AUA Update Series 2008
Lesson 33 Volume 27

Active Surveillance for Prostate Cancer: Patient Selection and Management

Learning Objective: At the conclusion of this continuing medical education activity, the participant will understand the rationale for active surveillance, the clinical and pathological criteria for considering surveillance as a management option, and the practical aspects of surveillance, including follow-up strategies, triggers for intervention and expected results with respect to the likelihood of eventual treatment and prostate cancer mortality in a favorable risk population.

Laurence Klotz, M.D.

Disclosures: Abbott: Meeting Participant/Lecturer, Scientific Study/Trial; AstraZeneca: Meeting Participant/Lecturer, Scientific Study/Trial, Consultant/Advisor; Aventis, Merck, GSK: Meeting Participant/Lecturer

Professor of Surgery
University of Toronto
Chief, Division of Urology
Sunnybrook & Women's College Health Sciences Centre
Toronto, Ontario, Canada

This self-study continuing medical education activity is designed to provide urologists, Board candidates and/or residents affordable and convenient access to the most recent developments and techniques in urology. The American Urological Association (AUA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AUA takes responsibility for the content, quality and scientific integrity of this CME activity.

Credit Designation Statement: The American Urological Association designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Each physician should only claim credit commensurate with the extent of their participation in the activity.

AUA Disclosure Policy: As a provider accredited by the ACCME, the AUA must insure balance, independence, objectivity and scientific rigor in all its activities. All faculty participating in an educational activity provided by the AUA are required to disclose to the audience any relevant financial relationships with any commercial interest to the provider. The intent of this disclosure is not to prevent faculty with relevant financial relationships from serving as faculty, but rather to provide members of the audience with information on which they can make their own judgments. The program planners must resolve any conflicts of interest prior to the commencement of the educational activity. It remains for the audience to determine if the faculty's relationships may influence the educational content with regard to exposition or conclusion. When unlabeled or unapproved uses of drugs or devices are discussed, these are also indicated.

Unlabled/Unapproved Uses: It is the policy of the AUA to require the disclosure of all references to unlabeled or unapproved uses of drugs or devices prior to the presentation of educational content. Please consult the prescribing information for full disclosure of approved uses.

Publication date: November 2008
Expiration date: November 2011

American Urological Association
Education and Research, Inc.
1000 Corporate Boulevard
Linthicum, MD 21090

KEY WORDS: prostatic neoplasms, surveillance

INTRODUCTION

Prostate specific antigen screening has led to a dramatic reduction in disease stage at diagnosis and identified more patients with curable cancers. Prostate cancer mortality has decreased about 25% in many regions, including the United States and Canada. The side effects of surgery and radiation are considerably less than they were 20 years ago due to improved surgical technique and expertise, and more precise radiation targeting.

However, early and repeated PSA testing results in many men being diagnosed with clinically insignificant prostate cancer that may pose little or no threat to life if left untreated. Unfortunately, the diagnosis of cancer typically results, at least initially, in ''cancer hysteria,'' that is fear of an aggressive, life threatening condition. This may lead to a quick and early treatment decision regardless of the risks and benefits. In fact, the condition most of these men have is far removed from a rampaging aggressive cancer. An alternative approach is presented which involves using the behavior of the disease over time to determine how aggressively a patient will be treated.

SCOPE OF PROBLEM AND RATIONALE FOR ACTIVE SURVEILLANCE

Prostate cancer screening based on PSA and prostate biopsy results in diagnosing many men with prostate cancer for whom the disease does not pose a threat to life. Welch recently modeled the rate of prostate cancer diagnosis. There are 2.74 million 50 to 70-year-old men in the United States with a PSA of >2.5. If all American men in this age group had a PSA test and PSA >2.5 was used as an indication for biopsy, 775,000 cases of PC would be diagnosed this year in the U.S. alone. **This is 543,000 more than the 232,000 cases diagnosed in 2005, and 25 times more than the 30,350 men expected to die of PC per year in the U.S.**[1]

Autopsy studies of men dying of other causes have documented the high prevalence (about 50% of those older than 50 years) of histological prostate cancer.[2] A large proportion of this histological or latent prostate cancer is never destined to progress or affect the life span of the patient. Since the introduction of PSA screening, the lifetime risk of being diagnosed with prostate cancer has almost doubled from around 10% in the pre-PSA era to 17%.[3] Many men with localized prostate cancer are overtreated, since most not destined to die of prostate cancer or experience its morbidity will be subjected to radical therapy.[4]

Autopsy studies have demonstrated that prostate cancer typically may begin in the third or fourth decade of life.[1] Therefore, in most patients there is likely a period of slow subclinical tumor progression that lasts approximately 20 years, followed by a period of clinical progression (potentially to metastatic disease and death) lasting about 15 years. The implication is that most patients have a long window of curability, particularly those with favorable risk, low volume disease.

The lifetime risk of dying of prostate cancer remains at less than 3%.[3] As the lifetime risk of being diagnosed approaches the known rate of histological (mostly insignificant) prostate cancer, there is a greater risk of overtreatment. At least 2 studies have attempted to model the rate of diagnosing clinically insignificant disease, suggesting that it ranges from 30% to 84%.[4, 5] The current incidence-to-mortality ratio of about 7:1 suggests that the higher (84%) figure is more likely. Factors contributing to this hypothesis are the increasing use of PSA screening and more extensive biopsy of 8 to 13 cores compared to the historical value of 6 cores.[6] Additionally, biopsies are often repeated until a cancer diagnosis is made. More biopsies mean more clinically insignificant and clinically important prostate cancer is diagnosed.

The PSA era (1990 to the present) has been characterized by a high level of enthusiasm for radical therapy, including surgery and radiation. This enthusiasm has been driven by high quality data from phase 2 prospective databases, population databases and randomized trials showing improved biochemical disease-free survival with aggressive treatment. Screening has also been accompanied by a 25% reduction in mortality in screened populations. However, this decrease has come at the cost of many patients being diagnosed and treated for a non-life threatening cancer. **Currently, 90% of men with low risk prostate cancer undergo radical treatment.** A situation in which 1 in 5 men is diagnosed vs 1 in 30 at risk for prostate cancer mortality, in the context of the impact of treatment on quality of life and the modest survival benefit for many patients who are cured, is not sustainable. An approach that would reduce unnecessary treatment is highly desirable. The fundamental approach is to screen aggressively, thereby detecting intermediate and high grade cancers earlier when treatment is clearly of benefit, but manage the low risk disease conservatively.

WHAT IS ACTIVE SURVEILLANCE?

Active surveillance is used to describe an approach to favorable risk prostate cancer characterized by initial observation, with close monitoring of PSA kinetics and serial biopsy. Over time a minority of patients will be reclassified as having higher risk disease and offered definitive radical treatment, and the remainder will continue to be followed. Watchful waiting, a phrase coined in the pre-PSA era, refers to conservative management until metastatic disease develops at which time patients are treated palliatively. The key distinction is the use of selected delayed definitive treatment in a subset of patients based on biological markers before the development of clinical disease progression.

Cancer aggressiveness can be predicted using existing clinical parameters, the most widely used of which are tumor grade or Gleason score, PSA and tumor stage. Favorable risk prostate cancer is characterized by a Gleason sum of 6 or less (ie no pattern 4 or 5 disease), PSA 10 ng/ml or less and T1c-T2a disease.[5] As a result of stage migration due to PSA screening, the proportion of newly diagnosed patients in the favorable risk category has increased, and now constitutes about 50%. While

ABBREVIATIONS: NNT (number needed to treat), PC (prostate cancer), PSA (prostate specific antigen), PSADT (prostate specific antigen doubling time)

patients with these characteristics have a much more favorable natural history and progression rate than those with a higher Gleason grade or PSA, advanced incurable prostate cancer and death will occur in a few.

REVIEW OF PREVIOUS STUDIES

A large group of patients in Connecticut were treated with watchful waiting, and outcomes at 20 years have been reported.[7] The study data confirm the powerful predictive value of Gleason score. In the pre-PSA screening cohort 23% of patients with untreated Gleason 6 and 65% with Gleason 7 disease died of prostate cancer within 20 years. In addition, there has been a shift in Gleason scoring[8] interpretation during the last 20 years largely due to the current practice of calculating the Gleason sum based on the presence of any high grade foci, even if they are scant. A pattern 3+3 cancer with 5% Gleason 4 would have been called a 6/10, 20 years ago and today it would be a 7.

Thus the Connecticut results likely represent a worst case scenario for the expected mortality from untreated Gleason 6 cancer. Furthermore lead time with PSA screening is about 10 years in men in their 60s, estimated from a variety of serum databases and modeling.[9, 10] **Therefore, it is plausible that in a serially screened population the cancer mortality of Gleason 6 cancer may be as low as 10% at 30 years.**

The results of a watchful waiting approach (no treatment until progression to metastatic or locally advanced disease) has been reported by many groups.[11-20] Although these studies describe non-progression in many patients, the results are difficult to apply in the current era because 1) the cohorts described are from the pre-PSA era, and constitute patients with more extensive disease at the time of diagnosis, and 2) patients were not offered the opportunity for selective definitive therapy. In the era of PSA monitoring patients who are treated conservatively receive periodic PSA tests, which raises the tantalizing prospect that treatment of favorable prostate cancer could be deferred indefinitely in the majority. Although effective, delayed therapy need only be offered to the patient subset in whom PSA progresses rapidly or the tumor grade increases.[21, 22]

Choo et al were the first to report a prospective active surveillance protocol incorporating selective delayed intervention for the subset of patients with rapid PSA progression or grade progression on repeat biopsy.[23, 24] The eligibility criteria for this therapy included T1c or T2a prostate cancer, Gleason ≤6 and PSA ≤10. For patients older than 70 years these criteria were relaxed to include Gleason ≤7 (3+4) and/or PSA ≤15. The core prospective cohort was 331 patients with a median follow-up of 8 years (range 2 to 11). Overall survival was 85%, and the disease specific and metastasis-free survival was 99%.

Only 3 of the 331 patients died of prostate cancer to date. All 3 patients had PSADT of <2 years and death occurred 3.0, 5.1 and 5.2 years after diagnosis. All 3 patients exhibited the same pattern of clinical progression, which included initial favorable prognostic factors; a rapid increase in PSA which led to treatment 6, 9 and 11 months after the initial diagnosis; a progressive increase in PSA; and clinically apparent bone metastases within a year after treatment, leading to androgen deprivation therapy. All 3 patients died within 3 years of the initiation of hormonal therapy. This rapid progression after diagnosis suggests that these patients had occult metastases at the time of initial disease presentation, and that the outcome would not have been altered by earlier treatment. Even in the Scandinavian trial there were almost no lives saved before 5 years had elapsed.[25]

PSADT, calculated by logarithmic regression, was <3 years in 22% and more than 10 years in 42% of patients (median 7), suggesting an indolent course of disease in these patients. Radical treatment was given to 35% of the patients for PSADT <3 years (20%), progression to Gleason 4+3 or higher on repeat

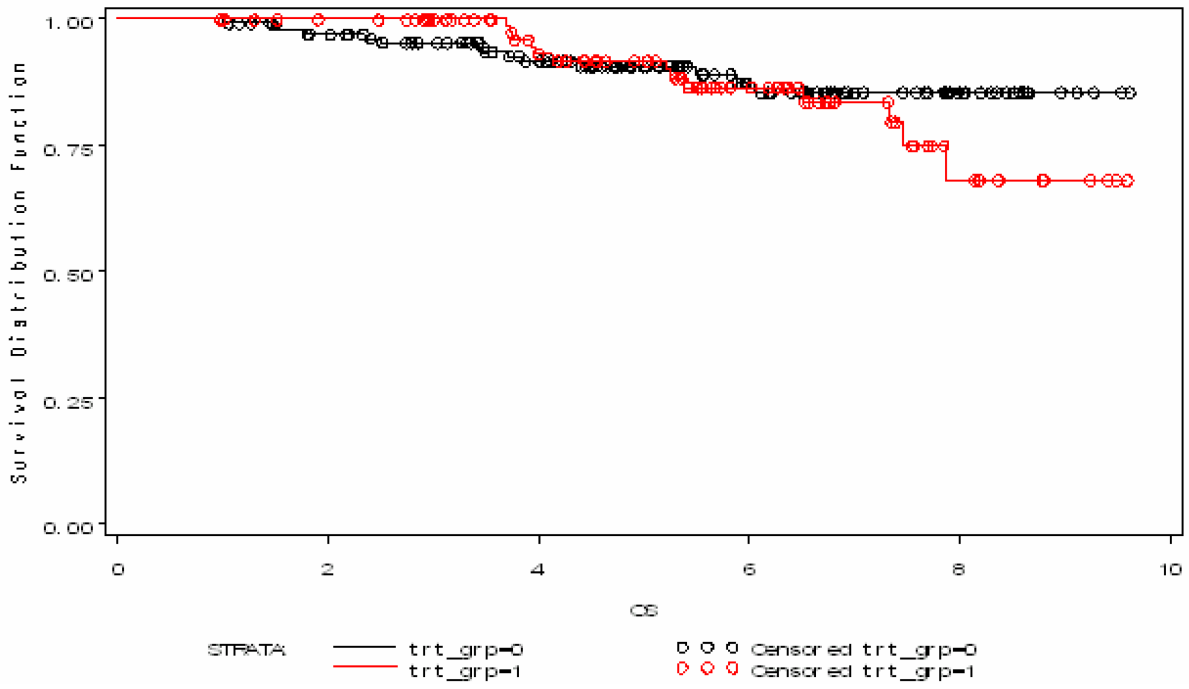

FIG. 1. Overall survival of 331 patients on active surveillance

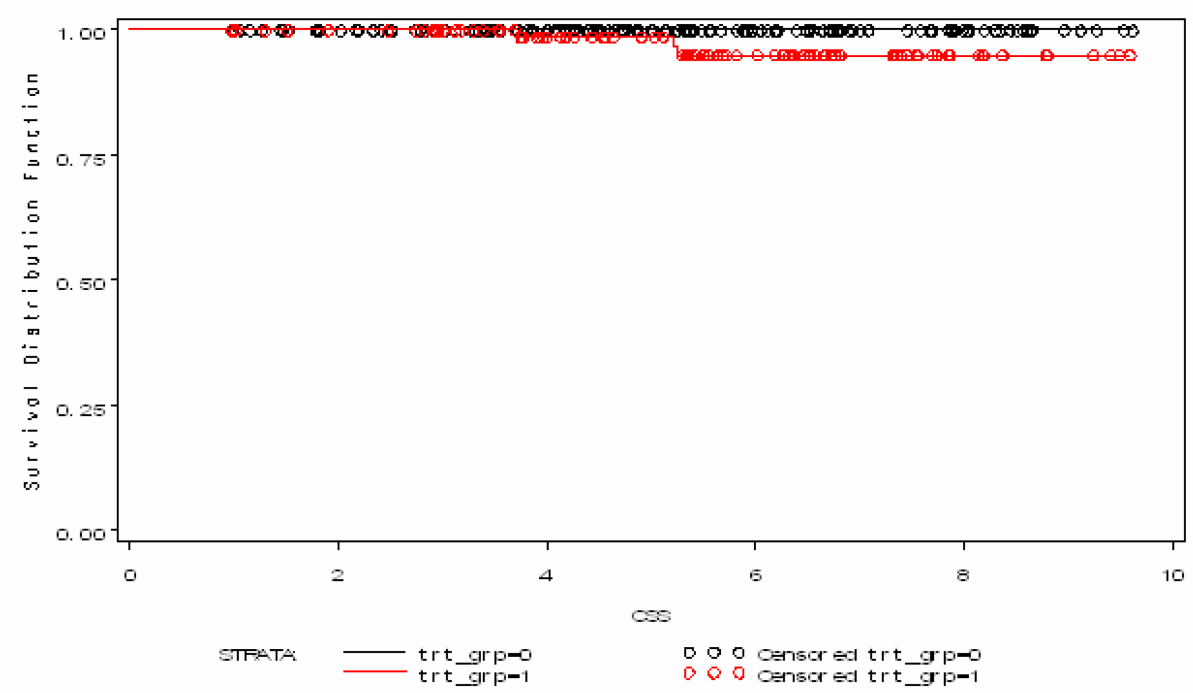

FIG. 2. Prostate cancer specific survival of 331 patients on active surveillance

biopsy (5%) and patient preference (10%). The remaining patients have not required any local or systemic therapy.

A number of other groups have now reported favorable results of active surveillance, including 270 patients diagnosed in the Swedish arm of the European screening trial.[26] Of the patients 39% have been treated and there were no prostate cancer deaths or metastatic progression. Of the 70 patients treated with delayed surgery 12% have had biochemical recurrence but none with PSADT >4 years has had recurrence after surgery. Soloway et al reported on 175 patients with a median follow-up of 4 years (range 1 to 12).[27] There were no prostate cancer deaths or metastatic disease, and only 8% of the patients received delayed radical intervention. Carter et al performed surveillance on 407 patients, and at a median follow-up of 3.4 years (range 0.4 to 12) there have been no prostate cancer deaths.[28]

These series confirm that this approach is associated with an extremely low rate of progression to metastatic disease and/or prostate cancer death, and that the majority of patients do not require intervention. The limitation of these studies in the context of the long natural history of this disease is the length of follow-up. It will require another 5 to 7 years before even the most mature of these studies will have a median 15-year follow-up. Nonetheless, the results are encouraging to date.

STUDIES SUPPORTING RADICAL INTERVENTION

The recent landmark trial from Scandinavia recently demonstrated, for the first time, that radical prostatectomy improves survival.[25] Treatment of about 630 patients was randomized between radical prostatectomy and watchful waiting. **The study revealed a 5% absolute survival benefit at 10 years** and a 50% reduction in prostate cancer mortality with surgery.

However, this cohort included many patients with intermediate to high risk disease, and only 5% were diagnosed based on PSA screening (median PSA 12.8). The volume of disease in these patients represented a pre-stage migration cohort. However, even in this group the PSA level needed to treat to prevent each prostate cancer death at 10 years was 19. The distribution of disease volume and grade was higher than the expected distribution in a contemporary screened population, in which a substantial proportion of newly diagnosed patients have small volume low grade disease.

The Scandinavian study should not be interpreted to mean that all patients with localized prostate cancer should be treated radically. Many studies emphasize that patients with Gleason 4-5 pattern disease are at the greatest risk for death from prostate cancer. In the Swedish study the mortality improvement began to appear at 5 years.[25] It would be most unusual for a patient with low grade, low volume disease to die within 5 years of diagnosis, and in the Toronto surveillance cohort this rate is 1% of patients.[23] Thus, the majority of the benefit seen in the Scandinavian trial likely represents mortality reduction in the high risk group. Importantly, the study showed no benefit in men older than 65 years.

We have used these data and the Connecticut watchful waiting data to estimate for each prostate cancer death averted at 20 years the number of patients with favorable risk prostate cancer that would have to be treated at the time of diagnosis. The number needed to treat for each death avoided at 10 years in the Swedish trial was 20. It is likely that with additional (ie 20 years) follow-up the survival benefit in the Swedish trial, now 10 years, will increase. In patients diagnosed by PSA screening this benefit is likely to be balanced by the additional 10-year lead time afforded by screening. Thus, in a screened patient with intermediate grade disease and PSA similar to the Swedish cohort, the NNT at 20 years is estimated to also be about 20.

Albertsen et al indicated that the mortality for intermediate risk disease (Gleason 7) was about 2.5 times greater at 20 years than it was for favorable risk disease.[7] If the shift in

contemporary Gleason scoring is factored in then this number may be an underestimate. Even so, compared to no treatment, about 50 favorable risk patients (Gleason 6 or less) would need to be treated for each death that would be prevented by surgery. However, if one offers selective delayed intervention to those patients with disease progression, it can be conservatively estimated that at least 50% can be salvaged. **The conclusion is that about 80 to 100 radical prostatectomies would be required for each prostate cancer death averted in cases of favorable risk disease.** Correcting the Connecticut data for grade migration, as referred to earlier, would increase this even further. A similar analysis has been performed by Parker et al, also confirming that for Gleason 6 or less virtually no reduction in prostate cancer mortality would be expected by radical treatment of all patients.[29]

Finally, how much benefit does that 1 patient whose prostate cancer death is averted by all of those radical treatments achieve? Experience with 2000 patients suggests that the prostate cancer deaths averted would have occurred on average 16 years after diagnosis, meaning that the number of life years saved in each of these 1 in 100 averted deaths is modest.[30] Unfortunately, no one lives forever. For the average 60-year-old man, life would be prolonged an average of 5 years by having prostate cancer death averted.[8] If each prostate cancer death averted adds 5years to that individual's life, each radical prostatectomy would add 0.6 months of life (60 months per 100 operations). This is of dubious merit.

DO WE HAVE CLINICAL TOOLS THAT MAKE ACTIVE SURVEILLANCE SAFE?

The 2 challenges with surveillance are to avoid excessive delay in patients who appear to be at higher risk for progression over time and avoid overtreating patients based on a transient change in PSA or other biomarkers. All groups have used a combination of PSA kinetics and serial biopsy, and the specific approach varies. The Toronto group uses a doubling time of 3 years or less based on multiple determinations at 3-month intervals calculated using a General Linear Mixed Model which corrects for baseline PSA, grade and age. This model is available free at http://psakinetics.sunnybrook.ca. Others use a calculated or actual PSA velocity >2.0 ng/ml per year.

Most groups advise serial biopsies at intervals varying from 1 to 4 years. The Toronto group recommends a confirmatory biopsy at 1 year to identify higher grade disease that was missed on the original biopsy, and subsequent biopsies are performed every 4 to 5 years to detect biological progression, a much more uncommon event. The Hopkins group performs biopsies annually or when an increase in PSA occurs.[28]

In the Toronto series patients with a PSADT of 3 years or less constituted 22% of the cohort. This cut point for intervention remains empirical and speculative. However, the 20% to 25% of patients with a 3-year doubling time represents a rough approximation of the proportion of good risk patients at risk for disease progression.[24] For patients with a PSA in the 6 to 10 range, it also approximates an annual increase of 2 ng/ml, which is an adverse predictor of outcome as described by D'Amico et al.[31] PSA kinetics are prone to artifact from biological variation, prostatitis, etc. There are a number of other promising biomarkers to identify patients at risk for disease progression, including PSA density, free vs total PSA ratio and PCA3. It is also likely that genetic biomarkers, including SNP chip arrays, will allow better prediction of patient risk within the next decade, and this remains an active area of research.

Prostate biopsy is also imperfect, since it is a limited sampling of the prostate. This issue has been addressed, in part, by serial biopsies with particular attention to the anterolateral horn, a common site for disease missed on routine biopsies. Some have advocated saturation biopsies, consisting of 50 or more cores performed with the patient under general anesthesia for those contemplating surveillance. This approach, which may identify some patients with higher risk disease, has not been embraced by most advocates of active surveillance and does not appear necessary in the majority of patients.[32]

The psychological effects of living for many years with untreated cancer are a potential concern. Does the cumulative effect, year after year, of knowing one is living with untreated cancer lead to depression or other adverse effects? **The best data on this come from a companion study by Steineck et al[33] to the Scandinavian randomized trial of surgery vs watchful waiting in Sweden.[25] Steineck et al found absolutely no significant psychological difference between the 2 groups after 5 years, and worry, anxiety and depression were equal between the 2 arms.**[33] The absence of any adverse effect compared to patients treated radically has been reported by others.[34] While surveillance may be stressful for some men, the reality is that most patients with prostate cancer, whether treated or not, are concerned about the risk of progression. Anxiety about PSA recurrence is common among treated and untreated men. Patients who are educated to appreciate the indolent natural history of most good risk prostate cancers may avoid much of this anxiety.

WHO IS A CANDIDATE?

Identifying patients for surveillance requires a knowledge of the natural history of prostate cancer, and the impact of age and comorbidity on life expectancy. While there are no absolute rules, some general considerations apply. Young age is not a contraindication. Rather, the longer the life expectancy, the more stringent the criteria. For example, men younger than 60 years should ideally fulfill the Epstein criteria for insignificant prostate cancer (no more than a third of all cores positive, no more than half of any 1 core involved and PSA density <0.15). Men older than 70 years, particularly with comorbidity, may have a PSA of >10 or minor elements of Gleason 4 pattern and still be appropriate candidates. Patient choice is a key component of decision making. Men younger than 70 years with any significant Gleason 4 pattern are not good candidates for surveillance. The evidence suggests that their likelihood of disease progression is about 3 times greater than those without Gleason 4 pattern.

FOLLOW-UP

The Appendix contains a suggested calendar for follow-up. It is the responsibility of the physician and patient to maintain regular follow-up on surveillance to monitor PSA kinetics and undergo periodic repeat biopsies (although these can be rela-

tively infrequent). A key task of the physician is to reassure the patient (in most cases) as to the indolent course of the disease.

CLINICAL TRIALS

There are currently about 8 prospective phase 2 trials of active surveillance that report ongoing results. In addition, the National Cancer Institute (Canada), in conjunction with 4 U.S. based cooperative oncology trial groups and the UK, have opened a trial entitled START (Surveillance Therapy Against Radical Treatment). This trial, which opened to accrual in September 2007, will randomize 2100 patients between the active surveillance approach described and patient choice of radical treatment (surgery or radiation). The primary end point is prostate cancer survival. The trial has a major correlative science component. Successful accrual to this trial will demonstrate conclusively whether active surveillance is equivalent to radical treatment in the favorable risk patient.

CONCLUSION

Conservative management has been resisted in many constituencies due to concern about the inaccuracies of clinical staging and grading. The advent of widespread PSA screening has the positive effect of identifying patients with life threatening prostate cancer when they are more curable, and the negative effect of identifying many patients with non-life threatening cancer who are susceptible to overtreatment. In a population subjected to regular screening the latter group is far more prevalent. PSA testing will result in hundreds of thousands of patients needlessly subjected to the side effects of therapy.

A rational approach is to offer definitive treatment (ie surgery or radiation) to the intermediate and high risk group, and little or no treatment to the low risk group. However, some apparently favorable risk patients harbor more aggressive disease, and there are benefits of curative treatment for them. A policy of close monitoring with selective intervention for those whose cancers exhibit characteristics of higher risk disease over time is appealing. Intervention is offered for PSADT <3 years (depending on patient age, comorbidity, etc) or grade progression to a predominant Gleason 4 pattern. This approach is currently the focus of several clinical trials, and preliminary analysis has demonstrated that it is feasible. Most patients who understand the basis for this approach will remain on long-term surveillance.

If patients are selected properly (ie good risk and low volume disease) and followed carefully to enable early intervention if there is evidence of progression, it is likely that the majority with indolent disease will not suffer from clinical disease progression or prostate cancer death, and the minority with aggressive disease will still be amenable to cure. We estimate that if all such patients were offered radical prostatectomy compared to the strategy described in this Update, the NNT would be approximately 100 for each patient who avoids a prostate cancer death. Thus, the proportion of patients who die of disease is not likely to be significantly different from the proportion dying despite aggressive treatment of all good risk patients at the time of diagnosis. This approach is currently being evaluated in a large-scale phase 3 study which is open in Canada, U.S. and Britain. The support of this trial and others evaluating the outcome of surveillance is a clear priority.

APPENDIX: SUGGESTED CALENDAR FOR FOLLOW-UP OF ACTIVE SURVEILLANCE

Follow-up schedule:

- PSA, digital rectal examination every 3 months x 2 years, then every 6 months assuming PSA is stable
- 10-12 core biopsy at 1 year, and then every 3 to 5 years until age 80
- Optional transrectal ultrasound on alternate visits

Intervention:

- For PSADT <3 years (in most cases based on at least 8 determinations, about 20% of patients)
- For grade progression to Gleason 7 (4+3) or higher (about 5% of patients)
- For patient anxiety about harboring untreated cancer (about 10% of patients)

These are guidelines and should be modified according to patient age and comorbidity

REFERENCES

1. Welch HG, Schwartz LM and Woloshin S: Prostate-specific antigen levels in the United States: implications of various definitions for abnormal. J Natl Cancer Inst 2005; **97:** 1132.
2. Sakr WA, Haas GP, Cassin BF et al: The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients. J Urol 1993; **150:** 379.
3. Jemal A, Tiwari RC, Murray T et al: Cancer statistics, 2004. CA Cancer J Clin 2004; **54:** 8.
4. Etzioni R, Penson DF, Legler JM et al: Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst 2002; **94:** 981.
5. D'Amico, 1998
6. Presti JC Jr: Prostate biopsy: how many cores are enough? Urol Oncol 2003; **21:** 135.
7. Albertsen P, Hanley JA and Fine J: 20-Year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005; **293:** 2095.
8. Albertsen PC, Hanley JA, Barrows GH et al: Prostate cancer and the Will Rogers Phenomenon. J Natl Cancer Inst 2005; **97:** 1248.
9. Draisma G, Boer R, Otto SJ et al: Lead times and overdetection due to PSA screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003; **95:** 868.
10. Tornblom M, Eriksson H, Franzen S et al: Lead time associated with screening for prostate cancer. Int J Cancer 2004; **108:** 122.
11. Hanash KA, Utz DC, Cook EN et al: Carcinoma of the prostate: a 15-year followup. J Urol 1972; **107:** 450.
12. Johansson JE, Holmberg L, Johansson S et al: Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. JAMA 1997; **277:** 467.
13. Lerner SP, Seale-Hawkins C, Carleton CE Jr et al: The risk of dying of prostate cancer in patients with clinically localized disease. J Urol 1991; **146:** 1040.
14. Handley R, Carr TW, Travis D et al: Deferred treatment for prostate cancer. Br J Urol 1988; **62:** 249.
15. Adolfsson J, Carstensen J and Lowhagen T: Deferred treatment in clinically localised prostatic carcinoma. Br J Urol 1992; **69:** 183.
16. Waaler G and Stenwig AE: Prognosis of localised prostatic cancer managed by 'watch and wait' policy. Br J Urol 1993; **72:** 214.
17. Whitmore WF Jr, Warner JA and Thompson IM Jr: Expectant management of localized prostatic cancer. Cancer 1991; **67:** 1091.

18. George NJ: Natural history of localised prostatic cancer managed by conservative therapy alone. Lancet 1988; **331:** 494.
19. Aus G, Hugosson I and Norlen L: Long-term survival and mortality in prostate cancer treated with noncurative intent. J Urol 1995; **154:** 460.
20. Sandblom G, Dufmats M and Varenhorst E: Long-term survival in a Swedish population-based cohort of men with prostate cancer. Urology 2000; **56:** 442.
21. Parker C: Active surveillance: towards a new paradigm in the management of early prostate cancer. Lancet Oncol 2004; **5:** 101.
22. Parker C: Active surveillance: an individualized approach to early prostate cancer. BJU Int 2003; **92:** 2.
23. Choo R, Klotz L, Danjoux C et al: Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol 2002; **167:** 1664.
24. Choo R, DeBoer G, Klotz L et al: PSA doubling time of prostate carcinoma managed with watchful observation alone. Int J Radiat Oncol Biol Phys 2001; **50:** 615.
25. Bill-Axelson A, Holmberg L, Ruutu M et al: Radical prostatectomy versus watchful waiting (update). N Engl J Med 1977; **352:** 1977.
26. Khatami A, Aus G, Damber JE et al: PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. Int J Cancer 2006; **120:** 170.
27. Soloway MS, Soloway CT, Williams S et al: Active surveillance; a reasonable management alternative for patients with prostate cancer: the Miami experience. BJU Int 2007; **101:** 165.
28. Carter HB, Kettermann A, Warlick C et al: Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. J Urol 2007; **178:** 2359.
29. Parker C, Muston D, Melia J et al: A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival. Br J Cancer 2006; **94:** 1361.
30. Pound CR, Partin AW, Eisenberg ME et al: Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; **281:** 1591.
31. D'Amico AV, Chen MH, Roehl KA et al: Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med 2004; **351:** 125.
32. Scattoni V, Zlotta A, Montironi R et al: Extended and saturation prostatic biopsy in the diagnosis and characterisation of prostate cancer: a critical analysis of the literature. Eur Urol 2007; **52:** 1309.
33. Steineck G, Helgesen F, Adolfsson J et al: Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002; **347:** 790.
34. Burnet KL, Parker C, Dearnaley D et al: Does active surveillance for men with localized prostate cancer carry psychological morbidity? BJU Int 2007; **100:** 540.

Study Questions Volume 27 Lesson 33

1. Aggressive PSA screening of the entire male population between ages 50 and 70 years would result in an incidence-to-mortality ratio of
   a. 3:1
   b. 6:1
   c. 15:1
   d. 25:1
   e. 50:1
2. The proportion of men older than 50 years who harbor microfoci of prostate cancer is approximately
   a. 10%
   b. 25%
   c. 50%
   d. 70%
   e. 90%
3. A 63-year-old man has a PSA of 4.5 and is diagnosed with 2 microfoci of Gleason 6 prostate cancer, stage T1c. Untreated the likelihood of prostate cancer mortality at 20 years is about
   a. 10%
   b. 20%
   c. 40%
   d. 60%
   e. 80%
4. The Scandinavian trial randomized patients between watchful waiting and radical prostatectomy. The absolute reduction in prostate cancer mortality at 10 years was
   a. 5%
   b. 10%
   c. 25%
   d. 50%
   e. 75%
5. Studies of the psychological impact of a conservative surveillance approach suggest that
   a. The psychological burden increases with time and frequently becomes intolerable
   b. There is no difference in psychological functioning between patients treated radically and those treated with surveillance
   c. The side effects of radical treatment have a greater adverse psychological effect than the burden of being on surveillance
   d. Surveillance is associated with significant anxiety and depression, which are relieved by radical treatment
   e. The psychological impact of surveillance has not been studied