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Active Surveillance for Early-stage Prostate Cancer

Review of the Current Literature

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The natural history of prostate cancer is remarkably heterogeneous and, at this time, not completely understood. The widespread adoption and application of prostate-specific antigen (PSA) screening has led to a dramatic shift toward the diagnosis of low-volume, nonpalpable, early-stage tumors. Autopsy and early observational studies have shown that approximately 1 in 3 men aged >50 years has histologic evidence of prostate cancer, with a significant portion of tumors being small and possibly clinically insignificant. Utilizing the power of improved contemporary risk stratification schema to better identify patients with a low risk of cancer progression, several centers are gaining considerable experience with active surveillance and delayed, selective, and curative therapy. A literature review was performed to evaluate the rationale behind active surveillance for prostate cancer and to describe the early experiences from surveillance protocols. It appears that a limited number of men on active surveillance have required treatment, with the majority of such men having good outcomes after delayed selective intervention for progressive disease. The best candidates for active surveillance are being defined, as are predictors of active treatment. The psychosocial ramifications of surveillance for prostate cancer can be profound and future needs and unmet goals will be discussed. *Cancer* 2008;112:1650-9. © 2008 American Cancer Society.

KEYWORDS: prostate cancer, active surveillance, review, risk stratification.

Prostate cancer is the most common form of noncutaneous malignancy among males in the U.S., and is the second leading cause of cancer mortality, accounting for more than 27,000 deaths in 2007.¹ However, the natural history of this disease is remarkably heterogeneous and, at this time, not completely understood. Autopsy studies have shown that approximately 1 in 3 men aged >50 years has histologic evidence of prostate cancer, with up to 80% of these tumors measuring <0.5 cm in size and low in grade, suggesting that the majority are clinically insignificant.² Approximately 3% of all men will die of prostate cancer, although the mortality from prostate cancer has declined by 31% over the past 13 years.¹ The relative contributions of factors responsible for this decline including prostate-specific antigen (PSA) screening, improved detection strategies, and improved treatments are not known.

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Widespread, repeated PSA testing and extended-core needle prostate biopsies have raised concerns over the possible overdiagnosis of prostate cancer. Overdiagnosis refers to the ability of a screening test to identify a condition that would have remained silent and caused a patient no morbidity during his lifetime if left untreated. Theoretically, this is consistent with the concept of length-time bias, a bias that would be expected to be most pronounced in a disease of such high prevalence and variable natural history. Currently, overdiagnosis rates are estimated to be between 27% and 56%.^{3,4} Despite earlier detection and, as a consequence, stage migration of newly diagnosed cases, active treatment remains the standard and the use of active surveillance has not increased.⁵ Any active treatment for prostate cancer, no matter how well delivered, may be associated with potential decrement in quality of life in multiple domains (eg, urinary function, sexual function, etc).⁶ Utilizing the power of improved contemporary risk stratification schema to better identify patients with a low risk of cancer progression, several centers are gaining considerable experience with active surveillance with delayed, selective, and curative therapy.⁷ Thus far, a limited number of men on active surveillance have required treatment and the majority of such men appear to have good outcomes after treatment. Therefore, in selected men delayed treatment does not, as yet, appear to compromise the outcome and care of these patients. The best candidates for active surveillance are being defined, as are predictors of active treatment. Unmet needs and future research strategies are being formulated.

The Rationale for Active Surveillance

Biology and natural history

Autopsy studies first described the significant prevalence of clinically undetected prostate cancer among men dying from unrelated causes. Rates were found to vary by age, race, and geography. Among men aged >50 years, for example, 21% of men in Japan had some element of prostate cancer at autopsy compared with 37% of black men in the U.S.² Prevalence was found to increase with age, with up to 67% of men aged >80 years having prostate cancer at the time of death.⁸ When comparing rates of autopsy-detected prostate cancers before and after the start of the PSA era, Konety et al.⁹ found a significant decrease in prevalence after the introduction and widespread use of PSA testing. These data suggest that a significant proportion of prostate tumors will never become clinically significant and that PSA screening likely identifies several of these cancers before death from other causes.

The ratio of prostate cancer incidence to mortality appears to be relatively high, with nearly 8 times as many men diagnosed with prostate cancer each year than will die of the disease. This is compared with only 1.3 and 2.1 times for lung and colorectal cancers, respectively.¹⁰ This disparity between prostate cancer incidence and mortality partly accounts for the high prevalence of prostate cancer noted today as more men live with the disease, the effects of its detection, and, for those treated, its therapies. The U.S. has the highest incidence of prostate cancer in the world, along with northern Europe and Australia.¹⁰ Mortality also varies geographically and is highest in northern Europe, Australia, and parts of sub-Saharan Africa followed closely by North America; Asian countries have the lowest mortality rates from prostate cancer.¹⁰ This worldwide variation in prostate cancer incidence and mortality likely reflects differences in genetic susceptibilities, variations in competing causes of death, environmental exposures including diet, and, importantly, screening practices. The comparatively high prostate cancer incidence in the U.S. compared with other countries suggests a potentially higher detection rate of clinically insignificant tumors.

Impact of changing diagnostic and screening practices

In 2003, data from the Prostate Cancer Prevention Trial demonstrated the prevalence of prostate cancer in a contemporary, screened population of men. The study found that 15% of men with PSA levels below the traditional cutoff of 4 ng/mL had prostate cancer, and that there existed no PSA threshold below which the risk of having cancer was zero.¹¹ These data prompted the trend toward lowering the PSA threshold for prostate biopsy. Clearly, as indications for biopsy are expanded more cancer will be found. Porter et al.¹² estimated that if all men in the U.S. between the ages of 62 and 75 years underwent prostate biopsy regardless of PSA, an additional 1.2 million of cases of prostate cancer would be diagnosed. Clearly, the impact of lowering PSA thresholds for biopsy can be significant, with nearly half of currently diagnosed prostate cancers classified as low risk.¹³ Recent studies, moreover, have found that beginning screening at earlier ages will lead to detection of significant numbers of tumors, some with aggressive features that merit early treatment.¹⁴ Indeed, the National Comprehensive Cancer Network's (NCCN) updated screening guidelines now recommend screening beginning at age 40 years, with subsequent screening schedule driven by the baseline value.¹⁵

In addition to lowering screening and PSA thresholds for biopsy, increases in the average num-

ber of cores taken at prostate biopsy also will increase cancer detection rates.¹⁶⁻¹⁸ As with lowering of PSA thresholds, the effect of extended pattern biopsies on the detection of clinically significant tumors is unclear. Although extended pattern biopsies have been shown to increase detection of smaller volume tumors independent of Gleason score or PSA, an analysis by Master et al.¹⁹ and Chan et al.²⁰ showed no difference in the grade distribution of tumors diagnosed with extended pattern biopsy. Similarly, Eskew et al.²¹ found no significant differences in Gleason score, pathologic stage, or tumor volume between cancers detected by sextant or extended needle biopsy schemes. When directly comparing biopsy Gleason score with pathologic Gleason score after radical prostatectomy, however, extended pattern biopsies appear to reduce the risk of clinical undergrading.²² Although the proportion of clinically low-risk tumors may remain the same with extended biopsies, the absolute number of tumors detected and potentially treated clearly increases, further compounding the potential problem of the overdiagnosis and overtreatment of prostate cancer.

Defining the magnitude of stage migration and lead-time bias

The widespread adoption and application of PSA screening has led to a dramatic shift toward the diagnosis of low-volume (≤ 1 of 3 cores positive), nonpalpable, early-stage tumors. The majority of tumors are now detected at clinical stage T1c, diagnosed by prostate biopsy after elevated PSA.¹³ Data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) has shown that the percentage of patients presenting with locally advanced (T3-T4) tumors fell over a 10-year period, from 11.8% in the early 1990s to only 3.5% by 2000.⁵ Clinical stage T1c-T2a tumors have increased from 65% to 77% over this same period. Moreover, whereas the proportion of tumors diagnosed as low risk under traditional criteria (as defined by a PSA < 10 ng/mL, a Gleason score ≤ 6 , and clinical stage $\leq T2a$) has been essentially constant since 2000, PSA and the percentage of positive biopsy cores have continued to fall since 2000 within the low-risk group, thus lowering overall risk as assessed by a current multivariate instrument.⁷

Such a stage migration from widespread screening correlates with considerable lead-time bias as tumors are diagnosed well before they would otherwise become clinically evident. A corollary to this observation is the finding that widespread screening may detect tumors that would otherwise never become clinically evident. Draisma et al.²³ estimated

lead-time bias and overdiagnosis rates based on results from the European Randomized Study of Screening for Prostate Cancer. Diagnosis lead times ranged from 9.9 to 13.3 years for men in PSA screening programs.^{24,25} Other authors report similar lead-time rates ranging from 5 to 10 years.^{4,26} Overdiagnosis estimates calculated by several models are approximately 50%, meaning that up to one-half of PSA-detected cancers may be clinically insignificant.⁴ The identification of high-risk cancers in younger patients is the most important goal of widespread screening efforts; however, these men are also at risk for the early detection and treatment of indolent cancers. Given young men's high pretreatment functional levels in multiple health-related quality of life (HRQOL) domains, they may experience greater absolute functional declines than men who are older with poorer baseline function (ie, those who have the most to lose, lose the most).⁵

Risk of delayed intervention

The reasons behind what is likely underutilization of active surveillance are multiple and complex. It must be acknowledged that prognostic risk assessment is not perfect and that one assumes some risk of disease progression while on active surveillance, which many physicians and patients may not be willing to accept. The issue becomes one of timing of definitive intervention for successful active surveillance of prostate cancer. Is there evidence that treatment can be delayed until absolutely necessary with no detriment to curability? Freedland et al.,²⁷ for example, reported no differences in adverse pathologic features or biochemical disease progression for men with low-risk prostate cancer who delayed radical prostatectomy for up to 180 days after diagnosis. Similarly, Warlick et al.²⁸ reported no differences in adverse pathologic features between a group of men undergoing delayed prostatectomy after a period of active surveillance and a group of men with similar risk disease undergoing immediate surgical intervention. The median time to intervention in the delayed group was 26.5 months.²⁸ These data suggest that well-characterized, early-stage tumors followed by experienced physicians and knowledgeable patients do not progress rapidly and deferring treatment appears not to alter their natural history.

Refined risk assessment and nomograms

Ideally, prostate cancer therapy will be reserved for men at greatest risk for cancer progression and morbidity or mortality from their disease. Determining which men fall into this category poses significant challenges. Many physicians estimate risk by inte-

grading Gleason score, pretreatment PSA, and clinical stage by physical examination or prostate ultrasound; many now also assess the extent of biopsy involvement with tumor. Tables and nomograms integrate clinical variables to help estimate risk of adverse outcomes from prostate cancer. Such risk assessment helps guide timing and choice of therapy. It must be emphasized that all such instruments require that the initial prostate biopsy be performed well. Common instruments include the Partin tables,²⁹ the D'Amico risk classification,³⁰ the Kattan nomograms,³¹ and the CAPRA score.³² With particular respect to low-risk tumors, Kattan et al.³³ have developed nomograms to predict tumors likely to be indolent based on pathologic characteristics, and the CAPRA score has proved to be an effective tool with which to stratify low-risk men in terms of likelihood of disease progression.⁷

An argument can be made that the overdiagnosis of prostate cancer is problematic primarily to the extent that it leads to overtreatment; a patient diagnosed with an indolent tumor that is not treated may suffer anxiety, but no other sequelae of disease or treatment. Despite evidence for an often prolonged natural course, however, the majority of tumors are actively treated with surgery, some form of radiotherapy, and/or hormonal ablation, with a significant risk of treatment-related detriments to quality of life.⁵ Data from CaPSURE demonstrate that the proportion of low-risk men electing surveillance has risen in recent years (2004–2006) to 10.2%, up from a nadir of 6.2% in 2000 through 2001, but still representing a small fraction of potentially eligible men.⁷

Observational cohort studies in men with prostate cancer diagnosed in the pre-PSA era provide important insight into the heterogeneous and often prolonged natural history of localized disease and demonstrate a clear correlation between Gleason score and mortality from prostate cancer.²⁶ With a median follow-up of 24 years, prostate cancer-specific mortality remains low and relatively stable for men with low-grade tumors. Johansson et al.⁴ reported progression-free and cause-specific survival rates at 15 years after diagnosis of 56% and 89%, respectively, for men with well-differentiated tumors diagnosed clinically in the pre-PSA era. Rates for all men were stable up to 15 years after diagnosis, after which they observed a 3-fold increase in cancer progression and mortality from prostate cancer. With a 5-year to 10-year estimated diagnosis lead-time afforded by PSA screening, these data suggest a very low prostate cancer-specific mortality, especially for a group of men with low-risk tumors who are treated conservatively.

Active Surveillance: Contemporary Experience

The last few years have witnessed a paradigm shift in conservative management for low-risk prostate cancer. Rather than reserving 'watchful waiting' (which suggested deferring intervention until the advent of symptoms), for older patients with limited life expectancy, a large fraction of men diagnosed today with low-risk disease might be offered 'active surveillance,' suggesting close monitoring of PSA kinetics and other parameters, and treatment with clinical interventions when/if necessary. Whereas many men on such a protocol may ultimately require active treatment, they often can delay therapy and preserve quality of life with the possibility of benefiting from further advances in available treatments.

Selection criteria

Critical to successful active surveillance programs is patient selection. Who are the best candidates for active surveillance? In general, active surveillance protocols attempt to identify men with good-risk prostate cancer who are most likely to be safely watched for a period of time and then treated when necessary. Published active surveillance series use different criteria largely based on personal preferences and individual clinical experiences with no hard data. Tables and nomograms based on a well-performed, extended pattern biopsy at the time of initial diagnosis and assessment should be used to integrate clinical variables and help estimate risk to guide timing and choice of treatment. It has been demonstrated that PSA, PSA density, and prostate needle biopsy parameters can be used to predict low-volume disease.³⁴ Greene et al.³⁵ reported that a higher number of cores involved with tumor correlates with biochemical failure after radical prostatectomy and thus may suggest higher risk disease. PSA velocity before treatment has been shown to be predictive of outcome and may be useful in evaluating patient risk.³⁶

The most common clinical data used to define low-risk prostate cancer include a Gleason score ≤ 6 (no pattern 4 or 5 disease), PSA level ≤ 10 ng/mL, and clinical stage T1 to T2a disease. Other characteristics to consider include PSA density (PSAD < 0.15), percent positive cores at biopsy ($< 33\%$), the extent of cancer in any core ($< 50\%$), and PSA kinetics (stable) before diagnosis (Table 1). Prospective studies comparing entry criteria for active surveillance protocols with subsequent disease progression and treatment patterns are needed to clarify the best candidates for active surveillance.

TABLE 1
Common Entry Criteria for Active Surveillance

Gleason sum	6 (no pattern 4 or 5)
PSA	≤10 ng/mL
% positive cores	≤33%
% single core involvement	≤50%
PSA kinetics	Stable

PSA indicates prostate-specific antigen.

Predicting progression

Identifying the early signs of significant disease progression is critical for providing appropriate therapy during the window of curability. What will serve as the best 'canary in the coal mine' for prostate cancer surveillance is a matter of ongoing debate. Mounting evidence suggests that PSA changes over time provide an important window into prostate cancer tumor biology. D'Amico et al.³⁶ showed in 2004 that men with rapidly rising PSA in the year before radical prostatectomy had a higher risk of dying from the disease. Among patients with biochemical recurrence after radical prostatectomy, PSA doubling time is a strong predictor of prostate cancer-specific mortality.³⁷ A recent analysis by Carter et al.³⁸ suggests that PSA velocity (PSAV) 15 years before diagnosis was significantly higher in men who died from prostate cancer than men who were never diagnosed with the disease or who were diagnosed and died of unrelated causes. Ali et al.³⁹ observed that PSA doubling time <2 years in men undergoing radical prostatectomy after a period of active surveillance was the greatest predictor of eventual biochemical recurrence. These findings suggest that PSA kinetics can be used to predict cancer behavior and perhaps provide an important endpoint for active surveillance protocols. By identifying only the less indolent, clinically significant tumors for surveillance, many men may be spared treatment.

Carter et al.⁴⁰ describe following PSA and digital rectal examination semiannually with annual prostate needle biopsy. Other investigators describe following PSA every 3 months for 2 years with a repeat prostate biopsy after 1 year of surveillance.⁴¹ Criteria for grade progression in a Canadian cohort include upgrading to Gleason 4 + 3 or greater on rebiopsy; however, only 4% of men were treated because of grade progression alone. PSA doubling time was the greatest trigger for intervention, with 21% of the cohort having a doubling time of <3 years.⁴² Data from CaPSURE also demonstrated that rising PSA is the greatest predictor of active treatment.⁴³ In the series by Zeitman et al.,⁴⁴ 71% of men treated after a

period of active surveillance had a rising PSA as the only driver for intervention. Stephenson et al.⁴⁵ found that men with stage progression detected by digital rectal examination while on active surveillance were more likely to have PSA doubling times of <2 years, again suggesting that PSA kinetics may act as an important surrogate for progressive disease. A retrospective analysis of 88 men with low-risk cancer who deferred initial active management reported that a positive first follow-up biopsy was predictive of disease progression and only 11% of men with negative rebiopsies developed disease progression compared with 40% of men with positive surveillance biopsies.⁴⁶ Predicting clinically significant disease progression is critical to providing appropriately selective treatment in a timely manner.

Prostate imaging by ultrasound or magnetic resonance may also have a role in following detected lesions. Although to our knowledge no published series used lesion size as a sole trigger for intervention, stage progression may provide insight into disease progression. It remains to be shown whether significant changes in lesion size occur in the isolation of PSA or grade progression. Emerging techniques in magnetic resonance imaging with spectroscopic imaging (MRI/MRSI) can integrate anatomic with molecular data to possibly improve prostate cancer detection and characterization.⁴⁷ By assessing tumor metabolism, such technology may enhance the prediction of tumor aggressiveness or disease progression for active surveillance protocols. Shukla-Dave et al.⁴⁸ incorporated MRI/MRSI findings with clinical variables to develop a nomogram for predicting clinically insignificant prostate cancers. Highly sensitive transrectal ultrasonography with 3-dimensional imaging and color flow Doppler is also being investigated for better characterization or prostate tumors.⁴⁹ Whether PSA kinetics or innovative imaging modalities can predict clinically meaningful tumors or disease progression in men with low-risk prostate cancer on active surveillance remains to be determined. Such tools must be tested rigorously in larger, prospective studies before being relied upon for predicting candidacy for active surveillance or for detecting disease progression.

Outcomes

Reported outcomes from several series have been promising, although follow-up remains limited. Treatment characteristics and indications for active therapy in selected surveillance series are presented in Table 2. Roemeling et al.⁵⁰ examined a cohort of 278 men with screen detected prostate cancer from the European Randomized study of Screening for

TABLE 2
Treatment Characteristics of Selected Active Surveillance Cohorts

Study	No. of patients	% Treated	Treatment criteria	Median follow-up, months
UCSF	321	21	Gleason score ≥ 7 on rebiopsy, rising PSA, increase in volume by biopsy parameters	24
Klotz et al. ⁴²	299	34	PSA DT <3 years	64
Warlick et al. ²⁸	320	31	Gleason score ≥ 7 on re-biopsy, any pattern 4,5 >2 cores involved, >50% any single core involved	23
Hardie 2005 ⁵¹	80	14	Rising PSA, clinical judgment	42
Patel 2004 ⁴⁶	88	35	Gleason score increase, PSAV>0.75/yr, increase DRE/TRUS detected lesion, increase biopsy volume	44

PSA indicates prostate-specific antigen; PSADT, PSA doubling time; PSAV, PSA velocity; DRE, digital rectal examination; TRUS, transrectal ultrasonography.

Prostate Cancer and found that 30% of men received delayed therapy after a median of 40 months on active surveillance. With a median follow-up of 82 months, no men in the active surveillance group developed metastatic disease or died of prostate cancer. With a median follow-up of 42 months, Hardie et al.⁵¹ reported that 80% of men remained on active surveillance with no prostate cancer-specific deaths. Five of the 80 enrolled men (6%) died from other causes and no men developed metastatic disease. Approximately 73% of the cohort had a PSA level <10 ng/mL and 91% had a Gleason score ≤ 6 . The median PSA doubling time for the active surveillance group was 12 years. Carter et al.⁴⁰ described evidence of clinical disease progression (primarily grade progression on repeat biopsy) in 31% of 81 men in an active surveillance program with a median follow-up of 23 months. Of the men undergoing radical prostatectomy for disease progression while on active surveillance, 23% had adverse pathologic features considered to represent <75% chance of remaining disease-free for 10 years after surgery.⁵² This rate did not differ from a similar group of low-risk men treated within 3 months of diagnosis, and likely represents underassessment of baseline risk rather than disease progression during surveillance. In what to our knowledge is 1 of the largest published series to date with nearly 300 patients and 8 years of follow-up, overall survival was 85%, with a disease-specific survival rate of 99.3%.⁴² Among more than 500 men on active surveillance at the University of California at San Francisco, 24% have received secondary treatment a median of 3 years (range, 1–17 years) after being placed on active surveillance. Thirty-eight percent of the cohort had an increased Gleason score on rebiopsy and increasing cancer grade was the greatest driver of treatment for the entire cohort. Given the often prolonged natural history of prostate

cancer, the median follow-up from these published series remains relatively short. Without longer-term data or validation of appropriate surrogate endpoints, results from these protocols must be interpreted with caution.

Psychosocial Impact

In contemporary series approximately 10% to 50% of men come off of active surveillance and are treated despite the absence of evidence of clinical disease progression.^{41,53} The psychosocial ramifications of careful surveillance for a disease such as prostate cancer can be profound. In the more than 10 years since Litwin et al.⁵⁴ first reported that men on active surveillance experienced limitations in their role function because of anxiety and uncertainty regarding their disease status, to our knowledge only a few studies have explored the psychosocial ramifications of this management option for men with prostate cancer. These studies reported that men undergoing watchful waiting experience anxiety, illness uncertainty, and a decreased quality of life.^{55–58} It is unclear whether these effects are worse than those experienced by men who have been treated radically. A companion study to the Holmberg randomized trial of surgery versus watchful waiting in Scandinavia, for example, demonstrated absolutely no significant psychologic difference after 5 years between the 2 groups.⁵⁹ Worry, anxiety, and depression all were equal between the 2 arms. Whereas surveillance may be stressful for some men, it appears that most patients with prostate cancer whether treated or not are concerned about the risk of progression, and anxiety regarding PSA recurrence is common among both treated and untreated patients. Cultural differences undoubtedly have an impact on patients' response to a cancer diagnosis, and the Scandinavian

experience may not be generalizable to other groups of men. Substantial clinical experience suggests that patients who are educated to appreciate the indolent natural history of good-risk prostate cancers may avoid much of these adverse psychologic effects. Indeed, anxiety can be a greater factor than PSA progression or other clinical factors in driving surveillance patients toward active intervention.⁶⁰

Studies of the role of support groups to decrease the negative impact of active surveillance have provided inconsistent results. Katz et al.⁶¹ observed that after adjusting for ethnicity, age, and type of treatment, men attending support groups reported better health-related quality of life than men who did not. Yet Chapple et al.⁶² reported that support groups intended to provide emotional support may produce a negative psychosocial response in men when they believe pressured by group members to initiate aggressive treatment. These studies underscore the need for psychosocial intervention to support men's emotional responses to active surveillance. It remains unclear as to whether traditional group programs are effective at meeting these needs.

Recent work by Bailey et al.⁶³ has supported the benefit of 1-on-1 nursing interventions for patients undergoing active surveillance and to our knowledge to date, their study remains the only published trial of the intervention. The intervention involves a process of rethinking about prostate cancer as a chronic illness rather than an instant killer (cognitive reframing) and changes in lifestyle that promote health. Preliminary results of the intervention are promising, but these results must be replicated in a large study of men in active surveillance programs. The goal of future work designed to provide psychosocial support for these men is the development of a clinical protocol focusing on the management of prostate cancer as a chronic condition for men considering or undergoing active surveillance for their disease.

Obstacles to Surveillance

Multiple pragmatic barriers to implementing active surveillance for prostate cancer exist and must be addressed. These include access to psychosocial support, appropriate clinical data tracking, medicolegal concerns, and financial constraints. Educational programs designed to increase health professional and community awareness of active surveillance for prostate cancer can begin to break down some of these barriers. Organizations that embrace active surveillance, including the American Cancer Society and the NCCN, represent invaluable resources to begin this process. Guidelines for offering active surveil-

lance for men with low-risk disease have been incorporated into current NCCN guidelines for prostate cancer. These guidelines function to support patients and clinicians interested in expectant management.

Lack of adequate psychosocial and financial support networks is not unique to prostate cancer. Increased public awareness combined with patient demand can work to focus existing cancer-oriented resources on the specific needs of men living with prostate cancer. Certain aspects of the monitoring protocol such as PSA measurements and digital rectal examination can be performed remotely with local providers utilizing telephone or internet-based communication to update more specialized centers. Careful and thorough patient monitoring is critical for active surveillance and the responsibility must lie on both the patient and the physician to ensure that appropriate tests are performed and interpreted appropriately. Such issues must be addressed before widespread implementation of active surveillance for prostate cancer and are currently the focus of multiple working groups internationally.

The Future

Despite ongoing research and active education, the overwhelming *minority* of eligible men and their physicians choose active surveillance for primary management of their disease. Although we are able to predict low-risk prostate cancer with increasing accuracy, the need for novel biomarkers for predicting the biologic behavior of individual tumors remains. Demichelis et al.,⁶⁴ for example, evaluated TMPRSS2:ERG gene fusion in prostate cancer tissue specimens from 111 men on active surveillance for what was considered low-risk prostate cancer. The gene fusion was detected in 15% of the specimens and was found to be significantly correlated with Gleason score and prostate cancer-specific mortality. Other researchers have investigated genomic alterations in prostate cancer and have correlated them with PSA recurrence after treatment. Paris et al.⁶⁵ used comparative genomic hybridization to investigate DNA alterations and their relation to postoperative PSA recurrence. They found gains (11q13.1) and deletions (8p23.2) associated with advanced stage and biochemical recurrence after prostatectomy independent of the grade and stage of the primary tumors. A 12-gene signature developed by Bismar et al.⁶⁶ was shown to discriminate aggressive prostate tumors by also predicting postoperative PSA recurrence. However, multi-institutional validation studies are required before the widespread clinical application of these techniques. Ideally, the concomitant use of novel biomarkers and standard clinical character-

TABLE 3
Recommended Surveillance Schedule

PSA	Every 3–4 mo
DRE	Every 3–6 mo
TRUS	Every 9–12 mo*
Prostate biopsy	After 1 y then every 1–2 y or as indicated by PSA or examination trends

PSA indicates prostate-specific antigen; DRE, digital rectal examination; TRUS, transrectal ultrasonography.

* Imaging not found beneficial in some studies.

istics will provide robust predictive value for safe and more emotionally secure active surveillance.

Conclusions

Active surveillance with delayed intervention appears to be a viable option for carefully selected men with low-risk prostate cancer. Answers from large randomized trials comparing expectant management or watchful waiting to active treatment such as START, PIVOT, and PROTECT will confirm and validate many of the criteria for patient selection and monitoring while providing insight into anticipated outcomes from such treatment strategies. Patterns in progression to active treatment and quality-of-life data from these trials will also identify important components for psychosocial interventions and support. However, results from these trials are several years from being obtained. Although these data are pending, we here-with put forward our conservative recommendations given the current state of knowledge. Men should have a low (<10 ng/mL) and stable PSA level, a Gleason grade ≤ 6 , clinical stage T1 to T2a disease, and low-volume disease as assessed by extended pattern (≥ 12 needle cores) biopsy. Men should be followed closely with frequent PSA measurements (every 3–4 months) with digital rectal examinations performed every 3 months to 6 months and imaging (if performed) every 9 months to 12 months (Table 3). Repeat prostate needle biopsy should be performed after 1 year of surveillance and then every 12 to 24 months or as indicated by changes in PSA or findings on digital rectal examination. Although a significant number of men may ultimately require other forms of therapy, active surveillance offers the opportunity to delay active treatment and its associated morbidities until evidence of clinical progression is found. The need for more research on this subject is evident given the incidence of prostate cancer and trends in stage migration described earlier.

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