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Platinum Priority – Brief Correspondence – Editor's Choice

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Risk of Becoming Lost to Follow-up During Active Surveillance for Prostate Cancer

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Abstract

Active surveillance (AS) has emerged as the preferred management strategy for many men with prostate cancer (PC); however, insufficient longitudinal monitoring may increase the risk of poor outcomes. We sought to determine rates of patients becoming lost to follow-up (LTFU) and associated risk factors in a large AS cohort. The Michigan Urologic Surgery Improvement Collaborative (MUSIC) maintains a prospective registry of PC patients from 44 academic and community urology practices. Over a 6-yr period (2011–2017), we identified patients managed with AS. LTFU was defined as any 18-mo period where no pertinent surveillance testing was entered in the registry. With a median surveillance period of 32 mo, the estimated 2-yr LTFU-free probability calculated by Kaplan-Meier method was 90% (95% confidence interval [CI] = 89–92%). Both African American race (hazard ratio [HR]: 2.77, 95% CI = 1.81–4.24) and Charlson comorbidity index $\geq$1 (HR: 1.55, 95% CI = 1.08–2.23) were independently associated with increased risk of LTFU. There was variability in rates of estimated 2-yr LTFU-free survival across MUSIC practices, ranging from 52% (95% CI = 21–100%) to 99% (95% CI = 97–100%), with a median of 96% (interquartile range: 94–98%), although this did not reach statistical significance ($p = 0.076$). These data reveal opportunities for urology practices to identify systems to reduce rates of LTFU and improve the long-term safety of AS.

Patient summary: With a median observation period of 32 mo, an estimated 10% of patients will be lost to follow-up at the 2 yr time point while on AS. African American men and generally unhealthy patients were at increased risk, and there was variability from one urology practice to another. There is ample opportunity to improve the quality of the performance of AS.

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As the name implies, active surveillance (AS) is a dynamic process requiring periodic monitoring for disease progression using tests such as digital rectal exam, serum prostate-specific antigen (PSA), prostate imaging, and prostate biopsy [1]. Despite the general success of this strategy, it is increasingly clear that a small proportion of

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patients choosing to avoid initial curative treatment will ultimately miss their window of curability, develop metastasis, and die of prostate cancer (PC) [2,3].

Urology practices should institute monitoring with sufficient frequency and rigor to avoid these failures; this is a facet of AS that is beginning to be explored [4]. An extension of these types of studies is to examine the frequency with which patients have no follow-up data at all, a situation called "lost to follow-up (LTFU)". Herein, we sought to define the proportion and characteristics of patients who initially chose AS but were subsequently no longer followed, and therefore, LTFU.

The Michigan Urological Surgery Improvement Collaborative (MUSIC) maintains a prospective registry of PC patients from 44 academic and community urology practices within the state of Michigan. Patients were included in this study if the managing physician indicated AS as the management strategy in the primary medical record. We defined LTFU as a period of at least 18 mo without any surveillance testing (PSA, PC imaging, or prostate biopsy) entered into the registry or the primary medical record. The date of the LTFU event was defined as the date of the last surveillance test entered into the registry. The surveillance period was defined as the start of AS to the date of data analysis. Patients had to have at least 18 potential months of surveillance to be included. To confirm that patients were truly LTFU, trained data abstractors at each clinical site re-reviewed the primary medical record of every patient with a LTFU event to confirm lack of clinical data not only in the registry but also in the primary medical record. The MUSIC Coordinating Center also searched across the registry for duplicate names, birth dates, and dates of diagnosis to determine if patients LTFU in one MUSIC practice were being followed by another. Further investigative efforts were made by two large urology practices to contact every LTFU patient and/or their family by telephone.

From 2011 to 2017, 2211 men met the inclusion criteria. Median age for the cohort was 66.2 yr (interquartile range [IQR]: 60.7–71.0; Supplementary Table 1). The median surveillance period for the entire cohort was 32.1 mo (IQR: 24.3–43.1). For the 1994 patients without LTFU, the median time from the initiation of surveillance to their most recent surveillance test was 22.2 mo (IQR: 15.3–32.5). During the study period, 217 patients were LTFU, with an estimated 2-yr LTFU-free probability calculated by Kaplan-Meier method of 90% (95% confidence interval [CI] = 89–92%; Fig. 1). Both African American (AA) race (hazard ratio [HR]: 2.77, 95% CI = 1.81–4.24) and Charlson comorbidity index (CCI) $\geq$1 (HR: 1.55, 95% CI = 1.08–2.23) were independently associated with increased risk of LTFU by cox regression modeling (Table 1). Values regarding men with LTFU and Gleason Score, age, PSA, greatest percent cancer involvement in individual cores, number of positive cores, or annual AS patient volume per practice or per urologist can be found in Supplementary Table 1.

Most (79/217) LTFU events occurred shortly after enrollment on AS, with fewer events per month thereafter (Supplementary Fig. 1). When patients had more than five surveillance tests entered into the registry, only 1.9% were LTFU compared with 6.9% for three to five tests and 26% for none to two tests.

After adjusting for age, PSA, Gleason score, race, and CCI, we noted variability in the calculated 2-yr LTFU-free survival among MUSIC practices, ranging from 52% (95% CI = 21–100%) to 99% (95% CI = 97–100%), with a median of 96% (IQR: 94–98%), although these differences between practices did not reach conventional statistical significance (p = 0.076; Fig. 2).

Although a patient may be LTFU within the MUSIC registry, he may be receiving oncologic care elsewhere, and therefore not LTFU from the perspective of the patient. To investigate this possibility, we repeatedly attempted to contact 42 LTFU patients and/or their families from two

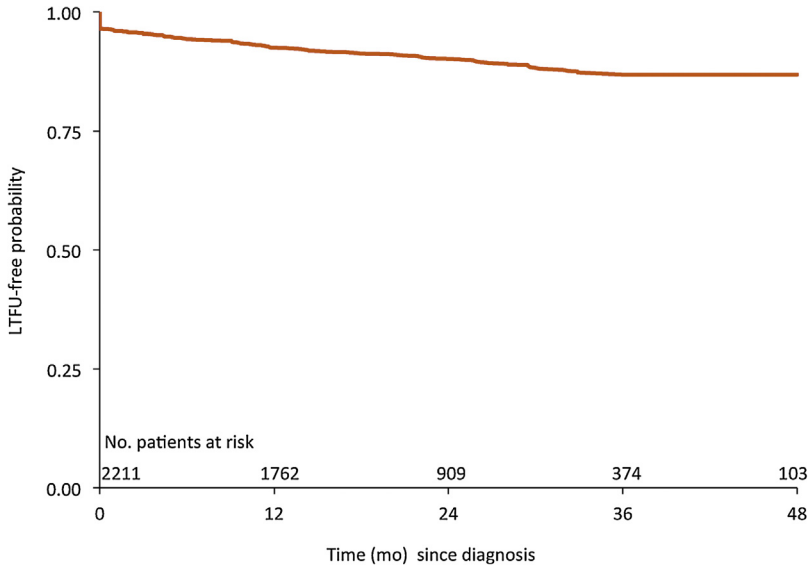

Fig. 1 – Kaplan-Meier curve of lost to follow-up free survival.
LTFU = lost to follow-up.

Table 1 – Multivariable cox regression model on time to lost to follow-up

	HR	95% CI	*p* value
Biopsy Gleason score			
6		Reference	
>6	1.40	(0.90–2.18)	0.1
Race			
White		Reference	
African American	2.77	(1.81–4.24)	<0.001
Other	1.44	(0.52–3.95)	0.5
Charlson comorbidity index			
0		Reference	
≥1	1.55	(1.08–2.23)	0.02
Age	1.00	(0.98–1.02)	0.9
PSA (logarithm)	0.92	(0.76–1.11)	0.4

CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
Note: Adjusted for practice (hospital) through random effect.

large practices using every available phone number, including emergency contact information. We successfully contacted or confirmed information on 22 (52%), of which 16 (73%) were confirmed to have no oncologic care. Three (14%) had oncologic care outside of MUSIC practices (all by urologists/none by radiation oncology or medical oncology) and three (14%) were registry errors (duplication in the registry or incorrect entries). These data suggest that LTFU estimates obtained from the MUSIC registry may overestimate LTFU rates from the patient perspective to a small degree.

Although AS is safe for most men, metastasis and death still occur [2,3]. Patients who are LTFU, theoretically, may have worse outcomes due to insufficient monitoring and missed opportunities to convert to definitive therapy. During a median surveillance period of 32 mo, we found that approximately 10% of patients will become LTFU when on AS for 2 yr. Most LTFU events seem to be early in the monitoring period, as indicated by a large number of patients LTFU immediately after being placed on surveillance. However, LTFU events persisted throughout the length of the study, consistent with the notion that patients remain at risk indefinitely.

Osterberg et al. [5] reported that at a safety-net hospital, 17% of patients ($n = 104$) were LTFU during a 10-yr study period. Kraus et al. [6] reported that 50% of patients were LTFU within the first 2 yr at their safety-net hospital compared with 16% at a neighboring cancer center. These findings, in concert with the findings of our study, provide a focus for intervention and quality improvement among urology practices to increase compliance with surveillance regimens.

There is concern that AA patients have more aggressive PC, increased risk of progression, and worse PC outcomes [7–9]. Race, socioeconomic status, and education have been shown to affect outcomes and utilization of healthcare in general, as well as cancer care [10,11]. The MUSIC registry does not capture potentially confounding factors, such as socioeconomic and educational statuses, that may underlie some of the differences in LTFU rates between AA and Caucasian patients. It is important to note that patients of all races, ages, and CCI are at risk for LTFU. Our data do not imply that certain patients should be excluded from AS.

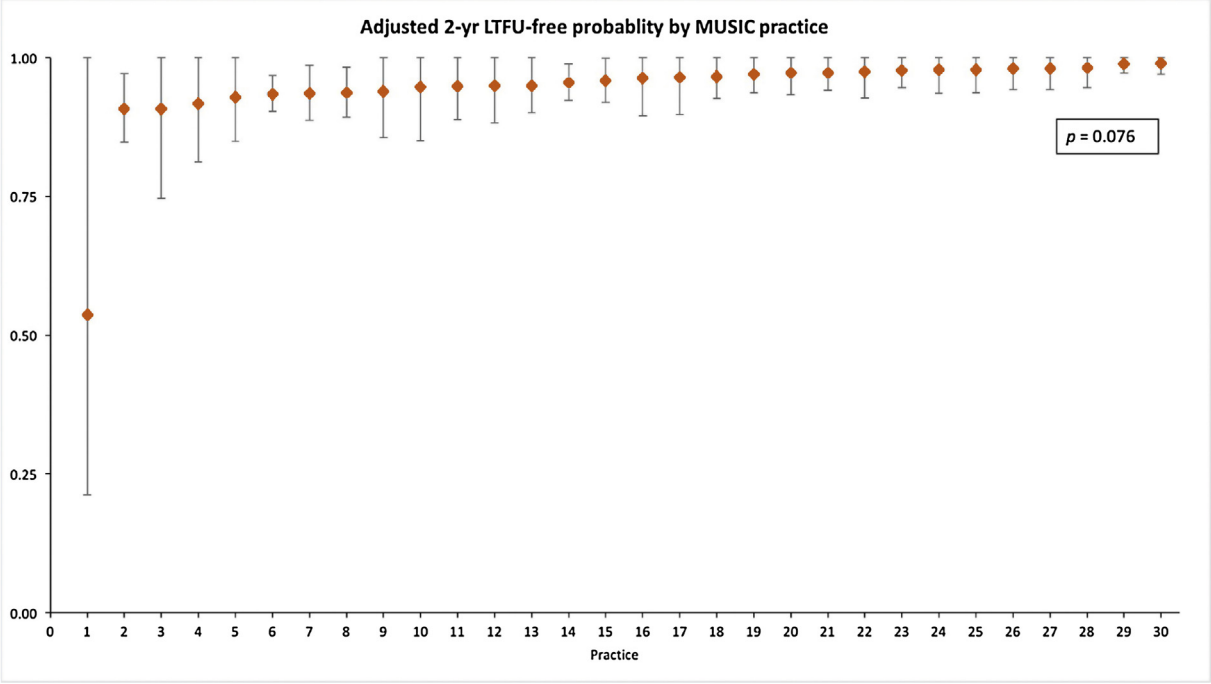

Fig. 2 – Practice-level adjusted 2-yr LTFU-free probability based on multivariable cox regression model controlling for age, race, comorbidity, PSA, and biopsy Gleason score. Error bars display the 95% confidence interval.
LTFU = lost to follow-up; MUSIC = The Michigan Urologic Surgery Improvement Collaborative; PSA = prostate-specific antigen.

However, the data may help identify patients that are at higher risk for becoming LTFU. These concerns can be relayed to the patient and help the physician and patient maintain diligent attention to surveillance schedules, with increased emphasis placed on patients who are at a higher risk for becoming LTFU, such as AA patients and patients with CCI $\geq$1.

In summary, we demonstrate that some patients placed on AS have major gaps in oncologic care. These patients are no longer on AS; instead, they are LTFU and may, therefore, miss an opportunity for intervention. The data we present reveal opportunities to identify systems of care to reduce LTFU events, thereby improving the quality and long-term safety of AS for men with early-stage PC. To this end, we developed a MUSIC "Roadmap" for the management of men with favorable-risk PC which includes suggested schedules for AS testing [12]. In addition, in 2017, a system was created within MUSIC to alert participating practices if a patient has not had clinical information entered into the registry within 19 mo of starting surveillance. We are optimistic that this automated system will increase compliance with longitudinal monitoring and decrease rates of LTFU.

Author contributions: Michael L. Cher had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ginsburg, Auffenberg, Cher, Qi.
Acquisition of data: Qi, Linsell.
Analysis and interpretation of data: Ginsburg, Auffenberg, Cher, Qi, Linsell, Powell, Montie, Miller.
Drafting of the manuscript: Ginsburg, Cher.
Critical revision of the manuscript for important intellectual content: Ginsburg, Auffenberg, Cher, Qi, Linsell, Powell, Montie, Miller.
Statistical analysis: Qi.
Obtaining funding: Miller, Montie, Linsell.
Administrative, technical, or material support: Qi, Linsell.
Supervision: Powell, Montie, Miller, Cher.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.08.010.

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