Oncology

Impact of Early Confirmatory Tests on Upgrading and Conversion to Treatment in Prostate Cancer Patients on Active Surveillance

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OBJECTIVES To assess the impact of confirmatory tests on active surveillance (AS) biopsy disease reclassification and progression to treatment in men with favorable risk prostate cancer (FRPC).

METHODS We searched the MUSIC registry for men with FRPC managed with AS without or with a confirmatory test. Confirmatory tests included (1) repeat prostate biopsy, (2) genomic tests, (3) prostate magnetic resonance imaging (MRI), or (4) MRI followed by a post-MRI biopsy. Confirmatory test results were deemed reassuring (RA) or nonreassuring (nonRA) according to predefined criteria. Kaplan-Meier curves and multivariable Cox regression models were used to compare surveillance biopsy disease reclassification-free survival and treatment-free survival.

RESULTS Of the 2,514 men with FRPC who were managed on AS, 1211 (48%) men obtained a confirmatory test. We noted differences in the 12-month unadjusted surveillance biopsy disease reclassification-free probability (68%, 83%, and 90%, $P < .0001$) and 24-month unadjusted treatment-free probability (55%, 81%, and 79%, $P < .0001$), for men with nonRA confirmatory tests, no confirmatory test, and RA confirmatory tests, respectively. Excluding patients with genomic confirmatory tests, men with RA confirmatory tests were associated with a lower hazard (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.38-0.84, $P = .005$) and men with nonRA confirmatory tests had an increased hazard (HR 1.97, 95% CI 1.22-3.19, $P = .006$) of surveillance disease reclassification compared with men without confirmatory tests in the multivariable model.

CONCLUSION These data suggest men with RA confirmatory tests have less surveillance biopsy reclassification and remain on AS longer than men with nonRA test results. Confirmatory tests may help risk stratify men considering active surveillance. UROLOGY 00: 1–10, 2020. © 2020 Elsevier Inc.

For men with newly diagnosed, favorable risk prostate cancer (FRPC), active surveillance (AS) has become the standard of care with the intent of delaying or avoiding overtreatment and its attendant morbidity.[1] Despite the previously demonstrated safety of AS in large cohorts,[2,3] some men with FRPC will still undergo immediate treatment.[4]

In order to aid in shared decision-making and facilitate the use of AS in appropriate men, MUSIC distributed a "Roadmap for FRPC" to all MUSIC practices based on previously developed appropriateness criteria for AS.[5,6] The Roadmap advocates for men with newly diagnosed FRPC to avoid immediate treatment and enter the Consideration Phase, a period after diagnosis during which consideration is given to AS. As part of the Consideration Phase, patients should undergo at least one confirmatory test within 6 months of diagnosis.[5] The purpose of confirmatory testing is to provide "confirmation," or increased confidence in the shared decision-making process.

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Options for confirmatory testing include: (1) repeat prostate biopsy (rBx), (2) a commercially available genomic test (Prolaris, Oncotype DX, or Decipher), (3) prostate magnetic resonance imaging (MRI) alone or (4) prostate MRI followed by post-MRI biopsy (pMRI-Bx). After appropriate shared decision-making, taking into account the results of confirmatory testing as well as many other factors, a decision is made to enter the "Surveillance Phase," during which long-term disease monitoring ensues, to embark on more testing, or to choose immediate treatment.

MUSIC has showed previously that men with reassuring confirmatory test results are more likely to choose AS,[7] demonstrating an impact of confirmatory testing on initial shared decision-making. Although other groups have investigated the association of MRI or genomics with surveillance outcomes,[8-11] to our knowledge, no other group has reported on their experience utilizing multiple types of confirmatory tests (rBx, genomics, MRI, and pMRI-Bx), as well as men without confirmatory tests, and their association with surveillance outcomes in a cohort of comparable size. Herein, we aim to describe the association of confirmatory test results with surveillance outcomes: surveillance biopsy disease reclassification and conversion to treatment during the Surveillance Phase.

MATERIALS AND METHODS

MUSIC maintains a prospective, state-wide registry of men undergoing prostate biopsy. Currently, 44 community, academic, and hospital-based practices contribute to the registry. The registry is maintained by trained data abstractors at each clinical site who review the primary medical record at fixed intervals and enter pertinent clinical and laboratory parameters. We analyzed registry data on men with newly diagnosed FRPC, which includes men whose diagnostic biopsy shows any volume Gleason Grade Group 1 (GG1) or low volume GG2 (≤3 cores positive, with no more than 50% involvement of any individual core of GG2).

A new round of counseling and shared decision-making is required following confirmatory testing. For this reason, results of confirmatory tests were deemed either reassuring (RA) or nonreassuring (nonRA). NonRA genomic studies were defined as ≥3% probability of prostate cancer mortality for Prolaris; >20% high-grade disease for OncotypeDx, or ≥0.45 for Decipher. While no clinically validated molecular classifier cut-points existed during the time period of this study, these cut-points have been published previously by others and are demarcated on the testing reports provided to patients and physicians.[12-14] A nonRA MRI was defined as PIRADS v2 score of 4 or 5.[15] A nonRA biopsy (whether rBx or pMRI-Bx) was defined as any volume of ≥GG2 if the diagnostic biopsy was GG1; or any volume of ≥GG3, >3 cores of GG2, or >50% of GG2 cancer involvement of any individual core if the diagnostic biopsy was low volume GG2. A biopsy was considered a pMRI-Bx if (1) the biopsy was obtained after the MRI and (2) was within 6-month of diagnosis regardless of whether performed with or without ultrasound/MRI fusion software. Patients with an MRI that was obtained prior to the diagnostic biopsy were excluded from analysis. Any biopsy that was obtained beyond 6-months of diagnosis, with or without an MRI prior, was considered a surveillance biopsy. For the purpose of this analysis, if more than one confirmatory test was obtained during the Consideration Phase, patients were grouped by their initial test. If the results of multiple tests were discordant, the initial test results were deemed nonRA vs RA based on consideration of all of the confirmatory tests together with this hierarchy: biopsy, then MRI, then genomics.

As defined by the MUSIC registry, patients were recorded as being on AS if (1) AS was explicitly described by the managing urologist as the primary management strategy in the primary medical record *and* (2) there was no definitive treatment within 6 months of the diagnostic biopsy. The outcome of disease reclassification on surveillance was defined as surveillance biopsy results being nonRA using the same criteria as described above.

Statistical Analysis

Patient demographics for patients with and without a confirmatory test were compared using the Chi-squared and Wilcoxon rank-sum test. Patients were classified into one of the three groups: (1) those with a nonRA confirmatory test, (2) those without confirmatory test, and (3) those with a RA confirmatory test. The primary outcomes of interest were freedom from disease reclassification at surveillance biopsy (among patients who received a surveillance biopsy), and freedom from definitive treatment (among all patients). We prefer the terminology "disease reclassification" instead of "disease progression" as we are unable to determine if the upgraded cancer found on the surveillance biopsy represents unsampled cancer which was missed on the diagnostic biopsy vs true grade progression. To avoid lead time bias, follow up time was calculated from the date of diagnosis to the date of surveillance biopsy reclassification or the date of the patient's last surveillance biopsy for patients that were not reclassified. For time to definitive treatment, follow up time was calculated as the date from diagnosis to the date of definitive treatment or last clinical contact for patients who remained on AS. Kaplan-Meier curves and the log rank test were used to compare the outcomes across the three groups. Sensitivity analysis was performed for both outcomes using the time from confirmatory test instead of time from diagnosis. To help account for differences in baseline demographic, clinical, pathologic factors between groups, multivariable Cox regression modeling was used to assess for an association between confirmatory test use and surveillance biopsy disease reclassification and transition from AS to curative treatment. Covariates included in the multivariable models were race, clinical T stage, biopsy Gleason score, family history of prostate cancer, age, insurance type, BMI, Charlson comorbidity index, prebiopsy Prostate Specific Antigen (PSA), number of cores positive for cancer, and maximal percent cancer involvement in a single core. Due to the unknown utility of genomic biomarkers in this disease space, analyses were repeated after excluding patients with a genomic test as confirmatory test. All statistical tests were two-sided with significance set at 0.05, and statistical analysis was performed with SAS 9.4.

RESULTS

From June 2016 through June 2018, 4192 men from 44 practices were diagnosed with FRPC, of which 1678 (40%) proceeded directly to treatment. Of the 2514 men who began AS, 1211 (48%) obtained a confirmatory test (Fig. 1). Median follow up from the time of diagnosis to the date of data analysis was 20.1

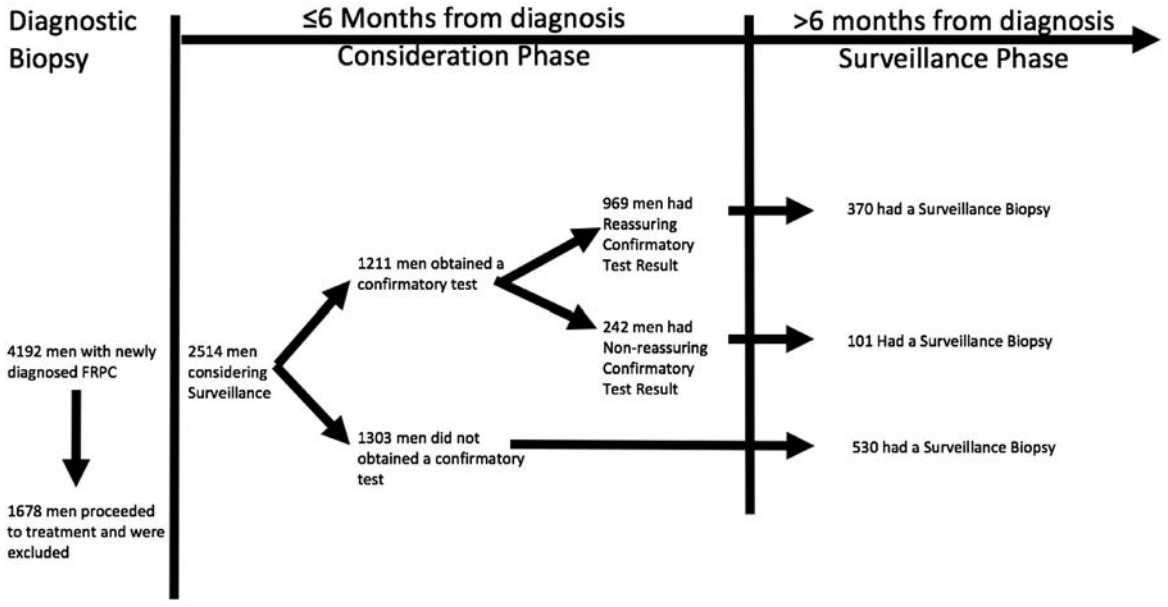

Figure 1. Study design flow chart of men with newly diagnosed favorable risk prostate cancer.

Table 1. Clinical and pathological demographics of patients with or without a confirmatory test

Variable	Confirmatory Test		*P*
	No	Yes	
	No. patients		
Race			
White	970 (82.1%)	950 (86.1%)	.009
Non-White	212 (17.9%)	154 (13.9%)	
Charlson comorbidity index			
0	935 (71.8%)	885 (73.1%)	.438
>=1	368 (28.2%)	325 (26.9%)	
cT			
T1c or less	1161 (90.0%)	1093 (91.2%)	.323
T2a or above	129 (10.0%)	106 (8.8%)	
Biopsy GS			
GS6	1167 (89.6%)	1004 (82.9%)	<.0001
GS7	136 (10.4%)	207 (17.1%)	
Family history			
Yes	356 (29.0%)	373 (31.9%)	.134
No	870 (71.0%)	798 (68.1%)	
Age			
<50	24 (1.8%)	34 (2.8%)	<.0001
50-60	252 (19.3%)	309 (25.5%)	
60-70	620 (47.6%)	586 (48.4%)	
>=70	407 (31.2%)	282 (23.3%)	
Insurance type			
Private	703 (54.5%)	688 (57%)	.284
Public	577 (44.7%)	514 (42.5%)	
None	11 (0.9%)	6 (0.5%)	
NCCN risk group			
Low	1019 (80.6%)	892 (75.1%)	.004
Int	232 (18.4%)	282 (23.8%)	
High	13 (1.0%)	13 (1.1%)	
BMI, median (IQR)	28.2 (25.8-31.7)	28.5 (25.8-31.7)	.843
Prediagnosis PSA, median (IQR)	5.5 (4.3-7.3)	5.3 (4.2-6.9)	.007
No. cores positive, median (IQR)	1 (1-2)	2 (1-3)	.010
Maximal % cancer involvement in a single biopsy core, median (IQR)	10 (5-20)	10 (5-25)	<.0001

BMI, body mass index; IQR, interquartile range.

Table 2. Clinical and pathological demographics of patients by the performance and result of confirmatory test

Variable	Performance and Result of Confirmatory test			*P*
	None	Nonreassuring	Reassuring	
No. patients	1303	242	969	
Race				
White	970 (82.1%)	186 (83.0%)	764 (86.8%)	.013
Non-White	212 (17.9%)	38 (17.0%)	116 (13.2%)	
Charlson comorbidity index				
0	935 (71.8%)	160 (66.1%)	725 (74.9%)	.018
>=1	368 (28.2%)	82 (33.9%)	243 (25.1%)	
cT				
T1c or less	1161 (90.0%)	214 (89.9%)	879 (91.5%)	.469
T2a or above	129 (10.0%)	24 (10.1%)	82 (8.5%)	
Biopsy GS				
GS6	1167 (89.6%)	169 (69.8%)	835 (86.2%)	<.001
GS7	136 (10.4%)	73 (30.2%)	134 (13.8%)	
Family history				
Yes	356 (29.0%)	71 (30.5%)	302 (32.2%)	.286
No	870 (71.0%)	162 (69.5%)	636 (67.8%)	
Age				
<50	24 (1.8%)	4 (1.7%)	30 (3.1%)	<.001
50-60	252 (19.3%)	52 (21.5%)	257 (26.5%)	
60-70	620 (47.6%)	116 (47.9%)	470 (48.5%)	
>=70	407 (31.2%)	70 (28.9%)	212 (21.9%)	
Insurance type				
Private	703 (54.5%)	123 (50.8%)	565 (58.5%)	.118
Public	577 (44.7%)	117 (48.3%)	397 (41.1%)	
None	11 (0.9%)	2 (0.8%)	4 (0.4%)	
NCCN risk group				
Low	1019 (80.6%)	134 (57.0%)	758 (79.6%)	<.001
Int	232 (18.4%)	94 (40.0%)	188 (19.7%)	
High	13 (1.0%)	7 (3.0%)	6 (0.6%)	
BMI, median (IQR)	28.2 (25.8-31.7)	28.4 (25.8-31.2)	28.6 (25.8-31.8)	.862
Prediagnosis PSA, median (IQR)	5.5 (4.3-7.3)	6 (4.4-8.2)	5.2 (4.2-6.7)	<.001
No. cores positive, median (IQR)	1 (1-2)	2 (1-3)	1 (1-2)	<.001
Maximal % cancer involvement in a single biopsy core, median (IQR)	10 (5-20)	20 (10-30)	10 (5-20)	<.001

(IQR 13.6-25.8) months. Clinical, demographic, and pathological characteristics of patients by the performance and result of confirmatory test are shown in Table 1 and Table 2, respectively. Clinical, demographic, and pathological factors by each type of confirmatory test are shown in Supplemental Table 1. Most factors were balanced between patients who did and did not obtain a confirmatory test. We found that more patients with low volume GS 7 and National Comprehensive Cancer Network (NCCN) intermediate risk disease obtained a confirmatory test compared with those that did not obtain a confirmatory test. Patients obtaining any confirmatory test tended to be younger than patients not obtaining confirmatory tests.

Surveillance Biopsy Disease Reclassification

Of the 1001 men who obtained a surveillance biopsy, median time to first surveillance biopsy was 10.9 months (interquartile range [IQR]: 7.5-13.9), 12.4 months (IRQ 9-15.6), and 13.0 months (11.7-15.2) for men with nonRA confirmatory tests, no confirmatory test, and RA confirmatory tests. Freedom from disease reclassification was the lowest among men with nonRA confirmatory tests, followed by men without confirmatory tests and RA confirmatory tests corresponding to an estimated unadjusted 12-month surveillance biopsy disease reclassification-free probability of 68%, 83%, and 90%, respectively (P <.0001, Fig. 2A). Sensitivity analysis showing freedom from surveillance biopsy disease reclassification calculated from date of the confirmatory test instead of date of diagnosis is shown in Supplemental Figure 1A.

Table 3 demonstrates clinical and demographic parameters associated with surveillance biopsy disease reclassification in the multivariable analysis. When all of the types of confirmatory tests were considered together, we noted men with nonRA confirmatory tests had a higher hazard of surveillance disease reclassification (hazard ratio [HR] 1.85, 95% confidence interval [CI] 1.32-2.61, P <.0001) compared with men without a confirmatory test. Men with RA confirmatory tests had lower hazard of surveillance biopsy disease reclassification compared with men without confirmatory tests, though this did not reach conventional statistical significance (HR 0.85, 95% CI 0.65-1.05, P = .125).

Due to the unknown utility of genomic biomarkers in this disease space,[1,9,16,17] sensitivity analysis was performed excluding the 289 patients with genomic confirmatory tests. Excluding these men, the unadjusted 12-month surveillance biopsy disease reclassification-free probability was 68%, 83%, and 92%, for men with nonRA, without, and RA confirmatory tests respectively (P <.0001, Fig. 2B). In multivariable analysis (Table 4), men with nonRA confirmatory tests had increased hazard of surveillance biopsy reclassification compared with men without confirmatory tests (HR 1.97, 95%

CI 1.22-3.19, $P = .006$). Additionally, we appreciated that men with a RA confirmatory test results had significantly lower hazard of surveillance biopsy reclassification (HR 0.57, 95% CI 0.38-0.84, $P = .005$) compared to those without confirmatory testing.

Treatment-Free Survival

The estimated unadjusted 24-month treatment-free probability was 55%, 81%, and 79% among those with a nonRA, without, and RA confirmatory tests, respectively ($P < .0001$, Fig. 2C). Sensitivity analysis showing treatment-free probability calculated

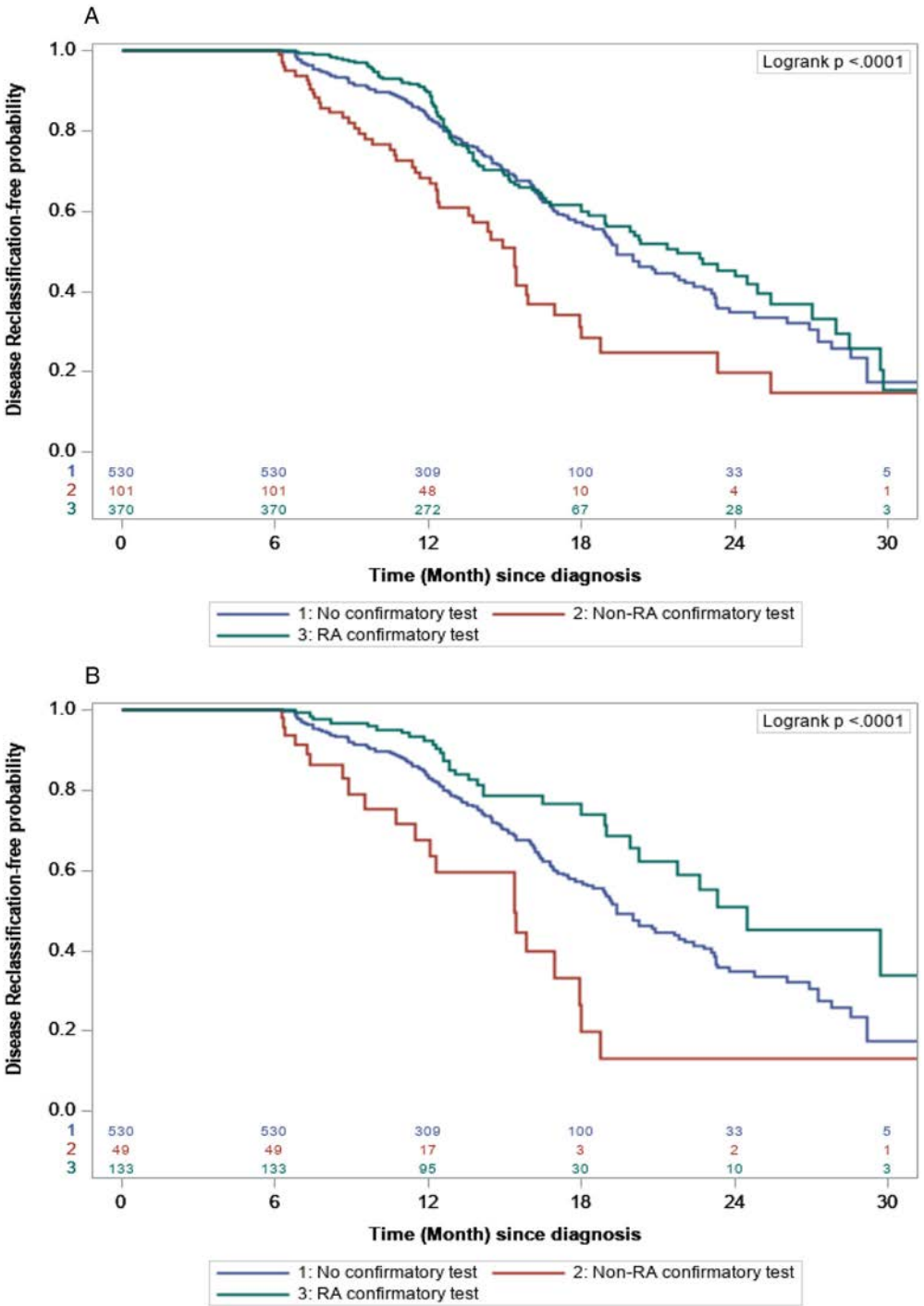

Figure 2. (**A**) Kaplan-Meier estimates of freedom from surveillance biopsy disease reclassification for AS patients by usage and result of confirmatory tests ($P < .0001$). (**B**). Kaplan-Meier estimates of freedom from surveillance biopsy disease reclassification for AS patients by usage and result of confirmatory tests, excluding patients with genomic confirmatory tests ($P < .0001$). (**C**). Kaplan-Meier estimates of freedom from treatment for AS patients by usage and result of confirmatory test ($P < .0001$). (**D**). Kaplan-Meier estimates of freedom from treatment for AS patients by usage and result of confirmatory test, excluding patients with genomic confirmatory tests ($P < .0001$). (Color version available online.)

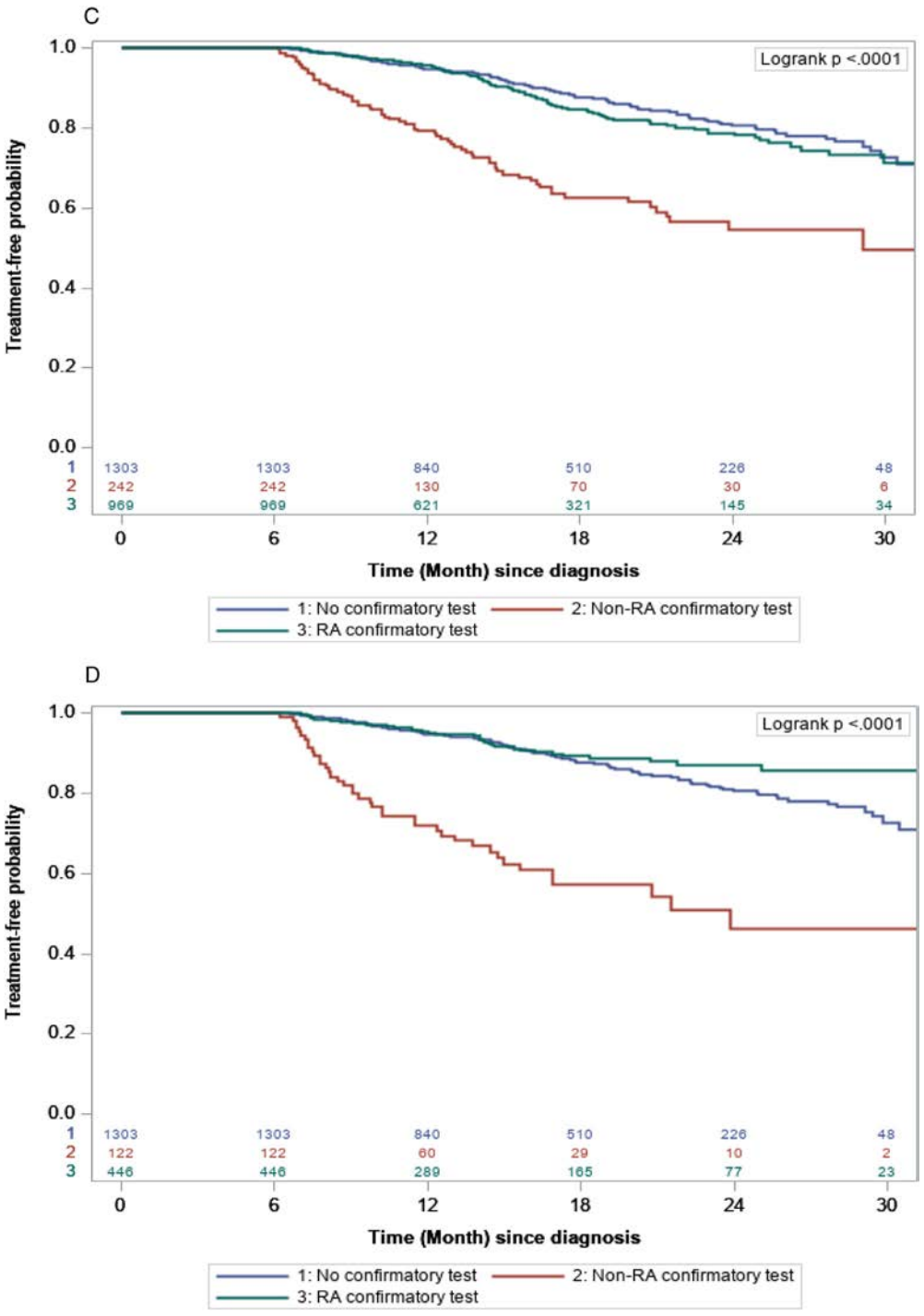

Figure 2. Continued

from date of the confirmatory test instead of date of diagnosis is shown in Supplemental Figure 1B.

On multivariable analysis, nonRA confirmatory tests were associated with decreased treatment-free probability (HR 2.45, 95% CI 1.79-3.34, P <.0001) compared with those without confirmatory tests (Tables 5). On the other hand, RA confirmatory tests were not found to be associated with the treatment-free probability (HR 1.06, 95% CI 0.82-1.36, P = .679). After excluding patients with genomic confirmatory tests (643 patients), the unadjusted 24-month treatment-free probability for the cohort was 46%, 81%, and 87% for patients with nonRA, without, and RA confirmatory tests (P <.0001, Fig. 2D). In multivariable analysis, nonRA confirmatory test results continued to be associated with decreased treatment-free probability (HR 3.19, 95% CI 2.17-4.69, p <0.001, Tables 6). Furthermore, with genomics excluded, RA confirmatory tests were associated with higher treatment-free

Table 3. Multivariable Cox regression model of factors associated with surveillance biopsy disease reclassification

Variable	HR	95% CI	*P*
Confirmatory test			
None		-Reference-	
Nonreassuring	1.85	(1.32, 2.61)	<.0001
Reassuring	0.83	(0.65, 1.05)	.125
Race			
White			
Non-White	1.04	(0.76, 1.42)	.809
Unknown	1.22	(0.84, 1.77)	.298
Charlson comorbidity index			
0			
≥1	1.24	(0.97, 1.57)	.080
cT			
T1c or less			
T2a or above	1.46	(0.98, 2.16)	.062
Biopsy GS			
GS6			
GS7	0.90	(0.66, 1.24)	.535
Family history			
No			
Yes	1.06	(0.83, 1.35)	.653
Unknown	1.06	(0.61, 1.83)	.832
Age			
<50			
50-60	0.56	(0.26, 1.17)	.123
60-70	0.69	(0.33, 1.43)	.320
≥70	0.89	(0.42, 1.88)	.752
Insurance type			
None			
Private	1.50	(0.60, 3.74)	.385
Public	1.47	(0.59, 3.66)	.406
BMI	1.02	(0.99, 1.04)	.147
Prediagnosis PSA	1.12	(0.87, 1.45)	.386
No. cores positive	1.07	(1.02, 1.13)	.010
Largest % cancer involvement	1.01	(1.01, 1.02)	<.0001

CI, confidence interval; HR, hazard ration.
Factors with HR >1 were associated with surveillance biopsy disease reclassification. Factors with HR<1 were protective against surveillance biopsy disease reclassification.

Table 4. Multivariable Cox regression model of factors associated with surveillance biopsy disease reclassification, excluding men with genomic confirmatory tests

Variable	HR	95% CI	*P*
Confirmatory test			
None		-Reference-	
Nonreassuring	1.97	(1.22, 3.19)	.006
Reassuring	0.57	(0.38, 0.84)	.005
Race			
White			
Non-White	1.15	(0.78, 1.71)	.486
Unknown	0.92	(0.55, 1.56)	.768
Charlson comorbidity index			
0			
≥1	1.12	(0.82, 1.52)	.486
cT			
T1c or less			
T2a or above	1.78	(1.05, 3.00)	.032
Biopsy GS			
GS6			
GS7	0.76	(0.48, 1.20)	.241
Family history			
No			
Yes	1.15	(0.86, 1.53)	.362
Unknown	1.02	(0.53, 1.97)	.946
Age			
<50			
50-60	0.57	(0.22, 1.46)	.240
60-70	0.65	(0.26, 1.66)	.371
≥70	0.95	(0.36, 2.48)	.918
Insurance type			
None			
Private	1.46	(0.58, 3.71)	.425
Public	1.34	(0.53, 3.40)	.535
BMI	1.01	(0.99, 1.04)	.271
Prediagnosis PSA	1.43	(1.02, 2.01)	.040
No. cores positive	1.05	(0.98, 1.12)	.139
Largest % cancer involvement	1.01	(1.01, 1.02)	<.001

Factors with HR >1 were associated with surveillance biopsy disease reclassification. Factors with HR<1 were protective against surveillance biopsy disease reclassification.

probability, though this did not reach conventional statistical significance (HR 0.71, 95% CI 0.49-1.04, $P = .08$)

COMMENT

The primary goal of active surveillance is to avoid treatment-related morbidity in patients in whom curative intervention in unlikely to yield benefit. However, it remains difficult to determine which newly diagnosed active surveillance candidates will be free of disease progression in the long term. MUSIC recommends a "Consideration Phase" after diagnosis during which at least one confirmatory test is obtained. The purpose confirmatory testing is to provide affirmation of AS candidacy and to aid in the shared-decision making process such that the patient can embark on surveillance with greater confidence.

We have previously demonstrated that confirmatory test results impact decision-making in patients with newly diagnosed FRPC[7]. The purpose of the current study was to determine whether results of confirmatory tests impact longer term surveillance outcomes in terms of freedom from disease reclassification and freedom from treatment, thus justifying their use and impact on shared-decision making.

Not surprisingly, patients with nonRA confirmatory tests had more disease reclassification and conversion to treatment during the surveillance phase compared with patients either with RA confirmatory tests or without confirmatory tests. Despite this fact, a significant portion of men with nonRA confirmatory tests still chose AS as their initial management strategy. This decision is supported by our data that shows only a small portion of men (~1/3) with nonRA confirmatory tests underwent surveillance biopsy disease reclassification during their first year on AS. The shared decision-making process while deciding on treatment vs AS for men with newly diagnosed FRPC is complex and involves innumerable factors with variable weights and importance from patient to patient. The

Table 5. Multivariable Cox regression model of factors associated with treatment-free survival

Variable	HR	95% CI	*P*
Confirmatory test			
None		-Reference-	
Nonreassuring	2.45	(1.79, 3.34)	<.0001
Reassuring	1.06	(0.82, 1.36)	.679
Race			
White			
Non-White	1.10	(0.80, 1.52)	.564
Unknown	1.48	(1.03, 2.12)	.036
Charlson comorbidity index			
0			
≥1	0.99	(0.77, 1.27)	.924
cT			
T1c or less			
T2a or above	1.54	(1.09, 2.19)	.015
Biopsy GS			
GS6			
GS7	1.43	(1.06, 1.93)	.021
Family history			
No			
Yes	0.94	(0.73, 1.20)	.595
Unknown	1.00	(0.54, 1.85)	.995
Age			
<50			
50-60	0.89	(0.43, 1.84)	.750
60-70	0.68	(0.33, 1.39)	.289
≥70	0.61	(0.28, 1.31)	.203
Insurance type			
None			
Private	1.05	(0.43, 2.57)	.919
Public	1.00	(0.40, 2.48)	1.000
BMI	1.00	(0.98, 1.02)	.908
Prediagnosis PSA	1.19	(0.95, 1.49)	.129
No. cores positive	1.05	(0.98, 1.12)	.200
Largest % cancer involvement	1.01	(1.01, 1.02)	<.0001

Factors with HR >1 were associated with conversion from active surveillance to treatment. Factors with HR <1 were protective against conversion from active surveillance to treatment.

Table 6. Multivariable Cox regression model of factors associated with treatment-free survival, excluding men with genomic confirmatory tests

Variable	HR	95% CI	*P*
Confirmatory test			
None		-Reference-	
Nonreassuring	3.19	(2.17, 4.69)	<.0001
Reassuring	0.71	(0.49, 1.04)	.080
Race			
White			
Non-White	1.07	(0.71, 1.61)	.748
Unknown	1.28	(0.79, 2.10)	.319
Charlson comorbidity index			
0			
≥1	0.96	(0.70, 1.32)	.809
cT			
T1c or less			
T2a or above	1.58	(1.02, 2.46)	.043
Biopsy GS			
GS6			
GS7	1.44	(0.96, 2.15)	.077
Family history			
No			
Yes	1.09	(0.82, 1.47)	.546
Unknown	1.12	(0.56, 2.23)	.744
Age			
<50			
50-60	1.04	(0.37, 2.89)	.943
60-70	0.84	(0.30, 2.33)	.738
≥70	0.85	(0.30, 2.44)	.763
Insurance type			
None			
Private	0.89	(0.36, 2.21)	.803
Public	0.92	(0.37, 2.31)	.865
BMI	1.01	(0.99, 1.04)	.389
Prediagnosis PSA	1.25	(0.92, 1.69)	.163
No. cores positive	1.04	(0.96, 1.13)	.331
Largest % cancer involvement	1.01	(1.01, 1.02)	<.0001

Factors with HR >1 were associated with conversion from active surveillance to treatment. Factors with HR <1 were protective against conversion from active surveillance to treatment.

patient must weigh their oncologic parameters, competing health issues, urinary and sexual function, and personal values and wishes. Confirmatory tests are just one of the many factors for patients to consider while choosing between AS and treatment. Confirmatory tests are meant to help patients have additional data regarding their treatment options, not to replace shared decision making and dictate their treatment and behavior. Therefore, certain men with nonRA confirmatory tests may still elect to pursue AS, though they might consider a more intensive surveillance protocol while on AS due to concern of increased risk of disease reclassification.

Regarding reassuring confirmatory test results, we initially found no significant difference in surveillance biopsy reclassification outcomes when comparing men with RA confirmatory test results to men without confirmatory tests. Based on the uncertain utility of genomic tests[1,9,16,17] we repeated the analysis excluding genomic tests. We then found that RA confirmatory tests were protective against surveillance biopsy disease reclassification. In addition, as mentioned above, men with nonRA confirmatory tests had increased hazard of surveillance biopsy reclassification in our multivariable model. Taken together, these data suggest that patients gain valuable information regarding future surveillance biopsies from both RA and nonRA results. We believe these data justify the concept of confirmatory testing as a method of providing confidence and aid in shared decision-making during the Consideration Phase; however, it is MRI and biopsy that provide the greatest value, rather than genomic testing.

Although disease reclassification and conversion to treatment are important surrogate endpoints, it remains unknown how the use of confirmatory tests affects the development of metastasis and prostate cancer-specific mortality. Furthermore, we advocate for the early use of confirmatory tests as we believe it seems logical to know if more aggressive disease is present around the time of diagnosis to aid in the shared decision-making process. It remains unknown whether patients harboring intermediate or high-risk prostate cancer

initially managed on AS and converting to treatment will have inferior outcomes compared with patients with higher risk disease identified and treated earlier.

Limitations of this study include its retrospective design and the registry nature of the data. Patients were not randomized and the choice of confirmatory test was determined by the managing physician. However, our study adds to the growing body of evidence investigating the association of genomics and MRI on future disease reclassification and ability to persist on AS. We acknowledge that, ideally, prospective, randomized trials are necessary to fully elucidate the effect of confirmatory tests on surveillance outcomes, yet these data are currently lacking. The structure of the registry does not record location or differentiate if the cores positive were from a systematic biopsy or targeted biopsy, leading to the possibility that an area may be sample twice or oversampled from multiple cores taken of a targeted lesion or the accompanied systematic biopsy. Furthermore, despite having one of the largest active surveillance cohorts, this sample was not large enough to do regression analysis with each type of confirmatory test (genomics, MRI, pMRI-Bx, or rBx) individually. Different clinicians and patients will have different thresholds for when to obtain a surveillance biopsy or transition to curative treatment, as potentially anxiety from not obtaining a confirmatory test may influence the timing of these outcomes. Due to the complexity of shared decision making, additional factors which likely influence the decision to obtain a surveillance biopsy or transition to treatment were not measured in this study and may influence the results.

CONCLUSION

Despite relatively short follow-up, our results regarding the use of early confirmatory test are encouraging. These data show that the concept of using confirmatory tests to influence shared decision-making is valid. Although the different confirmatory tests vary in their ability to predict disease reclassification and conversion to treatment, men with reassuring confirmatory tests can be more confident in their decision to pursue AS. Additionally, although nonreassuring confirmatory tests are cause for concern, such results should not reflexively exclude men from AS. Further research with longer follow-up on the impact of confirmatory tests on surveillance outcomes is needed.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2020.07.067.

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EDITORIAL COMMENT

The authors describe a large state-wide retrospective cohort of men diagnosed with favorable risk prostate cancer (FRPC) on active surveillance (AS) with or without follow up confirmatory testing within 6 months of diagnosis. Confirmatory testing included repeat prostate biopsy, MRI, MRI with biopsy or a tissue-based genomic classifier within 6 months of diagnosis. This study further evaluates the MUSIC initiative, a "Roadmap for FRPC," during AS and the role of additional testing for the "Consideration Phase" of AS to help determine appropriate candidates for the "Surveillance Phase."[1]

The authors found that nonreassuring confirmatory testing was associated with 12-month reclassification-free probability of 68% vs 90% for a reassuring (RA) confirmatory test. The 24-month treatment free probability for nonreassuring was 55% vs 79% for

reassuring confirmatory testing. Importantly, the authors acknowledge limitations including the lack of a uniform confirmatory testing protocol and instead describe a real-world scenario where the choice and utilization of confirmatory testing is determined by the managing physician. Many of the patients in the study did not have a surveillance biopsy. Additionally, this study excludes patients undergoing MRI prior to diagnostic biopsy, a practice that is becoming more common and, in this study, may result in a selected cohort more prone to misclassification.[2]

There is considerable latitude for urologist to consider confirmatory testing including somatic genetic testing and MRI in the NCCN guidelines.[3] MRI in the AS setting has been demonstrated in a prospective setting[4,5] and from a very practical standpoint can allow for targeting during surveillance biopsy. The data on utility of genomic confirmatory testing as the role in AS are maturing. How to combine these data leads to interesting possibilities — especially when the testing gives discordant results.

Importantly, this study begins to address a gap in our knowledge of the clinical utility of noninvasive confirmatory tests in AS. The use of nonreassuring noninvasive testing to bring a patient off AS should be approached with caution. Without longer term outcomes such as surgical pathology, recurrence, and ultimately survival it is unclear whether the use of confirmatory testing truly improves the safety of AS.

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