not associated with differences in upgrading by both definitions (Figure 2B).

Men who met criteria for PPSBx with either a reassuring confirmatory test or without a confirmatory test experienced less upgrading compared with men who met criteria for FCSBx (Figure 2C). However, among men with non-reassuring confirmatory tests, men who met criteria for PPSBx tended to have similar upgrading as men who met criteria for FCSBx for both definitions.

When stratified by the modality of confirmatory tests, we noted more men who met criteria for PPSBx with reassuring genomics tended to have more upgrading to ≥GG2 disease (28%) compared with men with RA MRI (17%) and RA confirmatory biopsy (13%, Figure 3A). For the outcomes of upgrading to ≥GG3 disease, we did not appreciate a statistically significant difference in the proportion of patients upgraded to GG3 disease or greater for men with reassuring genomics (4.5%), MRI (2.9%), and confirmatory biopsy (1.3%, Figure 3A). Of the 79 men with a reassuring confirmatory biopsy that met criteria for a PPSBx, only one patient was upgraded to ≥GG3 disease.

Lastly, we considered the influence of a reassuring surveillance MRI (MRI obtained during AS) on upgrading in men who met criteria for PPSBx. Compared with men without a confirmatory or a surveillance MRI ($n = 850$), men with a reassuring surveillance MRI who met criteria for a PPSBx ($n = 112$) had significantly less upgrading to ≥GG2 disease (17% vs. 30%, $p < 0.001$, Figure 3B). Additionally, men with a reassuring surveillance MRI who met criteria for a PPSBx had less upgrading to ≥GG3 compared with men without a surveillance MRI (1.8 vs. 7.4%, $p = 0.03$). Considering the unique situation in which men had a reassuring confirmatory MRI and a reassuring surveillance MRI ($n = 28$) who met criteria for a PPSBx, 14% (4/28) were upgraded to ≥GG2 and no patient (0/28) was upgraded to ≥GG3.

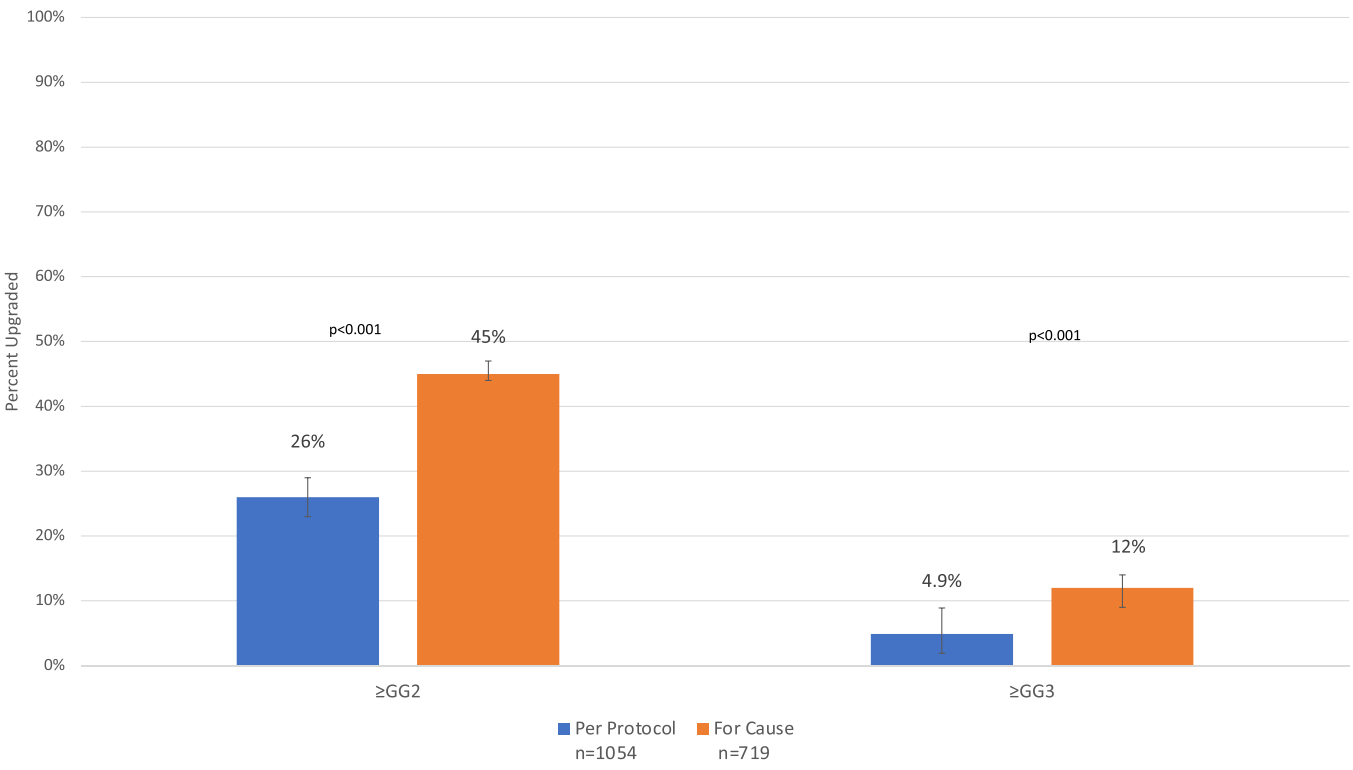

FIGURE 1 Proportion of patients upgraded for men meeting criteria for PPSBx versus FCSBx. Error bars display 95% CI interval. CI, confidence interval; FCSBx, For Cause surveillance biopsy; PPSBx, Per Protocol surveillance biopsy. [Color figure can be viewed at wileyonlinelibrary.com]

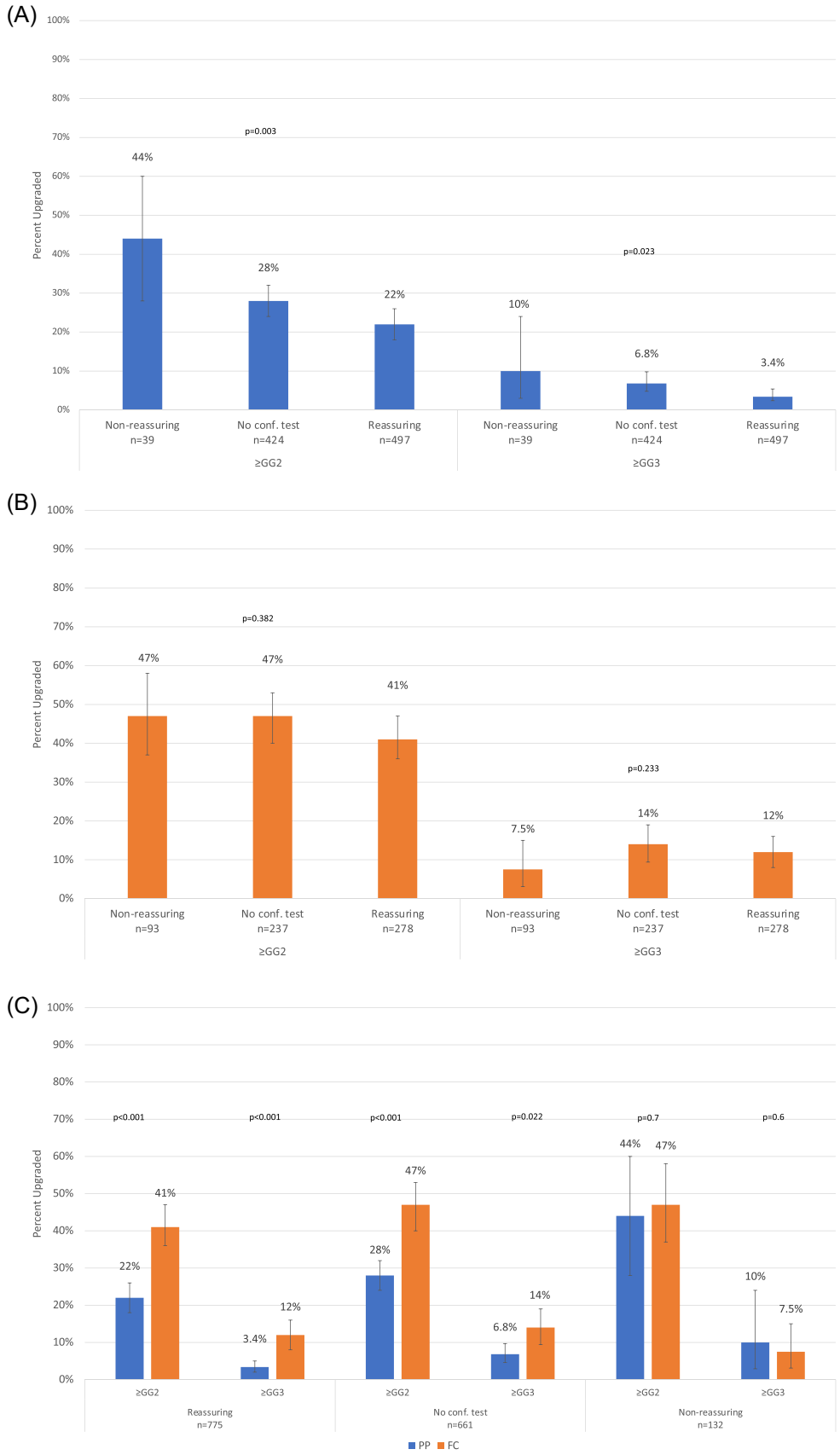

FIGURE 2 (A) Upgrading among men meeting criteria for PPSBx stratified by confirmatory test result. Error bars display 95% CI interval. (B) Upgrading among men meeting criteria for FCSBx stratified by confirmatory test result. Error bars display 95% CI interval. (C) Upgrading among men meeting criteria for PPSBx versus FCSBx stratified by confirmatory test result. Error bars display 95% CI interval. CI, confidence interval; FCSBx, For Cause surveillance biopsy; PPSBx, Per Protocol surveillance biopsy. [Color figure can be viewed at wileyonlinelibrary.com]

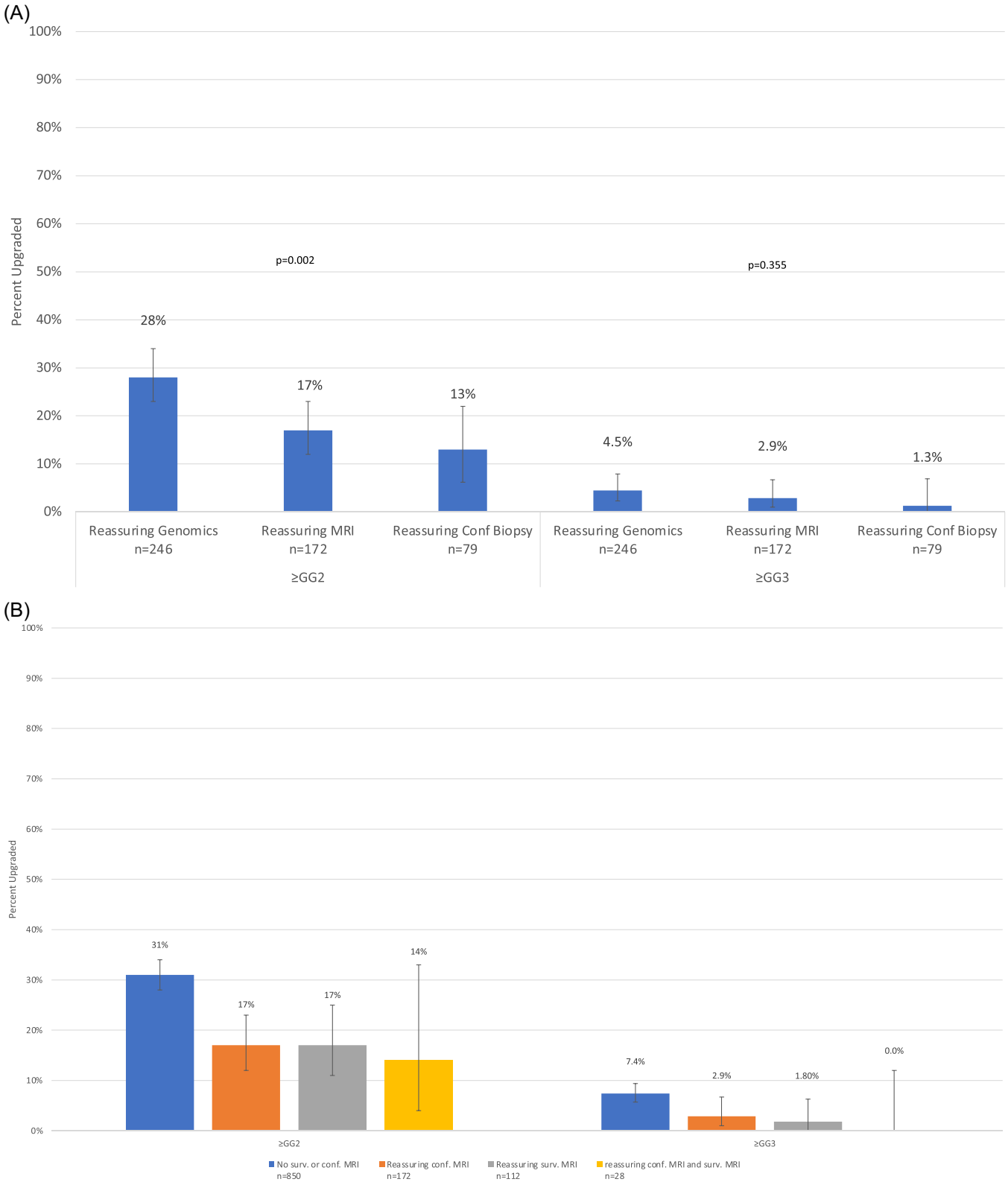

FIGURE 3 (A) Upgrading among men meeting criteria for PPSBx stratified by reassuring confirmatory tests type (Genomics, MRI, Confirmatory Biopsy). Error bars display 95% CI interval. (B) Upgrading among men with reassuring confirmatory or surveillance MRIs meeting criteria for PPSBx. Error bars display 95% CI interval. CI, confidence interval; MRI, magnetic resonance imaging; PPSBx, Per Protocol surveillance biopsy. [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

The defining characteristic of AS, as opposed to watchful waiting, is the intention to identify and treat clinically significant disease within the curative window. To this end, surveillance biopsy is integral to this process, even though it can be painful, costly, and potentially dangerous.[19,20] These risks are unappealing, especially in men whose management will not change after the surveillance biopsy, which is in fact the majority of men on AS. In an effort to decrease the burden of surveillance and reduce unnecessary surveillance biopsy in men on AS, we examined the proportion of men that would meet various upgrading and treatment thresholds for men meeting criteria for PPSBx compared with FCSBx.

We identified several clinical scenarios in which there was a considerably lower proportion of upgrading among men who met criteria for PPSBx. First, men with reassuring confirmatory tests had less upgrading than men without a confirmatory test or men with non-reassuring confirmatory tests. In particular, men with a reassuring confirmatory biopsy who met criteria for PPSBx had some of the lowest probability of upgrading seen in the cohort, with only 13% upgraded to ≥GG2% and 1.3% upgraded to ≥GG3 disease. Additionally, men with a reassuring surveillance MRI had a considerably lower yield of upgrading when meeting criteria for PPSBx, with 17% of men upgraded to ≥GG2 disease and 1.8% upgraded to ≥GG3. These data regarding the incidence of upgrading among men meeting criteria for PPSBx with a reassuring surveillance MRI in our cohort is very similar to the 15% of patients upgraded on surveillance biopsy with a PIRADS < 3 reported in the Memorial Sloan Kettering series.[21] An analysis of the PRIAS cohort also reported similar incidence of upgrading rates to ≥GG2 disease and ≥GG3 disease for patients with reassuring or non-reassuring prostate MRI.[22] Our study adds to this expanding field of knowledge by also examining the value of other confirmatory tests on upgrading, including genomic classifiers and repeat prostate biopsies. The prevailing thought in the urologic community is that surveillance biopsy cannot be excluded in men with reassuring MRI findings due to the potential of missing clinically significant disease. In our series of men with reassuring surveillance MRIs meeting criteria for a PPSBx, the number needed to biopsy (NNB) to upgrade one man to ≥GG2 disease is 5.8 and 56 for upgrading to ≥GG3 disease. We would conclude from these data that omitting a biopsy among men meeting criteria for PPSBx is reasonable and could be discussed with the patient due to the high number of "negative" biopsies would have to be performed to identify a small number of clinically significant cancers, especially if a man would continue AS if low volume GG2 disease were found (Supporting Information: figures).

Furthermore, we identified a group of men who should not forgo a biopsy when PPSBx criteria are met: men with non-reassuring confirmatory tests. In previous studies, we have shown that confirmatory tests may be influential in selecting AS versus treatment as well as time on AS.[23,24] In this study, we demonstrate the value of confirmatory tests by their ability to help triage the intensity of follow-up on AS. While upgrading was higher for men with non-reassuring confirmatory tests compared with men with reassuring confirmatory tests, this study suggests that men with GG1 disease and non-RA confirmatory tests are indeed appropriate for AS as most of these men will not be upgraded at their first surveillance biopsy.

To help contextualize the sum of our results, consider a hypothetical cohort of 100 men on AS. Assuming the distribution of PPSBx (59% of surveillance biopsy) and the results of confirmatory tests (52% of PPSBx had reassuring confirmatory tests) from our cohort is representative of these 100 men, if PPSBx were omitted only in men with reassuring confirmatory tests, 31 men would avoid a biopsy, at the cost of failing to upgrade 6 men to GG2 disease and only 1 man to ≥GG3 disease. With high-quality surveillance and diligent follow up in men that omit a PPSBx, it is likely that some clinical parameter will change and prompt a FCSBx. Given the prolonged natural history of prostate cancer, patients omitting PPSBx are unlikely to experience worse oncologic outcomes from the delay in upgrading by waiting for a change in clinical status, which would then have prompted a FCSBx.[25]

Our study has several notable limitations. First, this a retrospective registry study of patients undergoing surveillance biopsies. Biopsies were labeled as PPSBx or FCSBx in a retrospective fashion. Prostate MRIs and biopsy pathology were also not reviewed centrally. Second, the criteria of PPSBx were generated from reviewing prostate cancer and AS literature, but are arbitrary. Despite this limitation, these data help illustrate the utility of surveillance biopsies when clinical parameters remain stable on AS. Third, MUSIC provides a framework for active surveillance including the use of confirmatory testing, type of confirmatory test, and interval of surveillance testing, but ultimately the decision to use confirmatory tests, interval of surveillance testing, and decision to perform a surveillance biopsy was left to the discretion of the patient and physician, which may introduce bias. The participating urologists in MUSIC are also in a unique environment as they are familiar with the framework for active surveillance as provided in the *Roadmap*, which may limit the generalizability of this study. Fourth, certain subgroups of patients (such as patients with non-reassuring confirmatory tests or patients with confirmatory and surveillance MRIs) are small and limits the statistical power to detect differences among these groups.

Uniquely, our study allows us to provide several clinical recommendations about how to perform active surveillance follow-up, which should be interpreted in the context of the patients other clinical, demographic, and oncological factors. First, men with non-reassuring confirmatory test should not omit a surveillance biopsy, even when PPSBx criteria are met. Second, for men with reassuring confirmatory tests but have concerning changes in their clinical parameters on surveillance (FCSBx), these patients should obtain a surveillance biopsy. Third, men with reassuring confirmatory or surveillance MRIs meeting criteria for PPSBx can consider omitting surveillance biopsy after a thorough shared-decision-making process. The duration for which a surveillance biopsy can safely be delayed in men meeting PPSBx criteria remains unknown. We acknowledge that some men and urologists may not accept the uncertainty of omitting

a biopsy when there is a small chance of finding clinically significant cancer. Nonetheless, we believe these data will be informative to patients on AS and urologists considering the utility of a surveillance biopsy with stable surveillance parameters, such as an MRI. Fourth, for men who find reassurance and a reduction in anxiety by knowing their disease has not changed, these men may find value in performing a PPSBx despite a low probability in upgrading.

5 | CONCLUSIONS

Men meeting criteria for PPSBx had significantly less upgrading compared with men meeting criteria for FCSBx. The lowest probability of upgrading was seen among men with reassuring confirmatory biopsies, confirmatory MRIs, or surveillance MRIs meeting criteria for PPSBx. Men with non-reassuring confirmatory tests should not omit a surveillance biopsy, even if PPSBx criteria are met, due to the high proportion of men upgraded. These data may help providers and patients triage the intensity of surveillance testing and biopsies and be incorporated into future risk-adapted, data-driven AS protocols.

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CONFLICT OF INTEREST STATEMENT

Ji Qi, Arvin K. George, Stephanie Ferrante, Alice Semerjian, Kevin B. Ginsburg received salary support through MUSIC.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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