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REVIEW ARTICLE

Active Surveillance for Prostate Cancer: Progress and Promise

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ABSTRACT

Widespread prostate-specific antigen (PSA) –based screening and aggressive treatment of prostate cancer have reduced mortality rates substantially, but both remain controversial in large part because of high rates of overdiagnosis and overtreatment of otherwise indolent tumors. Active surveillance—or close monitoring of PSA levels combined with periodic imaging and repeat biopsies—is gaining acceptance as an alternative initial management strategy for men with low-risk prostate cancer. In reported series, rates of progression to active treatment with intermediate-term follow-up have ranged from 14% to 41%, and likelihood of subsequent cure with surgery or radiation does not seem to be compromised by an initial trial of surveillance. Two related challenges to broader acceptance of surveillance are better characterization at time of diagnosis of the risk of progression (including likelihood that given tumor may have been undersampled by diagnostic biopsy) and validation of optimal end points once surveillance begins. Both are subjects of intense ongoing investigation, with emerging biomarkers and novel imaging tests expected to facilitate decision making substantially. Recent reports have suggested active surveillance can be a cost-effective approach and preserve quality of life, but these questions must be assessed more definitively in prospective cohorts. Ultimately, by minimizing the harms of overtreating low-risk prostate cancer, active surveillance may help settle the controversy surrounding prostate cancer screening and management.

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RATIONALE FOR SURVEILLANCE

Although prostate cancer kills more men annually in the United States than any malignancy except lung cancer,[1] a substantial majority of men diagnosed ultimately die as a result of other causes. Indeed, many prostate cancers would never cause any impairment to quality or quantity of life if undetected and are thus said to be overdiagnosed.[2] In the era of prostate-specific antigen (PSA) –based screening, the percentage of prostate cancers overdiagnosed has recently been estimated, based on data from large screening trials, to be as high as 23% to 67%, depending on the specific definitions of overdiagnosis assessed.[3,4] In contemporary practice in the United States, diagnosis tends to lead to treatment; thus, as the proportion of prostate cancers diagnosed with low-risk characteristics has grown, overdiagnosis has been associated with high rates of overtreatment.[5,6]

Despite randomized controlled trials demonstrating survival benefits for prostate cancer screening among men with good life expectancy,[7-9] the harms of detection, primarily those related to overtreatment, underlie the negative opinions on screening promulgated by the US Preventive Services Task Force[10] and others. Although the new recommendation by the American Urological Association to begin screening at age 40 years for most men[11] might be expected to identify a higher proportion of lethal tumors at an earlier, curable stage, it will likely be associated with risks of further overdiagnosis of indolent tumors among men at even younger ages. Therefore, treatment must be applied selectively, and the timing and intensity of treatment should reflect disease and patient characteristics.

An emerging consensus now supports deferring treatment initially for a growing proportion of men diagnosed with low-risk (ie, low volume, stage, and grade) prostate cancer. Under the management strategy of active surveillance, men are observed carefully with serial PSA assessments, repeat biopsies, and other tests intended to identify early signs of progression. The term active surveillance has supplanted watchful waiting, but the two are not synonymous. The latter term generally applied to older men with significant comorbidity; they were advised to defer treatment unless symptoms developed, at which point palliative androgen deprivation could be offered. Active surveillance, on the other hand, rests on the presumptions that the lead time from diagnosis to clinical progression is usually long for

low-risk disease,[4] and at the first signs of higher-risk disease, the cancer can be treated, likely well within the window of opportunity for cure. The distinction is particularly important in that neither oncologic nor health-related quality of life (HRQOL) outcomes from patients assigned to observation in older randomized trials,[12] nor those identified in population-based registries as receiving conservative management,[2] can be considered representative of those expected with contemporary active surveillance.

STATE OF THE FIELD

Several academic institutions have been prospectively accruing growing cohorts of men on defined active surveillance protocols over the past several years. The largest of these now includes more than 500 men, and in total, short- to intermediate-term results have been reported for more than 2,800 men (Table 1). Median follow-up ranges from less than 2 to nearly 7 years. However, it is important to stress that even the cohort with the longest median follow-up time has been observed for too short a time to draw definitive conclusions regarding mortality risks. The proportions of men moving from surveillance to active treatment range from 14% to 41%. These figures are not necessarily associated with length of follow-up and may reflect different selection criteria, early identification in all cohorts of higher-risk disease that was initially undersampled, or variation in patient and clinician decision-making preferences for treatment.

Multiple studies have compared outcomes for men undergoing treatment after a period of surveillance with those for comparable, risk-matched men undergoing immediate treatment. Results seem to be essentially similar. No report yet published has provided evidence of impaired likelihood of cure after a period of careful surveillance.[17,19,27] In the University of Toronto cohort, five men died as a result of prostate cancer. However, all were noted early in their management course to have rapid PSA kinetics (< 1.6 years) and were offered active treatment. Two declined, and three were treated within 1 year of original diagnosis. Only one, in retrospect, who had a delay of 2 years from diagnosis to treatment (radiation therapy), could be considered to have possibly missed an opportunity for cure. He died 7 years after his delayed treatment.[21] Among men undergoing surgery after surveillance, biochemical recurrence-free survival was 100% at 3 years in the University of California San Francisco (UCSF) cohort ($n = 74$)[19] and University of Miami cohort ($n = 12$),[15] 96% at 2 years in the Johns Hopkins cohort ($n = 96$),[17] and 91% at 3 years in the ERSPC (European Randomized Study of Screening for Prostate Cancer) cohort ($n = 81$).[23]

The START (Surveillance Therapy Against Radical Treatment) trial, sponsored jointly by the National Cancer Institute of Canada and four US cooperative oncology groups, is currently randomly assigning patients to surveillance versus the patient's choice of surgery or radiation therapy.[28] The ProtecT (Prostate testing for cancer and Treatment) study randomly assigned men to surgery, external-beam radiation, or surveillance and completed accrual at nine centers in the United Kingdom between 1999 and 2008. Among approximately 3,000 men diagnosed with prostate cancer through a national screening trial, 88% had localized disease, and of these, 63% accepted random allocation.[29,30] Although results from both studies will take years to mature, they are expected to yield important information regarding the safety and efficacy of surveillance in a controlled setting.

TWO PAIRED CHALLENGES

In the interim, two related challenges have limited widespread acceptance of active surveillance: defining eligibility and identifying progression. Diversity of approaches to both questions is pervasive in the literature, and as yet, there exists no clear consensus as to how to resolve the uncertainty.

Defining Eligibility

Each large surveillance cohort includes slightly different inclusion criteria (Table 1), although most reflect variations on the theme

Table 1. Summary of Surveillance Studies

Institution	Principal Investigator	Most Recent Reports	Total No.*	Strict No.*	Median Age (years)	Inclusion Criteria
Royal Marsden	Parker	2007[13,14]	326	326	67	Gleason ≤ 3 + 4; PSA ≤ 15 ng/mL; cT stage ≤ 2a; ≤ 50% of cores positive
University of Miami	Soloway	2010[15,16]	230	230	64	Gleason ≤ 6; PSA ≤ 10 ng/mL; cT stage ≤ 2; ≤ two cores; ≤ 20% of any core positive
Johns Hopkins	Carter	2011[17,18]	769	633	66	Gleason ≤ 3 + 3; PSAD ≤ 0.15 ng/mL/mL; cT stage 1; ≤ two cores positive; ≤ 50% of any core positive
University of California San Francisco	Carroll	2011[19,20]	640	376	62	Gleason ≤ 3 + 3; PSA ≤ 10 ng/mL; cT stage ≤ 2; ≤ 33% of cores positive; ≤ 50% of any core positive
University of Toronto	Klotz	2010[21,22]	453	453	70	Gleason ≤ 6; PSA ≤ 10 ng/mL (until January 2000, for men age > 70 years: Gleason ≤ 3 + 4; PSA ≤ 15 ng/mL)
European Randomized Study of Screening for Prostate Cancer sites	Schröder	2009[23,24]	988	616	66	Gleason ≤ 3 + 3; PSA ≤ 10 ng/mL; PSAD ≤ 0.2 ng/mL/mL; cT stage 1c to 2; ≤ two cores positive
Memorial-Sloan Kettering	Eastham	2011[25,26]	238	238	64	Gleason ≤ 3 + 3; PSA ≤ 10 ng/mL; cT stage ≤ 2a; ≤ three cores positive; ≤ 50% of any core positive
Total			3,644	2,872	67	

Abbreviations: cT, clinical tumor; PSA, prostate specific antigen; PSAD, prostate specific antigen density.
*Total No. indicates total No. of men undergoing surveillance; strict No. is No. reported who met institutional criteria for surveillance. In all cases, outcomes reported are based on strict No.

of low-grade, low-volume disease associated with low PSA. The eligibility criteria vary. In one comparative study of a cohort of 1,097 men undergoing prostatectomy, the percent of men who would have been eligible for surveillance based on various sets of criteria ranged from 4% for the Johns Hopkins definition[18] (most restrictive) to 82% for the Royal Marsden definition[13] (most permissive). Rates of upgrading from biopsy to prostatectomy ranged from 23% to 35% among men meeting the various criteria. Rates of upstaging ranged from 7% to 19% for extracapsular extension and from 2% to 9% for seminal vesicle invasion.[31]

The likelihood of undersampled high-grade disease falls with a more extended biopsy. A minimum 12-core biopsy is now recommended, including cores sampling the anterior prostate.[32,33] Some have advocated routine saturation biopsy for men embarking on surveillance,[34] but this is not generally practiced in most high-volume surveillance centers. On the other hand, most centers do recommend confirmatory biopsy if the diagnostic biopsy was not performed with an extended template or otherwise seems to be of questionable quality. The Memorial Sloan-Kettering Cancer Center criteria explicitly require confirmatory biopsy for all men before surveillance—and notably, 58% of these repeat biopsies in fact did not demonstrate cancer.[25]

The obvious candidate for active surveillance is an older man with low-risk prostate cancer—and indeed, in clinical practice, age is a strong driver of treatment selection. However, even among men older than 75 years of age with low-risk disease, most in the United States receive treatment rather than surveillance.[6,35,36] In reality, age does not need to be a primary determinant of surveillance eligibility. For younger men with low-risk, low-volume disease, active surveillance may be reasonable, with the understanding that surveillance may mean delayed rather than avoided treatment. Autopsy series have demonstrated histologic prostate cancers in 30% of men in their 30s,[37] so if men are indeed to be screened at younger ages as has been proposed,[11] reflexive treatment should be avoided for young men with low-risk disease, whose period of tumor latency may be prolonged.

Criteria for surveillance may often be more liberal for older men (eg, including those with low-volume Gleason 3 + 4 disease).[21] It is important to recognize, on the other hand, that for men with aggressive disease, cancer-specific mortality rates are quite high, even for men diagnosed in their 80s.[2] Cancer risk, comorbidity, and life expectancy should receive greater consideration than chronologic age per se in treatment decision making.[36] Of note, the UCSF series, which has been relatively liberal in terms of accruing men with intermediate-risk disease who do not meet the UCSF strict criteria for surveillance, also has the youngest median age at accrual, although men not meeting strict criteria were somewhat older than those with strictly low-risk disease (median age, 65 *v* 62 years).[19]

A number of nomograms have been published purporting to identify indolent prostate cancer.[38-40] In fact, these merely predict low-volume, low-grade, organ-confined tumors identified at time of radical prostatectomy, although they seem to be superior to the criteria defined by Epstein et al[41] (no pattern 4 disease, no extracapsular extension or lymph node invasion, and tumor volume < 0.5 cm^3) in predicting indolent or insignificant cancers. Indeed, although the 0.5 cm^3 threshold is frequently cited as an indicator of clinical insignificance, this has never been validated.[42] A recent study based on ERSPC has suggested that a more appropriate cut point for clinically insignificant disease is Gleason 6 cancer less than 1.3 cm^3 in volume.[43] The CAPRA (Cancer of the Prostate Risk Assessment) score, likewise, has been proved able to further substratify low-risk patients, but only in terms of likelihood of recurrence after surgery.[5] Prospective studies of nomograms and other prognostic tools using data from patients undergoing surveillance rather than surgery are sorely needed.

Defining Risk Progression

Although there exists significant variation in identifying the ideal patient for active surveillance, determining risk progression among men undergoing surveillance is equally challenging. In all surveillance programs, men are observed periodically with PSA and digital rectal examination (DRE) as well as prostate biopsy, usually every 1 to 2 years. Common types of definitions for risk progression include biochemical (ie, PSA threshold or kinetic parameters), histologic (increase in Gleason grade and/or extent of biopsy core involvement), stage (by DRE findings or imaging), and therapeutic (moving to surgery, radiation, or other modalities for any reason).

However, none of these end points is entirely satisfactory. PSA can reflect benign prostate processes; crossing a threshold (eg, from 9.5 to 10.2 ng/mL) may not be clinically meaningful, and there is no PSA kinetic definition that consistently reflects progression. Likewise, PSA kinetics are not consistently associated with an increase in Gleason grade.[44,45] In fact, most risk progression tends to be grade progression and is usually identified on the first or second repeat biopsy. Identification of histologic progression, however, may be no less likely to reflect resampling of the prostate than true progression, especially on the first follow-up surveillance biopsies—although resampling cannot easily be distinguished from true progression of disease. Increase in stage is uncommon. Finally, treatment may occur in the absence of biologic progression because of anxiety or other HRQOL considerations (eg, urinary symptoms resulting from benign disease); conversely, many men who meet established criteria for risk progression opt to continue surveillance despite counseling in favor of treatment.

Rates for each of these outcomes vary across cohorts (Table 2). Drivers of treatment also vary. In the Toronto cohort, for example, the most common reason for active treatment was rapid PSA kinetics,[21] whereas in the Johns Hopkins cohort, PSA kinetics have been felt to be noninformative,[44] and tumor grade and/or volume progression were more important drivers of progression.[17] Overall, grade progression seems to be the most consistent driver of progression. Reported rates of progression- and treatment-free survival range from 54% to 86%, although these are not actuarial figures, and depend to a significant extent on duration of follow-up.

ECONOMICS OF SURVEILLANCE

Rates of initial surveillance in one recent study of 30 clinical practices across the United States varied from 0% to 28%.[46] From the clinician's standpoint, active surveillance is labor intensive and reimbursed relatively poorly; these financial concerns, together with perceived medicolegal risks and cultural biases in favor of aggressive treatment, may conspire to keep active surveillance a relatively uncommon management strategy.[6,46] Conceivably, modifying relative financial incentives may help increase uptake of active surveillance.

Table 2. Outcomes of Surveillance Series

Institution	Median Follow-Up (months)	Progress by Grade/Volume (%)	Progress by PSA/PSA Kinetics (%)	Treatment Without Progression (%)	OS	CSS	PFS
Royal Marsden	22	13	18	2	98	100	73
University of Miami	32	10	NR	NR	100	100	86
Johns Hopkins	32	14	NR*	9	98	100	54
University of California San Francisco	47	35	5 of 11†	8	97	100	54
University of Toronto	82	9‡	14‡	3	68	97	70
European Randomized Study of Screening for Prostate Cancer sites	52	NR§	13	18	91	99	68
Memorial-Sloan Kettering	22	13	14	11	NA	NA	NA

NOTE. Outcomes given reflect those for men meeting criteria for surveillance at each institution. University of California San Francisco and Johns Hopkins have reported outcomes for men with higher-risk disease (ie, those not meeting criteria); these are not included in table but are discussed in text. All progression/survival figures are raw, not actuarial.

Abbreviations: CSS, prostate cancer–specific survival; NA, not applicable; NR, not reported; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.

*Johns Hopkins studies do not use PSA-based definition of progression, but PSA outcomes for cohort have been reported in detail.[44]

†Progression based on PSA doubling time $<$ 24 months/$<$ 36 months.

‡Figures for University of Toronto do not include those who progressed but continued undergoing surveillance.

§Repeat biopsy information reported for only subset (23%) of European Randomized Study of Screening for Prostate Cancer cohort.

A recent decision analysis modeling men diagnosed at age 65 years with low-risk disease found that surveillance was associated with greater quality-adjusted life years than those for patients treated with surgery or radiation. The absolute difference was small ($<$ 1 year), and the analysis did not include costs. However, the study was the first to our knowledge to study surveillance along with active treatment in a formal decision model.[47]

Two other reports have demonstrated substantially lower costs for active surveillance: one based on Medicare reimbursement rates for a single high-volume center with costs calculated to 15 years,[48] and the other based on utilization data in a large community-based registry, with costs calculated over the patient's lifetime.[49] The actual cost estimates in the two studies differed markedly, but in both cases, costs were lower than those associated with active treatment. In both studies, the analyses admixed patients undergoing watchful waiting with those undergoing surveillance, so they may not necessarily be applicable to a contemporary surveillance protocol. The single-center study did model a more active surveillance protocol, which included follow-up biopsies and a 5% to 7% conversion rate to prostatectomy. Costs were still lower than those associated with surgery in this case, given discounting applied to prostatectomy costs after a period of surveillance.[48] However, the actual conversion rate to active treatment over a 15-year period of observation is likely higher than that estimated in this study; rates of progression to treatment in the reported series range from 14% to 41%, with follow-up much shorter than 15 years (Table 2).

Surveillance is often assumed to preserve HRQOL, but HRQOL has rarely been assessed formally in surveillance cohorts. Indeed, HRQOL has been shown to deteriorate over time among men in the watchful waiting arm of at least one older study, in large part because of progression of urinary symptoms.[50] Early results from one contemporary cohort also note a decline over time in erectile function among surveillance patients.[15] Psychologic health is usually preserved on surveillance,[51] but some patients undergoing surveillance experience disutility related to anxiety,[47] and serial biopsies do carry small but significant risks of sepsis and long-term HRQOL decline.[52,53]

THE FUTURE

Biomarkers and Imaging

The biology underlying the nonprogression of indolent prostate cancers is likely complex, reflecting germline (host) genetic factors, such as androgen pathway polymorphisms, acquired tumor genetics, and dietary and other environmental influences. Some tumors may lack telomerase or other immortalizing pathways, resulting in senescence. Others may lack growth factors required to induce angiogenesis, limiting their proliferative potential. Micronutrient ingestion or hormonal influences may induce differentiation or apoptosis. As these mechanisms and pathways are elucidated more clearly, markers interrogating their status in an individual tumor will be developed. Although no biomarkers or novel imaging examinations have yet been validated for use in the active surveillance setting, development of such markers and imaging tests for men with clinically low-risk prostate cancer is a major goal of multiple ongoing research efforts.

A key caveat for biomarker research, however, remains the lack of an accepted gold standard for outcome. None of the indicators of progression among men undergoing surveillance have been well validated. For this reason, marker studies are often designed first as studies of upgrading and/or upstaging among men with clinically low-risk tumors who undergo prostatectomy, because surgery provides the true pathology. Another advantage to this design is a greater abundance of tumor tissue, in most cases. However, whether upgrading/upstaging at surgery is a reasonable surrogate for progression during surveillance remains to be determined, and prospective studies in surveillance cohorts are still required.

The Canary Foundation and National Cancer Institute Early Detection Research Network have jointly sponsored the multicenter cohort study PASS (Prostate Active Surveillance Study), which is currently accruing patients undergoing surveillance at five North American academic centers.[54] Biospecimens (including blood, post-DRE

urine, and biopsy tissue) and HRQOL data will be collected prospectively and banked for future studies, conforming to the prospective specimen collection, retrospective blinded evaluation study design.[55] Identifying men who are relatively likely to have been undersampled by biopsy would reduce the likelihood not only of inappropriate surveillance of an aggressive tumor but also of undertreatment (eg, by omission of lymphadenectomy or whole-pelvis radiation therapy). Although the approach of testing and/or validation of biomarkers to select those most appropriate for active surveillance is still in its infancy, some have evaluated, as an example, the potential usefulness of urinary prostate cancer antigen 3 (PCA3) to identify men with indolent disease. In two small series, PCA3 scores were correlated with tumor volume and Gleason score, suggesting that PCA3 should be evaluated more formally, prospectively, and in larger series of men.[56,57]

A multiparametric magnetic resonance imaging examination was recently shown to identify men with low-risk disease who were relatively likely to be undergraded based on the presence of a visible lesion on imaging examination (which was not case for transrectal ultrasound findings).[58] Others have specifically advocated this imaging modality to avoid missing significant anterior disease.[33] Diffusion-weighted imaging seems particularly promising among currently available magnetic resonance sequences,[59] and next-generation magnetic resonance spectroscopy based on hyperpolarized ^{13}C has shown significant promise in in vitro models in providing metabolic data of tumor versus normal tissue at an unprecedented level of detail, yielding in effect a virtual biopsy.[60]

The major goal for biomarkers and imaging research in the setting of surveillance is to detect occult high-risk disease and thus avoid undertreatment. However, ultimately, if truly indolent disease can be identified with greater precision and confidence, then some men could be selected for relatively inactive surveillance and be spared the risks and anxiety of the close follow-up specified in contemporary protocols. One as yet unanswered—and rarely asked—question quite relevant to this area of research is the extent to which novel biomarkers will actually affect clinical practice. If, for example, a new marker or imaging test were to increase the accuracy of a nomogram or other prognostic tool from 80% to 90% in the prediction of indolent disease, how many men who otherwise would have been treated would opt for surveillance, given that test result?

Focal Therapy: An Alternative to Both Active Surveillance and Radical Treatment?

Interest in the active surveillance approach is driven, in large part, by the morbidity and cost of currently available radical therapies. As such, any effective active treatment that produces minimal or no adverse effects and is reasonably inexpensive could replace surveillance. Advocates of focal therapy (ie, treating only dominant cancer-containing region of prostate) claim this potential.[61] The limitations of focal therapy at this point, however, are similar to those of surveillance, namely patient selection and identification of the dominant cancer focus. Specifically, some patients with favorable clinical parameters harbor higher-risk disease and may be inadequately treated with focal therapy. Indeed, the risk of focal therapy is that it could prove most effective primarily among patients who do not require treatment and inconsistently effective among those who do. The appeal of active surveillance is the ability to use the observed natural history of patient disease over time to identify those who in fact have more aggressive disease; focal therapy could contaminate those observations. Only 13% to 38% of prostate cancers are unifocal,[62] so a means of monitoring the remainder of the prostate reliably is essential.

Given the negligible mortality rate identified to date for low-risk prostate cancer managed with active surveillance, advocates for focal therapy face a major challenge in demonstrating that the natural history is improved by such an approach. Focal therapy may have a role in treating some patients undergoing surveillance who are reclassified as higher risk based on an increase in cancer volume on biopsy. A clear need is better imaging; many dominant tumors still cannot be identified consistently and precisely, even with the best contemporary scans. When imaging can more reliably rule out the presence of significant missed disease, it is likely that active surveillance and focal therapy will play complementary roles.

5α Reductase Inhibitors

Finasteride and dutasteride have been shown in large randomized trials to reduce the risk of prostate cancer diagnosis.[63,64] Moreover, these agents seem to improve the receiver operating curve characteristics of PSA testing and prostate biopsy, primarily because of their effects on PSA produced by benign prostate tissue.[65] Many men in these studies harbored undiagnosed prostate cancer at entry.[66] Thus, these drugs may act to stabilize or reduce the volume of existing low-grade prostate cancer. Indeed, the REDEEM (Reduction by Dutasteride of Clinical Progression Events in Expectant Management) study[67] randomly assigned men otherwise managed with active surveillance to dutasteride or placebo. A preliminary presentation of the results of the trial suggested a role for dutasteride in reducing the risk of disease progression.

Although longer follow-up and more robust data are required, 5α reductase inhibitor treatment may prove a low-cost, minimal-risk intervention for men suitable for active surveillance. Other advantages with this approach are treatment of frequently coexistent, symptomatic, benign prostatic hyperplasia and reduction and stabilization of PSA levels, thus allaying PSA-associated anxiety. However, these medications cannot be considered definitive therapy. Patients treated still require close monitoring and periodic biopsies; PSA kinetics are recalibrated from the new baseline once a nadir is reached.

Diet, Lifestyle, and Psychosocial Interventions

Other low-cost and minimal-risk interventions for men with low-risk prostate cancer are the subject of growing interest. For example, a recent study demonstrated that intensive dietary and lifestyle modifications can affect prostate cancer gene expression patterns[68] and clinical outcomes.[69] Another ongoing study is examining the utility of a less intense (and therefore more broadly accessible) telephone-based dietary intervention.[70] One particularly appealing aspect of such diet and lifestyle interventions is that no matter what the magnitude of impact on prostate cancer risk and progression, the interventions tend to be heart healthy. Because most men with low-risk prostate cancer—like those in the general population—die as a result of cardiac disease, these interventions may well have dual benefits.

In one cohort study, increasing cancer anxiety was the strongest predictor, aside from PSA kinetics, of active treatment among

men initially managed with watchful waiting or surveillance.[71] Psychosocial interventions to manage this anxiety may be a key component of future surveillance programs. Along similar lines, more systematic measurement of uncertainty[72] will help determine the best ways to integrate emerging biomarkers into clinical practice and may help define the cost effectiveness of such novel markers as they are introduced.

For some men (or their partners), however, no matter how clearly a clinician explains that Gleason 3 + 3 cancer found in 1% of a single core of 20 represents minimal-risk disease that does not require immediate treatment, the conversation about surveillance ends at the word cancer. Thus, one recent editorial called for designating these minimal-volume, low-grade tumors as indolent lesions of epithelial origin (ie, IDLE tumors) rather than as cancer, specifically to allay the anxiety engendered by the word itself.[73] An analogy familiar to urologists and genitourinary pathologists might be found in the papillary urothelial neoplasm of limited malignant potential terminology for low-risk bladder tumors or the existing atypical small acinar proliferation designation for prostatic precursor lesions.

Expanding the Criteria for Surveillance?

A substantial majority of men reported in surveillance cohorts to date have presented with disease that would be considered low risk by most classification systems—and indeed, most centers select men for surveillance who have quite low-risk disease. However, some men with higher-risk disease characteristics may opt for surveillance as well, either in the setting of comorbidity and decreased overall life expectancy or, in some cases, a strong motivation to preserve HRQOL, even in the face of a higher chance of progression.

A recent report from the UCSF cohort identified 90 men considered to be at intermediate risk based on presence of Gleason 3 + 4 disease and/or CAPRA scores in the range of 3 to 5 (eg, based on higher PSA levels and/or numbers of biopsy cores involved).[74] Compared with those with low-risk disease, the intermediate-risk men were older and had higher baseline PSA levels (mean, 10.9 *v* 5.1 ng/mL). They had more rapid PSA kinetics, and among those ultimately undergoing surgery, they were more likely to be upstaged, although neither of these differences was statistically significant. They were no more likely to progress than low-risk patients. However, the major caveat to that finding is the fact that upgrading was the most common reason for progression, and it is more probable that a low-risk patient (Gleason 3 + 3 by definition) will upgrade to Gleason 3 + 4 than that an intermediate-risk patient (often low-volume Gleason 3 + 4) will upgrade to Gleason 4 + 3 or higher.[19]

A recent update of the Johns Hopkins cohort likewise reported outcomes for men observed with surveillance who did not met strict criteria for the program. Rates of progression to active treatment were higher (40% *v* 31% for those meeting criteria; $P = .03$), and rates of upgrading or increase in tumor volume were also higher. However, a majority of men not meeting criteria remained on surveillance, and the proportion was not statistically different from those who met criteria.[17] Similarly, 19% of the University of Toronto cohort had intermediate-risk disease characteristics, and among these, 58% remained treatment free at last follow-up.[21]

It should also be noted that with changing pathology standards, a Gleason 7 cancer today may have been called a Gleason 6 in the past[75] and is perhaps more likely to be a biologically indolent tumor than a Gleason 7 tumor identified a decade ago. To be clear, the numbers of men undergoing surveillance reported to date with intermediate-risk disease characteristics are small, and no formal criteria have yet been proposed. Although it would certainly be premature to offer surveillance to all men with intermediate-risk disease, the question of expanded criteria will be an important area of investigation at academic centers in the years to come. Surveillance may eventually prove a viable option for carefully selected and highly motivated men who do not meet existing strict criteria for surveillance, with the understanding that surveillance may connote delayed rather than avoided treatment.

SUMMARY

Through all the controversy regarding the efficacy of prostate cancer screening and treatment shines the fact that since the early 1990s, the mortality rate for prostate cancer in the US population —not simply the proportion of diagnosed cases that are ultimately lethal—has fallen by approximately 40%.[1] This trend has occurred during a time in which men are living longer and are less likely to die as a result of cardiovascular disease, so in theory there should be a greater risk of prostate cancer mortality. There is no identifiable environmental factor analogous to declining smoking trends in the case of falling lung cancer mortality that readily explains this trend. How much of the drop in prostate cancer mortality is attributable to screening and how much to improved treatment remains controversial.[76] However, it seems clear that aggressive management—including both screening and treatment— of aggressive prostate cancers has saved thousands of lives in the past decade.

However, there is little question that the price of this progress has been high, in that for every man saved, others have been exposed unnecessarily to the risks and adverse effects of treatment. Some have been seriously harmed in pursuit of a cure of a histologic finding that never would have become clinically apparent if undetected. More work is needed to identify biomarkers or imaging tests predictive of occult aggressive disease and to identify early those who are likely to need intervention. However, even with standard clinical data readily available and applied carefully, low-risk prostate cancer can be identified with reasonable consistency.

Active surveillance is still a relatively new treatment approach. Even the largest cohorts summarized in this review have reported follow-up durations quite short in the context of the natural history of prostate cancer, and there remain important open questions in terms of both selecting patients and identifying those undergoing surveillance who should move to active treatment. Nonetheless, the data to date are sufficient to conclude that most men with low-risk disease—and likely most with intermediate-risk disease and significant comorbidity—should be offered at least a trial of active surveillance. Reflexive radical treatment of all new diagnoses is increasingly difficult to justify. For men on surveillance who ultimately require treatment, moreover, the window of opportunity for cure appears to be measurable in years and decades. Consistent utilization of risk assessment tools and appropriate risk-adapted treatment, including greater use of initial active surveillance low-risk disease, will decrease overtreatment with its attendant costs and harms—and may by extension ameliorate much of the screening controversy.

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