NIH State-of-the-Science Conference

Role of Active Surveillance in the Management of Men With Localized Prostate Cancer

Program and Abstracts

December 5–7, 2011

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Sponsors

National Cancer Institute, NIH
Centers for Disease Control and Prevention
Office of Medical Applications of Research, NIH

Partner

The Agency for Healthcare Research and Quality provided additional conference development support.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

About the Program

The National Institutes of Health (NIH) Consensus Development Program has been organizing major conferences since 1977. The Program generates evidence-based consensus statements addressing controversial issues important to healthcare providers, policymakers, patients, researchers, and the general public. The Program is administered by the Office of Medical Applications of Research within the NIH Office of the Director. Typically, the conferences have one major NIH Institute or Center sponsor, with multiple cosponsoring agencies.

Topic Selection

NIH Consensus Development and State-of-the-Science Conference topics must satisfy the following criteria:

- Broad public health importance. The severity of the problem and the feasibility of interventions are key considerations.

- Controversy or unresolved issues that can be clarified, or a gap between current knowledge and practice that can be narrowed.

- An adequately defined base of scientific information from which to answer conference questions such that the outcome does not depend primarily on subjective judgments of panelists.

Conference Type

Two types of conferences fall under the purview of the NIH Consensus Development Program: State-of-the-Science Conferences and Consensus Development Conferences. Both conference types utilize the same structure and methodology; they differ only in the strength of the evidence surrounding the topic under consideration. When it appears that there is very strong evidence about a particular medical topic, but that the information is not in widespread clinical practice, a Consensus Development Conference is typically chosen to consolidate, solidify, and broadly disseminate strong evidence-based recommendations for general

practice. Conversely, when the available evidence is weak or contradictory, or when a common practice is not supported by high-quality evidence, the State-of-the-Science label is chosen. This highlights what evidence about a topic is available and what directions future research should take, and alerts providers that certain practices are not supported by good data.

Conference Process

Before the conference, a systematic evidence review on the chosen topic is performed by one of the Agency for Healthcare Research and Quality's Evidence-based Practice Centers. This report is provided to the panel members approximately 6 weeks prior to the conference, and posted to the Consensus Development Program website once the conference begins, to serve as a foundation of high-quality evidence upon which the conference will build.

The conferences are held over 2-1/2 days. The first day and a half of the conference consists of plenary sessions, in which invited expert speakers present information, followed by "town hall forums," in which open discussion occurs among the speakers, panelists, and the general public in attendance. The panel then develops its draft statement on the afternoon and evening of the second day, and presents it on the morning of the third day for audience commentary. The panel considers these comments in executive session and may revise its draft accordingly. The conference ends with a press briefing, during which reporters are invited to question the panelists about their findings.

Panelists

Each conference panel comprises 12 to 16 members, who can give balanced, objective, and informed attention to the topic. Panel members:

- Must not be employees of the U.S. Department of Health and Human Services.

- Must not hold financial or career (research) interests in the conference topic.

- May be knowledgeable about the general topic under consideration, but must not have published or have a publicly stated opinion on the topic.

- Represent a variety of perspectives, to include:

  – Practicing and academic health professionals

  – Biostatisticians and epidemiologists

  – Clinical trialists and researchers

  – Nonhealth professionals with expertise in fields relevant to the specific topic (ethicists, economists, attorneys, etc.)

  – Individuals representing public-centered values and concerns

In addition, the panel as a whole should appropriately reflect racial and ethnic diversity. Panel members are not paid a fee or honorarium for their efforts. They are, however, reimbursed for travel expenses related to their service as panel members.

Speakers

The conferences typically feature approximately 21 presentations: 3 cover the information found in the Evidence-based Practice Center's systematic review of the literature; the other 18 presentations feature experts in the topic at hand, who have likely published on the topic, and who may have strong opinions or beliefs on the topic. Where multiple viewpoints on a topic exist, every effort is made to include speakers who address all sides of the issue.

Conference Statements

The panel's draft report is released online late in the conference's third and final day. The final report is released approximately 6 weeks later. During the intervening period, the panel may edit its statement for clarity and to correct any factual errors that might be discovered. No substantive changes to the panel's findings are made during this period.

Each Consensus Development or State-of-the-Science Conference Statement reflects an independent panel's assessment of the medical knowledge available at the time the statement is written; as such, it provides a "snapshot in time" of the state of knowledge on the conference topic. It is not a policy statement of the NIH or the Federal Government.

Dissemination

Consensus Development and State-of-the-Science Conference Statements are broadly disseminated:

- A press briefing is held on the last day of the conference to assist journalists in preparing news stories on the conference findings.

- The statement is published online at **consensus.nih.gov.**

- The conference statement is published in at least one major peer-reviewed journal.

- Print copies are mailed to a wide variety of targeted audiences and are available at no charge through a clearinghouse.

Contact Us

For conference schedules, past statements, and evidence reports, please contact us:

NIH Consensus Development Program
  Information Center
P.O. Box 2577
Kensington, MD 20891

1–888–NIH–CONSENSUS (888–644–2667)
consensus.nih.gov

Upcoming Conferences

NIH Consensus
Development Conference: **Diagnosing Gestational Diabetes Mellitus**
October 29–31, 2012

To receive registration notifications and updates about conferences and other program activities, please join the NIH Consensus Development Program Information Network at **consensus.nih.gov/alerts.htm.**

Recent Conferences

NIH Consensus
Development Conference: **Inhaled Nitric Oxide Therapy for Premature Infants**
October 27–29, 2010

NIH State-of-the-Science
Conference: **Preventing Alzheimer's Disease and Cognitive Decline**
April 26–28, 2010

NIH Consensus
Development Conference: **Vaginal Birth After Cesarean: New Insights**
March 8–10, 2010

NIH Consensus
Development Conference: **Lactose Intolerance and Health**
February 22–24, 2010

NIH State-of-the-Science
Conference: **Enhancing Use and Quality of Colorectal Cancer Screening**
February 2–4, 2010

NIH State-of-the-Science
Conference: **Diagnosis and Management of Ductal Carcinoma In Situ (DCIS)**
September 22–24, 2009

NIH State-of-the-Science
Conference: **Family History and Improving Health**
August 24–26, 2009

NIH Consensus
Development Conference: **Management of Hepatitis B**
October 20–22, 2008

NIH Consensus
Development Conference: **Hydroxyurea Treatment for Sickle Cell Disease**
February 25–27, 2008

NIH State-of-the-Science
Conference: **Prevention of Fecal and Urinary Incontinence in Adults**
December 10–12, 2007

NIH State-of-the-Science
Conference: **Tobacco Use: Prevention, Cessation, and Control**
June 12–14, 2006

NIH State-of-the-Science
Conference: **Multivitamin/Mineral Supplements and Chronic Disease Prevention**
May 15–17, 2006

NIH State-of-the-Science
Conference: **Cesarean Delivery on Maternal Request**
March 27–29, 2006

To access previous conference statements, webcasts, evidence reports, and other conference materials, please visit **consensus.nih.gov.**

General Information

Financial Disclosures

The National Institutes of Health, the Centers for Disease Control and Prevention, our planners, and our presenters wish to disclose that they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters, with the exception of the following:

Speakers	Company	Financial Relationship
Andriole, Gerald L., M.D.	Amgen	Honorarium, Consultant
	Augmenix	Stock, Consultant
	Bayer	Honorarium, Consultant
	Cambridge Endo	Stock, Consultant
	Caris	Honorarium, Consultant
	Envisioneering Medical	Stock, Investor/Medical Director
	Ferring Pharmaceuticals	Honorarium, Consultant
	France Foundation	Honorarium, Consultant
	GenProbe	Honorarium, Consultant
	GlaxoSmithKline	Honorarium, Consultant
	Myriad Genetics	Honorarium, Consultant
	Ortho-Clinical Diagnostics	Honorarium, Consultant
	Steba Biotech	Honorarium, Consultant
	Viking Medical	Stock, Medical Director
Lucia, M. Scott, M.D.	GenProbe	Honorarium, Consultant
	GlaxoSmithKline	Honorarium, Consultant
Newcomer, Lee, M.D.	United Healthcare	Salary/Stock, Employee
Roach, Mack III, M.D., FACR	American Cancer Society	N/A, Board Member
	AstraZenca	Honorarium, Lecturing
	CareCore National, LLC	Consulting Fee, Board Member
	Ferring Pharmaceuticals	Honorarium, Lecturing
	Handbook of Evidence-based Radiation Oncology	Royalties, Educational Materials
	Molecular Insight Trofex	Research Support
	National Comprehensive Cancer Network, Prostate Cancer Guidelines	N/A, Member Guidelines Committee
	University of Pennsylvania	Honorarium, Consultant
	UpToDate, Prostate Cancer	Royalties, Educational Materials

All other planners and presenters signed statements that they have no financial or other conflicts of interest.

There is no commercial support for this activity.

Policy on Panel Disclosure

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

Videocast

Live and archived videocasts may be accessed at **videocast.nih.gov.** Archived videocasts will be available approximately 1 week after the conference.

Dining

The dining center in the Natcher Conference Center is located on the main level, one floor above the auditorium. It is open from 6:30 a.m. to 2:30 p.m., serving hot breakfast and lunch, sandwiches and salads, and snack items. An additional cafeteria is available from 7:00 a.m. to 3:30 p.m., in Building 38A, Level B1, across the street from the main entrance to the Natcher Conference Center.

Online Content

All materials issuing from the NIH Consensus Development Program are available at **consensus.nih.gov.** In addition, remote participants will have the opportunity to provide comments on the panel statement by visiting **consensus.nih.gov/comments.htm** from 8:30 a.m. to 11:30 a.m. on Wednesday, December 7, 2011.

Contents

I.   How have the patient population and the natural history of prostate cancer diagnosed in the United States changed in the last 30 years?

Background

Prostate cancer is the second leading cause of cancer-related deaths among men in the United States. It is estimated that in 2010, approximately 32,000 American men died of prostate cancer and 218,000 were newly diagnosed with the disease. Most prostate cancers are detected by a blood test that measures prostate-specific antigen (PSA), a tumor marker. More than half of cancers detected with PSA screening are localized (confined to the prostate), not aggressive at diagnosis, and unlikely to become life-threatening. However, 90 percent of patients receive immediate treatment for prostate cancer, such as surgery or radiation therapy. In many patients, these treatments have substantial short- and long-term side effects without any clinical benefit. Appropriate management of screen-detected, early-stage, low-risk prostate cancer is an important public health issue given the number of men affected and the risk for adverse outcomes, such as diminished sexual function and loss of urinary control.

Tools that can reliably predict which tumors are likely to progress and which are unlikely to cause problems are not available at present. Currently, clinicians rely on two observational strategies as alternatives to immediate treatment of early-stage prostate cancer: watchful waiting and active surveillance. Watchful waiting involves relatively passive patient follow-up, with palliative interventions if and when any symptoms develop. Active surveillance typically involves proactive patient follow-up in which PSA levels are closely monitored, prostate biopsies may be repeated, and eventual treatment is anticipated. Yet, it is unclear which men will most benefit from each approach and whether observational strategies will yield outcomes similar to immediate treatment when managing low-risk prostate cancer.

To better understand the benefits and risks of active surveillance and other observational management strategies for PSA-screening-detected, low-grade, localized prostate cancer, the National Institutes of Health has engaged in a rigorous assessment of the available scientific evidence. This process, sponsored by the National Cancer Institute, the Centers for Disease Control and Prevention, and the Office of Medical Applications of Research, will culminate in a State-of-the-Science Conference on December 5–7, 2011, that focuses on these key questions:

- How have the patient population and the natural history of prostate cancer diagnosed in the United States changed in the last 30 years?

- How are active surveillance and other observational strategies defined?

- What factors affect the offer of, acceptance of, and adherence to active surveillance?

- What are the patient-experienced comparative short- and long-term health outcomes of active surveillance versus immediate treatment with curative intent for localized prostate cancer?

- What are the research needs regarding active surveillance (or watchful waiting) in localized prostate cancer?

A multidisciplinary planning committee developed the questions, which will be addressed in an evidence report prepared through the Agency for Healthcare Research and Quality's Evidence-based Practice Centers program. During the conference, invited experts, including the authors of the report, will present scientific evidence. Attendees will have opportunities to ask questions

and provide comments during open discussion periods. After weighing the evidence, an unbiased, independent panel will prepare and present a statement addressing the key questions. The statement will be widely disseminated to practitioners, policymakers, patients, researchers, the general public, and the media.

About the Artwork

The illustration depicts the relationship between the healthcare provider and the patient, in this case a man diagnosed with localized prostate cancer. White lines symbolize active surveillance and multicolored triangles depict the diversity of patients and the wide range of factors influencing a man's access to, acceptance of, and adherence to alternatives to treatment. Active surveillance is an example of an alternative to immediate treatment and involves proactive patient follow-up and close monitoring.

The image was conceived and created by the National Institutes of Health's Division of Medical Arts and is in the public domain. No permission is required to use the image. Please credit "Bryan Ewsichek/NIH Medical Arts."
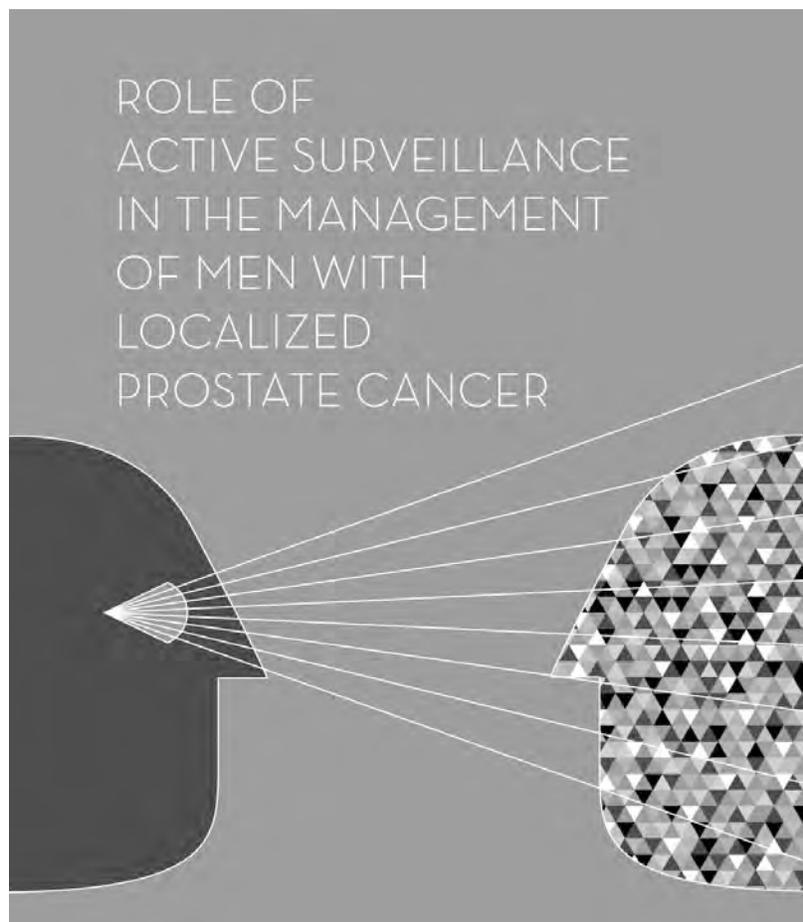
Agenda

Monday, December 5, 2011

8:30 a.m.　　　　Opening Remarks
　　　　　　　　James H. Doroshow, M.D., FACP
　　　　　　　　Director
　　　　　　　　Division of Cancer Treatment and Diagnosis
　　　　　　　　National Cancer Institute
　　　　　　　　National Institutes of Health

8:40 a.m.　　　　Charge to the Panel
　　　　　　　　Paul M. Coates, Ph.D.
　　　　　　　　Director
　　　　　　　　Office of Dietary Supplements and
　　　　　　　　Acting Director
　　　　　　　　Office of Disease Prevention
　　　　　　　　Office of the Director
　　　　　　　　National Institutes of Health

8:50 a.m.　　　　Conference Overview and Panel Activities
　　　　　　　　Patricia A. Ganz, M.D.
　　　　　　　　Panel and Conference Chairperson
　　　　　　　　Professor
　　　　　　　　University of California, Los Angeles Schools of Medicine
　　　　　　　　　and Public Health
　　　　　　　　Division of Cancer Prevention and Control Research
　　　　　　　　Jonsson Comprehensive Cancer Center

9:00 a.m.　　　　You're Kidding....I Have Cancer? A Patient's Perspective on
　　　　　　　　　Coping With Prostate Cancer and Why "Active Surveillance"
　　　　　　　　　Was Not Chosen
　　　　　　　　David A. Lipton, J.D.
　　　　　　　　Director
　　　　　　　　Securities Law Program
　　　　　　　　Catholic University of America School of Law

9:20 a.m.　　　　A Urologist's Personal Experience With Prostate Cancer
　　　　　　　　Paul F. Schellhammer, M.D., FACS
　　　　　　　　Professor
　　　　　　　　East Virginia Medical School
　　　　　　　　Medical Director
　　　　　　　　Virginia Prostate Center

9:40 a.m.   Cancer Diagnosis and Overdiagnosis
                   Gerald L. Andriole, M.D.
                   Robert K. Royce Distinguished Professor
                   Chief of Urologic Surgery
                   Washington University School of Medicine
                   Barnes-Jewish Hospital
                   Siteman Cancer Center

10:00 a.m.   **Discussion**
                   *Participants with questions or comments for the speakers should
                   proceed to the designated microphones and wait to be recognized by
                   the panel chairperson. Please state your name and affiliation.
                   Questions and comments not heard before the close of the discussion
                   period may be submitted on the computers in the registration area.
                   Please be aware that all statements made at the microphone or
                   submitted later are in the public domain.*

**I.   How have the patient population and the natural history of prostate cancer
       diagnosed in the United States changed in the last 30 years?**

10:30 a.m.   Temporal Trends in the Epidemiology of Prostate Cancer
                   Otis W. Brawley, M.D.
                   Chief Medical Officer
                   American Cancer Society

10:50 a.m.   Evidence-based Practice Center Presentation I: Systematic Review
                     Methods and the Natural History of Prostate Cancer Diagnosed in
                     the Last 30 Years
                   Issa Dahabreh, M.D., M.S.
                   Research Associate
                   Tufts Evidence-based Practice Center
                   Tufts Medical Center

11:10 a.m.   Temporal Changes in the Pathologic Assessment of Prostate Cancer
                   M. Scott Lucia, M.D.
                   Associate Professor and Director
                   Prostate Diagnostic Laboratory
                   Co-Director
                   Prostate Cancer Research Laboratories
                   Co-Director
                   Colorado Molecular Correlates Laboratory
                   University of Colorado Denver School of Medicine

I.	**How have the patient population and the natural history of prostate cancer diagnosed in the United States changed in the last 30 years?** *(continued)*

11:30 a.m.   Temporal Changes in the Clinical Approach to Diagnosing Prostate
        Cancer: How the Cancer of Today Differs From the Cancer
        of Yesterday
Ian M. Thompson, Jr., M.D.
Professor and Chair
Department of Urology
Executive Director
Cancer Therapy and Research Center
University of Texas Health Science Center at San Antonio

11:50 a.m.   **Discussion**

12:30 p.m.   **Lunch—Panel Executive Session**

II.	**How are active surveillance and other observational strategies defined?**

1:30 p.m.   What Is the Risk Posed by Prostate Cancer?
Peter Albertsen, M.D.
Medical Director
UConn Medical Group
Associate Dean
Clinical Research Planning and Administration
Associate Dean
Clinical Affairs
Division of Urology
University of Connecticut Health Center

1:50 p.m.   Tumor and Patient Metrics, Eligibility, and Inclusion for Active
        Surveillance for Prostate Cancer
H. Ballentine Carter, M.D.
Professor
Urology and Oncology
Johns Hopkins Medicine
Director
Division of Adult Urology
Bradley Urological Institute
The Johns Hopkins Hospital

Monday, December 5, 2011 *(continued)*

II.   How are active surveillance and other observational strategies defined? *(continued)*

2:10 p.m.   Active Surveillance: Inclusive Approach
                   Laurence Klotz, M.D.
                   Chief
                   Division of Urology
                   Sunnybrook Health Sciences Centre
                   Professor of Surgery
                   University of Toronto

2:30 p.m.   **Discussion**

III.   What factors affect the offer of, acceptance of, and adherence to active surveillance?

3:00 p.m.   Evidence-based Practice Center Presentation II: Definitions of
                     Observational Strategies and the Factors That Affect the Use of
                     Active Surveillance
                   Stanley Ip, M.D.
                   Associate Director
                   Tufts Evidence-based Practice Center
                   Tufts Medical Center

3:20 p.m.   Presenting Treatment Options to Patients With Localized
                     Prostate Cancer
                   Jenny Donovan, Ph.D.
                   Head of School
                   School of Social and Community Medicine
                   University of Bristol

3:40 p.m.   Improving the Communication of the Benefits and Harms of
                     Treatment Strategies
                   Richard M. Hoffman, M.D., M.P.H.
                   Professor of Medicine
                   University of New Mexico School of Medicine
                   Staff Physician
                   New Mexico Veterans Affairs Health Care System

Monday, December 5, 2011 *(continued)*

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III. What factors affect the offer of, acceptance of, and adherence to active surveillance? *(continued)*
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4:00 p.m.   Active Surveillance for Early-Stage Prostate Cancer—The University
                  of California, San Francisco Experience
                  Peter R. Carroll, M.D., M.P.H.
                  Ken and Donna Derr – Chevron Distinguished Professor
                  Department of Urology
                  University of California, San Francisco (UCSF)
                  Associate Dean
                  UCSF School of Medicine
                  Director of Clinical Services and Strategic Planning
                  UCSF Helen Diller Family Comprehensive Cancer Center

4:20 p.m.   **Discussion**

5:00 p.m.   **Adjournment**

Tuesday, December 6, 2011

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III. What factors affect the offer of, acceptance of, and adherence to active surveillance? *(continued)*
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8:30 a.m.   Factors Influencing Patients' Acceptance of and Adherence to Active
                  Surveillance
                  David F. Penson, M.D., M.P.H.
                  Professor of Urologic Surgery
                  Director
                  Center for Surgical Quality and Outcomes Research
                  Institute for Medicine and Public Health
                  Vanderbilt University

8:50 a.m.   Regional, Provider, and Economic Factors Associated With the Choice
                  of Active Surveillance in the Treatment of Men With Localized
                  Prostate Cancer
                  Ann S. Hamilton, Ph.D.
                  Associate Professor of Clinical Epidemiology
                  Department of Preventive Medicine
                  Division of Epidemiology
                  Keck School of Medicine
                  University of Southern California

9:10 a.m.   **Discussion**

IV. **What are the patient-experienced comparative short- and long-term health outcomes of active surveillance versus immediate treatment with curative intent for localized prostate cancer?**

9:30 a.m.   Overview of Randomized Controlled Trials for Localized
              Prostate Cancer
              Mack Roach III, M.D., FACR
              Professor
              Departments of Radiation Oncology and Urology
              Chairman
              Department of Radiation Oncology
              University of California, San Francisco
              Helen Diller Family Comprehensive Cancer Center

9:50 a.m.   Results From the Scandinavian Prostate Cancer Group 4
              Trial (SPCG-4)
              Lars Holmberg, M.D., Ph.D.
              Professor of Cancer Epidemiology
              Division of Cancer Studies
              King's College London School of Medicine
              Guy's Hospital

10:10 a.m.   Results From the Prostate Cancer Intervention Versus
              Observation Trial
              Timothy J. Wilt, M.D., M.P.H.
              Professor of Medicine and Core Investigator
              Minneapolis Veterans Affairs Center for Chronic Disease Outcomes
              Research and the University of Minnesota School of Medicine

10:30 a.m.   Impact of Different Management Strategies on Quality of Life in
              Localized Prostate Cancer
              Mark S. Litwin, M.D., M.P.H.
              Professor of Urology and Health Services
              Chair-Designate
              Department of Urology
              David Geffen School of Medicine at the University of California, Los
              Angeles (UCLA)
              UCLA School of Public Health

10:50 a.m.   Economic Analysis of Different Management Strategies for Localized
              Prostate Cancer
              Daniella J. Perlroth, M.D.
              Research Associate
              Center for Health Policy
              Center for Primary Care and Outcomes Research
              Stanford University

Tuesday, December 6, 2011 *(continued)*

> **IV. What are the patient-experienced comparative short- and long-term health outcomes of active surveillance versus immediate treatment with curative intent for localized prostate cancer?** *(continued)*

11:10 a.m.   Evidence-based Practice Center Presentation III: Comparative Effectiveness of Active Surveillance Versus Radical Prostatectomy or Radiation Therapy in Men With Localized Prostate Cancer
Mei Chung, Ph.D., M.P.H.
Assistant Director
Tufts Evidence-based Practice Center
Tufts Medical Center

11:30 a.m.   **Discussion**

12:30 p.m.   **Adjournment**

Wednesday, December 7, 2011

9:00 a.m.   **Presentation of the Draft Consensus Statement**
The panel chairperson will read the draft statement to the assembled audience.

9:30 a.m.   **Discussion**
The panel chairperson will call for questions and comments from the audience on the draft statement, beginning with the introduction and continuing through each subsequent section, in turn. Please confine your comments to the section under discussion. The chairperson will use discretion in proceeding to subsequent sections so that comments on the entire statement may be heard during the time allotted. Participants with comments should proceed to the designated microphones and wait to be recognized by the panel chairperson. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted on the computers in the registration area. For participants viewing the remote webcast, comments may be submitted online at **consensus.nih.gov/comments.htm.** *Comments will not be accepted after 11:30 a.m. Please be aware that all statements made at the microphone or submitted later are in the public domain.*

11:00 a.m.   **Adjournment**

Panel Meets in Executive Session
The public portion of the conference ends at 11:00 a.m. The panel meets in its last executive session to review public comments on the draft statement.

2:00 p.m.   **Press Telebriefing**

The panel will provide a summary of its findings to the press and will answer questions from reporters via telebriefing. Only members of the press are permitted to ask questions of the panel during this time. Interested conference participants who are not members of the press may call in (from a remote location) to listen to the live telebriefing. Please go to **consensus.nih.gov** *for instructions on joining the call.*

The panel's draft statement will be posted to **consensus.nih.gov** *as soon as possible after the close of proceedings, and the final statement will be posted 4 to 6 weeks later.*

Panel

Panel Chairperson: **Patricia A. Ganz, M.D.**
Panel and Conference Chairperson
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 Administration
Associate Dean
Clinical Affairs
Division of Urology
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Farmington, Connecticut

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Robert K. Royce Distinguished Professor
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Siteman Cancer Center
St. Louis, Missouri

Otis W. Brawley, M.D.
Chief Medical Officer
American Cancer Society
Atlanta, Georgia

Peter R. Carroll, M.D., M.P.H.
Ken and Donna Derr – Chevron Distinguished
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Associate Dean
UCSF School of Medicine
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Abstracts

The abstracts are designed to inform the panel and conference participants, as well as to serve as a reference document for any other interested parties. We would like to thank the speakers for preparing and presenting their findings on this important topic.

The organizers would like to thank the planning committee, the panel, the Tufts Evidence-based Practice Center, and the Agency for Healthcare Research and Quality. We also would like to thank the National Cancer Institute and the Centers for Disease Control and Prevention. We appreciate your continued interest in both the National Institutes of Health Consensus Development Program and the area of active surveillance of men with localized prostate cancer.

Please note that where multiple authors are listed in an abstract, the underline denotes the presenting author.

You're Kidding....I Have Cancer? A Patient's Perspective on Coping With Prostate Cancer and Why "Active Surveillance" Was Not Chosen

David A. Lipton, J.D.

Introduction and Scope of Talk

I teach. In fact, I teach law. One might guess that my training has led me to approach life's challenges with a somewhat defined methodology.

As happens to others, the news that I had prostate cancer pretty much took my breath away. After I became resigned to the disappointing news, I hunkered down to a familiar pattern of investigation and evaluation. Perhaps I was a tad compulsive. Perhaps I was excessive. But, as the saying goes, "this was MY cancer." Whether formally or informally, I suspect I spoke with probably 10 physicians in the field of urology, oncology, and radiology. In retrospect, my goals appeared to be to educate myself on the pluses and minuses of the variety of choices with which I was confronted and then to evaluate which physician I thought I could work with best. Obviously, there were issues that I overlooked and with which I became concerned only after I had undergone my treatment. Three days from now will be the third anniversary of my robotic radical prostatectomy.

The process of selecting the physicians with whom I sought to consult was perhaps as mysterious and tangled as the information that I culled. I remain in contact with several of the doctors from this convoluted web of consultations. Possibly, I gained a friend or two. As events unfolded, sometime after my procedure, two of the doctors who were willing to share with me both time and information came to play a role in the preparation of this program that we are attending today. Apparently, after consultation with one another, they decided to ask me to speak and give some sense of what it felt like to be the patient in the process that I think of as a decision tree for deciding on both a treatment and a treatment provider for prostate cancer. When asked to speak here, I naively assumed that the ideal talk I could present would be to focus on the selection process I had engaged. I had hoped that in discussing this uncertain and anxiety-producing process, which indeed was not without its flaws, thoughts might be generated regarding possible missing tools in the universe of workshops for educating prostate cancer patients.

As I focused more on the significance of the conference's theme of active surveillance, it became increasingly apparent that an "ideal talk" would have to include a discussion of why I did not choose active surveillance. The release of additional studies in the past several years suggesting that there is marginal or no difference in the rate of mortality between active surveillance and intervention made more pressing the need to include in my talk significant discussion of why active surveillance was not my treatment of choice. As fate, or more likely, reason would have it, the two discussion topics proved to be integrally tied. The discussion of my treatment selection inexorably led to a companion analysis of why active surveillance was not a compelling choice.

What Was Learned From Engaging in a Treatment Selection Process

What is it that might be gleaned from an analysis of a decisionmaking process for responding to a diagnosis of prostate cancer, which was conducted by a relatively rational, educated, academic, cancer patient?

For starters, at least this patient felt confused by the literature, the Internet sites, and the information that existed.[1] This patient found it necessary to create his own "decision tree" to discern how to proceed. If this anecdotal account is typical of other similarly situated patients, then there is something lacking in the decisionmaking materials that are provided or are available for the patient. The missing "something" might be as simple as an informed physician assistant or nurse practitioner who is willing to sit down with the patient and help the patient determine what is important to him and which approach might best preserve his lifestyle. That informed medical extender would be helping the patient to frame the decisions that would have to be made. I remember feeling like I was shooting craps over the issue of did I want to take the risk of immediate erectile dysfunction that might be the outcome of surgery, or was I more willing to wait the 2 to 5 years after radiation therapy to discover that I had ended up in the same place? Ultimately, we all have to make that decision. But it turned out that it also was my task to construct the inquiry.

In retrospect, a fascinating discovery for me was that not all intervention treatment providers were created equal. Needless to say, I expected skill differentials, many of which would be difficult to assess. What I had not anticipated was the wide spectrum of personalities, ranging from "warm and fuzzy" to "intolerable." Among those on the less positive end of the scale was the brachytherapist who did not explain to me, until a second visit, that he would be working in tandem with a urologic surgeon and that I would alternate between the two in posttherapy treatment. Should I have figured that out on my own? I do not believe so. For different reasons, I felt disappointed with a robotic surgeon who waited for a second visit to tell me that I had to remember, regardless of my preferences, that he was "in charge." I walked away from both of those physicians. Could a physician assistant or nurse practitioner have alerted me to these issues ahead of time? Probably not. But certainly, a thoughtful adviser might have said, "Figure out what matters to you. Do you want someone who shares with you exactly how a procedure will work or are you willing to say 'let the doctor decide'? "

Not surprisingly, my exploration process failed to explore all issues that would prove vital. Most significantly, I did not inquire about the chosen doctor's availability were something to go wrong after the operation. In hindsight, perhaps I should have recognized that a top surgeon with a warm patient manner and user-friendly personality was going to be terribly popular, busy, and perhaps difficult to get hold of if it was determined, as indeed it was, that I was experiencing postoperation internal bleeding. Were I to do it over, I would have inquired whether the surgeon had good back-up that would be available to assist me at the hospital emergency room during my two late night visits. Again, a guide, helping me to formulate my selection methodology, might have urged me to make such inquiries. After my bleeding was attended to through follow-up surgery, I did share with my surgeon my concerns about dealing with emergency room personnel who were unfamiliar with my surgery. Hopefully, my experience has benefited others who came after me.

Why the Selection Process Did Not Lead This Patient To Choose "Active Surveillance"

Let us assume that this patient fashioned a vaguely competent approach for deciding on his prostate cancer treatment and the selection of his physician. Let us also assume that the perceived need itself, to engage in such a process, reflects deficiencies in the available resources to assist patients in making these decisions. We understand that there might not be agreement with either of these assumptions. For the purpose of this conference, however, the question is, "How is it that the process of searching for the proper treatment did not lead me to the selection of active surveillance?" More importantly, why was active surveillance not a serious consideration? And finally, and this is very much a matter of an individual preference, how is it that if I had it to do over again, I still would chose intervention rather than active surveillance?

These are not difficult questions from my perspective. When I learned of my prostate cancer, I was advised of my choices by the urologist who had first suggested that I get a biopsy. He briefly outlined the different approaches and some of the advantages and drawbacks of each approach. Active surveillance was not given prominence. Perhaps I indicated that I would probably seek intervention. But one way or the other, active surveillance, which was then called "watchful waiting," was not given the emphasis given to intervention. Within my investigations, I saw one other urologist/surgeon for general advice. Again, perhaps it appeared to him that my mind was set, but there was no urging of active surveillance. Indeed, had I chosen active surveillance, I would not have known of a urologist who would have provided the surveillance. Then as now, I did not and do not have the sense that there are a large number of active surveillance physicians, although there are certainly some and they certainly must recommend active surveillance. On the other hand, there clearly are substantial numbers of radical prostatectomy surgeons, robotic surgeons, radiologists, and brachytherapists. It is quite possible that the ratio of active surveillance practitioners to "interventionists" has increased in the past 3 years. But, in 2008, it was difficult to find a practitioner who was a strong proponent of the active surveillance strategy.[2]

The apparent absence of promoters of active surveillance should not be surprising. Physicians train to be surgeons, to be radiologists, or perhaps to learn new robotic skills. Having learned those skills, it would be counterintuitive to expect the physician not to promote the chosen studied treatment. In addition, hospitals promote intervention treatment. Financial investments in robotic surgery equipment and new radiation devices stimulate hospitals to advertise these procedures. In July of this year, *The Washington Post* reviewed a study by Martin Markary about hospital advertisement of new technology. Markary, a pancreatic surgeon at Johns Hopkins School of Medicine, found that "among 164 U.S. hospital websites featuring robotic technology, 18 percent made use of what the study termed 'emotionally appealing phrases,' 73 percent used manufacturer-provided images or text, and 33 percent linked directly to a manufacturer's website."[3]

In some regards, the information about what active surveillance entails seems surprisingly limited. Although it was a clever linguistic move to reconfigure and expand the terminology from "watchful waiting" to "active surveillance," it is not always clear to the patient what makes it "active." When informed that one has cancer, there is a very human inclination to do "something." Active surveillance, in fact, does not feel active, except for those who perceive undergoing frequent prostate-specific antigen (PSA) tests, rectal exams, and periodic biopsies as "doing something." There is also very little discussion of what the survival rates are when active surveillance reveals a spike in a patient's PSA (although I have been advised that these

informational gaps will be filled by ongoing studies). The fact that several studies show no or limited impact on mortality rates as a result of intervention[4] might indicate that mortality rates after a spike in PSA of a patient pursuing active surveillance should be no different than mortality rates were a rise in PSA found after intervention.[5] In addition, the studies might indicate that the likelihood of PSA spiking during surveillance should not differ from the likelihood of it spiking after intervention. Those are difficult concepts to swallow, and all the more difficult to digest when it is "your cancer" in the balance. But they are important points to bring home if active surveillance is going to be viewed as an attractive option.[6]

Why This Patient Would Still Not Choose Active Surveillance

To be totally honest, were I to make my treatment decision today, I do not believe I would choose active surveillance. Indeed, I would have been a fairly good candidate for active surveillance (PSA less than 6, Gleason of 6 before the operation and revised to 7 after the operation, biopsy showing cancer in 1 of 12 needles, tumor size of 1 cm). Ultimately, however, the decision was very visceral and personal. The longevity of my parents and their siblings suggests that I have a fair chance of living another 30 years. I frankly plan to teach another 23 or 24 years…depending upon how much I am enjoying myself. There is one gland in my body that could have produced prostate cancer. That gland has been removed. I did not want to wake up each morning wondering if the previous night was the night that a cancer cell "flew" from my prostate and invaded other reaches of my body. I understand full well, and the studies cited confirm, that the cancer cell might already have flown. The fact that I continue to have my PSA tested every 6 months brings that point home to me twice a year. And statistically speaking, my decision lacks a certain amount of logic. But that is "statistically speaking." If indeed that cancer cell did not travel from my prostate into my body before 3 years ago, there no longer is a prostate gland, invaded by cancer, from which a life-threatening cell may depart to cause me concern. That gives me some comfort, even though a number of studies suggest it should not.

Statistics do not necessarily control treatment decisions for prostate cancer. Gut perceptions also play an important role. If active surveillance is to become a more prevalently adopted treatment, it well may be that the medical profession will have to discover how to influence that gut perception.

Notes

1. The reference book that I found most helpful was Walsh P, Farrar J. *Dr. Patrick Walsh's Guide to Surviving Prostate Cancer*, 2nd ed. New York: Warner Wellness; 2007. Since my treatment, a new book has been published that focuses more on creating a decision tree: McHugh JC. *The Decision: Your Prostate Biopsy Shows Cancer. Now What? Medical Insight, Personal Stories, and Humor by a Urologist Who Has Been Where You Are Now.* Gainesville, GA: Jennie Cooper Press USA; 2010. The essay that provided me with the greatest comfort was Lange PH, Schellhammer PF. Reflections on prostate cancer: personal experiences of two urologic oncologists. In: Kirby RS, Partin AW, Feneley M, et al., eds. *Prostate Cancer: Principles and Practice.* London: Taylor and Francis; 2006. This essay allowed me to understand that the decision I faced was difficult, even for medical providers in the field.

2. It is of interest to note that the National Institutes of Health/National Cancer Institute online patient version of the pamphlet *Prostate Cancer Treatment (PDQ[®]),* last modified in June 2011, provides, in the treatment option overview section, two lines to describe the active surveillance treatment option (still referred to as watchful waiting). See cancer.gov/cancertopics/pdq/treatment/prostate/Patient/page4#Keypoint14. Surgery, radiation, and hormone treatment have considerably greater coverage. In the health professional version of the pamphlet, although there is a discussion of studies suggesting limited or no advantages from intervention over active surveillance, the actual list of treatment options for prostate cancer does not include a mention of active surveillance. See cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional/page4. Accessed August 11, 2011.

3. Torres C. Robotic surgery extends its reach in health care, hospital marketing. *The Washington Post.* July 18, 2011. Available at: washingtonpost.com/national/robotic-surgery-extends-its-reach-in-health-care-hospital-marketing/2011/06/15/gIQAnw6HMI_story.html. Accessed August 11, 2011.

4. Stattin P, Holmberg E, Johansson JE, et al. Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. *J Natl Cancer Inst.* 2010;102(13):950–958. Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. *JAMA.* 2009;302(11):1202–1209. Bill-Axelson A, Holmberg L, Filén F, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. *J Natl Cancer Inst.* 2008;100(16):1144–1154. Charnow JA. Active surveillance offers PCa survival similar to treatment. *Renal and Urology News.* May 17, 2011 (discussion of a report by Dr. Kiranpreet Khurana, presented at the May 2011 meeting of the American Urological Study in Washington, DC).

5. The Stattin, Holmberg, Johansson study cited above and discussed online in the health providers' version of the National Institutes of Health/National Cancer Institute *Prostate Cancer Treatment (PDQ[®])* pamphlet does indeed suggest that there is no difference in mortality between those who choose immediate prostatectomy as opposed to those choosing a prostatectomy only after surveillance indicates the need. See the treatment overview section in the online patient version of the pamphlet available at: cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional/page4. Accessed August 11, 2011.

6. As close as the health providers' version of the National Institutes of Health/National Cancer Institute online pamphlet on *Prostate Cancer Treatment (PDQ[®])* cited above comes to suggesting the wisdom of active surveillance is the following sentence which precedes a discussion of one of the studies cited above: "Many men with screen-detected prostate cancer are candidates for active surveillance, with definitive therapy reserved for signs of tumor progression." From cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional/page4#Reference4.38. Accessed August 11, 2011.

A Urologist's Personal Experience With Prostate Cancer

Paul F. Schellhammer, M.D.

Words matter, and words voiced by a physician during a patient interaction have a profound effect on the individual patient's attitude and well-being.

The word "cure," derived from the Latin "to care," has evolved to imply that a procedure or medication will address the disease process such that it will be successfully resolved. When a patient hears that a disease is cured, in his mind it becomes past history. It no longer occupies attention or is a cause for anxiety. However, if the disease recurs, as is too often the case in the world of cancer, the caring that is required may not materialize—the cure and its expectations have failed, but the caring has been lost in translation. This conference will discuss the concept of "active surveillance." Surveillance implies a proactive process to monitor rather than to initially render treatment for a selected cohort of men with newly diagnosed prostate cancer. It describes a strategy where the term "cure" largely loses relevance. Caring, with appropriate guidance and reassurance, on the other hand, rises front and center.

Other words that have found their way into common and frequent usage for the patient with cancer are "war" and "survivor." War against cancer was declared legislatively by the President of the United States, Richard M. Nixon, in 1971, when he signed the National Cancer Act. Convention identifies those left standing during and after a war as "the survivors." Prostate cancer is a disease that runs a long-time course. Virtually 100% of patients diagnosed with this disease survive 5 years and greater, and more than 90% survive 10 years. War requires a hypervigilant state of readiness; it is resource depleting and often exhausting. For the prostate cancer patient, a war mentality may very well deprive him of the opportunity to learn to live well and to live long with his cancer, both very realistic possibilities. Again, in the context of a surveillance strategy, war and survivorship do not find traction. Patience, partnership, and participant are more appropriate.

At the time of diagnosis, the word "cancer" is often too toxic to allow a "living well with cancer" discussion or a discussion of a surveillance strategy. I can personally attest to this based on a personal experience.[1,2] Like so many men I have encountered, I too have experienced the two most common illnesses of aging, namely a cardiac event and the diagnosis of prostate cancer. I find it helpful to compare the emotions generated by each. At age 58, without any prior symptomatology, I experienced crushing chest pain. Prompt angioplasty and stents minimized cardiac damage. After my coronary occlusion, my mindset was one of establishing a program to heal my heart. Through diet modifications, exercise, and careful surveillance, I was committed to a partnership for mutual recovery with the injured organ. Implementing this lifestyle change was both satisfying and comforting. Reactions generated by my prostate cancer diagnosis were totally different. The sense of betrayal and hostility toward the offending organ was overpowering and was followed immediately by a commitment to destroy it by whatever means. Ironically, even though I intellectually recognized that the immediate and short-term threat to life was much greater secondary to coronary artery disease, this was overcome by my visceral reaction; my attention and anxiety were focused on the cancer diagnosis. My impression is that the majority of patients with both of these common diseases experience a similar emotional stance. The word "cancer" becomes the driving force in a patient's view of his diagnosis and future. The astute diagnostician William Ostler recognized this emotionally driven mindset years

ago when he advised that it is as important to know about the patient who has a disease as it is to know about the disease the patient has.

It has been 11 years since my diagnosis of prostate cancer. The prostate-specific antigen (PSA) clock has continued to tick up with regularity (Table 1). So the disease has not been cured. However, I am thankful that I have not been at war over this past decade and have attempted to adopt the same partnership stance with regard to prostate cancer that was my initial reaction in response to my cardiac event. And again, returning to the theme of "words matter," I now like to consider myself a partner and participant rather than a war-weary survivor. I am a partner with my physicians in addressing the disease process; I am a participant in the strategies developed to address the disease whose presence has been identified by a series of PSA rises.[3]

Table 1. Tale of a Prostate Cancer Participant

Radical prostatectomy *Rising PSA*	2000
Salvage radiation and androgen deprivation *Rising PSA*	2002
Clinical trial (Phase 2) *Rising PSA*	2006
Intermittent to continuous combined androgen blockade *Rising PSA*	2007
Secondary hormone therapy—ketoconizole/GMCSF	2008
Transdermal estradial	2009
Stable PSA	2010
? ? ?	2011

PSA = prostate-specific antigen; GMCSF = granulocyte macrophage colony-stimulating factor.

Active surveillance is not an intuitive pathway for a patient to accept on receiving a diagnosis of cancer. Active surveillance does not describe a battle but rather a partnership with and participation in living well with a cancer game plan. To convincingly discuss the active surveillance strategy/game plan will take all the counseling skills of a physician, both at diagnosis and at the follow-up intervals. The vocabulary of cancer includes a term that physicians and scientists use to identify gaps in treatment protocols or pathways. The gap is termed an "unmet need." This conference will present the option of active surveillance to address this unmet need. It will address the education of the patient and family so that they are comfortable with a discussion and decision that some prostate cancers—yes, even though the word "cancer" is spoken—may best be managed initially with a surveillance strategy rather than surgical or radiation or medicinal intervention.

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Cancer Diagnosis and Overdiagnosis

Gerald L. Andriole, M.D.

There is an enormous pool of prostate cancer prevalent in middle-aged and older men as shown in autopsy studies by Sakr et al.[1] and Powell et al.[2] (see Table 1) and in a series of studies evaluating cystoprostatectomy specimens (reported rates of incidental prostate cancer from 27% to 60% and clinically significant cancers from 18% to 53%).[3–7] It is becoming clear that prostate-specific antigen (PSA) testing as commonly performed in the United States (annual PSA and digital rectal examination) results in overdetection of some prostate cancers that are not apt to ever become clinically relevant.

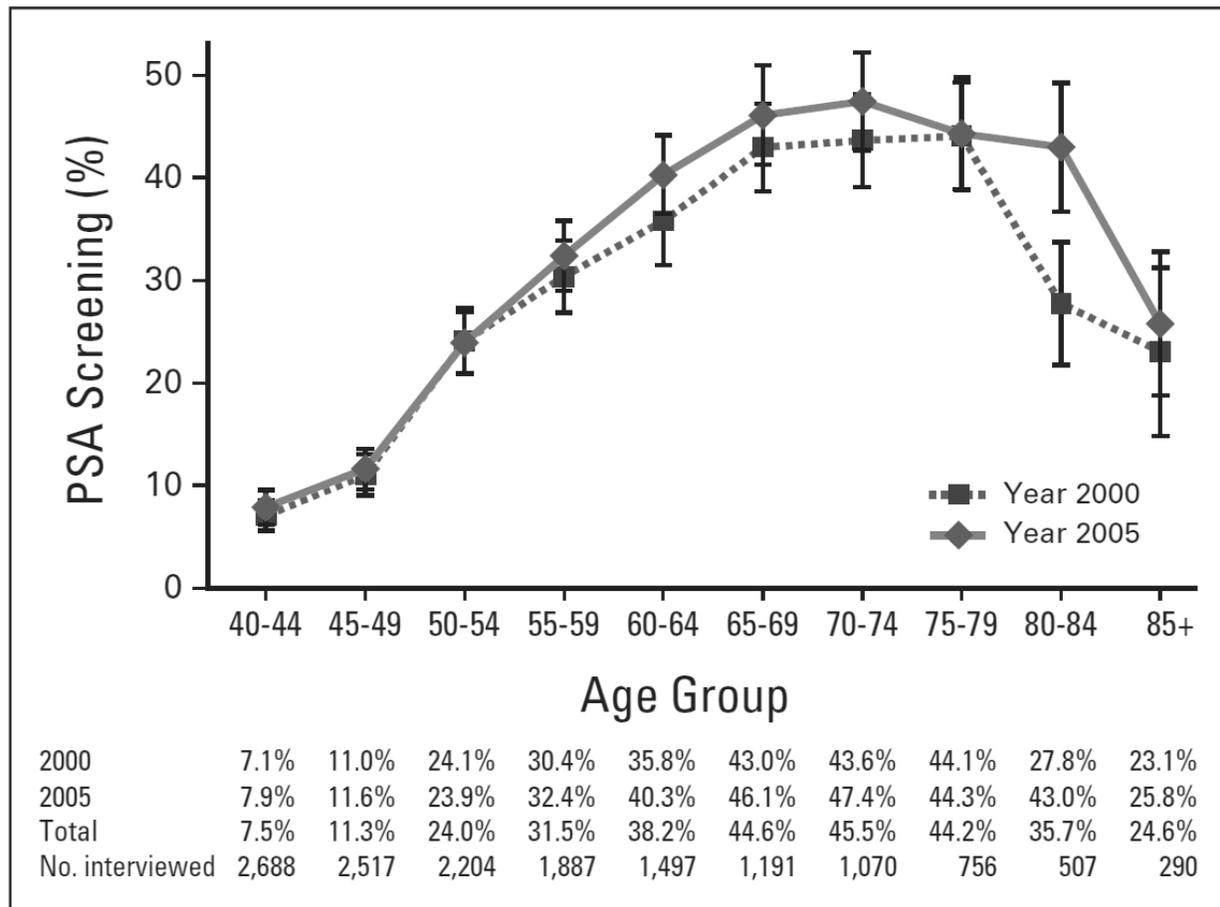**Table 1.** Prevalence of Prostate Cancer in Men at Autopsy

Percentage With Prostate Cancer at Autopsy		
Age Group	**Black**	**White**
20–29	8	11
30–39	31	31
40–49	43	38
50–59	46	44
60–69	72	68
70–79	77	68

From Powell IJ, Bock CH, Ruterbusch JJ, et al. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity. *J Urol.* 2010;183(5):1792–1796. Reprinted with permission. Copyright ©2010 American Urological Association. All rights reserved.

The magnitude of overdetection can be estimated by comparing a man's current lifetime risk of prostate cancer (approximately 17%) with his approximate 3% risk of prostate cancer mortality. Others have estimated the magnitude of overdiagnosis by examining various cohorts of men. Welch and Black estimated that 60% of screen-detected cancers in the European Randomized Study of Screening for Prostate Cancer (which evaluated PSA testing every 4 years) met the definition of overdiagnosis based on the finding of 58 prostate cancers per 1,000 men in the screened arm versus 34 prostate cancers per 1,000 men not undergoing screening.[8] Draisma et al. used a simulation analysis and reported that age of diagnosis heavily influenced the estimate of overdiagnosis, which ranged from 27% for young men to 56% for men age 75.[9] These data are especially relevant for elderly men in light of the observations of Drazer et al. where, as seen in Figure 1, substantial PSA testing occurs among men age 65 and older.[10] Etzioni et al. evaluated racial differences and estimated overdiagnosis was more common in black men than white men (44% vs. 29%).[11] They also estimated that the use of PSA would identify up to 15% of autopsy cancers in white men and 37% in black men. McGregor et al. reported an

overdiagnosis rate of 84% when only lethal prostate cancer was defined as a clinically significant cancer.[12] Moreover, overdiagnosis may be even higher when one considers the impact of comorbidity on a man's chance of dying of prostate cancer as is illustrated by Albertsen et al. (see Table 2).[13] Any diagnosis of prostate cancer substantially reduces men's quality of life.[14]

Figure 1. Population-Based Prevalence of Prostate-Specific Antigen Screening in the United States

	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2000	7.1%	11.0%	24.1%	30.4%	35.8%	43.0%	43.6%	44.1%	27.8%	23.1%
2005	7.9%	11.6%	23.9%	32.4%	40.3%	46.1%	47.4%	44.3%	43.0%	25.8%
Total	7.5%	11.3%	24.0%	31.5%	38.2%	44.6%	45.5%	44.2%	35.7%	24.6%
No. interviewed	2,688	2,517	2,204	1,887	1,497	1,191	1,070	756	507	290

From Drazer MW, Huo D, Schonberg MA, et al. Population-based patterns and predictors of prostate-specific antigen screening among older men in the United States. *J Clin Oncol.* 2011;29(13):1736–1743. Reprinted with permission. Copyright ©2011 American Society of Clinical Oncology. All rights reserved.

A cancer diagnosis frequently results in aggressive treatment, and for many men this may be overtreatment. In the United States, approximately 90% of men with newly diagnosed prostate cancer, including those with low-risk factors, undergo aggressive treatment.[15,16] In a typical radical prostatectomy series, about 20% of patients with a PSA <4 and 16% of those with a PSA >4 have trivial small-volume tumors.[17]

PSA is not prostate cancer specific; since it inevitably rises as men age, many men undergo biopsies of the prostate and are discovered to have incidental cancers merely because their benign prostatic hyperplasia is progressing. One way of potentially avoiding overdiagnosis in men on the basis of PSA is to consider using PSA in a different way. An analysis by Lilja et al. suggests that it is possible to identify a population of men at high risk of prostate cancer on the

basis of their serum PSA level during their 40s and 50s, a time when PSA levels are not apt to be significantly confounded by benign prostatic hyperplasia.[18] Other strategies might include the use of PSA-related kallikreins[19] and nomograms to predict an individual man's risk of prostate cancer and to intensively screen those at the highest risk for prostate cancer mortality while not screening those at low risk. Another option might be to improve the ability of PSA to identify aggressive cancer by use of 5-alpha reductase inhibitors.[20–22] Since 5-alpha reductase inhibitors "stabilize" the amount of PSA produced by benign prostatic elements, PSA rises in men receiving 5-alpha reductase inhibitors are especially worrisome for high-risk prostate cancer.

Table 2. Risk of Prostate Cancer and Overall Mortality in Men Without Initial Treatment for Prostate Cancer

Gleason Grade	Medical Comorbidity	10 Year Prostate Cancer Mortality (%)	10 Year Overall Mortality (%)
5–7	0	4.8	28.8
	1	2.0	50.5
	>1	5.3	83.1
8–10	0	25.7	55.0
	1	20.2	52.0
	>1	13.7	64.3

Five-alpha reductase inhibitors, in addition to improving PSA, reduce a man's chance of being diagnosed with a low-grade cancer by 25% to 30%.[23,24] However, the exact role of 5-alpha reductase inhibitors remains uncertain given some concerns that they may predispose men to developing high-grade prostate cancer.[25]

Potential strategies to eliminate overtreatment include more widespread implementation of active surveillance protocols,[26] better identification of aggressive tumors based on improved biopsy,[27,28] use of molecular markers,[29] and potentially focal ablation of small tumors.[30] Using conventional biopsy and considering men for active surveillance on the basis of relatively small-volume Gleason 6 tumors, active surveillance seems to be a safe option, although many men on active surveillance defect to aggressive treatment out of anxiety. Focal ablation therapy may be a valid adjunct to active surveillance as it may prevent biopsy progression. The use of 5-alpha reductase inhibitors also may be plausible agents to reduce biopsy progression of men on active surveillance.[31]

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Evidence-based Practice Center Presentation I: Systematic Review Methods and the Natural History of Prostate Cancer Diagnosed in the Last 30 Years

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Introduction

Radical prostatectomy and radiation therapy for prostate cancer have adverse effects, and their relative survival benefit over no treatment is unclear for men with localized and low-risk disease. Prostate cancer often has an indolent natural history, making observational management strategies, including active surveillance, potentially appealing. Throughout this report, we use the term "active surveillance" to describe management strategies of deferred treatment with monitoring of triggers to begin active treatment with curative intent.

Objectives

The objectives are to summarize the systematic review methods we used to address all sections of our report and to summarize changes in the natural history of prostate cancer in the United States over the last 30 years (Key Question 1).

Review Methods

The key questions were developed prior to the systematic review by a conference planning committee, which included experts in the field from the Federal Government, academia, and the clinical practice community. Guidance to the Tufts Evidence-based Practice Center was provided by an external Technical Expert Panel, separate from the conference planning committee. We searched MEDLINE® and the Cochrane Database of Systematic Reviews for relevant English-language publications, from inception through August 2011, using search terms related to prostate cancer, active surveillance, watchful waiting, expectant management, and other related strategies. We also searched for studies based on specific databases sourced from the U.S. population, such as the Surveillance, Epidemiology and End Results (SEER) and Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) databases. Additional studies were identified from reference lists of eligible articles and technical experts. We selected studies for inclusion by first reviewing titles and abstracts of all citations identified through our searches and then by reading the full text of potentially relevant citations. We also relied on two completed evidence reports on treatments for localized prostate cancer conducted for the Agency for Healthcare Research and Quality (AHRQ).[1,2]

For the question on the natural history of prostate cancer (Key Question 1), we included studies using large databases sourced from the U.S. population and reporting information on trends over time during the period between 1980 and 2011. For the question on definitions of observational management strategies (Key Question 2), we included primary studies of any design or study protocols that reported on observational management strategies (i.e., no immediate curative treatment) for patients with prostate cancer. For the question on the implementation (offer, acceptance, and adherence) of active surveillance or other observational

management strategies (Key Question 3), three types of studies were considered eligible: (1) studies that used quantitative methods to identify predictors of the offer of, acceptance of, or adherence to observational management strategies; (2) studies that used qualitative research methods (e.g., focus groups or surveys) to obtain information on factors that affect the implementation of observational management strategies; and (3) experimental studies evaluating the effect of tools such as decision aids on the implementation of observational management strategies. For the question of the effectiveness of active surveillance compared with radical prostatectomy or radiation therapy (Key Question 4), we included all longitudinal comparative studies, whether randomized or nonrandomized, prospective or retrospective, that were performed in a multicenter setting, together with selected existing systematic reviews. To be included, nonrandomized studies of treatment efficacy had to use multivariable methods to adjust for possible confounding (including specifically adjustments for age and tumor stage). The population of interest was men with clinically localized prostate cancer (T1 or T2), without known lymph node (N0-X) or metastatic (M0-X) cancer spread. Outcomes of interest included prostate cancer mortality, all-cause mortality, morbidity of primary treatment, metastatic disease, quality of life, satisfaction with treatment, and costs.

From all eligible studies, we extracted data on study design, population demographics, the interventions or predictive factors assessed, and the outcomes of interest. For studies of treatment effectiveness, we assessed methodological study quality and rated the overall strength of evidence regarding active surveillance versus active treatment using established AHRQ Evidence-based Practice Center methods.[3] We did not assess the quality of studies considered eligible for other key questions due to their largely descriptive (noninferential) nature.

Results: 30-Year Trends in the Natural History of Prostate Cancer in the United States

We identified 64 primary observational studies and one systematic review reporting data relevant to temporal trends in prostate cancer incidence; mortality/survival; or patient-, tumor-, and system-level characteristics at diagnosis. The majority of observational studies analyzed the SEER database of the National Cancer Institute or a subset of its component registries; other commonly used data sources were the linked SEER-Medicare database, the CaPSURE database, and the National Cancer Database. Given the extensive overlap in included populations across studies, the number of publications included in this review is not directly indicative of the amount of available evidence.

Prostate cancer incidence rose between 1975 and 1992 and then fell until around 1995. After a period of nonsignificant increase from 1995 to 2000, rates declined again from 2000 to 2007. These trends were observed both overall and among men age 65 or older (i.e., the age group in which the majority of prostate cancers are diagnosed). Prostate cancer incidence also increased in all racial/ethnic groups since the mid-1980s and peaked in the early 1990s. Studies consistently demonstrated that localized and regional prostate cancer cases were mainly responsible for the observed increase in prostate cancer incidence from the mid-1980s up to the mid-1990s. Studies also consistently demonstrated a decrease in incidence rates for all disease stages from the mid-1990s to 2000.

Studies generally reported a trend toward younger age at diagnosis. Studies also reported a decrease in the number of patients with low-grade and high-grade tumors, and a concomitant increase in patients with intermediate-grade tumors at diagnosis. Prostate-specific antigen (PSA) values at diagnosis have decreased over time such that an increasing number of patients

diagnosed have PSA concentrations below 10 ng/ml. The proportion of prostate cancer patients diagnosed through biopsy (compared with those diagnosed through other procedures, such as transurethral resection of the prostate) also has increased over time.

For the overall U.S. population, prostate cancer mortality rates increased from 1975 to 1991 and decreased from 1994 to 2007. Deaths due to prostate cancer as a proportion of all deaths among patients diagnosed with the disease have decreased over time (i.e., prostate cancer patients are increasingly likely to die of non-prostate cancer causes), particularly for patients with early-stage disease at diagnosis or patients who were diagnosed at an older age. Blacks have been at higher risk for prostate cancer death compared with non-Hispanic whites, although the difference between the two groups appears to have decreased over time.

Most studies demonstrated decreasing trends in the proportion of patients being managed with observational management strategies of no active treatment (active surveillance, watchful waiting, or expectant management, with or without androgen deprivation therapy). The proportion of patients receiving active surveillance or watchful waiting has remained low, even among patients with low-risk disease.

Conclusions

Over the past 30 years in the United States, patients with prostate cancer have been increasingly diagnosed with early-stage, low-risk disease. Only a small proportion of men with prostate cancer are managed with observational strategies. Studies indicate that patients diagnosed with prostate cancer in recent years are more likely to die of non-prostate-cancer-related causes.

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Temporal Changes in the Pathologic Assessment of Prostate Cancer

M. Scott Lucia, M.D.

In 30 years, there have been dramatic changes in the manner in which we diagnose and manage prostate cancer. The advent of the prostate-specific antigen (PSA) screening in the late 1980s, coupled with increased public awareness of the disease, has resulted in a marked shift in stage toward clinically localized disease.[1–3] Pathologically, pre-PSA-era tumors tended to be large, occupying the majority of the glandular volume, and often had extensive extraprostatic extension. In contrast, tumors of today are typically smaller in volume, organ confined, and associated with improved therapeutic outcomes.[2,3] Concern arises that we are now detecting more clinically insignificant cancers, cancers that might be better managed expectantly.

Prostate cancer is a multifocal disease: large tumors often result from the assimilation of multiple smaller tumors as they grow to confluence.[4] Individual tumors may display marked differences in grade, molecular markers, and DNA ploidy from region to region even within a single tumor.[5] The most important pathologic prognostic factor for prostate cancer on biopsy is the Gleason grade. The Gleason system is a five-tiered classification that categorizes tumors by their architectural pattern of growth rather than cytologic features. Since its first description by Donald Gleason in 1966,[6] the grading system has undergone a number of modifications over time by Gleason and others.[7,8] Tumors often display more than one pattern of growth. This was originally addressed by the Gleason system by adding the two most prominent patterns, a primary pattern (majority of tumor) and a secondary pattern (second most extensive pattern), together to obtain a Gleason "score." If only one pattern was present, then the grade was doubled with the resulting sums between 2 (grade 1 + grade 1) and 10 (grade 5 + grade 5).

Years of experience with Gleason grading in relation to disease outcomes, along with changes in the diagnostic tools available, have produced shifts in grading practices among academic genitourinary pathologists. In 2005, 80 genitourinary pathologists of the International Society of Urological Pathology participated in a practice survey and consensus conference to document and address trends in and refine the guidelines for Gleason grading.[8] Most notable of the changes to the classic Gleason grading system included (1) restrictions on the assignment of very low grades (patterns 1 and 2) to biopsy specimens, (2) refinement of the separation of pattern 3 from pattern 4, (3) guidelines for assigning grade to cribriform patterns, (4) Gleason grading of variant carcinomas, and (5) Gleason scoring of biopsies when minor amounts of high-grade tumor or tertiary-grade patterns are present.

In the classic Gleason system, a grade pattern had to represent at least 5% of the tumor to be included in the Gleason score as a secondary pattern. In the 2005 modified system, higher grade patterns, regardless of quantity, were included in the score (98% pattern 3 and 2% pattern 4 is scored as 3+4 = 7). If more than two grades existed for a tumor on biopsy, then the most extensive pattern (the primary pattern) and the highest pattern of those remaining regardless of relative amount were included in the score (e.g., a tumor with 70% pattern 3, 25% pattern 4, and 5% pattern 5 is scored as 3+5 = 8). Theoretically, this could result in a trend toward higher Gleason scores on biopsy when the modified Gleason grading system is used. Conversely, these modifications could ultimately result in fewer prostate cancers being upgraded upon prostatectomy, a situation that occurs frequently when comparing biopsy grade with final tumor grade on prostatectomy.[9] The refinements documented in the 2005 International

Society of Urological Pathology Consensus Conference represent an attempt to standardize grading trends already practiced by leading genitourinary pathologists around the world rather than a new approach to Gleason grading.

Ultimately, the goal of pathologic examination of prostate biopsies is to (1) establish a diagnosis of cancer, and (2) help determine the aggressiveness (grade) and extent of the tumor to guide management decisions. Since most prostate tumors of today are not clinically palpable, prostate biopsies are taken systematically but randomly from the right and left sides of the prostate from base to apex. What began as sextant biopsies in the 1980s has been extended to 10, 12, or more biopsies concentrating on lateral portions of the gland in attempts to improve tumor detection. Nevertheless, even extended biopsy schemes sample a limited portion of the prostate and frequently miss tumors.[10] Consequently, many men undergo repeat biopsies that may or may not be necessary. Moreover, the Gleason score as determined on biopsy may not be the same as, and is often lower than, that determined on subsequent prostatectomy when the entire gland is examined.[9] Furthermore, although the number of cores positive for cancer in a given set of biopsies correlates with tumor volume, the finding of small amounts of tumor on a single biopsy does not always indicate a clinically inconsequential tumor.[11]

The most commonly used definition of "insignificant" tumor is a tumor confined to the prostate with a volume of <0.5 cm^3 and a Gleason score of 6 or less (no pattern 4 or 5) at prostatectomy.[12] Epstein et al. define a tumor at biopsy as being "potentially insignificant" if the following criteria are met: (1) stage T1c, (2) PSA density <0.15 ng/ml/gm, (3) Gleason score ≤6 (no pattern 4 or 5), and (4) tumor involving less than three cores with no core having more than 50% tumor involvement.[13] However, attempts to predict clinical significance using biopsy criteria are imperfect with sensitivities ranging from 35% to 83% and specificities ranging from 68% to 98%.[14]

In an era when more conservative management options exist for prostate cancer, including targeted focal therapy and expectant management, it becomes more crucial to be able to determine the aggressiveness and extent of tumors accurately. The pathologist's ability to do this is hampered by limitations in the amount of information obtainable from routine prostate biopsies. The tissue obtained on biopsy is a static view of a tumor at a particular point in the course of a dynamic process in which the tumor continues to evolve over time. Predicting the behavior of a tumor from a single biopsy is much like trying to define the slope of a curve from a single data point. It is therefore critical that improved diagnostic techniques be developed to optimize management decisions.

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Temporal Changes in the Clinical Approach to Diagnosing Prostate Cancer: How the Cancer of Today Differs From the Cancer of Yesterday

Ian M. Thompson, Jr., M.D.

Prior to the mid-1980s, prostate cancer was largely a disease that presented with symptoms. A small series of screenings using digital rectal examination were performed, but these demonstrated that as many as two-thirds of cases diagnosed were extraprostatic at the time of diagnosis and thus potentially incurable.[1] With the advent of prostate-specific antigen (PSA), a dramatic series of initial changes in diagnosis occurred.[1] An increasing fraction of men participated in early detection activities, reaching about 50% of men at the present time.[2] A significantly greater fraction of men underwent prostate biopsy as approximately 8% of the general population has a PSA >4.0 ng/ml, the initial upper limit of normal for prostate biopsy.

With the rapid adoption of PSA screening in the United States, an enormous increase in the incidence of prostate cancer occurred, from about an 8% lifetime risk to an estimated 16% to 17% lifetime risk at this time. Although a steady-state detection rate would have initially been predicted, including a "harvest" of early cases leading to both a stage shift and an "age shift" toward a lower and lower age at diagnosis, several other events occurred that changed patterns of care.

The first of these events was in the mid-1990s as it became evident that a four-core prostate biopsy missed many prostate cancers. With the initial report on the "sextant" biopsy, further increases in detection of cancers occurred.[2] Thereafter, a 10-core and then a 12-core biopsy were recommended by various subject matter experts. It is not uncommon in some settings to now see as many as 20 cores and, with "saturation" biopsies, as many as 30 to 40 cores. Obviously, with a high background rate of small, low-grade prostate cancers in the general population, what would be expected is an increase in the detection of these small tumors and thus a further increase in disease incidence.

The next event that affected rates of detection was in 2004 when the results of the Prostate Cancer Prevention Trial were presented.[3] In this study, all men, regardless of PSA, underwent prostate biopsy. An overall rate of prostate cancer in the population of men with a PSA <4.0 ng/ml was found to be 15% with as high as 30% rates in men with a PSA of 3.5–4.0 ng/ml. Additional investigation found that older men and African American men as well as men with a family history of prostate cancer had a further increase in risk, thus increasing the number of men undergoing biopsy with PSA values <4.0 ng/ml.

As a result of these changes in clinical activities, an increase in the number of small, low-grade tumors has been witnessed. With about 90% of these patients undergoing treatment, an increasing number of whom have radical prostatectomy, fewer older men "at risk" of prostate cancer are present in the population, leading to significant changes in age at diagnosis of the disease.

Changes in patterns of detection are to be expected in the years to come. With the increased understanding that the detection of a low-volume, low-grade tumor in many men may actually not be a benefit but a harm (risk of complications of biopsy, treatment, anxiety without a measurable benefit vis-a-vis cancer risk), increased focus is being placed on methods to reduce

biopsies in men who have a low risk of aggressive prostate cancer. New biomarkers such as PCA3 or TMPRSS2:ERG fusion protein show considerable promise to help select those men who may benefit most from prostate biopsy.[4,5]

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What Is the Risk Posed by Prostate Cancer?

Peter Albertsen, M.D.

For the past century and a half, prostate cancer has challenged clinicians and researchers. Prior to Thompson's 1852 monograph, *The Enlarged Prostate,* prostate cancer was an unknown disease.[1] Forty years later, Von Recklinghausen reported that prostate cancer could present as a small local lesion and that metastases had a preference for bone.[2] Improvements in microscopy resulted in growing numbers of case reports of prostate cancer, so that by 1900 most clinicians recognized the presenting symptoms of this disease. Urologists of the early 20th century were often called to palliate symptoms of prostate cancer. Radiation seed implants were used to alleviate bladder outlet obstruction. Benjamin Barringer, a prominent urologist in New York City, recognized that most patients with symptoms had advanced disease that was uniformly lethal.[3] Only 36 of his first 352 patients lived more than 5 years.

The dismal prognosis associated with prostate cancer changed following the report by Huggins and Hodges in 1941 that prostate cancer was an endocrine-dependent tumor.[4] By the 1950s, orchiectomy and/or diethylstilbestrol had become the treatment of choice for men with clinically symptomatic disease. Although the average patient responded for only 3 years, many responded for much longer. The prognosis for this disease improved dramatically.

The Veterans Administration Cooperative Urologic Research Group was organized in the early 1960s to determine the appropriate treatment of prostate cancer. Researchers had no difficulty recruiting to trials involving men with metastatic disease, but they had difficulty identifying men with localized disease. Probably the most significant accomplishment of these trials was the Gleason scoring system used to evaluate tumor histology. Gleason's scoring system provided significant prognostic information, and the diagram developed by Gleason (Figure 1) helped standardize the evaluation of prostate cancer. This system remains the most powerful predictor of clinical prognosis for this disease.

The 1987 manuscript by Stamey et al. concerning prostate-specific antigen (PSA) began the modern era of prostate cancer diagnosis and management.[5] This publication along with Catalona's 1991 report advocating PSA testing to screen for prostate cancer dramatically altered the incidence of this disease.[6] Since 1987, the number of incident cases has doubled, although the death rate from this disease has declined about 20%.[7] The PSA era has produced a dramatic change in how men present with this disease. Before PSA testing, most men complained of either back pain or difficulty voiding. These men often had metastatic disease and were treated with some type of androgen deprivation. Now more than 80% of men present with localized disease as a result of a biopsy recommended because of an elevated PSA.

Researchers have attempted to describe the natural history of prostate cancer. Albertsen et al. published a series of graphs (Figure 2) depicting the competing risks of prostate cancer and other causes stratified by patient age at presentation and Gleason score.[8] Men with low-grade tumors rarely died from their disease compared with men with high-grade tumors who often died within 5 to 10 years of diagnosis.

Figure 1. The Gleason Scoring System

PROSTATIC ADENOCARCINOMA
(Histological Patterns)
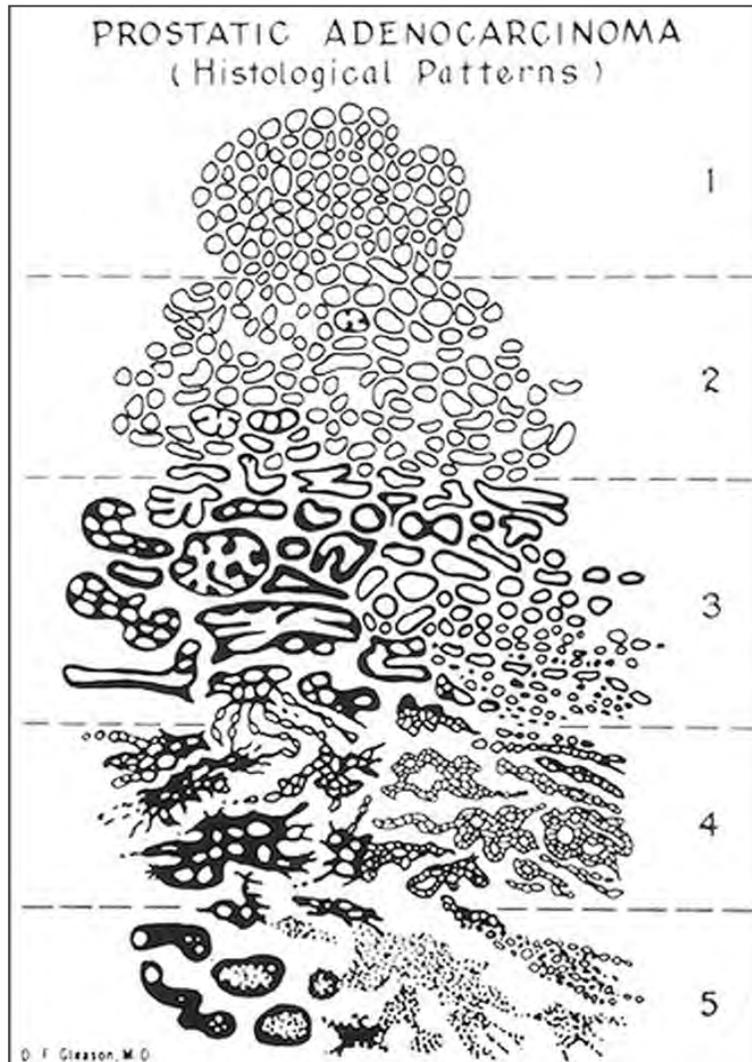
Reprinted from Gleason D. Classification of prostate carcinomas. *Cancer Chemother Rep.* 1966;50:125–128.

These studies, however, do reflect contemporary outcomes. Annual PSA testing has advanced the date of diagnosis for the majority of patients. Draisma et al. estimate that the lead time for men age 55 is approximately 12 years and for those age 75 approximately 6 years.[9] Equally important is the recognition that PSA testing leads to the discovery of indolent disease never destined to become clinically significant. Draisma et al. estimate that 27% of cancers diagnosed at age 55 and 56% of cancers diagnosed at age 75 are clinically unimportant.[9] These estimates support the findings of Sakr et al., who showed from autopsy studies that the incidence of small-

Figure 2. 20-Year Survival Estimates of Men Diagnosed in the Pre-Prostate-Specific Antigen Era
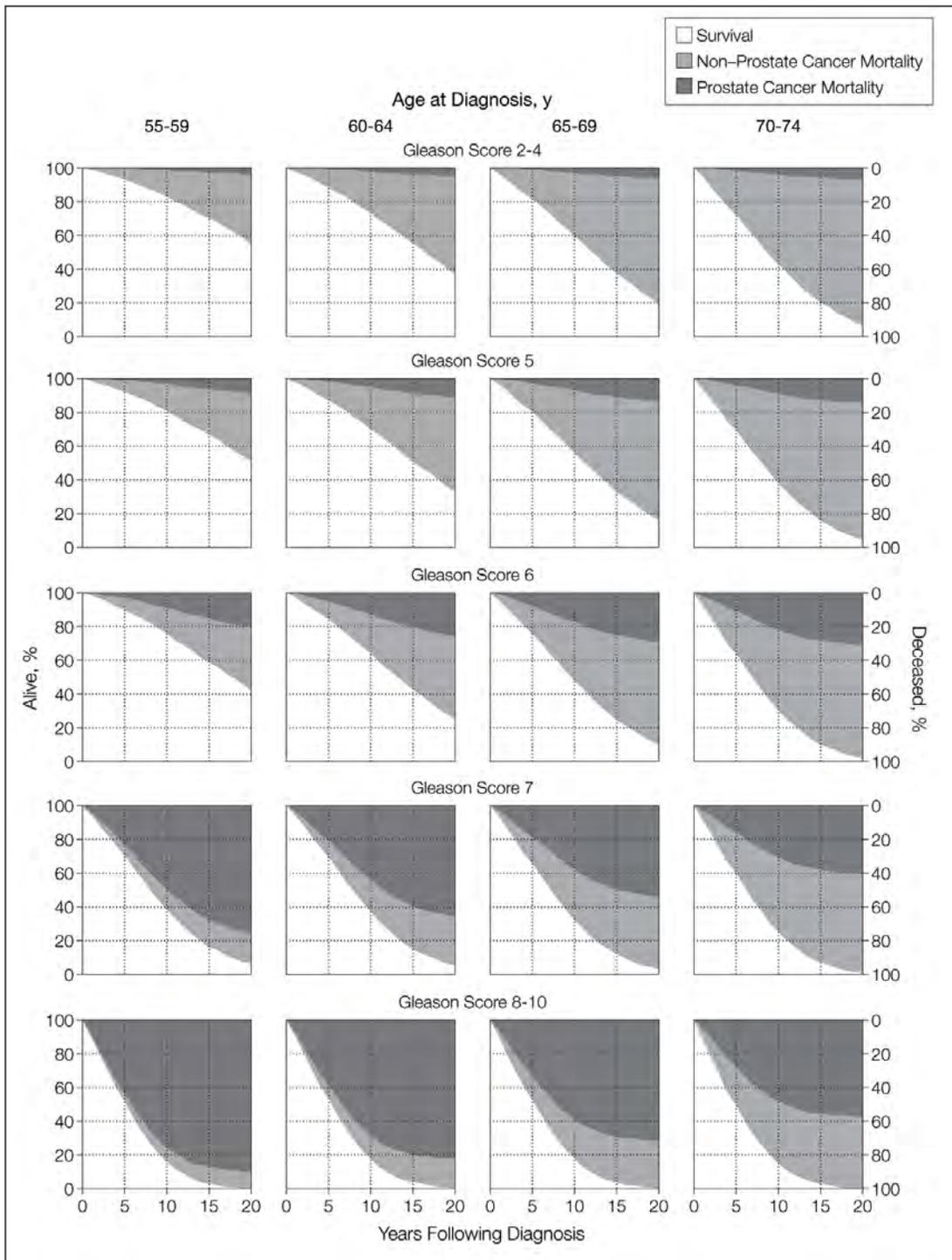
volume, low-grade cancers increased by 10% per decade so that a man age 50 has about a 50% chance of harboring a small, indolent prostate cancer.[10] The finasteride chemoprevention trial also demonstrated that small-volume, low-grade prostate cancers are very prevalent.[11] More than 20% of men originally noted to have PSA values within the normal range at the time of enrollment were eventually found to harbor prostate cancer. Three-quarters of the cancers were low-volume, low-grade tumors.

Another factor influencing our understanding of the natural history of prostate cancer is the changing interpretation of the Gleason scoring system. Contemporary pathologists no longer utilize Gleason patterns 1 and 2, and many features that were originally part of pattern 3 are now considered pattern 4.[12] These changes in the classification system have resulted in a significant upgrading of disease during the past two decades (Figure 3).

Figure 3. Change in the Interpretation of Gleason Score Patterns: Results Recorded in 1990 Versus Results Recorded in 2007
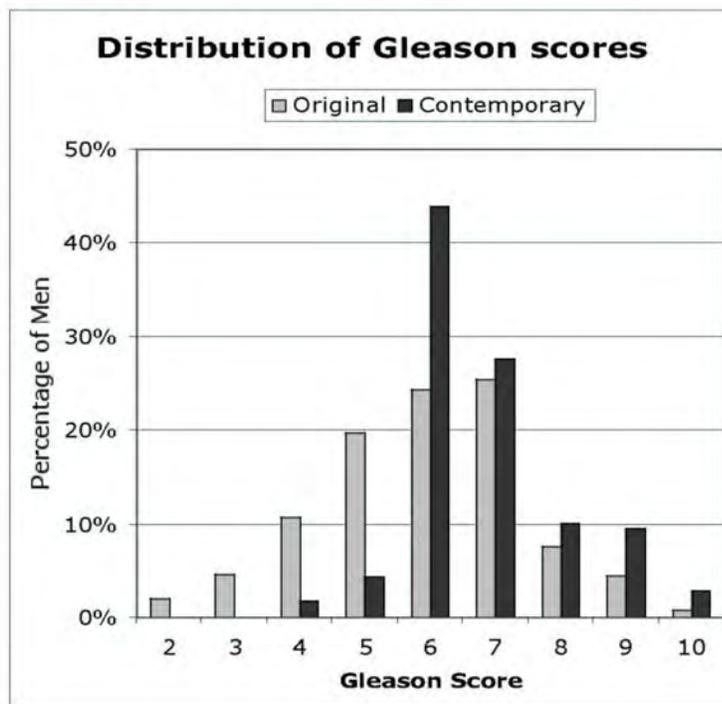
To adjust for the lead time introduced by PSA testing and the changes in the interpretation of the Gleason scoring system, Lu-Yao et al. analyzed the clinical outcomes of men diagnosed with localized prostate cancer who received no treatment for their disease at the time of diagnosis.[13] These results are presented in Figure 4. She and her colleagues also explored the impact of patient comorbidity in another competing risk analysis.[14] These 10-year survival curves reflect the current best estimates of the risk posed by prostate cancer diagnosed in contemporary practice in the United States.

Figure 4. Contemporary 10-Year Survival Estimates for Men With Gleason 5–7 Disease
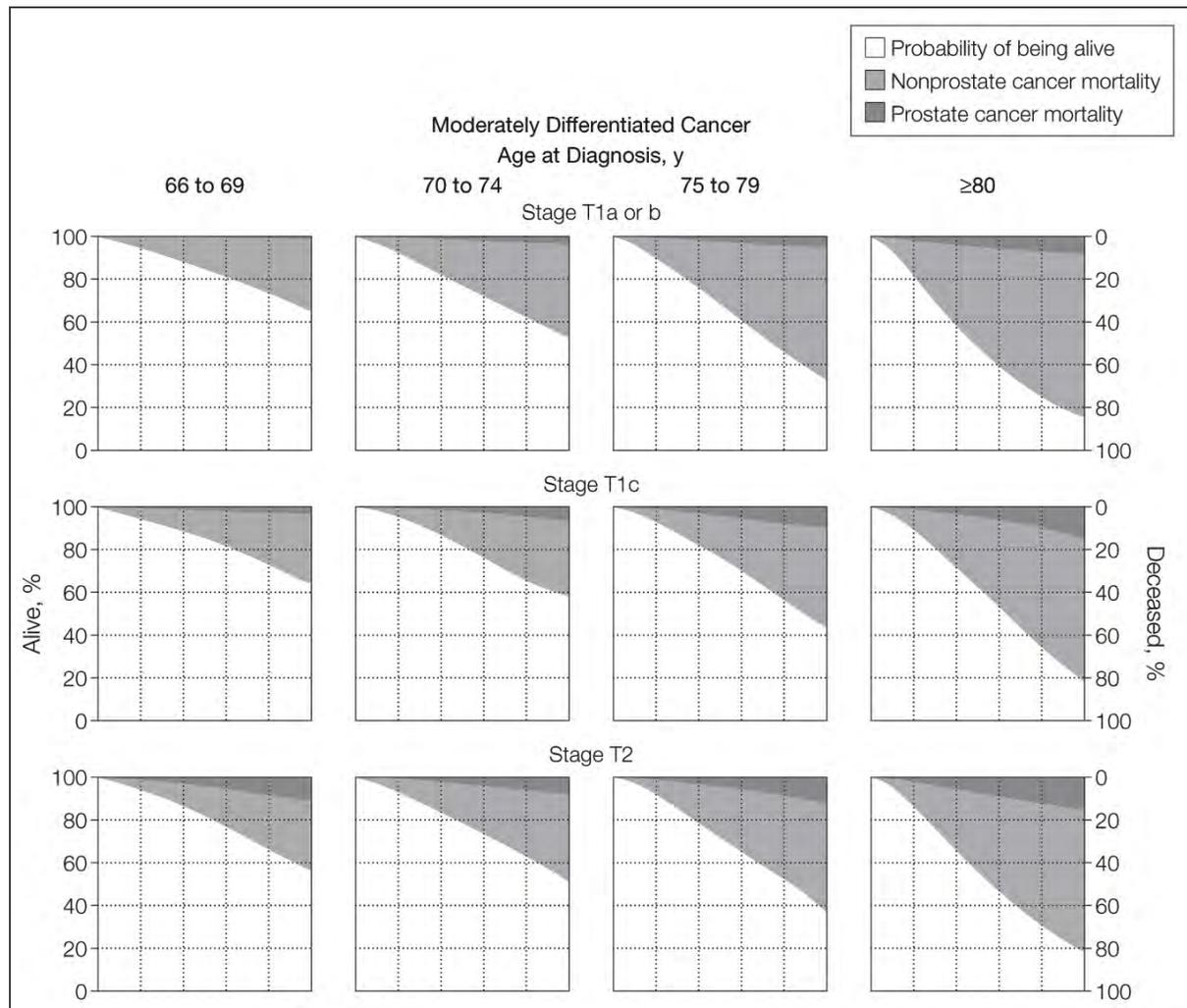
From Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. *JAMA* 2009;302:1202–1209. Reprinted with permission. Copyright ©2009 American Medical Association. All rights reserved.

The natural history of prostate cancer is extraordinarily variable. Before prostate cancer screening with PSA, most men presented with clinical evidence of prostate cancer and often succumbed to their disease several years later following treatment with hormonal manipulation. Since the advent of screening with PSA, most men are diagnosed with localized disease. The most powerful predictor of long-term outcome is the Gleason scoring system. Over the past two decades, however, pathologists have modified their use of this system such that men previously classified with Gleason 2–5 tumors are now classified as Gleason 6 disease and men with Gleason 6 disease are often now classified as Gleason 7 disease. Men with high-grade cancers (Gleason 8–10) often progress to metastatic disease and death despite treatment. Men with low-grade cancers have an excellent prognosis even in the absence of treatment. Unfortunately, we are still unable to predict accurately the risk posed by a specific prostate cancer.

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Tumor and Patient Metrics, Eligibility, and Inclusion for Active Surveillance for Prostate Cancer

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The management of favorable-risk prostate cancer is controversial and, in the absence of controlled trials to inform best practice, choices are driven by personal beliefs with resultant wide variation in practice patterns. Men with favorable-risk prostate cancer diagnosed today often undergo treatments that will not improve overall health outcomes. A shared decision approach for selecting optimal management of favorable-risk disease should account for (1) individual tumor metrics, (2) patient age and overall health, and (3) patient preferences that consider living with a cancer and the potential side effects of curative treatments.

Tumor Metrics

Gleason score (cancer grade) based on prostate biopsy, cancer stage, and prostate-specific antigen (PSA) have been used as tumor metrics to risk stratify men with newly diagnosed prostate cancer before recommending management. Based on these criteria, the National Comprehensive Cancer Network recognizes favorable-risk prostate cancer as a low-risk or very low-risk disease[1] (Figure 1). Most published prostate cancer surveillance programs have preferentially included men with favorable-risk tumor metrics using the criteria below (Figure 1)—or similar criteria[2]—thought to identify men with a low risk of cancer progression in the absence of treatment.

Figure 1. Criteria for Identifying Favorable-Risk Prostate Cancer (Low Risk and Very Low Risk)
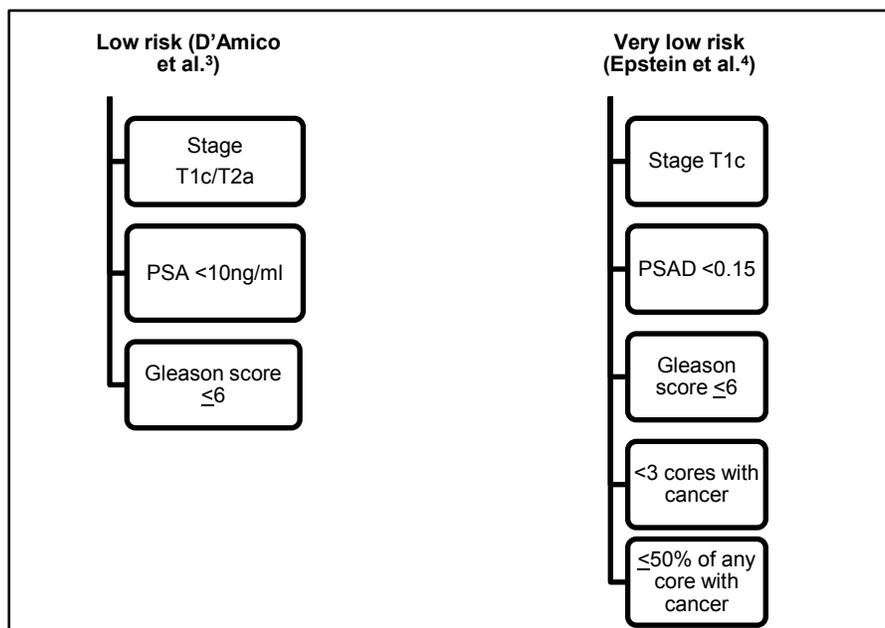
PSA = prostate-specific antigen; PSAD = PSA density (PSA/prostate volume).
Note: Core refers to prostate biopsy tissue.

The most recent update of the Johns Hopkins Active Surveillance Program begun in 1995 includes 769 men (median age 66), of whom 80% met the criteria for very low-risk disease[5] (Figure 1). The median survival time free of intervention was 6.5 years after diagnosis. Overall, 33% underwent curative intervention at a median of 2.2 years after diagnosis triggered by biopsy reclassification in 74% of men. The estimated 15-year prostate-cancer-specific mortality adjusted for competing risks ranged from 1.1% to 1.8% and 1.7% to 2.7% for men enrolled in the program 5 and 10 years, respectively.

Patient Age and Overall Health

The recently published 15-year follow-up data from the Scandinavian Prostate Cancer Group Study 4 comparing surgery to watchful waiting for men *without* screen-detected prostate cancers demonstrated no cancer-specific or metastatic-free survival advantage for surgery among men over age 65.[6] Thus, these data suggest that for favorable-risk prostate cancer diagnosed with screening, most men over age 65 to 70—especially those with comorbidities—should defer treatment based on life expectancy and the long natural history of prostate cancer. Yet, 71% of men age 75 years and older with favorable-risk prostate cancer undergo some form of active treatment.[7]

Patient Preferences

In decision analyses comparing active surveillance with curative intervention for management of prostate cancer using Monte Carlo simulations, individual patient preferences are critical in determining the optimal approach for favorable-risk prostate cancer.[8,9] Two important considerations are the ability to live with untreated disease without significant anxiety and utilities for side effects of treatment such as urinary, bowel, and sexual problems. Thus, in addition to tumor metrics that help identify men for surveillance, a shared decision approach that explores a man's preferences for living with cancer and the potential side effects of treatment should be included when a choice of surveillance or curative intervention is being considered.

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Active Surveillance: Inclusive Approach

Laurence Klotz, M.D.

Introduction

The world of prostate cancer has changed dramatically in the last 20 years. Prostate-specific antigen (PSA) first became available in the mid-1980s and was not introduced in Canada until about 1988. In both the United States and Canada, PSA was immediately embraced as a biomarker for the early identification of patients at risk for prostate cancer. The result was a sharp increase in the incidence of prostate cancer. This initial spike in incidence was due to the diagnosis of the many prevalent slow-growing, previously undiagnosed cases in the population. Many of these patients had substantial volume of disease; if serial PSA screening had been available, they would have been diagnosed years before.

With the passage of time, the prevalent cases were diagnosed and treated, and the median volume of prostate cancer in newly diagnosed patients began to fall. This process took about 5 years. By the mid-1990s, the "incident" cases began to predominate. A dramatic increase occurred in the number of patients with minimal low-grade disease on biopsy. Other than stage T1a prostate cancer seen following a transurethral resection of the prostate, such patients had previously been uncommon.

Discussion

My colleagues and I who worked together in a multidisciplinary genitourinary oncology group at Sunnybrook Health Sciences Centre were very cognizant of the high rate of prostate cancer found at autopsy and also were influenced by the excellent results of conservative management of T1a disease. Surprisingly, a widespread and relatively unremarked-on consensus existed that T1a prostate cancer (<5% of chips showing Gleason 6 or less prostate cancer on a transurethral resection of the prostate specimen) should not be treated. Yet this consensus was not applied to the diagnosis of T1c prostate cancer. Patients diagnosed with any prostate cancer at all based on an elevated PSA and transrectal ultrasound-guided prostate biopsy were offered radical therapy. In the United States, based on Cancer of the Prostate Strategic Urologic Research Endeavor data, 90% to 95% of such patients received radical treatment.[1]

It seemed obvious to us that there was an incongruity between the conservative approach taken successfully and without fanfare for T1a disease and the insistence on radical therapy for T1c disease. Many of the arguments by knowledgeable individuals seemed specious. For example, it was argued that American men diagnosed with cancer demanded treatment, yet this had not been the case for T1a disease. Another rationale was that some of these patients would progress and die of disease, even though their baseline parameters were favorable; this also had been true for T1a disease, which had a 15% progression rate at 10 years.[2] It was argued that patients managed with watchful waiting were deprived of an opportunity for cure, but experience suggested curative therapy offered after several years of observation might still be effective. Thus, we reasoned, perhaps an initial conservative approach of expectant management using the natural history of the patient's own disease, including PSA kinetics and serial biopsy to determine treatment, might go a long way toward reducing the overall morbidity of treatment. PSA kinetics was an appealing tool in managing these patients, based on emerging data at the time that PSA kinetics correlated with tumor aggressivity and volume. The

concept of personalized therapy also was beginning to emerge and further drove support for the concept.

Active surveillance has evolved to become a standard of care for favorable-risk prostate cancer. It is advocated as the treatment of choice for favorable-risk disease in several national guidelines (National Comprehensive Cancer Network, National Institute for Health and Clinical Excellence). The published experience with surveillance now encompasses approximately 2,000 patients (Table 1). While the median follow-up of some of these studies is short, collectively at least 400 patients have been followed for more than 10 years. The prostate cancer mortality in these patients remains low.

Table 1. Summary of Seven Active Surveillance Series

Author	Year	Number	Median Age	Median F/U Mo	pT3 in Radical Prostatectomy Patients	OS	CSS	On Surveillance (%)
Van As[3] *Cancer J.*	2007	326	67	22	8/18 44%	98	100	73
Carter[4] *J Urol.*	2007	407	66	41	10/4 20%	98	100	59
van den Bergh[5] *Eur Urol.*	2008	533	70	48	4/24 17%	90	99	50
Soloway[6] *BJU Int.*	2008	99	66	45	0/2 0%	100	100	92
Roemeling[7] *Eur Urol.*	2007	278	70	41		89	100	71
Khatami[8] *Int J Cancer*	2007	270	64	63		Not stated	100	61
Klotz[9] *J Clin Oncol.*	2010	452	70	73	14/24 58%	82	97 at 10 yrs	53
Total		**2,130**	**68**	**43**		**90**	**99.7**	**64**

F/U Mo = follow-up months; OS = overall survival; CSS = cause-specific survival.

Advocates for surveillance generally agree that patients with small-volume Gleason 6 prostate cancer (based on extended biopsies) with PSA <10 are candidates. In these patients, over time, approximately one-third are eventually reclassified as higher risk and treated radically. The likelihood of cancer death is, at 10 years, about 1/20th the risk of other cause mortality in patients managed this way.[9] Although the risk of prostate cancer death will increase over time, so will that of other-cause mortality. This large excess of other-cause mortality suggests that more patients may be candidates than just those with a small volume of disease and PSA <10. It is very plausible that some patients with higher volume Gleason 6 disease, PSA >10, or small elements of Gleason 4 pattern also may be at low risk for disease mortality during their lifetime and therefore are candidates for surveillance.

Since November 1995, 453 patients at our center have been managed with active surveillance.[9–13] Median follow-up is 8.0 years (range 1–16 years). Overall survival is 78.6% (Figure 1a), and 10-year prostate cancer actuarial survival is 97.2% (Figure 1b). Five of 450 patients (1.1%) have died of prostate cancer, and 30% of patients have been reclassified as higher risk and offered definitive therapy (Figure 2a). The most common indication for treatment was a PSA doubling time <3 years (44%) or Gleason upgrading (26%). Of 117 patients treated radically, the PSA failure rate was 50% (Figure 2b). This represents 13% of the total cohort. Most PSA failures occurred early; at 2 years, 44% of the treated patients had PSA failure. The hazard ratio for nonprostate cancer to prostate cancer mortality was 18.6 at 10 years (Figures 3a and 3b).

In the initial Toronto experience (1995–2000), we included, in patients older than age 70, men with Gleason 3+4 or PSA 10–15. Since 2000, we restricted the group to men with Gleason 6 and PSA <0. In fact, in multivariate analysis of predictive factors for progression, Gleason score was not an independent predictor. This likely reflected the fact that for most of these patients, the Gleason 4 pattern was <10% of the cancer present.

A detailed analysis of the five men who died of prostate cancer after being entered on surveillance revealed that (1) the PSA doubling time was <2 years in all five; (2) all had Gleason 7 or higher disease on repeat biopsy; (3) three of the five were treated within 1 year of diagnosis and had metastatic disease within 1 year of treatment; (4) one had an early trigger for diagnosis (upgrading at 1 year) and refused treatment; and (5) only one had radical treatment after a period of observation of 2 years and went on to a late prostate cancer death, possibly avoidable by earlier treatment.[13]

The recent large experience of radical prostatectomy patients reported by Eggener et al. supports the view that Gleason pattern 3 (i.e., Gleason score 6) has little or perhaps no metastatic potential.[14] In 12,000 patients with pathologic Gleason 6 or less only (i.e., no pattern 4 disease in the radical prostatectomy specimen), the 20-year prostate cancer mortality rate was 0.2%. Indeed, according to the author, even these few patients dying of disease had some Gleason 4 pattern (personal communication). Although there is a major treatment effect, one would expect that a disease with some lethality would result in a few deaths from disease in spite of treatment. One would not expect surgery to be curative in 100% of patients with a lethal disease.

Figure 1a. Overall Survival
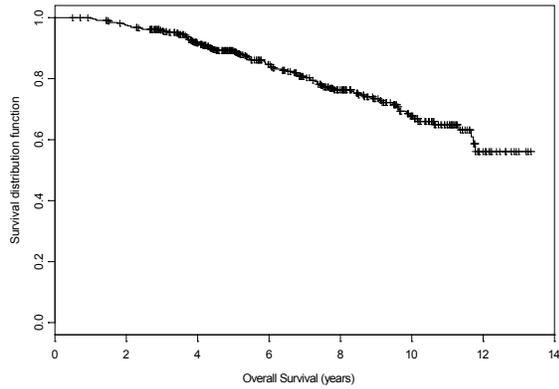
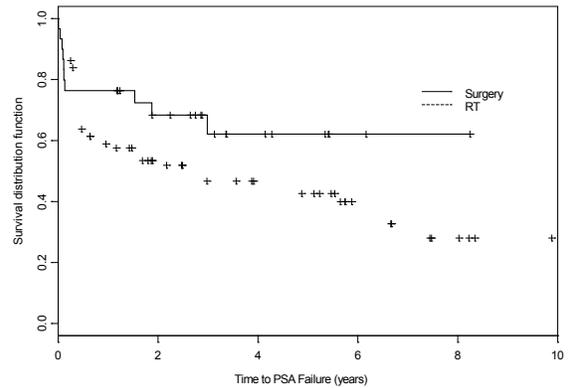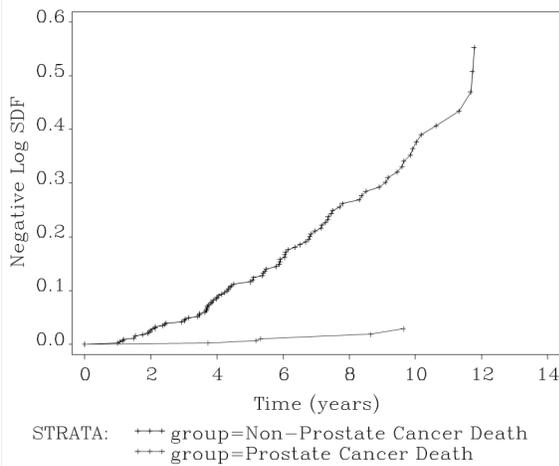**Figure 1b.** Cause-Specific Survival
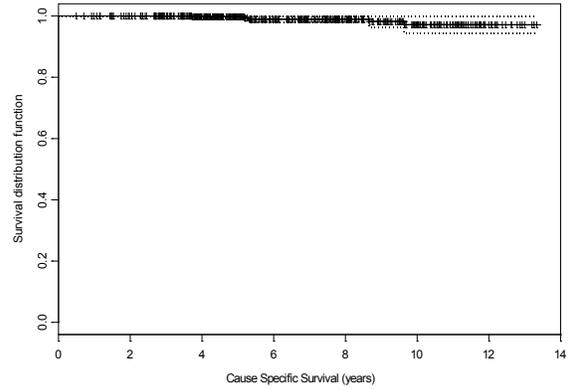
Figure 2a. Likelihood of Remaining Alive and on Surveillance
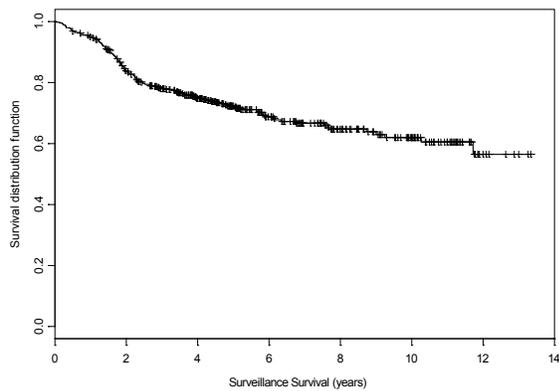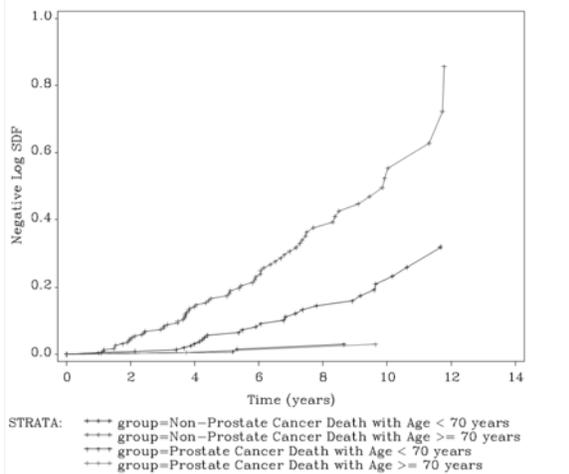

Figure 2b. PSA Failure in 117 Patients Treated With Surgery or Radiation After a Period of Surveillance

Figure 3a. Cumulative Hazard Ratio for Nonprostate Cancer to Prostate Cancer Mortality

Figure 3b. Cumulative Hazard Ratio for Mortality by Cause and Age, Stratified Around Age 70

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Another recent analysis by Wolters et al. examined the European Randomized Study of Screening for Prostate Cancer data to derive a contemporary definition of "clinically insignificant" prostate cancer using the same approach taken by Stamey in 1979, who arrived at the figure of <0.5 cc of Gleason 6 or less disease.[15] Their conclusion was that a more realistic threshold was <1.3 cc of cancer.[15] In fact, their analysis suggests that there may be no minimum threshold for clinically insignificant Gleason 6 disease.

Table 2 summarizes the current approaches to surveillance taken by various groups, from very stringent to very inclusive. Biomarkers and better imaging offer the promise of more accurate identification of both indolent and aggressive disease. There are two fundamental decision points where biomarkers and predictive tools would enhance the current approach to surveillance. First is the accurate identification of candidates for active surveillance. More accurate predictive tools would allow an even more inclusive approach to surveillance, assuming that the minority with aggressive disease could be identified at the outset.

Table 2. Active Surveillance: Who Is a Candidate?

1. Very stringent approach:	Age >65, Gleason 6, <3 positive cores, no core >50% involved, PSA <0 (Epstein criteria)
2. Stringent approach:	Any age, Epstein criteria
3. Inclusive approach:	Any age, all Gleason 6, PSA <10
4. Very inclusive approach:	Inclusive approach plus, in men >70, PSA <15, and/or Gleason 3+4 = 7

PSA = prostate-specific antigen.

The second challenge is to improve the early identification of those apparently favorable-risk patients who harbor more extensive or higher grade disease. Approximately 20% of patients are found to have Gleason 4 elements on first rebiopsy, and an additional 10% are identified on subsequent biopsies. In a smaller proportion, very aggressive disease was missed on initial biopsy. Earlier identification of these patients is a major priority. We used a PSA doubling time as a trigger for intervention between 1995 and 2008.[13] The initial PSA doubling-time threshold was 2 years; in 2000, this was increased to 3 years, as the 2-year doubling-time threshold appeared overly stringent (encompassing <10% of patients). We used the generalized linear mixed model (GLMM) to adjust for baseline PSA. Other PSA triggers (velocity >2 ng/ml per year or PSA doubling time <3 years by linear regression) resulted in inappropriate triggers for intervention in up to 50% of stable patients.[16] Although the GLMM approach seemed reasonably successful, recent analysis of PSA kinetics suggests that it is an unreliable guide in this setting.[17] Thus we now use a short PSA doubling time as an indication for further evaluation, either multiparametric magnetic resonance imaging (MRI) or repeat biopsy with biomarker evaluation if necessary.

Multiparametric MRI has recently shown tremendous progress in identifying higher grade and higher volume cancer. Multiparametric MRI encompasses T2 weighted image, dynamic contrast-enhanced imaging, and diffusion-weighted imaging. This approach offers the appealing combination of high sensitivity for high-grade or high-volume disease, and low sensitivity for unwanted low-grade or low-volume disease.[18] Recent reports suggest that the negative predictive value for high-grade prostate cancer in sectors of the prostate that show no abnormal

signal is as high as 97%. If confirmed, this negative predictive value is sufficient to make this technology a critically important partner in the management of men on surveillance. If the "new" threshold for clinically insignificant disease is indeed 1.3 cc, one can expect MRI to have an extremely high accuracy for detecting lesions of this size.

Several biomarkers have been evaluated in patients on surveillance. The two challenges are to identify those few patients with only Gleason 6 disease whose disease has metastatic potential, and (more importantly), the 25% of those who harbor higher grade disease. PCA3, a urine-based analysis of RNA expression-associated prostate cancer, has shown definite correlation with increased grade and increased cancer volume in surveillance patients. The negative predictive value of this assay for high-grade cancer in the low-risk population has not yet been established. Some studies have linked the TMPRSS2-ERG translocation to a more aggressive disease phenotype, although no consistent associations have been identified between the presence of ETS alteration and clinical outcome, with the possible exception that duplication of the ETS-related gene, reflecting aneuploidy, is associated with poor outcome.[19,20] In a recent radical prostatectomy series,[21] the TMPRSS2 translocation was associated with lower grade and not with biochemical recurrence, metastases, or death. The Aureon test, a systems pathology approach to biopsy tissue, is able to predict more aggressive natural history. Utilizing prostate needle biopsy specimens from men with T1c–T3 stage prostate cancer, who had been treated by curative-intent radical prostatectomy and followed for 8 years, the risk of systemic metastasis was predicted with 74% accuracy and a hazard ratio of 5.12.[22] Single-nucleotide polymorphism analysis, while able to identify a high-risk population for prostate cancer, has not yet been demonstrated to be able to predict more aggressive disease in men with low-risk prostate cancer.

Conclusions

Active surveillance for Gleason 6 prostate cancer for men of all ages, and Gleason 3 plus a small element of Gleason 4 disease in men over age 70, is feasible and appears safe in the 10- to 15-year timeframe. Common sense dictates that the uncertain increased risk of disease progression in those with high-volume Gleason 6 cancer should be weighed against patient age and comorbidity. This strategy provides the benefit of an individualized approach based on the demonstrated risk of clinical or biochemical progression with time. In this cohort, the likelihood of dying of other causes was 18.6 times greater than the likelihood of prostate cancer death. Uncertainty remains regarding the long-term impact of delayed treatment in men reclassified as higher risk after a period of observation and repeat biopsy.

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Evidence-based Practice Center Presentation II: Definitions of Observational Strategies and the Factors That Affect the Use of Active Surveillance

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Introduction

Active surveillance and watchful waiting are two observational follow-up strategies that forego immediate therapy in patients with prostate cancer. Two key questions asked by the conference planning committee were (1) how are these strategies defined, and (2) what factors influence the offer of active surveillance by physicians, the acceptance of active surveillance, and the adherence to active surveillance by patients?

Objectives

The objectives were to review the various definitions and protocols of active surveillance and other observational management strategies in research studies (Key Question 2) and to examine the factors that affect their use in clinical practice (Key Question 3).

Review Methods

We searched MEDLINE® and the Cochrane Database of Systematic Reviews for relevant English-language publications, from inception through August 2011. We used search terms related to prostate cancer, active surveillance, watchful waiting, expectant management, and other related strategies. For the review of definitions of observational strategies, we considered studies that reported data on observational management strategies (i.e., no immediate active treatment), enrolled patients based on predefined eligibility criteria, and used prespecified protocols for follow-up.

It was clear at the start of the review that the two terms (active surveillance and watchful waiting), in addition to others, have been used by investigators to denote various and often inconsistent general strategies. Therefore, for the purpose of this review, we divided protocols into those where the intent of subsequent treatment had been clearly described as curative, and those where the intent of subsequent treatment was either unclear or primarily palliative, regardless of the terminology originally used by the study investigators. We extracted data on parameters monitored as triggers for recommending treatment and the definitions of prostate cancer progression.

For the question on the use of observational management strategies, three types of studies were eligible: (1) studies that used quantitative methods to analyze databases or cohorts of patients to identify predictors of the offer of, acceptance of, or adherence to observational strategies; (2) studies that used qualitative research methods (e.g., focus groups or surveys) to obtain information on factors that affect the use of observational strategies; and (3) experimental studies evaluating the effect of tools such as decision aids on the use of observational strategies.

Results

Definitions of Observational Management Strategies

Fifteen unique cohorts reported selection criteria and follow-up protocols for monitoring triggers other than symptom progression for curative treatment of prostate cancer.[1–15] Other than the restriction to men with clinically localized prostate cancer (stage T1 or T2), the exact eligibility criteria had little in common across cohorts. The most commonly used patient selection criteria were based on Gleason score, prostate-specific antigen (PSA) value, and number of biopsy cores positive for cancer. All 15 cohorts included regular PSA testing in the follow-up protocol, but there was no uniform monitoring frequency; many also included regular digital rectal examinations and rebiopsies, also at various frequencies.

Seven unique cohorts of other observational strategies where subsequent treatment was of palliative intent were formed during the current PSA-screening era.[7,16–21] The commonly used patient selection criteria were based on PSA (five cohorts), disease stage (four cohorts), age (four cohorts), Gleason score (four cohorts), and bone scan findings (four cohorts). We compared the 15 unique cohorts reporting protocols with curative intent with the 7 cohorts of other observational strategies. Compared with other observational strategies, the protocols with curative intent more commonly had selection criteria based on Gleason score thresholds. They also often used selection criteria based on the number or percentage of cores positive for cancer, whereas none of the other observational strategies used such criteria. Both sets of strategies used PSA-based criteria, but PSA thresholds in curative-intent cohorts were generally lower (typically 10–15 ng/ml) compared with other observational strategies (either 15 or 50 ng/ml). Protocols with curative intent had more clearly defined follow-up protocols compared with other observational strategies, with explicit indications for treatment including increase in Gleason scores, number and percentage of positive cores (on rebiopsy), and/or PSA values. In contrast to other observational strategies, protocols with curative intent generally performed prostate rebiopsies but did not include imaging tests as part of their follow-up procedures. Other observational strategies typically included bone scans and chest radiography, but not rebiopsy.

Factors That Affect the Use of Active Surveillance

For the question on active surveillance practice, studies generally did not directly analyze the offer of, acceptance of, and adherence to active surveillance. Instead, most studies reported analyses of men who were either not treated or not initially treated. In most cases, we could not determine whether these men were on an active monitoring protocol with triggers for curative treatments. The common method for analyzing "adherence to active surveillance" in the literature is the use of the outcome "interruption of active surveillance" to seek definitive treatment. This approach does not distinguish between men who meet predefined criteria of the active surveillance protocol (indicative of disease progression) that call for curative treatment and men who elect to stop active surveillance and pursue curative treatment for other reasons (i.e., without having met disease progression criteria). Although the former could be considered "adherent" (the person is following the protocol), the latter would be considered "not adherent."

Only two studies specifically examined men who were enrolled in an active monitoring protocol with triggers for curative treatments (as opposed to other non-active surveillance observational management strategies).[22,23] The study by van As et al. found that free-to-total PSA ratio and T stage were independent predictors of time to radical treatment in patients on the protocol, but initial PSA, PSA density, Gleason score, number of positive cores, and prostate volume were not.[23] The study by Mills et al. found that decreased baseline anxiety and higher socioeconomic

status were both associated with a decreased probability of willingness to consent to active surveillance randomization (i.e., these men refused randomization and proactively selected active surveillance).[22]

Some findings from the remaining 35 heterogeneous studies concerning observational management strategies in men with prostate cancer include:

- Physician recommendations have been reported to be important elements in the decisionmaking process of men with localized prostate cancer.

- The following patient and clinical variables have been reported to be associated with an increased probability for a patient to receive observational management: older age, presence of comorbidities, lower Gleason score, lower tumor stage, lower PSA values at diagnosis, and membership in a lower risk group.

- The following patient and clinical variables have been reported to be associated with an increased probability for a patient to interrupt observational management strategies to seek definitive treatments: younger age, higher tumor stage, higher diagnostic PSA, higher PSA velocity, membership in a higher risk group, and increased anxiety.

- The desire to avoid treatment-related side effects is reported to be a predictor of electing observational management.

Conclusions

There is no standardized definition of active surveillance. The selection criteria and follow-up protocols with curative intent used similar monitoring elements, but the triggering parameters for curative treatments differed across protocols. Older age, presence of comorbidities, lower Gleason score, lower tumor stage, lower PSA value at diagnosis, and lower risk group are associated with increased likelihood of not receiving initial active treatments. It is plausible that similar factors would also affect the receipt of active surveillance, but these associations have not been formally examined.

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Presenting Treatment Options to Patients With Localized Prostate Cancer

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Treatment options for patients diagnosed with clinically localized prostate cancer were transformed following the introduction of prostate-specific antigen (PSA) testing in the mid-1980s. As incidence rates of prostate cancer rose steeply, so did rates of radical prostatectomy and radiotherapy, with radical prostatectomy rising to become the treatment of choice for 30% of all incident prostate cancers in the United States by 1990.[1] During those decades, clinicians in the United States and the United Kingdom overwhelmingly recommended radical intervention to patients: urologists favored radical surgery, and radiation oncologists favored external beam radiotherapy.[2–4] Watchful waiting was recommended mainly for older men and those with short life expectancies (≤10 years).

At the turn of the century, however, concerns began to be raised about whether this strategy of intensive detection and immediate radical intervention was leading to overdiagnosis and overtreatment.[5,6] The capacity for radical interventions to produce serious adverse events also was documented.[7] Important long-term outcome studies showed that watchful waiting could lead to survival outcomes comparable with those from attempted cure.[8–10] Groups began to explore whether prostate cancer could be stratified into different levels of risk, and safe but less radical forms of treatment could be devised. Several definitions of "no immediate intervention" emerged, ranging from delayed intervention and timing of palliative treatment to active monitoring/surveillance programs.[11]

Currently, men with prostate cancer can be offered and accept treatments from the most radical to the least invasive/intensive without clear evidence to guide them. Randomized controlled trials (RCTs) initiated in the PSA era including the Prostate Cancer Intervention Versus Observation Trial,[12] Prostate Testing for Cancer and Treatment (ProtecT),[13] and Standard Treatment Against Restricted Treatment[14] provide better comparative evidence, but most patients have to rely on a variety of sources of information about treatments—for example, the media (including professional and commercial documents on the Internet), family doctors, and friends and relatives, as well as specialist clinicians. Uncertainty around treatment and outcome for PSA-detected prostate cancer means that many patients face the dilemma of having to weigh the risks of immediate radical intervention with the potential for cure but also adverse events, versus the opportunity to avoid the risks of radical intervention but undergo regular testing and take the chance of incurring increased and possibly only palliative treatment in older age. Various nomograms and algorithms can indicate probabilities of the occurrence of these events, but for any single patient the essential dilemma of having to make a choice between treatments without robust evidence remains, often causing considerable anxiety.[15,16] There is little guidance about how treatment options are best presented to patients.

When the United Kingdom National Institute for Health Research's ProtecT trial was initiated in 1999, there were many who believed that men with PSA-detected prostate cancer (and their clinicians) would not accept randomization between radical surgery, radical conformal radiotherapy, and conservative management. As a consequence, a feasibility study was undertaken with a nested RCT to investigate recruitment to a three-arm or two-radical-arm trial.[17] Integrated qualitative research (interviews with patients and clinicians and recordings of recruitment appointments) was undertaken to explore patients' treatment preferences, the

presentation of study information by recruiters (urologists and nurses), and the interpretation of the information by trial participants.[18]

The study information was considered fully by the ProtecT trial management group and ethics committees, and meetings were held with recruiters to agree on the information to be presented, with a checklist provided of topics to be covered. In the first few months, most patients rejected randomization and opted for radical surgery.[19] Scrutiny of recruitment appointments showed that surgery was always presented first, in considerably greater detail and with more enthusiasm than radiotherapy, and the arm that should have been referred to as "conservative management" was called "watchful waiting."[19] Interviews with patients revealed several crucial issues: that watchful waiting was unacceptable as it was seen to be a form of neglect; that terms used by recruiters such as "trial" and "random" were confusing; and that the purpose of the study was not well described or understood.[19] The trial management group responded quickly: the protocol for the conservative option was refined and renamed "active monitoring" to reflect the regular PSA tests and review appointments needed by patients; recruiters were instructed to present active monitoring first so that it was fully explained; and they were provided with tips about how to avoid problematic terminology and better describe the purpose of randomization.[19] Randomization rates rose from 30% to 70% of eligible participants,[19] and recruitment to the full-scale three-arm treatment trial was then able to be completed.[13] The ProtecT study has shown that the presentation of study information clearly influenced randomization rates and the treatments selected,[19] and further research has provided evidence about treatment preferences[20] and the impact on patient engagement of styles of information provided.[21]

Publications most recently from the Scandinavian Prostate Cancer Group Study 4 treatment trial,[22] European screening trial (European Randomized Study of Prostate Cancer),[23] and U.S. screening trial (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial)[24] have added very important information to our understanding of prostate cancer, but they have not resolved the key dilemma of how to balance detecting and treating life-threatening prostate cancer while avoiding overdiagnosis and unnecessary treatment. While we await evidence from the RCTs under way, patients and clinicians still have to choose between treatment options. There is now evidence that great care needs to be taken in interactions with patients because the way in which treatments are presented by clinicians can be highly influential, and also that the impact of these influences can only be fully understood by listening to patients' interpretations. The lack of definitive evidence about the most effective and appropriate treatment, particularly for a man diagnosed with the most common low-grade and small-volume PSA-detected prostate cancer, means that clear and fair presentation of information about treatments is crucial if men are to make informed choices.

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Improving the Communication of the Benefits and Harms of Treatment Strategies

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The optimal treatment strategy for localized prostate cancer is unclear because there is a dearth of clinical trial data on comparative survival benefits. However, treatment complications, which occur frequently and can be long lasting, are recognized to vary by modality.[1] Therefore, a man facing the complex decision of whether and how to treat a localized prostate cancer should ideally be engaging in a shared decisionmaking process. Treatment decisions should reflect a man's personal values for the various potential outcomes and his attitudes toward risk.[2] To achieve this goal, clinicians should discuss the patient's role in the decisionmaking process, the nature of the decision, treatment alternatives, the potential benefits and harms of the alternatives, and the probabilities for various outcomes, as well as assess the patient's understanding of the discussion and his preferences.[3] Unfortunately, patient preferences do not consistently reflect careful consideration of the evidence.[4] Prostate cancer treatment decisions are most strongly influenced by physician recommendations, which are often for the therapy that the particular specialist provides.[5,6] In addition, patients do not routinely seek treatment opinions from multiple specialists or discuss options with primary care providers.[4,6] Decisions can be driven by feelings of fear and uncertainty, and unduly influenced by anecdotes, misperceptions,[7] and family and friends.[8]

One strategy for delivering comprehensive, objective information to support decisionmaking is to provide a health decision aid, which can be written or electronic.[2] These aids should describe alternative options, provide information on the probabilities of benefit and harm for each option, help patients clarify their values, and guide them toward achieving shared decisionmaking.[2,9] However, although a systematic review published in 2001 concluded that the content of educational material on prostate cancer treatment was generally accurate, balanced, and readable, most materials failed to provide sufficient information about the risks and benefits of each treatment to support quality decisionmaking.[10] Recently, the International Patient Decision Aids Standards (IPDAS) Collaboration developed an instrument to measure the quality of a decision aid that encompassed 10 dimensions.[11] A systematic review of 55 decision aid trials, though, found that few of the IPDAS dimensions were consistently evaluated.[12]

The effectiveness of decision aids in supporting clinical decisionmaking has been evaluated by several systematic reviews.[13,14] Overall, using decision aids for treatment or screening decisions improved knowledge, created more realistic expectations, reduced decisional conflict, increased the level of involvement in decisionmaking, and reduced the chance of being undecided.[13] Prostate cancer treatment decision aids specifically increased knowledge, encouraged more active involvement in decisionmaking, reduced decisional conflict, and reduced the proportion of patients undergoing surgery.[13–16] However, few trials were randomized, decision aids did not consistently present all treatment options or provide exercises to help patients clarify their preferences, and the effects of decision aids on treatment selection were inconclusive.[14]

Interpreting the literature on decision aids is also problematic because the primary alternative to active treatment is presented as watchful waiting, which has the often unwelcome connotation of just palliating progressive symptoms. Acceptable decision aids must define active surveillance as a strategy to defer active treatment, allowing patients to avoid treatment complications in the absence of clinical evidence of tumor progression.

Research on decisionmaking for treatment of localized prostate cancer should use decision aids that meet expected quality standards and accurately define active surveillance. These decision aids need to be rigorously evaluated in clinical practice, and investigators should address issues about content (e.g., including patient testimonials, displaying risk information, tailoring presentations), format (e.g., written, video, web-based), the logistics of implementing decision aids (e.g., timing, setting, responsible provider, costs), and acceptability by patients and providers. Appropriate outcomes (e.g., decision quality, treatment selection, treatment decision satisfaction/regret) should be measured with validated instruments. Study designs also should account for the repeated decisions occurring during active surveillance. Effective decision aids could better align patient preferences with treatment selection, an important goal of patient-centered healthcare, and potentially improve health outcomes.

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Active Surveillance for Early-Stage Prostate Cancer—The University of California, San Francisco Experience

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The widespread use of serum prostate-specific antigen (PSA) and extended pattern biopsy for the early detection of prostate cancer has led to profound stage and grade migration with the attendant consequences of overdetection and overtreatment. Active surveillance is an alternative to immediate treatment in well-selected patients.[1,2]

At the University of California, San Francisco to date, more than 650 men have been followed on an active surveillance regimen, which includes period serum PSA, clinical examination, ultrasound imaging, and repeat biopsy.[3] Of these men, 80% met criteria as having low-risk disease, 18% as intermediate-risk disease, and 2% as having high-risk disease. Mean age at entry was 62 years, and mean PSA was 6.1 ng/ml.

Treatment-free survival (Figure 1) at 5 years is 64%, with upgrading at biopsy the most significant predictor of treatment. Overall survival at 5 years is 97%. No man has died of prostate cancer. Results at radical prostatectomy for those found to have progressed are no different from those found in a parallel cohort treated with surgery at the time of diagnosis.[4,5] The most common indication for treatment has been a change in Gleason score. Changes in serum PSA have not predicted upgrading.[6–8] Active surveillance appears to be a safe alternative to immediate treatment in properly selected—and followed—men with prostate cancer. Although men with very low-risk disease appear to be excellent candidates for surveillance, such an option may be appropriate for men with slightly higher risk disease.[9] Prospective evaluation of predictors of treatment/risk (serum, tissue biomarkers, imaging) is currently under way. In addition, such men may be candidates for novel, low-morbidity treatment strategies (lifestyle, pharmacologic) that delay or prevent progression.

Figure 1. Treatment-Free Survival

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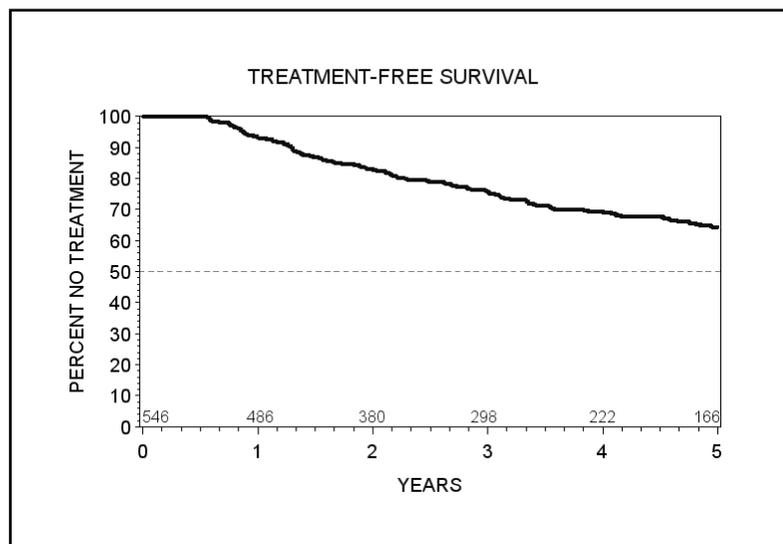
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Factors Influencing Patients' Acceptance and Adherence to Active Surveillance

David F. Penson, M.D., M.P.H.

Clinical decisionmaking in localized prostate cancer is a complicated, multidimensional process in which men often consider their own personal preferences, the advice of their healthcare providers, the opinions of their family and friends, and outside information sources. They synthesize all of this within the framework of their own unique socioeconomic situation, their social support network, and their preconceived impressions of their health and the healthcare system. Our prior systematic review of the literature on decisionmaking in prostate cancer identified a number of consistent themes men consider when choosing therapy.[1] These include cancer eradication, treatment side effects (and their impact on quality of life), and out-of-pocket economic costs. Importantly, the way the decision is framed by the healthcare provider plays a critical role in decisionmaking as well. The last point has a strong influence on patient acceptance of active surveillance as a therapeutic strategy for localized prostate cancer.

Previous studies have documented that the specialty of the counseling physician strongly influences the primary recommendation for treatment—urologists tend to recommend radical prostatectomy, whereas radiation oncologists tend to recommend radiation therapy.[2] To this end, if there were "invested" providers who advocated for active surveillance in the setting of localized prostate cancer, acceptance of active surveillance likely would increase. Evidence supporting this hypothesis comes from qualitative research performed by Davison et al.[3] They interviewed 25 men with low-risk prostate cancer who opted for active surveillance and found that physician recommendation played an important role in a patient's accepting active surveillance as a management strategy. Specifically, the way the physician described the cancer influenced the patient's perception of the seriousness of his condition and set the tone for the decisionmaking process. Study participants also noted that initial physician reassurance regarding active surveillance as a viable treatment choice and obtaining additional provider opinions that confirmed active surveillance as an option also increased their acceptance of active surveillance. A full list of the factors identified in the study that influenced men to go on active surveillance is shown in the table below.

Table 1. Factors Influencing Men To Go on Active Surveillance

Patient perception of prostate cancer
Physician recommendation
Decision control: Who made the decision?
Avoiding the side effects of therapy
Seeking information to make a treatment decision
Advice from family and friends
Pre-existing medical conditions
Age
Coping strategies for active surveillance

Although there is no doubt that all of these factors play a role in the acceptance of active surveillance, one factor in particular bears special mention: seeking outside information to make a treatment decision. Our group assessed the relationship between information seeking and treatment choice in 804 men with newly diagnosed localized prostate cancer from three clinical sites on the west coast.[4] Men electing active surveillance were statistically significantly influenced by media stories and reports about prostate cancer (odds ratio = 1.86, confidence interval 1.12–3.10). This illustrates a possible "leverage point" that public health advocates can possibly use to increase acceptance of active surveillance in the general population.

Once a man elects active surveillance, he must deal with a number of issues. Some might believe that men on active surveillance are more likely to experience anxiety and/or fear of disease recurrence. Recent studies indicate that this may not actually be the case. A study by van den Bergh et al. assessed uncertainty, anxiety, and depression in 129 European men who elected active surveillance for localized prostate cancer.[5] Among these men, 81% to 93% of the patients scored better than reference values for these outcomes, indicating that men who stayed on active surveillance protocols did not experience increased disease-specific anxiety. Of course, this likely represents an element of selection bias, as patients who experience increased anxiety are more likely to undergo an aggressive intervention. Acknowledging this, these data dispel the notion that active surveillance itself causes increased anxiety.

Little is known about what influences adherence to active surveillance protocols. A qualitative study by Oliffe and colleagues sheds light on ways that men cope with the uncertainty of active surveillance and provides some insight into factors that may influence adherence.[6] They interviewed 25 men on active surveillance and identified the two most common strategies these men used to cope with uncertainty. First, the men tended to frame their prostate cancer as benign through stoicism. This, in turn, underscored their determination to "live a normal life." Second, men often committed to "doing something extra" to complement active surveillance protocols. Importantly, they often involved their wives and focused on diet as an adjunct therapy. It seems that two of the factors that influence acceptance of active surveillance as a viable therapy—patient perception of disease and advice/support from family—also influence adherence.

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Regional, Provider, and Economic Factors Associated With the Choice of Active Surveillance in the Treatment of Men With Localized Prostate Cancer

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The physician has been shown to play a major role in the choice of active surveillance.[1] However, active surveillance appears to be underused among eligible patients (with only 9% of eligible patients opting for active surveillance in the Cancer of the Prostate Strategic Urologic Research Endeavor study), and the role of the physician in the treatment decisionmaking process requires further study.[2] Similarly, no treatment within the first 6 months after diagnosis was found for 9% of men with clinically localized prostate cancer from a 2002 patterns of care study based on the National Cancer Institute's Surveillance, Epidemiology and End Results cancer registries.[3] Earlier studies of men diagnosed between 1994 and 2002 indicated that men relying on primary care physicians as opposed to specialists were more likely to be followed by what was termed "expectant management."[4] Since then, the indications for surveillance as a treatment option have changed, with the earlier approach suggested for elderly men without curative intent. More recently, active surveillance is indicated for younger men with low-risk disease; it involves very rigorous follow-up and includes curative intent.[5] Thus, the viewpoint of physicians and their understanding of this option may be changing.

The variation in use of surveillance (with various definitions) according to provider, regional factors, and rural/urban residence has been assessed from the Breast and Prostate Cancer Data Quality and Patterns of Care (PoC-BP) study, which was funded by the National Program of Cancer Registries of the Centers for Disease Control and Prevention (CDC) and involved researchers from CDC and seven states (California, Georgia, Kentucky, Louisiana, Minnesota, North Carolina, and Wisconsin). Conducted in 2007–2009, the PoC-BP study used registry data from cancer cases diagnosed in 2004 and included reabstraction of cancer data from hospitals and outpatient facilities (i.e., pathology laboratories, radiation facilities, free-standing surgery centers, long-term care facilities, physicians' offices). Information on the demography of the cancer patient, characteristics of the cancer, work-up information, and data on the first course of cancer-directed treatment (i.e., therapy regimen that was given or planned at the time of the initial cancer diagnosis, before disease recurrence or progression) and its outcome were collected.

From all participating registries, 11,679 cases of invasive prostate cancer (*International Classification of Diseases for Oncology,* 3rd Edition, code C61.9) were randomly selected across strata defined by race/ethnicity and state-specific factors such as Appalachian versus non-Appalachian region, type of facility, and patient volume of the facility. The methods and quality of the data have been previously described.[6] Linkages with hospital and physician provider files to obtain health system measures were completed. Census tract of residence was linked to variables associated with socioeconomic status and access to care including urbanization (urban [100% urban], rural [100% rural], urban-rural mix), working class (<66% in working class vs. ≥66%), and poverty level (20%+ below poverty vs. <20% below poverty level). The data were weighted by the sampling fractions using SAS Proc Survey to represent the source population.

Abstracts were completed for 77.2% (9,017) of the selected cases, and 8,376 of them had clinically localized disease (after excluding those with T3 or T4 disease, positive nodes, metastases, or missing data required for risk-group definition). Among these patients, 13.9% did not receive therapy in the first 6 months after diagnosis (Table 1). If no mention was made of active surveillance, watchful waiting, expectant management, or other surveillance plan in the records reviewed, they were classified as having "no plan/no therapy" (9.3%); if a specific surveillance plan was mentioned, they were classified as having "active surveillance" (4.6%).

Both types of surveillance were more likely to occur among those age 75 and older than among those diagnosed at younger ages (Table 1). Nonwhites were more likely than whites to not receive therapy within 6 months; this was due largely to having no plan rather than being followed by active surveillance. Men with lower clinical risk were more likely to receive no therapy due to both active surveillance and having no specific plan.

Little difference was seen in the percentage receiving surveillance of either type by urban/rural residence; however, having no plan was more common among those from areas with a greater percentage in the working class and from areas where 20% or more were below the poverty level than from higher socioeconomic status areas (Table 1). The average number of physicians (both primary care physicians and urologists) was higher in areas where men received active surveillance compared with areas where men received no therapy without a specific plan (Table 2).

In summary, although active surveillance may be underutilized in general, when it is used, it occurs more commonly among those with lower risk tumors, which would be considered appropriate, and where the ratio of physicians per 100,000 men is higher. In contrast, receiving no therapy with no specific plan occurs more commonly in lower socioeconomic status areas. Additional results on association of surveillance type with physician specialty will be presented, as well as multivariable analyses to identify factors that independently predict receipt of either active surveillance or no therapy with no plan.

Table 1. Weighted Percentage of Demographic, Clinical, and Area Characteristics for Men With No Therapy: Localized Prostate Cancer, 2004, Centers for Disease Control and Prevention's Breast and Prostate Cancer Data Quality and Patterns of Care Study, Preliminary Data

Characteristics	All Patients Total % Distribution[*]	Patients Receiving No Therapy in 6 Months		
		% of Total With No Therapy[†]	% With Active Surveillance[‡]	% With No Plan/No Therapy[§]
Number	8,376	1,211	392	819
Weighted number	24,513	3,406	1,133	2,273
% of total	100.0	13.9	4.6	9.3
Age at diagnosis				
<60	26.4	9.0	2.0	7.0
60–64	17.5	8.9	2.7	6.2
65–69	20.2	12.4	3.0	9.4
70–74	17.0	15.2	3.9	11.3
75+	18.8	25.8	12.5	13.3
Race/ethnicity				
White	73.6	12.6	4.7	7.9
African American	17.4	15.9	3.7	12.2
API, AI/AN	2.5	17.2	6.1	11.1
Hispanic	6.6	21.0	5.1	15.9
Insurance				
None	1.4	11.3	3.0	8.3
Private	60.8	12.5	3.8	8.7
Medicaid	5.6	18.6	3.6	15.0
Medicare/other public	27.0	16.1	6.8	9.3
Unknown	5.3	14.8	4.8	10.0

Table 1. Weighted Percentage of Demographic, Clinical, and Area Characteristics for Men With No Therapy: Localized Prostate Cancer, 2004, Centers for Disease Control and Prevention's Breast and Prostate Cancer Data Quality and Patterns of Care Study, Preliminary Data *(continued)*

Characteristics	All Patients Total % Distribution[*]	Patients Receiving No Therapy in 6 Months		
		% of Total With No Therapy[†]	% With Active Surveillance[‡]	% With No Plan/No Therapy[§]
Clinical risk group				
Low	42.0	18.8	6.8	12.0
Intermediate	41.2	9.9	3.2	6.7
High	16.7	11.5	2.7	8.8
Rural/urban				
100% urban	50.2	15.6	5.0	10.6
100% rural	14.3	14.4	5.5	8.9
Urban/rural mix	35.1	10.9	3.7	7.2
Working class				
<66% working class	45.8	12.7	4.5	8.2
≥66% working class	53.8	14.7	4.7	10.0
Poverty level				
<20% below poverty level	82.4	12.8	4.5	8.3
≥20% below poverty level	17.2	18.1	5.0	13.1

API, AI/AN = Asian Pacific Islander, American Indian/Alaska Native.

[*]Totals may not equal 100% due to rounding and missing data.

[†]No therapy includes those with active surveillance and no plan.

‡Active surveillance = active surveillance plan specifically mentioned in medical record.

§No plan/no therapy = no mention of active surveillance and no therapy received in first 6 months after diagnosis.

¶Definitions of risk groups: Low = T1–T2a and Gleason score 2–6 and PSA <10 ng/ml; Intermediate: T2b–T2c or Gleason score 7 or PSA 10–20 ng/ml; High: Gleason score 8–10 or PSA >20 ng/ml.

Table 2. Mean Number of Office-Based Primary Care Physicians and Urologists per 100,000 Men by Initial Therapy: Localized Prostate Cancer, 2004, Centers for Disease Control and Prevention's Breast and Prostate Cancer Data Quality and Patterns of Care Study, Preliminary Data

Initial Therapy	Mean Number of Office-Based Physicians per 100,000 Men		
	Primary Care Physicians (PCP) (95% CI)	Urologists (95% CI)	PCP + Urologists (95% CI)
Active surveillance	102.0 (97.5–106.5)	6.7 (6.2–7.2)	108.7 (103.8–113.6)
No plan/no therapy	98.8 (96.2–101.4)	6.0 (5.7–6.4)	104.8 (102.0–107.7)

CI = confidence interval.

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Overview of Randomized Controlled Trials for Localized Prostate Cancer

Mack Roach III, M.D., FACR

The argument for active surveillance is influenced critically by whether treatment is proven to be effective. This point was emphasized in an open forum on prostate cancer screening published in the January 18, 2002, edition of the *San Francisco Chronicle* by Yamey and Wilkes.[1] They wrote, "For a screening test to be valuable, there must be a proven treatment that will alter the course of the disease…. There is no research to show that among the various treatment options…any option is better…. In fact, not giving any treatment may be just as good." It is this last comment that I address in my presentation. In Tables 1 through 4, I summarize most of the major phase III randomized trials addressing men with localized prostate cancer. Based on these data, the following conclusions can be drawn:

1. Radical prostatectomy prolongs survival compared with "watchful waiting."

2. There is no role for androgen deprivation therapy before radical prostatectomy.

3. Postoperative external beam radiation therapy reduces recurrences after radical prostatectomy and may improve survival.

4. Higher dose external beam radiation therapy improves prostate-specific antigen control, but there is no overall advantage yet.

5. External beam radiation therapy with androgen deprivation therapy is better than external beam radiation therapy alone for intermediate-risk and high-risk patients.

6. High-risk patients benefit from long-term androgen deprivation therapy (more than 2 years), but those with intermediate-risk disease appear to require only 4 to 6 months.

7. Androgen deprivation therapy with external beam radiation therapy is better than androgen deprivation therapy alone for men with locally advanced disease.

Table 1. Major Trials of Radical Prostatectomy for Clinically Localized Prostate Cancer

First Author (Year)	Design	Conclusions	Comments
Bill-Axelson (2011)[2]	RP vs. watchful waiting	RP associated with better survival	Most benefit for men <65 years of age
Studer (2006)[3]	RP ± adjuvant ADT	Small improvement in overall survival	No improvement on cause-specific survival or quality of life
Klotz (1999)[4]	RP vs. ADT + RP	Similar rate of PSA failure and no survival advantage	Does not support the use of ADT with RP
Aus (1998)[5]	RP vs. ADT + RP	Similar rate of PSA failure and no survival advantage	Does not support the use of ADT with RP
Soloway (2002)[6]	RP vs. ADT + RP	Similar rate of PSA failure and no survival advantage	Does not support the use of ADT with RP
Schulman (2000)[7]	RP vs. ADT + RP	Similar rate of PSA failure and no survival advantage	Does not support the use of ADT with RP
Homma (1997)[8]	RP vs. ADT + RP	Similar rate of PSA failure and no survival advantage	Does not support the use of ADT with RP
Van Poppel (1995)[9]	RP vs. estramustine + RP	Similar rate of PSA failure and no survival advantage	Does not support use of estramustine with RP

RP = radical prostatectomy; PSA = prostate-specific antigen; ADT = androgen deprivation therapy.

Table 2. Postoperative Radiotherapy After Radical Prostatectomy for Localized Prostate Cancer

First Author (Year)	Design	Conclusions	Comments
Thompson (2009)[10]	pT3 ± adjuvant RT	Improved PSA control, clinical failure, and overall survival	Longest follow-up
Wiegel (2009)[11]	pT3 ± adjuvant RT	Improved PSA control	Follow-up too short to address survival?
Bolla (2005)[12]	pT3 or + margins ± adjuvant RT	Improved PSA control, clinical failure, and metastasis-free survival	Follow-up too short to address survival?

RT = radiation therapy; PSA = prostate-specific antigen.

Table 3a. Radiation Dose Escalation

First Author (Year)	Design	Conclusions	Comments
Kuban (2011)[13]	70 vs. 78 Gy EBRT	Patients with PSA >10 ng/ml or high risk benefit from 78 Gy	78 Gy decreased PSA, clinical failure, and, in a post-hoc analysis, prostate cancer deaths compared with 70 Gy
Zietman (2010)[14]	70.2 Gy EBRT vs. 79.2 Gy with protons	5-year bFFS: Low risk: 84% to >98% Intermediate risk: 79% to >91%	No impact on survival yet
Peeters (2006)[15]	68 vs. 78 Gy EBRT	PSA control better in the 78 Gy arm	No impact on survival yet
Dearnaley (2007)[16]	64 vs. 74 Gy EBRT	Improved PSA control at 5 years with 74 Gy	No impact on survival yet
Beckendorf (2011)[17]	70 vs. 80 Gy EBRT	Improved 5-year PSA failure with 80 Gy benefit greatest if PSA >15	No impact on survival yet
Sathya (2005)[18]	66 Gy EBRT vs. 40 Gy + 35 Gy Ir-192 implant	Improved PSA control with addition of higher doses with implant	No impact on survival yet

EBRT = external beam radiation therapy; PSA = prostate-specific antigen; bFFS = biochemical failure-free survival.

Table 3b. Completed Major Phase III Radiation Therapy Oncology Group Prostate Cancer Trials: Radiation ± Androgen Deprivation Therapy

First Author (Year)	Design	Conclusions	Comments
Shipley (2011)[19]	RT vs. RT + bicalutamide 150 mg for rising PSA after prostatectomy	Improved PSA control, reduced metastasis rate	Pending assessment of primary end point due to short follow-up
Jones (2011)[20]	± NHT 2 months prior and during RT (66 Gy)	Overall and cause-specific survival advantage	Benefit of ADT greatest for intermediate risk
Roach (2008)[21]	RT ± ADT 2 months prior and during WPRT	Cause-specific survival advantage	High-risk patients require longer term ADT
Pilepich (2005)[22]	RT ± long-term adjuvant ADT	Overall survival advantage	Essentially all subsets with high risk benefited
Hanks (2003)[23]	RT + 4 or 28 months ADT	Survival advantage GS = 8–10	High-risk patients require longer-term ADT
Roach (2003)[24]	RT + 4 months ADT started either before or after RT and ± WPRT	Improved PFS with WPRT and ADT started before RT	Trial to confirm value of WPRT (RTOG 0924) under way

RT = radiation therapy; PSA = prostate-specific antigen; NHT = neoadjuvant hormonal therapy; ADT = androgen deprivation therapy; GS = Gleason score; PFS = progression-free survival; WPRT = whole-pelvic radiation therapy; RTOG = Radiation Therapy Oncology Group.

Table 3c. Completed Major Phase III Non-Radiation Therapy Oncology Group Prostate Cancer Trials: Radiation ± Androgen Deprivation Therapy

First Author (Year)	Design	Conclusions	Comments
Armstrong (2011)[25]	70 Gy + 4 vs. 8 months neoadjuvant ADT	No advantage	Included mostly high-risk patients
Denham (2011)[26]	66 Gy to prostate ± 3 or 6 months ADT	ADT for 6 months improves overall survival	Need at least 6 months of ADT?
Bolla (2007)[27]	70 Gy (50 Gy WP) 6 months vs. 3-year HT	Improved survival with 3 years	Long term > short term
D'Amico (2004)[28]	70 Gy ± 6 months ADT	Improved survival	Need at least 6 months of ADT?
Crook (2009)[29]	66–67 Gy + 3 months vs. 8 months ADT	Overall, no advantage in disease-free survival	Improved disease-free survival in subset of high-risk patients on 8-month arm
Bolla (2002)[30]	70 Gy ± 3 years ADT	Improved survival for very high-risk patients	

ADT = androgen deprivation therapy; WP = whole pelvis; HT = hormone therapy.

Table 4. Completed Contemporary Phase III Prostate Cancer Trials: Androgen Deprivation Therapy ± Radiation

First Author (Year)	Design	Conclusions	Comments
Widmark (2009)[31]	ADT ± RT for locally advanced disease	Better survival with addition of RT	Used primarily anti-androgens
Mason (2010)[32]	ADT ± RT for locally advanced disease	Better survival with addition of RT	Used LHRH drug

ADT = androgen deprivation therapy; RT = radiation therapy; LHRH = luteinizing hormone-releasing hormone.

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Results From the Scandinavian Prostate Cancer Group 4 Trial (SPCG-4)

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Introduction

The Scandinavian Prostate Cancer Group 4 (SPCG-4) trial started in 1989 when there was no conclusive evidence from previous studies to introduce radical treatment for early prostate cancer.[1] The trial aimed to test whether radical removal of the prostate could lower prostate cancer mortality in men with clinically localized disease with what, in those days, was considered medium- and low-risk prostate cancer. During the course of the trial, studies of side effects and quality of life in long-term survivors have come increasingly into focus. The trial started well before prostate-specific antigen (PSA) testing became widespread in the studied Nordic population, but with the knowledge that diagnostic intensity was increasing and a swing from conservative to active management was happening without empirical evidence of benefit. By today's standards, none of the participating centers were high-volume prostatectomy surgical units.

Methods

The study design and methods of estimation of main effects on overall, cause-specific, and distant metastasis-free survival have been described in a series of publications.[2–5] From 1989 to 1999, 695 men with early prostate cancer were randomized to watchful waiting or to radical prostatectomy. Men were eligible for inclusion if they were younger than age 75, were deemed to have a life expectancy of more than 10 years, and had a localized well- or moderately well-differentiated tumor of stage T1b–T2 and a PSA level of less than 50 ng/ml. Follow-up is complete through December 2009. A team of study pathologists reviewed biopsy and radical prostatectomy specimens. Throughout the study, an independent review committee blinded to study arm allocation classified causes of death. The reports include relative risk and absolute risk difference estimates with 95% confidence intervals.

The methods for assessing symptom burden and self-assessed quality of life have been described in detail earlier.[6–8] Physical symptoms, symptom-induced stress, and self-assessed quality of life were evaluated by study-specific questionnaires. In a first follow-up, all living Swedish men enrolled in the SPCG-4 trial 1989 through February 1996 were approached.[6] In a second long-term follow-up, all 400 living men randomized to the SPCG-4 trial in Sweden and Finland from 1989 to 1999 were included.[8] For this second follow-up, a population sample of 300 men without prostate cancer were in an age- and region-matched control group. Longitudinal data were provided for men in the SPCG-4 trial participating in both assessments.

Results

The long-term follow-up of survival and recurrence is based on 367 deaths, of which 136 were attributed to prostate cancer.[5] Stable 15-year estimates show a difference between the study

arms of 6.1 percentage points in prostate cancer mortality (95% confidence interval [CI], 0.2–12.0), corresponding to a relative risk with surgery of 0.62 (95% CI, 0.44–0.87). These results have remained stable over the follow-up and have been shown in exploratory subgroup analyses to be confined primarily to men younger than age 65, but also observed among men with a low-risk prostate cancer. Tumor size, PSA levels, and Gleason grade at time of diagnosis all have prognostic impact but do not modify the effect of radical prostatectomy.[9] During a median follow-up of 12 years, the overall cost in the radical prostatectomy group was 34% higher (p <0.01) than in the watchful waiting group, corresponding to €6,123 in Sweden. The difference was driven almost exclusively by the cost of the surgical procedure.[10]

In men who underwent radical prostatectomy and had extracapsular tumor growth in the operative specimen, the risk of death from prostate cancer was about seven times that of men without extracapsular tumor growth. In a study of PSA as a marker of progressive disease in men in the watchful waiting group, both PSA value at baseline and the rate of PSA change were associated with the development of lethal prostate cancer.[11] However, the accuracy of classifying the disease as either indolent or aggressive was low, regardless of the cut-off point chosen for initial PSA level or rate of change in PSA level.

In the first follow-up of symptoms and quality of life, erectile dysfunction was more common after radical prostatectomy, although urinary obstruction was less common than among men on watchful waiting. The prevalence of depression, well-being, and subjective quality of life were similar in the two groups.[6] In the long-term follow-up, the prevalence of erectile dysfunction was 84% and 80% in the radical prostatectomy and the watchful waiting group, respectively. The corresponding figures for urinary leakage were 41% and 11%, respectively. Distress from these symptoms was significantly more severe among men allocated to radical prostatectomy than among those allocated to watchful waiting. Men who provided information at two points of follow-up reported an increase in bothersome symptoms and a reduction in quality of life. However, the level of self-assessed quality of life was similar between the groups. The prevalence of symptoms and the level of anxiety were considerably higher in the SPCG-4 groups than among population controls, for example, with a relative risk of 1.42 for presence of anxiety in the SPCG-4 groups compared with controls.[8]

Discussion

The SPCG-4 trial is the first study to provide randomized evidence that radical treatment of early prostate cancer confers a survival benefit. Several factors limit the direct generalizability of these results to the present situation. The SPCG-4 trial was undertaken among men with clinically detected prostate cancer. Today, PSA screening introduces long lead times and possibly diagnosis of cancers from a qualitatively different biological domain. The surgery in SPCG-4 was done in the pioneering period of the present surgical technical development and, by today's standards, by low-volume surgeons. The comparison group was managed by watchful waiting, not active surveillance.

Nevertheless, the study provides clinically highly relevant information from many points of view. In many regions of the world, PSA testing is still not prevalent for policy reasons or will not be feasible for a very long time. Among men with a clinically detected prostate cancer, no routinely assessed clinical parameters (besides, tentatively, age) modify the effect of radical prostatectomy. In a watchful waiting group, PSA does not seem to be a safe indicator of whom to treat early. As for the effect modification by age, we caution that this is a finding in an exploratory subgroup analysis; a more detailed investigation shows that there is no sharp cut-off of the effect by age 65 but rather indicates a slowly diminishing survival benefit in the age span

65–75.[12] The poor prognosis among men with extracapsular growth indicates that they may be suitable candidates for postoperative adjuvant treatment.

The quality-of-life studies show that the effects of leaving the tumor *in situ* with ensuing higher risk of being treated with androgen deprivation impacts quality of life similarly to the sequelae of radical prostatectomy.[7] Thus, it is important for decisionmaking and patient information that choice of therapy is guided by complete information and understanding of patient preferences because the interventions involve complex scenarios that are not directly comparable.

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The Prostate Cancer Intervention Versus Observation Trial (PIVOT): U.S. Department of Veterans Affairs/National Cancer Institute/Agency for Healthcare Research and Quality Cooperative Studies Program #407: A Randomized Trial Comparing Radical Prostatectomy to Observation for Men With Clinically Localized Prostate Cancer

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Background

The comparative effectiveness of surgery versus observation for men with localized prostate cancer detected since the initiation of prostate-specific antigen (PSA) testing is not known.

Methods

Between November 1994 and December 2002, we randomly assigned 731 men (mean age 67, median PSA=7.8 ng/ml) with clinically localized (T1–T2NxMO) prostate cancer to radical prostatectomy or observation. We achieved complete follow-up through January 2010. The primary end point was all-cause mortality, and the secondary end point was prostate cancer mortality.

Results

During the median follow-up of 10.0 years (interquartile range 7.3 years to 12.6 years), 171 (47.0%) of 364 men in the radical prostatectomy group and 183 (49.9%) of 367 men in the observation group died (hazard ratio [HR] = 0.88; 95% confidence interval [CI] = 0.71–1.08; p = 0.22; absolute risk reduction (ARR) = 2.9%; 95% CI = –4.3–10.1). Overall, 52 men (7.1%) had a death attributed to prostate cancer or prostate cancer treatment. Among men in the radical prostatectomy group, 21 (5.8%) died of prostate cancer or prostate cancer treatment versus 31 (8.4%) men in the observation group (HR = 0.63; 95% CI = 0.36–1.09; p = 0.09; ARR = 2.7%; 95% CI = –1.1–6.5). In predefined subgroups, all-cause mortality did not differ by treatment assignment according to age, race, comorbidity, health status, or tumor histology categories. A reduction in all-cause mortality was limited to men with baseline PSA >10 (p = 0.043 for interaction) and borderline reduction in those with intermediate-risk prostate cancer (p = 0.073 for interaction). Prostate cancer mortality was rare in men with baseline PSA values $\leq$10 ng/ml and those with low-risk prostate cancer, and did not differ by treatment assignment (p $\geq$0.1 for all groups). Radical prostatectomy reduced prostate cancer mortality among men with PSA values >10 ng/ml (5.6% vs. 12.8%; p = 0.02) and those with high-risk prostate cancer (9.1% vs. 17.4%; p = 0.04).

Conclusions

In men with localized prostate cancer detected during the early PSA era, radical prostatectomy compared with observation produced reductions in all-cause and prostate cancer mortality that were not significant and less than 3% in absolute terms through 12 years. While a larger reduction may occur in men with higher PSA or higher risk disease, surgery did not reduce

mortality compared with observation in men with PSA values 10 ng/ml or less or men with low-risk prostate cancer.

Impact of Different Management Strategies on Quality of Life in Localized Prostate Cancer

Mark S. Litwin, M.D., M.P.H.

The clinical indolence of prostate cancer begets uncertainty regarding the role of initial therapy. Men diagnosed with low-risk prostate cancer are typically offered three treatment options: radical prostatectomy, radiation therapy, or active surveillance (formerly called "watchful waiting"). Because affected men are much more likely to die *with* than *of* their disease, the decision between active treatment and active surveillance may hinge on factors other than expected cause-specific survival. As Harry Herr noted in 1987, "The goal of any treatment strategy for cancer is to improve not only patient survival but also quality of that survival."[1]

Research on health-related quality of life (HRQOL) in men with early-stage prostate cancer has focused primarily on the impact of active treatment with sparse attention to active surveillance. Although little is known about the psychosocial impact of active surveillance, one study found that patient uncertainty over treatment outcomes, support from physicians, and concerns about side effects often influence men to choose watchful waiting.[2] Yet many men perceive watchful waiting as "doing nothing," which they consider inherently unacceptable.[3–10] In some studies, men on watchful waiting report higher levels of stress and worse HRQOL than those receiving active treatment.[11] The few studies focused specifically on active surveillance indicate that the main predictor of abandoning active surveillance for active treatment is patient anxiety, a central domain of HRQOL.[12–14] One recent study found that men on active surveillance use two strategies to overcome active surveillance-related angst. First was considering the cancer *benign* and living a normal life, and second was *doing something extra,* which included diet modifications and complementary and alternative medicine.[15] Overall, the emergent literature suggests that barriers to choosing active surveillance are anxiety, uncertainty, and lack of education.[12–14,16–18]

Prospective Randomized Controlled Trials

The only large, prospective randomized controlled trial published to date in which HRQOL has been compared between men receiving active treatment versus active surveillance is the Scandinavian Prostate Cancer Group Study 4 (SPCG-4),[19] which has shown a durable and significant survival benefit of prostatectomy over watchful waiting.[20] Comparing the surgery and watchful waiting groups in the first 5 years after randomization, HRQOL differences were mainly limited to more erectile dysfunction (80% vs. 45%) and urinary leakage (49% vs. 21%) but less urinary obstruction (28% vs. 44%) in men undergoing prostatectomy. Bowel function, anxiety, depression, well-being, and overall HRQOL were similar in the two groups. However, subsequent analyses at 6–8 years have shown that watchful waiting is associated with worse late deterioration in other domains of HRQOL, such as anxiety and depression.[21]

Prospective National Observational Trials

Two multicenter cohort studies have been particularly fruitful in prostate cancer. Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) is a national, longitudinal disease registry of more than 10,000 men with prostate cancer in community and academic settings across the United States, led by Dr. Peter Carroll at the University of California, San Francisco,

which has provided valuable insights into evolving practice patterns, technology diffusion, outcomes, and severity of disease from data collected.[22–24]

As reported in the recent CaPSURE review by Porten et al., CaPSURE enrollees who underwent radical prostatectomy had lower scores on both disease-specific and general HRQOL instruments immediately postoperatively, which improved significantly at 1 year after treatment and continued to improve in the domain of sexual function in the second year.[25] Men who were treated with external beam radiation therapy, active surveillance, or primary androgen deprivation therapy had scores that were relatively stable, except for sexual function, which declined with time. Overall, patients who underwent surgery had the greatest decline initially and also the greatest degree of recovery. Most men experienced the greatest recovery of both urinary and sexual functions within 2 years of treatment, with little change in reported HRQOL scores after 3 years.[26] Those who received multimodal therapy appeared to have greater declines in urinary and sexual functions than those who were treated with monotherapy.[27]
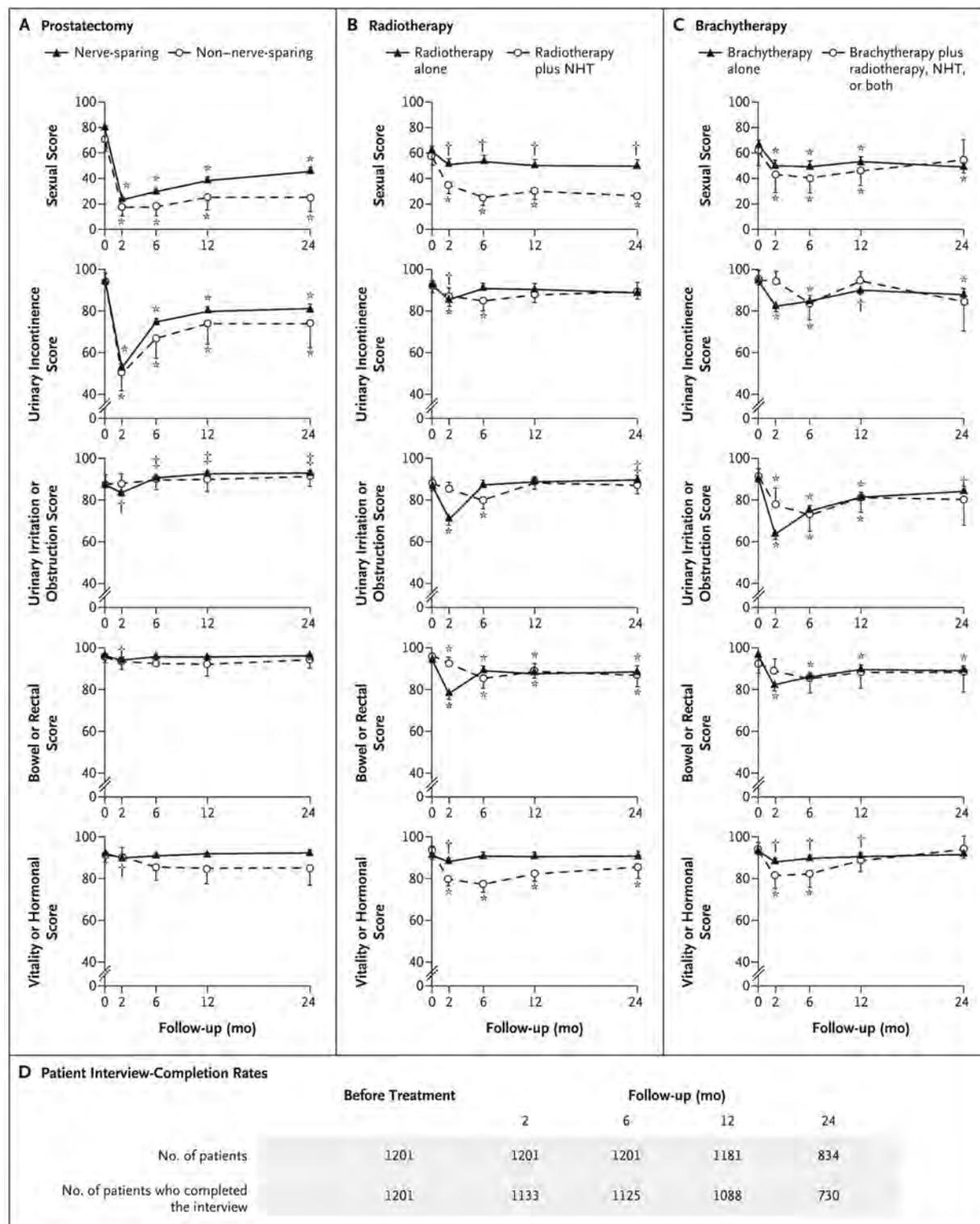
Prostate Cancer Outcomes and Satisfaction With Treatment Quality Assessment is a consortium of nine academic centers, led by Dr. Martin Sanda at Harvard Medical School, which has tracked more than 1,800 patients and spouses for several years with a specific focus on quality-of-life outcomes after surgery, external beam radiation, or interstitial brachytherapy.[28] As Figure 1 illustrates in part, Sanda found that "patients in the brachytherapy group reported having long-lasting urinary irritation, bowel and sexual symptoms, and transient problems with vitality or hormonal function. Adverse effects of prostatectomy on sexual function were mitigated by nerve-sparing procedures. After prostatectomy, urinary incontinence was observed, but urinary irritation and obstruction improved, particularly in patients with large prostates. No treatment-related deaths occurred, and serious adverse events were rare. Treatment-related symptoms were exacerbated by obesity, a large prostate size, a high prostate-specific antigen score, and older age. Black patients reported lower satisfaction with the degree of overall treatment outcomes. Changes in quality of life were significantly associated with the degree of outcome satisfaction among patients and their spouses or partners."

Retrospective National Observational Trials

Building on Fowler's early cross-sectional work in Medicare patients,[29] Carroll's national CaPSURE registry,[23,24] Talcott's early prospective single-institution series,[30,31] and the availability of validated instruments,[32–34] Potosky and colleagues at the National Cancer Institute undertook the Prostate Cancer Outcomes Study (PCOS). Drawing subjects from Surveillance, Epidemiology and End Results (SEER) registries across the United States, PCOS was the first nationally representative, population-based, longitudinal cohort study examining outcomes and HRQOL from the patient perspective in men who had undergone active treatment for prostate cancer.

Initial PCOS results indicated that 2 years after radical prostatectomy, more than 90% of men were continent, and about half were (by some definition) potent.[35] This represented a dramatic improvement over the era before Walsh and Donker reported their now-classic description of the cavernous erectile nerves.[36]

Figure 1. Changes in Quality of Life After Primary Treatment for Prostate Cancer

NHT = neoadjuvant hormonal therapy.
From Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med.* 2008;358(12):1250–1261. Reprinted with permission. Copyright ©2008 Massachusetts Medical Society. All rights reserved.

Subsequent PCOS results revealed that 5 years after treatment, men who had undergone surgery reported stable urinary function, but those who had undergone radiation experienced progressive urinary impairment. Just as striking was the finding that 3–5 years after treatment, those who had been irradiated saw a much sharper decline in sexual function than did those who had been operated on,[37] thus providing empirical evidence for the widely held observation that time homogenizes sexual outcomes after surgery or radiation. This may be due to the effects of aging, cumulative radiation injury, postoperative nerve recovery, or all three.

Penson's 2005 update to the 5-year PCOS data featured several important observations for men undergoing radical prostatectomy.[38] First, significant urinary leakage, uncommon although not trivial, remains fairly constant between 11% at 2 years and 14% at 5 years postoperatively. Associated urinary distress is commensurate with leakage, occurring in only 13% of surgical cases. Second, Penson reiterated our understanding of how vastly different sexual outcomes are between urologists in general and those in referral centers with high-volume subspecialty practices.[39] Third, sildenafil appears to aid in the postoperative return of erections for men who are potent at baseline and who undergo bilateral nerve sparing. Fourth, for the majority of men, functional outcomes remain fairly stable between 2 and 5 years after surgery. Finally, even though only 28% of respondents overall report erections firm enough for intercourse, almost twice as many (54%) state that they are sexually active at least once a month. This clarifies that the nature of sexual function in prostate cancer survivors includes activities beyond coitus alone, an observation that has clinical relevance for men whose sexual partner is unable or unwilling to have intercourse.

Single-Institution Series

In a prospective longitudinal study of recovery profiles in 475 men before and through 4 years after prostatectomy, external beam radiation, or interstitial brachytherapy, Gore and colleagues compared changes in mean HRQOL scores and the probability of regaining baseline HRQOL across treatment groups (Figure 2).[40] Urinary incontinence was more common after prostatectomy, while voiding and storage urinary symptoms were more prevalent after brachytherapy. Sexual dysfunction profoundly affected all treatment groups, with a relatively low likelihood of regaining baseline function among prostatectomy subjects. Bowel dysfunction was more common after radiation. Capturing baseline function prior to treatment permitted comparison of interval mean scores with pretreatment function.

Wei and colleagues reported results from a cross-sectional survey of 902 men who underwent radical prostatectomy, external beam radiation, or brachytherapy at an academic medical center and from 112 age-matched controls.[41] The authors summarized their HRQOL results: "Compared with controls, each therapy group reported bothersome sexual dysfunction; radical prostatectomy was associated with adverse urinary HRQOL; external beam radiation was associated with adverse bowel HRQOL; and brachytherapy was associated with adverse urinary, bowel, and sexual HRQOL. Hormonal adjuvant symptoms were associated with significant impairment. More than 1 year after therapy, several HRQOL outcomes were less favorable among subjects after brachytherapy than after external radiation or radical prostatectomy. Progression-free subjects reported better sexual and hormonal HRQOL than subjects with increasing prostate-specific antigen." Figure 3 highlights these results.

Figure 2. Longitudinal Mean Scores for Health-Related Quality of Life Across Treatment Groups
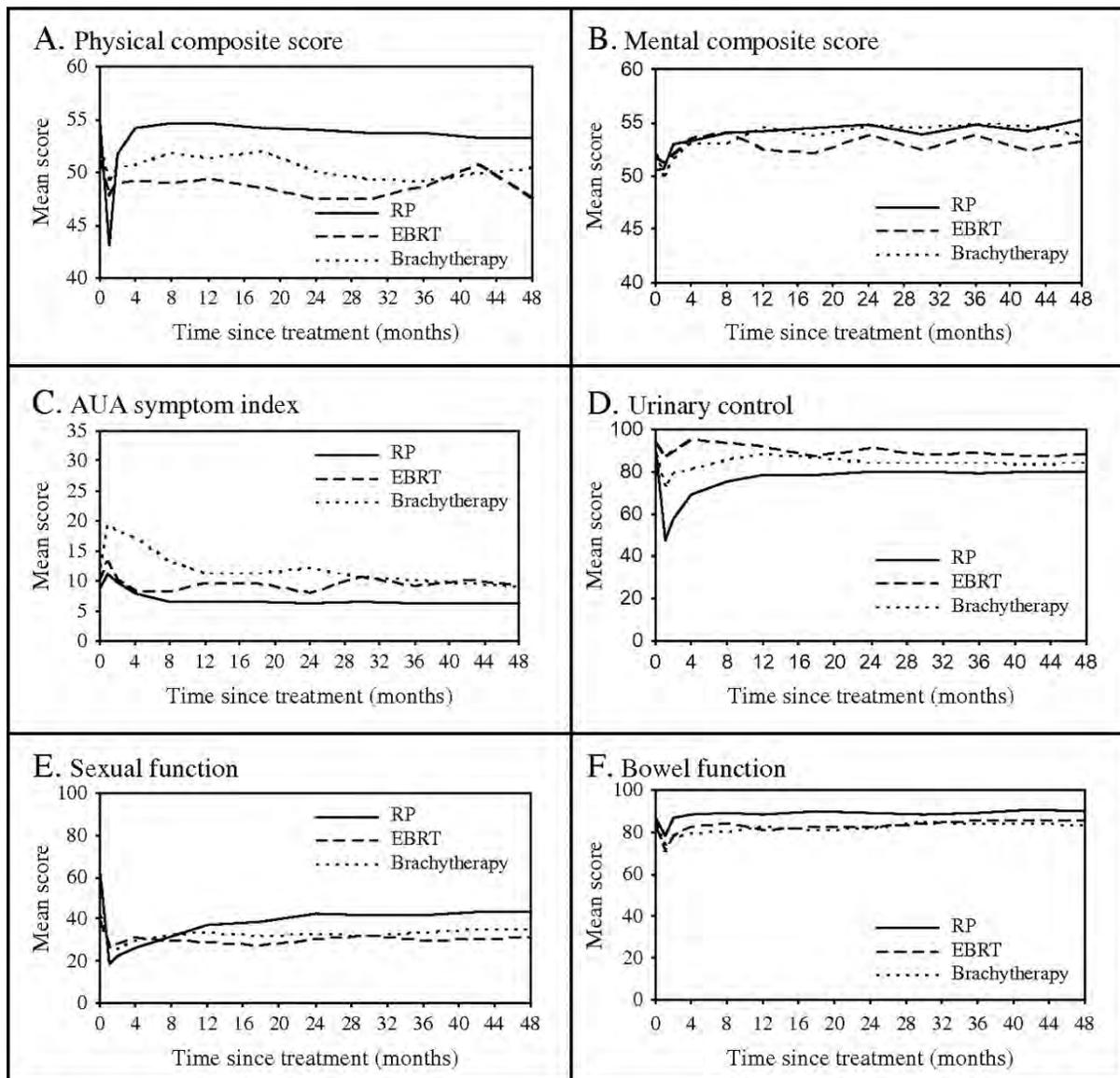

Time (Months):	0	1	2	4	8	12	18	24	30	36	42	48
Sample size (No.)	475	400	420	412	402	392	385	357	341	329	303	290

RP = radical prostatectomy; EBRT = external beam radiation therapy; AUA = American Urological Association.
From Gore JL, Kwan L, Lee SP, et al. Survivorship beyond convalescence: 48-month quality-of-life outcomes after treatment for localized prostate cancer. *J Natl Cancer Inst.* 2009;101(12):888–892. Reprinted with permission. Copyright ©2009 Oxford University Press. All rights reserved.

Figure 3. Severity of Overall Urinary, Bowel, and Sexual Bother After Localized Prostate Cancer Therapy and in Age-Matched Controls
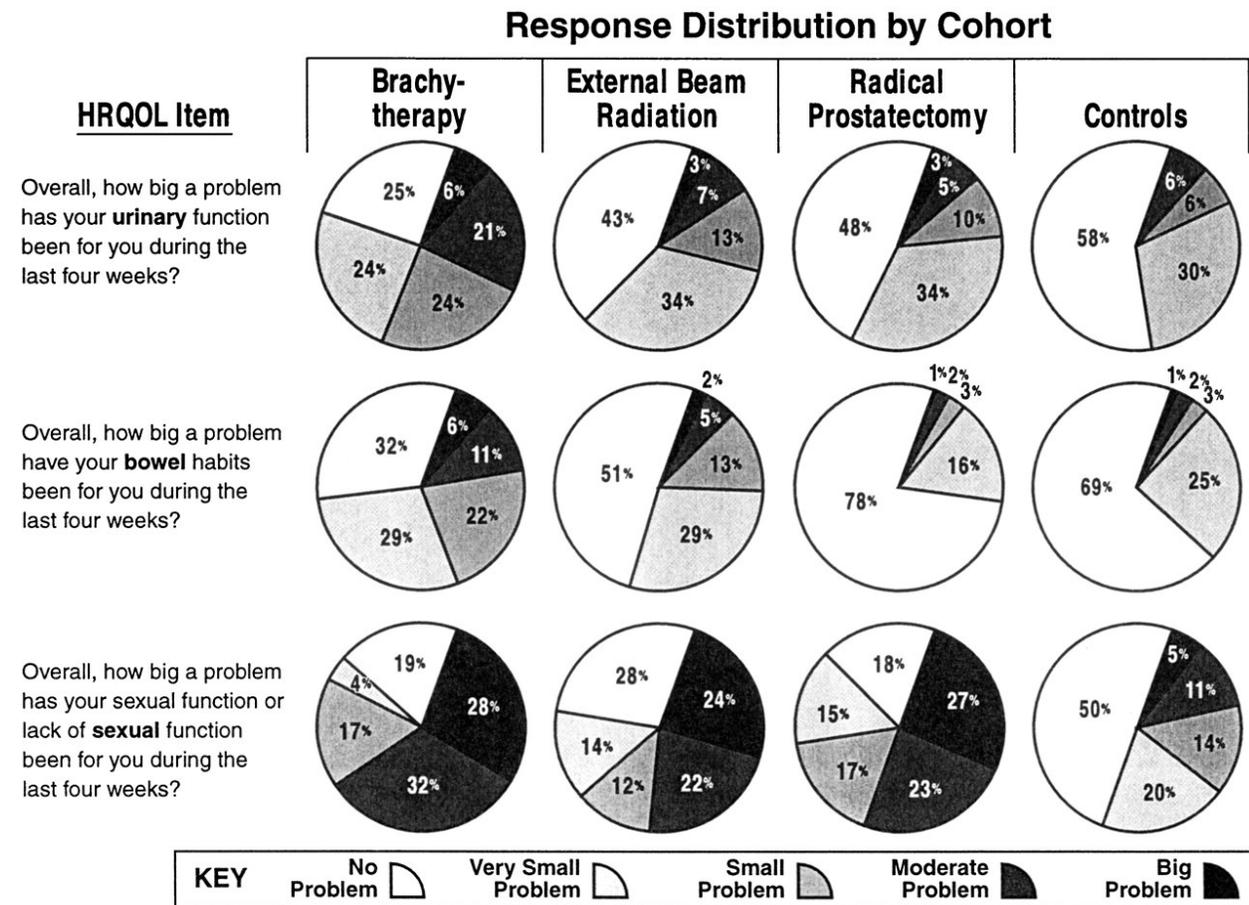
From Wei JT, Dunn RL, Sandler HM, et al. Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer. *J Clin Oncol.* 2002;20(2):557–566. Reprinted with permission. Copyright ©2002 American Society of Clinical Oncology. All rights reserved.

Special Populations

Results from low-income, underserved populations with prostate cancer have been reported primarily in men enrolled in a large, state-funded program, Improving Access, Counseling, and Treatment for Californians With Prostate Cancer (IMPACT). IMPACT enrollees' HRQOL scores are significantly worse at baseline in all domains of the 12-Item Short Form Survey from the RAND Medical Outcomes Study than men in the general population. Subsequently, sexual bother worsens significantly but bowel domains improve.[42,43] Nurse case management appears to improve patients' HRQOL.[44] Enrollees with low self-efficacy fare worse over a range of psychosocial outcomes and both general and disease-specific HRQOL.[45]

Conclusions

Physicians interacting with prostate cancer patients should advise them that treatment is unlikely to affect general HRQOL, but it may be associated with clinically significant changes in

sexual, urinary, or bowel function. Treatment decisions should continue to be individualized. Any survival gains from surgery or radiation must be balanced with expected decrements in some areas of function and bother. With richer information on HRQOL, in addition to duration of survival, patients will be able to make better informed decisions and feel more comfortable proceeding with therapy or observation for localized prostate cancer.

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Economic Analysis of Different Management Strategies for Localized Prostate Cancer

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Community management of low-risk localized prostate cancer is characterized by a proliferation of treatment options. This may partly reflect the paucity of high-quality evidence to guide treatment selection for most patients.[1] Conservative management with active surveillance is considered a reasonable and recommended initial management for many patients with localized prostate cancer.[2,3] Despite this, conservative management is less frequently used than active treatments in current clinical practice. The frequency of initial treatments provided within 9 months of diagnosis for patients with localized prostate cancer is shown in Figure 1. This illustrates that the use of conservative management as initial treatment has not increased during the recent period (2003–2007), at approximately 20% of patients. Notably, the largest increase in use was for intensity-modulated radiation therapy, from 8% to 14% as single therapy, and 7% to 16% when used in combination with brachytherapy.

Figure 1. Use of Primary Treatment Options for Localized Prostate Cancer by Year of Diagnosis (2003–2007) in SEER-Medicare Data
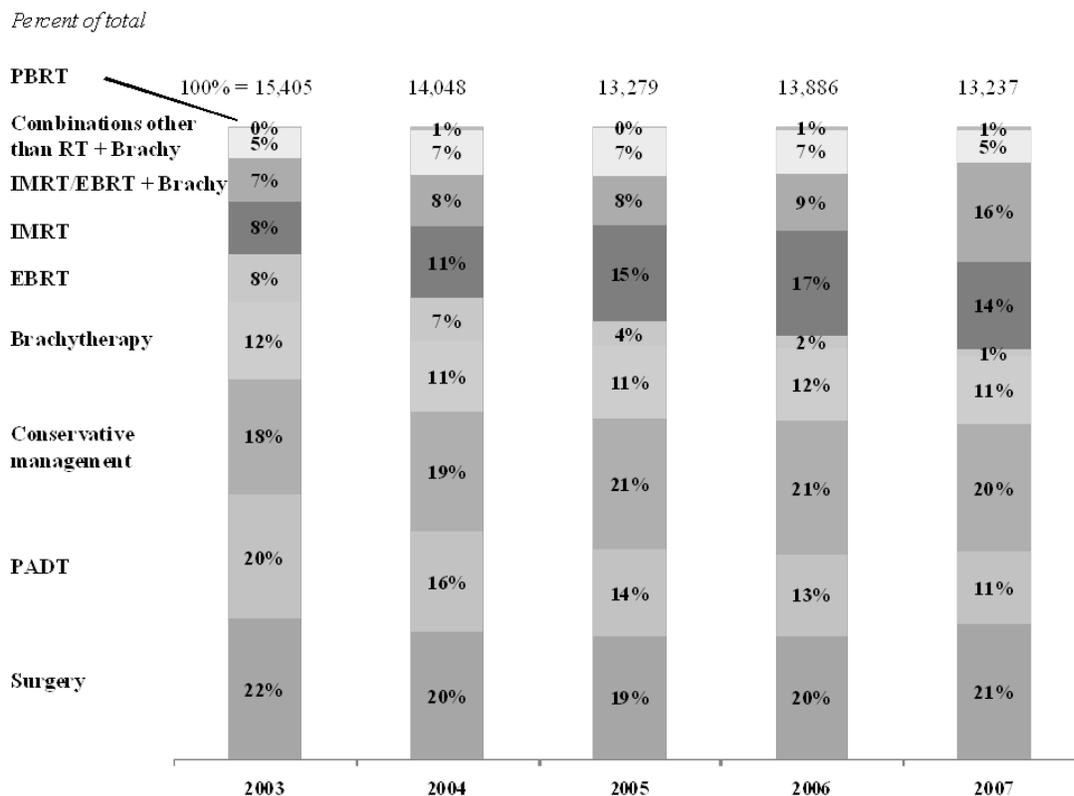
PBRT = proton beam radiation therapy; RT = radiation therapy; Brachy = brachytherapy; IMRT = intensity-modulated radiation therapy; EBRT = external beam radiation therapy; PADT = primary androgen deprivation therapy.

Initial treatment costs for prostate cancer were estimated to be $4.5 billion for 213,000 patients newly diagnosed in 2010, and forecast to increase to $6.02 billion for 283,000 patients by 2020.[4] This would result in a total of $57.5 billion spent on initial treatment for prostate cancer over this decade. The majority of these expenditures will be for localized disease (80% to 90% of diagnosed patients), and most patients will have low- to intermediate-risk profiles (70% to 75%).[5]

The choice of initial management differs substantially in both treatment-related and long-term costs. Snyder et al. found wide variation in initial treatment costs for patients diagnosed in 2000 with localized prostate cancer based on Surveillance, Epidemiology and End Results (SEER) Medicare data, with initial (1-year) costs ranging from $4,270 (in 2000 U.S. dollars) for watchful waiting to $17,474 for radiation plus hormonal therapy; 5-year total costs were $9,130 for watchful waiting and $26,896 for hormonal therapy alone.[6] The difference in costs for active treatments over watchful waiting dissipated by year 3 after diagnosis, except for patients receiving initial hormonal therapy whose costs remained elevated throughout the 5-year analytic period.

We performed a similar cost analysis for patients diagnosed with nonmetastatic prostate cancer between 1998 and 2006 based on analysis of a commercial database containing claims for 42 large employers (Ingenix in Eden Prairie, Minnesota).[7] Initial treatment was assigned based on claims for treatment procedures present in the data within 6 months of diagnosis. Patients were required to have a new code for prostate cancer following a code for prostate biopsy, with a prior 1-year period devoid of prostate-cancer-related claims. Annual median costs by initial treatment groups incremental to conservative management were adjusted for comorbid conditions, age, year, region of diagnosis, preceding 12-month health expenditures, median household income, marital status, percent black population in patient's three-digit ZIP Code, and a National Cancer Institute comorbidity index for prostate cancer.[8] Median incremental annual costs of active treatments are reported in Table 1.

All active treatment groups cost more than conservative management, even over 5 years of analysis. The combined treatment group (the most frequent being radiation therapy plus brachytherapy) and intensity-modulated radiation therapy initial treatment incurred the highest initial cost; costs for primary androgen deprivation therapy remained consistently higher in all years following diagnosis than conservative management.

To compare long-term costs of initial treatment strategies, how long should the analytic period extend? A recent long-term prospective cohort study in the United States reported that the mean time to treatment for patients (mean age 72.7) initially managed with active surveillance was 3.9 years; at a mean follow-up of nearly 8 years, 49% had progressed to treatment.[9] According to this study, most patients who will eventually be treated will do so within 5 years of diagnosis. Furthermore, both cost analyses described above find no difference in annual costs for initial active treatment compared with conservative management after the first several years from diagnosis (with the exception of primary androgen deprivation therapy), providing reassurance that a 5-year period of analysis is adequate for the goals of most cost estimation.

Table 1. Marginal Cost of Initial Treatments Over Conservative Management by Year From Diagnosis With Localized Prostate Cancer (2006 U.S. Dollars; 95% Confidence Intervals)

Initial Treatment Group	Year 1	Year 2	Year 3	Year 4	Year 5
RP	14,362 (13,295, 15,430)*	−385 (−800, 30)	−554 (−997, −112)	15 (−750, 780)	−89 (−1,237, 1,059)
Brachytherapy	27,065 (25,522, 28,608)*	−771 (−1,370, −172)	−428 (−1,075, 217)	−445 (−1,624, 733)	1,008 (−890, 2,907)
EBRT	17,869 (14,617, 21,210)*	63 (−1,197, 1,325)	−288 (−1,544, 968)	−272 (2,273, 1,728)	2,137 (−808, 5,084)
IMRT	45,925 (43,154, 48,695)*	−654 (−1,731, 422)	362 (−1,006, 1,731)	−810 (−3,901, 2,280)	9,435 (1,662, 17,208)
Combined treatments[†]	60,046 (57,167, 62,925)*	799 (−337, 1,895)	1,301 (54, 2,548)*	1,752 (−566, 4,071)	950 (−3,348, 5,250)
PADT	35,450 (34,092, 36,869)*	7,192 (6,652, 7,732)*	3,398 (2,854, 3,942*	3,183 (2,282, 4,083)*	3,173 (1,841, 4,505)*
Number	5,512	5,512	3,611	2,519	1,708

RP = radical prostatectomy; EBRT = external beam radiation therapy; IMRT = intensity-modulated radiation therapy; PADT = primary androgen deprivation therapy.
*Statistically significant at the 5% level.
[†]45% of patients in combined treatment group received radiation therapy plus brachytherapy.

I modeled health expenditure savings based on the previous incremental cost estimates for treatment of a hypothetical cohort of patients diagnosed in 2010 with localized disease, assuming that active surveillance replaced current rates of treatment. Assuming equal cost across risk groups for localized disease, estimated savings from shifting patients with low risk, intermediate risk, and all risks of disease are reported in Table 2. Since local geographic treatment norms have been found to be the primary determinant of treatment choice, rather than disease or risk characteristics, the assumption of equal costs across risk groups may in fact be valid.[10] This analysis concludes that 18% to 49% of 5-year treatment costs for localized disease could be saved should active surveillance become the initial management strategy of choice. Although this estimate may seem high, studies do report surprisingly high rates of initial active treatment (75%) for even very low-risk populations (prostate-specific antigen <4.0 ng/ml), where many are probably suitable for active surveillance.[11] These estimates suffer from limitations of observational analysis, particularly the influence of immeasurable factors on treatment selection.

Table 2. Estimated U.S. Health Expenditures Savings* (5-Year Net Present Value) From Shifting Active Treatment to Active Surveillance for a Single Annual Cohort Diagnosed With Localized Prostate Cancer (2010 U.S. Dollars for Low-Risk, Intermediate-Risk, and All Risk Groups, Respectively)

Active Treatment Group	Scenarios								
	Base Case			**Increase in Localized Disease**			**Increase in Rates of Active Treatment**		
IMRT	260	490	690	275	515	730	350	665	940
Brachytherapy	135	250	355	140	265	375	150	280	395
Combined treatments	235	445	625	250	470	660	190	280	505
PADT	210	395	560	220	420	590	285	535	755
Total	840	1,580	2,225	885	1,670	2,355	975	1,840	2,595

IMRT = intensity-modulated radiation therapy; PADT = primary deprivation therapy.
*Assumes 219,000 new cases of prostate cancer with 75% below age 75. Base case scenario assumes 80% of diagnosed cases are localized disease and 68% are locally treated (excluding PADT), with IMRT accounting for 20% of active treatments. Increase in localized disease scenario assumes 90% of cases are localized disease. Increase in rates of active treatment assumes 75% are locally treated and IMRT accounts for 33% of those treatments.

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Evidence-based Practice Center Presentation III: Comparative Effectiveness of Active Surveillance Versus Radical Prostatectomy or Radiation Therapy in Men With Localized Prostate Cancer

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Introduction

The comparative effectiveness of active surveillance versus either immediate radical prostatectomy or radiation therapy for reducing morbidity and mortality among men with localized prostate cancer is not known. For this review, active surveillance was characterized as an observational management strategy with patients receiving deferred curative treatment based on cancer progression.

Objectives

The objectives were to review primary studies and selected relevant existing systematic reviews, evidence reports, and technology assessments that compared the effectiveness of active surveillance versus radical prostatectomy or radiation therapy in terms of clinical outcomes and costs (Key Question 4).

Review Methods

We searched MEDLINE® and the Cochrane Database of Systematic Reviews for relevant English-language publications, from inception through August 2011. We also relied on two previously completed Agency for Healthcare Research and Quality (AHRQ) evidence reports on treatments for localized prostate cancer[1,2] and two economic evaluations of these treatments prepared by the Institute for Clinical and Economic Evaluation.[3,4] We supplemented the evidence summarized in these documents with comparative studies performed in a multicenter setting and with studies analyzing databases sourced from the U.S. population. The population of interest was men with clinically localized prostate cancer (T1 or T2), without known lymph nodes (N0-X) or metastases (M0-X). No more than 20% of the study sample could have more advanced-stage disease. For observational studies exclusively including patients with T1 or T2 disease, we required statistical adjustment for age. For studies also including patients with non-T1 or non-T2 disease (up to 20% of the total population), we also required adjustment for disease severity (e.g., stage or Gleason score). Studies had to compare observational management strategies (without androgen deprivation therapy) to active treatment, including radical prostatectomy, external beam radiation therapy, or brachytherapy, all with or without androgen deprivation therapy. Androgen deprivation therapy monotherapy was not considered an active treatment. Outcomes of interest included prostate cancer mortality, all-cause mortality, morbidity of primary treatment, metastatic disease, quality of life, satisfaction with treatment, and costs. We assessed the studies' methodological quality and rated the strength of evidence regarding active surveillance versus active treatment using established AHRQ Evidence-based Practice Center methods.

Results

No study reported clinical outcomes specifically for active surveillance management strategies versus immediate definitive treatment. Therefore, the strength of evidence is insufficient regarding the comparative effectiveness of active surveillance versus immediate definitive treatment for men with localized prostate cancer.

Due to the lack of studies comparing active surveillance with immediate treatment, we evaluated studies that compared other observational management strategies (largely resembling watchful waiting) with immediate treatment.

Observational Management Strategies Versus Radical Prostatectomy

Two randomized controlled trials (RCTs) that were included in previous systematic reviews compared observational management strategies with radical prostatectomy: the Scandinavian Prostate Cancer Group Study 4 (SPCG-4)[5] and the Veterans Administration Cooperative Urological Research Group (VACURG)[6] trials. These trials enrolled mostly patients with prostate cancer diagnosed in the pre-prostate-specific antigen screening era. We did not identify any new RCTs, but we found two publications reporting recent data on clinical outcomes[7] and treatment costs[8] from the SPCG-4 trial. We also identified nine additional observational studies.[9–17]

Generally, the results from observational studies indicated that men treated with radical prostatectomy had lower all-cause and prostate-cancer-specific mortality rates than men on watchful waiting. These findings are consistent with the latest update from the SPCG-4 trial, which followed 695 men with localized prostate cancer for a median of 12.8 years.[9–12] However, the VACURG trial followed 142 patients for a median of 23 years and found no difference in mortality between the watchful waiting and radical prostatectomy groups.[6] The development of metastatic disease was assessed only by the SPCG-4 trial, which found a significant benefit for radical prostatectomy compared with watchful waiting.[7] Morbidity of primary treatment was reported by two observational studies that suggested an increased risk for urethral stricture (and procedures to treat it) among patients treated with radical prostatectomy versus those managed with watchful waiting.[13,14] The findings for quality of life reported in two observational studies varied across different domains of the quality-of-life measure.[15,17] One study reported that the percentage of patients satisfied with treatment were similar for the watchful waiting and radical prostatectomy groups.[16]

Observational Management Strategies Versus Radiation Therapy

No RCTs comparing observational management strategies with radiation therapy were identified. For this comparison, we relied on an AHRQ report (which included nine observational studies),[2] and seven additional observational studies identified through our update search.[11,12,14–18] It should be noted that studies in the evidence report may have included some men treated with androgen deprivation therapy in the observational management arms, which would have been excluded based on this review's eligibility criteria. Two of the seven observational studies in our update reported that men treated with radiation therapy had lower all-cause mortality rates than men on watchful waiting.[11,12] One study reported prostate-cancer-specific mortality information and did not find a statistically significant difference between radiation therapy and observational management.[12] No study reported on treatment comparisons for the development of metastatic disease. One study did not find a significant difference in treatment-related morbidity between observational management and

brachytherapy or external beam radiation therapy.[14] The findings for quality of life reported in three studies varied across different domains of the quality-of-life measure.[15,17,18] One study reported that the proportion of patients satisfied with treatment was lower in the watchful waiting group than in the radiation therapy group.[16]

Observational Management Strategies Versus Combined Treatment Modalities or Active Treatments Considered in Aggregate

One observational study in our update reported that patients who received active treatment (radical prostatectomy, radiation therapy, and/or brachytherapy considered together) had significantly lower risks of all-cause and prostate-cancer-specific mortality compared with those on observation.[11] Morbidity of primary treatment was reported by only one study, which found a higher rate of receiving treatments for urethral stricture in men treated with both external beam radiation therapy and brachytherapy compared with those on watchful waiting.[14] No study reported incidence of metastatic disease or quality-of-life outcomes for this comparison.

Costs

We did not identify any primary study comparing the cost of active surveillance with active treatment strategies; economic modeling using U.S. prices suggests that active surveillance may be associated with higher costs compared with radical prostatectomy or brachytherapy, but lower costs compared with intensity-modulated radiation therapy or proton-beam radiation therapy.[19]

Two studies using observational data from the United States and one based on a subgroup of patients enrolled in the SPCG-4 trial reported on cost comparisons between observational management strategies (watchful waiting) and immediate active treatment for localized prostate cancer. Short- and long-term costs were higher for active treatment strategies (radical prostatectomy or radiation therapy) compared with watchful waiting; however, studies were small and used heterogeneous measurement methods.

Conclusions

No published studies have compared active surveillance (monitoring with the intent of curative intervention upon disease progression) versus immediate active treatment. Thus, the strength of evidence is insufficient regarding the comparative effectiveness of active surveillance versus immediate definitive treatment for men with localized prostate cancer. Randomized and observational studies suggest that active treatment may be more effective than watchful waiting for reducing overall and prostate-cancer-specific mortality. However, we caution that confounding bias is likely in observational studies of treatment effectiveness because patients managed with observational strategies and those who received active treatments differ in many characteristics that are also associated with the outcomes of interest. Ongoing clinical trials are expected to provide information on the comparative effectiveness of active surveillance compared with immediate active treatment, but they will require long-term follow-up.

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