Oncology

Overtreatment and Underutilization of Watchful Waiting in Men With Limited Life Expectancy: An Analysis of the Michigan Urological Surgery Improvement Collaborative Registry

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OBJECTIVE To determine rates of watchful waiting (WW) vs treatment in prostate cancer (PCa) and limited life expectancy (LE) and assess determinants of management.

MATERIALS AND METHODS Patients diagnosed with PCa between 2012 and 2018 with <10 years LE were identified from the Michigan Urologic Surgery Improvement Collaborative registry. Multinomial logistic regression models were used to identify factors associated with management choice among NCCN low-risk PCa patients. Data from high-volume practices were analyzed to understand practice variation.

RESULTS Total 2393 patients were included. Overall, WW was performed in 8.1% compared to 23.3%, 25%, 11.2%, and 3.6% who underwent AS, radiation (XRT), prostatectomy (RP), and brachytherapy (BT), respectively. In men with NCCN low-risk disease (n = 358), WW was performed in 15.1%, compared to AS (69.3%), XRT (4.2%), RP (6.7%), and BT (2.5%). There was wide variation in management among practices in low-risk men; WW (6%-35%), AS (44%-81%), and definitive treatment (0%-30%). Older age was associated with less likelihood of undergoing AS vs WW (odds ratio [OR] 0.88, $P < .001$) or treatment vs WW (OR 0.83, $P < .0001$). Presence of ≥cT2 disease (OR 8.55, $P = .014$) and greater number of positive biopsy cores (OR 1.41, $P = .014$) was associated with greater likelihood of treatment vs WW and Charlson comorbidity score of 1 vs 0 (OR 0.23, $P = .043$) was associated with less likelihood of treatment vs WW.

CONCLUSION Wide practice level variation exists in management for patients with low- and favorable-risk PCa and <10-year LE. Utilization of WW is poor, suggesting overtreatment in men who will experience little benefit. UROLOGY 00: 1–7, 2020. Published by Elsevier Inc.

While the widespread practice of prostate-specific antigen (PSA)-based screening, along with the drive and adoption of genomic testing and MRI for cancer detection, has undoubtedly led to an increase in prostate cancer diagnosis, variable data exist to suggest a reduction in mortality associated with screening.[1,2] This is not unexpected, however, given the largely indolent nature of prostate cancer, with 10-year disease-specific survival estimates >95% with conservative management for low-risk disease.[3-5] Additionally, concerns regarding overdiagnosis and overtreatment of the general population remain, as screening and definitive therapy is not without harm. In fact, previous studies have shown a significant reduction in quality-of-life measures and diminished mortality benefit due to long-term effects of PSA-screening and treatment, and changes in quality-of-life were significantly associated with

Ψ *Co-first authors.*

Funding: *The Michigan Urological Surgery Improvement Collaborative is supported by the by Blue Cross Blue Shield of Michigan as part of the Blue Cross Blue Shield of Michigan Value Partnerships Program.*

Author Contributions: *U.S., J.J.T., J.Q., and A.K.G. conceived the study and analyses; J.Q. performed data processing and data analysis with assistance from U.S., J.J.T., A.K.G., and all other authors; U.S., J.J.T., J.Q., and A.K.G. wrote the manuscript. All authors discussed results, commented, edited and agreed on the submission of the manuscript.*

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Submitted: March 24, 2020, accepted (with revisions): July 20, 2020

patient-related satisfaction.[6-9] Given these factors, a consensus regarding the management of clinically localized prostate cancer remains elusive.[10]

Active surveillance (AS) has thus emerged as a practical approach to minimize risk of overtreatment without compromising oncological safety, and growing evidence suggests integration of this strategy into community-based practices.[11] Furthermore, utilization of AS in the appropriately selected patient has yielded favorable long-term outcomes, with low rates of metastasis and prostate cancer mortality.[12-15] However, there are limited data on the utility of watchful waiting (WW), or observation until presence of symptoms, as a viable management option, especially in those patients with limited life expectancy (LE). While AS aims to defer or delay curative treatment in eligible men, WW intends to avoid the morbidity associated with treatment in men with limited LE unlikely to benefit from treatment at any point. In 2017, the Michigan Urological Surgery Improvement Collaborative (MUSIC) introduced the concept of a "roadmap" for support in management of favorable-risk prostate cancer (https://musicurology.com/wp-content/uploads/2016/12/MUSIC-AS-Roadmap-Patient-Facing_v2.pdf), suggesting that men with limited LE be followed with annual PSA alone, without the need for tumor volume re-assessment (biopsy or prostate MRI) unless clinically indicated.[16,17] Through dissemination of the roadmap, the maturation of long-term surveillance data, and various quality improvement activities, appropriate selection to AS has increased. However, the effect on use of WW in clinical practice is still unclear.

MUSIC is a physician-led partnership of community and academic urology practices within the state of Michigan, with the goal of improving the quality of urological care. Using this unique resource, we sought to better understand the current landscape of management options being utilized in patients with localized prostate cancer and limited LE and understand the factors that guide management decisions in these patients.

METHODS

Data Registry and Study Population

Data were obtained from the MUSIC prostate cancer registry. MUSIC is a physician-led quality improvement collaborative of 44 academic and community urology practices, including over 250 urologists, within the state of Michigan. Data are prospectively collected by trained abstractors at participating sites and is routinely updated and validated. For this analysis, patients with prostate cancer between January 2012 and September 2018 with LE <10 years were included. LE was calculated as previously described by Hawken et al.[18] Briefly, this calculator was initially developed as a comorbidity-adjusted model to improve cancer screening strategies using Medicare claims data by Cho et al.[19] However, data regarding at what age patients would have <10 years LE, the most relevant metric for prostate cancer risk-stratification when making treatment decisions, were difficult to derive. As a result, this was streamlined to facilitate LE incorporation for clinical decision-making for patients with prostate cancer. Comorbidities were assigned point values based on their relative impact on survival, and the ages where LE was <10 years was reported, stratified by comorbidity group and race. This allowed providers to easily determine at what age patients were expected to have <10 years LE.[18] Risk-stratification was performed in accordance with NCCN guidelines for prostate cancer management, with favorable-risk being Gleason Grade 1 or low-volume Gleason Grade 2 (1-3 cores positive, no cores with >50% of 3 + 4).[20] Patients were considered to be on WW or an AS protocol only if explicitly stated as such in documentation by their provider. Institutional review board approval was not needed, as each practice was of exempt or nonregulated status.

Statistical Analysis

Management decisions were summarized for the entire cohort and by NCCN risk group. Among patients with NCCN low-risk cancer, clinical and demographic characteristics of patients were compared by management group (WW vs AS vs definitive treatment) using Wilcoxon rank-sum test for continuous variables and chi-squared test for categorical measures. To measure practice-level management variation, we calculated management decisions across participating practices. Predictors of management choices were identified using a multinomial logistic regression model. All analyses were performed in SAS 9.4, and statistical significance was set at 0.05.

RESULTS

The study population included 2393 patients with prostate cancer and <10 years LE at the time of diagnosis. The median patient age among those who underwent WW, AS, and definitive treatment was 79.5 years (interquartile range [IQR] 74.5-81.9), 74.2 (IQR 70.2-80.5), and 72.8 (IQR 68.6-78.9), respectively. A total of 14.9% of patients harbored NCCN low-risk prostate cancer, as compared to 40.7% with intermediate-risk and 41.5% with high-risk disease. Among the overall cohort, WW was performed in 194 (8.1%) men and AS in 558 (23.3%). An additional 647 (27.0%) underwent primary androgen-deprivation therapy (ADT), 598 (25.0%) underwent external beam radiation therapy (EBRT), 268 (11.2%) underwent radical prostatectomy (RP), and 85 (3.6%) underwent brachytherapy. The remaining 41 (1.7%) patients underwent chemotherapy (0.2%), cryotherapy (1.5%), high-frequency ultrasound ablation (HIFU), or immunotherapy (Table 1).

Among the 358 NCCN low-risk patients with <10 years LE, 54 (15.1%) were managed with WW, 248 (69.3%) with AS, and 56 (15.6%) underwent treatment. We explored demographic and clinical factors across management type (Table 2). As compared to AS and treatment, men who underwent WW were older (median age 79.5 vs 74.2 vs 72.8 years, $P < .0001$), less likely to harbor cT2 disease (5.6% vs 12.1% vs 25%, $P = .007$), and had a lower median number of positive biopsy cores (1 vs 1 vs 3, $P < .0001$). We performed multivariable analysis to identify patient-level factors associated with type of management. Age was the only significant factor in comparing the WW vs AS subgroups (Table 3). For each additional year of age, the odds of undergoing WW as compared to AS increased by a factor of 1.13 (95% confidence interval [CI] 1.06, 1.21). As compared to undergoing treatment, the odds of undergoing WW were significantly decreased in men with clinical stage T2 disease

Table 1. Treatment type for patients with a life expectancy <10 years, overall and by NCCN risk groups

		NCCN Risk Group			
Treatment Option	Overall (n = 2393)	Low (n = 358)	Favorable Intermediate (n = 351)	Unfavorable Intermediate (n = 623)	High (n = 994)
Active surveillance	558 (23.3%)	248 (69.3%)	139 (39.6%)	111 (17.8%)	26 (2.6%)
Watchful waiting	194 (8.1%)	54 (15.1%)	37 (10.5%)	44 (7.1%)	41 (4.1%)
ADT	647 (27.0%)	7 (2.0%)	18 (5.1%)	88 (14.1%)	533 (53.6%)
Brachytherapy	85 (3.6%)	9 (2.5%)	19 (5.4%)	33 (5.3%)	23 (2.3%)
Chemotherapy	4 (0.2%)	-	-	2 (0.3%)	2 (0.2%)
Cryotherapy	37 (1.5%)	1 (0.3%)	5 (1.4%)	13 (2.1%)	18 (1.8%)
EBRT	598 (25.0%)	15 (4.2%)	70 (19.9%)	235 (37.7%)	270 (27.2%)
HIFU	1 (0.0%)	-	-	1 (0.2%)	-
Immunotherapy	1 (0.0%)	-	-	-	1 (0.1%)
RP	268 (11.2%)	24 (6.7%)	63 (18.0%)	96 (15.4%)	80 (8.0%)

Table 2. Patient characteristics by treatment type among NCCN low-risk group

Variable	Watchful Waiting	Active Surveillance	Treatment	*P*
No. patients	54	248	56	
Family history of PCa	13 (27.1%)	52 (22.3%)	12 (22.2%)	.767
Race				
White	46 (85.2%)	210 (84.7%)	49 (87.5%)	.880
African American	7 (13.0%)	33 (13.3%)	7 (12.5%)	
Other	1 (1.9%)	5 (2.0%)		
Clinical T stage				
T1	51 (94.4%)	218 (87.9%)	42 (75.0%)	.007
T2a	3 (5.6%)	30 (12.1%)	14 (25.0%)	
Charlson comorbidity index				
0	11 (20.4%)	35 (14.1%)	9 (16.1%)	.651
1	23 (42.6%)	105 (42.3%)	20 (35.7%)	
≥2	20 (37.0%)	108 (43.5%)	27 (48.2%)	
Age, median (IQR)	79.5 (74.5-81.9)	74.2 (70.2-80.5)	72.8 (68.6-78.9)	.000
No. positive cores, median (IQR)	1 (1-2)	1 (1-2)	3 (1-4)	<.0001
PSA, median (IQR)	6.1 (4.6-7.4)	5.5 (4.2-6.8)	5.6 (4.1-7.4)	.439

Table 3. Predictors of treatment among low-risk patients

	AS vs WW		Treatment vs WW	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Family history of PCa	0.69 (0.31,1.54)	.363	0.68 (0.24,1.91)	.466
Non-White vs White	1.14 (0.43,3.00)	.791	0.91 (0.26,3.20)	.886
cT2 (vs cT1)	3.63 (0.75,17.68)	.111	8.55 (1.55,47.20)	.014
Charlson 1 vs 0	0.55 (0.20,1.52)	.247	0.23 (0.06,0.96)	.043
Charlson ≥2 vs 0	0.68 (0.23,2.03)	.493	0.39 (0.09,1.72)	.215
Age	0.88 (0.83,0.94)	.000	0.83 (0.76,0.91)	<.0001
No. positive cores	1.08 (0.84,1.39)	.531	1.41 (1.07,1.85)	.014
PSA (logarithm)	0.99 (0.54,1.80)	.966	1.00 (0.46,2.16)	.996

(odds ratio [OR] 0.12 vs cT1, 95% CI 0.02, 0.65), and more positive biopsy cores (OR 0.71 per additional core, 95% CI 0.53, 0.93). The odds of undergoing WW were significantly higher in older men (OR 1.20 per year, 95% CI 1.10, 1.32) and those with higher Charlson comorbidity score (OR 4.29 for score 1 vs 0, 95% CI 1.04, 17.62). In patients with low-risk disease, those undergoing AS underwent a greater proportion of MRI, biopsies, and genomic tests than those undergoing WW at 1-year follow-up (Supplementary Table 1).

There were 13 MUSIC practices that managed at least 10 patients with low-risk prostate cancer and limited LE and thus were included in the practice-level analysis. The proportion of men managed with WW varied across practices, ranging from 6% to 35% (median 14%). Similarly, the use of AS (44%-81%) and definitive treatment (0%-30%) varied widely (Fig. 1).

DISCUSSION

While prostate cancer remains a widely heterogeneous disease, for men with clinically localized prostate cancer

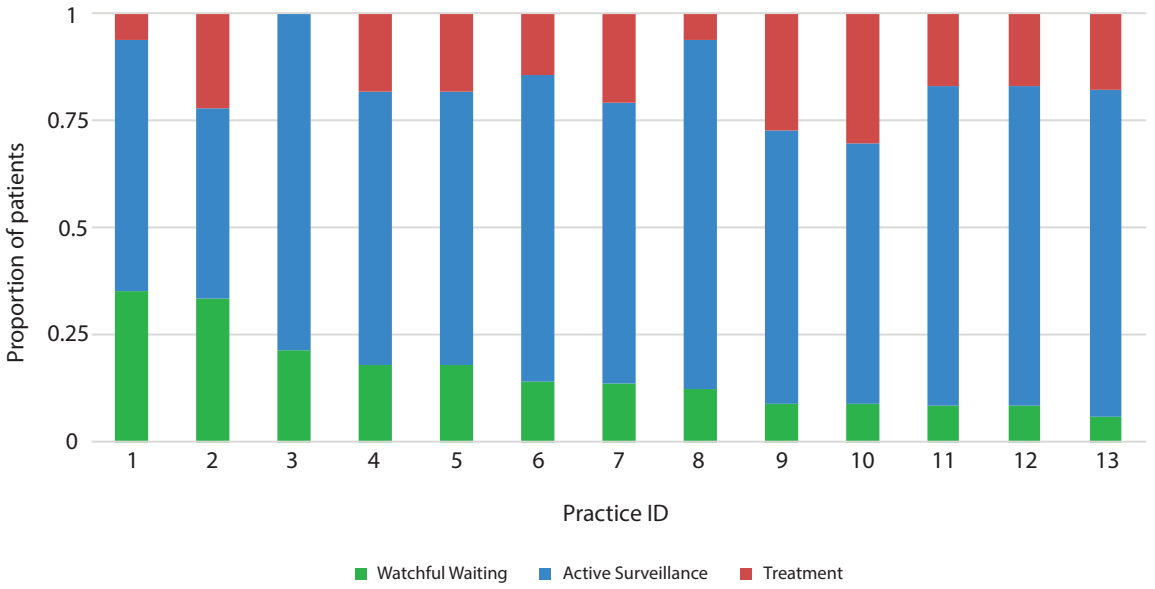

Figure 1. Practice level variation among treatment decision in low-risk PCa: Among MUSIC PCa patients with limited life expectancy, there was wide practice-level variation in rates of WW (6%-35%), AS (44%-81%), and definitive treatment (0%-30%).

randomized clinical trials have not been able to demonstrate a significant survival advantage with definitive treatment compared to conservative management.[21,22] The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) showed treatment with radical prostatectomy, compared with WW, improved survival outcomes, but these results were largely limited to those <65 years of age with intermediate-risk disease, and 30% of patients within the WW cohort had Gleason 7-10 cancer.[23-25] The Prostate Cancer Intervention Versus Observation Trial (PIVOT) showed no reduction in prostate cancer-specific mortality or overall mortality with surgery when compared to WW, and this held true through nearly 20 years of follow-up. Small differences in mortality, if present, were again likely limited to those with intermediate and high-risk disease, though the study was not adequately powered to detect these distinctions between subgroups.[21,22]

Though SPCG-4 and PIVOT were conducted in contrasting eras of PSA-screening, suggesting longer follow-up is needed for a true delineation of outcomes between observation and surgery due to lengthier lead-time in the PIVOT cohort, these data nonetheless provide a foundation for WW as a reliable route for patients with low-risk, clinically localized prostate cancer and limited LE. Current guidelines recommend LE calculation as a critical tool to inform clinical management of prostate cancer, with generally more conservative approaches recommended in those with <10 years LE.[20] Despite this, observational studies have shown utilization of WW as a primary treatment modality is <10% among clinical practices.[10]

Combined with data suggesting the lifetime risk of prostate cancer diagnosis is 11% with corresponding risk of death only 2%, the basis for WW in select patients is substantial, especially in those with limited LE.[13] Therefore, we evaluated the contemporary landscape of primary management in a prospectively monitored cohort of men with clinically localized prostate cancer and limited LE, and sought to identify the determinants of management selection.

Analysis of our cohort suggests WW remains underutilized in men with life expectancy <10 years, with rates of 8.1% in the overall population and 15.1% of those with low-risk disease. As could be expected, there was decreased utilization of WW with increasing disease severity; the use of WW was 15.1% in low-risk men, 10.5% in favorable-intermediate risk men, 7.1% in unfavorable-intermediate risk men, and 4.1% in high-risk disease. Notably, primary ADT remained commonly used in this setting, despite previous data showing no survival improvement in a majority of men and clinical guidelines recommending against primary ADT.[26] It is important to note all patients included in this analysis harbored localized cancer and limited life expectancy <10 years using a previously developed LE calculator to help inform treatment decisions in prostate cancer.[18] As such, the entire cohort is theoretically of good candidacy for WW, and therefore the reported utilization rate represents substantial underutilization of WW and overtreatment of patients. Not only does this have implications for patients due to adverse effects associated with treatment, but also for the population at-large due to increased healthcare costs of definitive treatment.[27]

Furthermore, we observed that older men and those with lower disease volume were more likely to pursue WW. While this is congruent with prior observations in this space, our data suggest wide variation in clinical practice across individual sites—a finding that remained consistent in those with low-risk cancer.[28] Specifically,

the use of WW ranged from 6% to 35% of patients across participating MUSIC practices. These data suggest that clinical decision-making is likely dependent on both clinicopathologic parameters and nondisease-related factors. These may include physician training, geography, payer reimbursement patterns, medico-legal considerations, availability of resources, and personal patient experiences contributing to shared decision-making, among others. In fact, this is consistent with prior data highlighting that nonclinical socioeconomic factors, such as ethnicity and income, are associated with use of WW rather than definitive treatment.[29]

Our study is not without limitations. First, although LE was based upon a previously validated calculator, this remains difficult to predict and may introduce substantial uncertainty in clinical decision-making. Additionally, we were unable to confirm how, or even if, providers are calculating LE prior to making clinical management decisions. Second, we were unable to identify patients that are symptomatic from their disease, and consequently unable to understand whether presence of symptoms contributed to high rate of definitive treatment. Still, this is only likely to apply in a minority of cases. Additionally, the MUSIC registry does not track any measures of mobility or functional status. Patient-reported outcomes are now being collected within the MUSIC collaborative, and future studies will be needed to understand the impact of these measures into clinical decision-making. Furthermore, WW patients within the MUSIC registry are only followed for 1 year, and as a result, long-term oncological outcomes were not assessed. Additionally, identification of patients who were on WW was performed based on designation within documentation by providers, lending to the presumption that urologists distinguish between WW and AS, though this may not always be the case. While this continues to be a challenge, the strength of the MUSIC cohort is the ability to leverage its specialized, trained data abstractors to achieve greater granularity within the database. Additionally, substantial provider education has been disseminated regarding AS/WW candidacy and surveillance strategies for each via in-person practice site visits, triannual collaborative-wide meetings, and provider/practice-level reports that would significantly mitigate misclassification. Additionally, our data show that those undergoing AS undergo greater number of biopsies, MRIs, and genomic tests compared to those on WW, suggesting providers are distinguishing between these patients. Finally, the MUSIC registry does not track various socioeconomic factors within the registry, such as patient income and physician training, among others. Therefore, it is difficult to draw conclusions as to the factors contributing to these observations.

These limitations notwithstanding, this is the first study to our knowledge evaluating the landscape and determinants of primary management in patients with clinically localized prostate cancer and limited LE. Given the indolence of low-risk prostate cancer, the question arises as to whether men should be subjected to the burden of testing of AS or treatment, specifically in those with limited LE. Further studies are needed to understand if LE calculation prior to treatment would result in increased utilization of conservative measures, such as WW and AS. Our data suggest that utilization of WW within this specific cohort is low, implying overtreatment of patients who are likely to experience minimal benefit.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2020.07.047.

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EDITORIAL

Results from several key randomized trials have contributed enormously to our understanding of the natural history of localized prostate cancer and the relative impact of treatment. Three screening trials, the Prostate, Lung, Colon and Ovarian (PLCO) trial, the European Randomized Screening for Prostate Cancer (ERSPC) trial, and the Cluster randomized trial of PSA testing for prostate cancer (CAP) trial have clearly shown us the prostate-specific antigen (PSA) testing can identify clinically significant prostate cancer in an early phase, but over 75% of the cases identified by screening are likely to be low-risk Gleason Grade Group 1 and 2 disease.[1-3] Less than 25% of men with screen detected prostate cancer will harbor intermediate or high-grade disease. Results from 3 treatment trials, the Scandinavian Prostate Cancer Group 4 (SPCG4) trial, the Prostate Intervention Versus Observation (PIVOT) trial and the Prostate testing for cancer and treatment (ProtecT) trial have all shown us the radical prostatectomy is only likely to benefit men with intermediate grade disease AND who have at least a 15-year potential survival.[4-6] It is unlikely that radiation provides better outcomes.

Based upon these findings, the MUSIC has once again highlighted an important area for improvement in clinical management. In their manuscript entitled *Overtreatment and underutilization of watchful waiting in men with limited life expectancy*, the authors raise the concern that many men are undergoing screening and treatment for a disease that is highly unlikely to cause any morbidity during their life time. The primary outcome of aggressive assessment and treatment protocols for these men is decreased quality of life and greater expense to the patients and greater costs to the health care system.

For men with a life expectancy less than ten or even 15 years, the threshold for prostate biopsy should be significantly higher than for younger men. Before considering a biopsy in older men PSA values should be at least 10 ng/mL or higher and should show evidence of exponentially increasing values.[7] These are the older men more likely to harbor clinically significant disease and therefore who might benefit from anti-androgen therapy should they develop evidence of metastatic disease. For those who are found to have intermediate and high grade disease, annual PSA testing is sufficient to identify those who may eventually require antiandrogen intervention. This is the essence of watchful waiting as suggested by the MUSIC collaborative. Active surveillance protocols including multiparametric magnetic resonance (MRI) testing, repeat biopsies and genomic testing are only appropriate for men with at least a fifteen year potential survival and who are likely to benefit from surgery or radiation in the future should they demonstrate evidence of clinically significant disease. For all others, these tests accomplish little other than exposing men to complications, increasing their anxiety and decreasing their quality of life since the likelihood they will benefit from surgery or radiation is remote. The MUSIC group deserves considerable praise for providing appropriate clinical guidance concerning the management of localized prostate cancer.

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https://doi.org/10.1016/j.urology.2020.07.052
UROLOGY 00: 6–7, 2020. Published by Elsevier Inc.