History of Prostate Cancer: Diagnosis and Treatment Timeline, 1904 to 2012

1904  Radical perineal prostatectomy (Hugh Hampton Young)
1913  Direct implantation of radium into prostate
1936  Elevated acid phosphatase in PCa (Ethel and Alexander Gutman)
1941  Beneficial effects of castration and oestrogen in men with advanced PCa (Charles Huggins)
1947  Retropubic radical prostatectomy (Terrence Millin)
1962  Megavoltage radiation for localized PCa (Malcolm Bagshaw)
1966  Gleason scoring developed
1973  National Veterans study reports benefits of hormonal therapy
1975  First RTC using chemotherapy in prostate cancer (W.W. Scott, et al.)
1980  PSA found elevated in serum of men with prostate cancer
1981  LHRH analogues first used
1983  Nerve-sparing prostatectomy preserves erectile function (Patrick Walsh)
1985  Transperineal implantation of radioactive seeds (H. Holms)
1986  FDA approves Leuprolide® to treat PCa
1987  Researchers identify new specific sub-set of prostate tumors (neuroendocrine, also called small-cell tumors that grow and react to treatment differently than to the common form of PCa adenocarcinomas)
1988  Ultrasound guided biopsy device approved
1989  FDA approves antiandrogen flutamide
1990  Watchful waiting (active surveillance) introduced to avoid unnecessary radical treatments 3-D conformal radiation therapy developed
1994  FDA approves PSA for screening to detect early PCa
1995  Meta-analysis trial of androgen blockade concludes no significant benefit from combining these drugs
1996  FDA approves anthracenedione Novantrone® to treat advanced prostate cancers that do not respond to hormone therapy
1997  Combination of radiation and hormone therapy to improve PCa survival become standard
2003  Two large clinical trials report Proscar® and Avodart® reduce the risk of developing prostate cancer by up to 25 percent
2004  FDA approves antimicrotubule agent Taxotere® for hard-to-treat prostate cancers
2008  FDA approves CellSearch®, a test for predicting survival and monitoring the impact of treatment for men with advanced prostate cancer
2009  Radiation after surgery or hormone therapy improves survival
2012  FDA approves anti-androgen Xtandi® for late stage cancer

References

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http://www.fda.gov
Special Feature

Peter Scardino, MD, Chief of Surgery at Memorial Sloan-Kettering Cancer, Talks About the Practicality of Prostate Cancer Screening

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An Interview with UroToday Reporter Karen Roberts

“Long term follow-up of the results of the good randomized trials screening for prostate cancer, especially the European trial and subsets across Europe, are showing a substantial decrease in the risk of dying among men followed for longer periods of time. In particular, the Swedish randomized trial involving 20,000 men shows greater than a 50% reduction in risk of dying after 14 years for men who were screened versus those men who were not screened in this study. There is better and better data showing the effects of screening are very powerful. Foregoing screening for prostate cancer should be taken with great caution.”

“Look at what has been wrong with how we do prostate cancer screening in America. Men get a DRE and PSA starting at age 50 (or at age 45 if in a higher risk group, like African Americans or those with family history) and those tests are repeated each year. Good long-term studies of men in their 40s indicate it’s very important to get the first PSA test at age 40 or 45 because that test provides reasonable accuracy as to whether men will develop prostate cancer in their lifetimes. You don’t need to screen every year if the man has a very low PSA (below 1), instead screen every 5 years until age 60s and if the PSA is still below 1. This man’s risk for developing prostate cancer in this lifetime is very low.

The Memorial Sloan-Kettering Cancer Center Prostate Cancer Disease Management Team developed risk-adjusted prostate screening guidelines posted on the MSKCC.org website, stating, “Men interested in the early detection of prostate cancer should be informed about their risk and be advised to consider screening according to guidelines.”

Memorial Sloan-Kettering’s prostate cancer guidelines are based on the following principles:

- Many men with prostate cancer do not need to be treated and can be followed by active surveillance. A diagnosis of prostate cancer is information used to help make decisions, not an indication for immediate treatment.
- Compliance with screening will increase if men are told whether they are at high, intermediate, or low risk and are informed about their need for subsequent screening.
- There is a balance between the harms and benefits of screening. By focusing screening on men at highest risk of life-threatening prostate cancer, we can better achieve this balance.


The guidelines were developed at Memorial Sloan Kettering Cancer Center by James Eastham, chief, urology service; Andrew Vickers, statistician, Dept. of Epidemiology and Biostatistics; Hans Lilja, Dept, of Laboratory Medicine and Surgery and an investigator on the European Randomized Study of Prostate Cancer screening (ERSPC); and Peter Scardino, chair, Dept. of Surgery.

The MSKCC team states, “There is clear evidence that screening with a PSA test can reduce the number of deaths from prostate cancer. Many men with cancers detected by the PSA test are treated even though their cancer is not aggressive and would not become apparent during the course of their natural lives if it was not detected by screening.” Dr. Scardino adds, “Better markers as well as smarter forms of the PSA test are rapidly becoming available (Prostate Health Index, 2ProPSA, and a panel of 4 markers) and are proving to be much more specific than PSA while remaining as sensitive. These new assays are currently being commercialized, and we should have access to these tests in the next year or so.”

Active surveillance—“If you end up doing the biopsy for whatever reason (based on the PSA or DRE) think carefully before you recommend radical therapy for that treatment. Often you can put the patient on active surveillance and the risk that a cancer will grow and become serious over time is very low. We should always stop and think about active surveillance instead of active treatment. If we do those things, we will continue to save the lives of men while reducing the number of false-positive tests and reducing overtreatment.”

“The benefit is becoming more certain, and we can eliminate harm if we screen much smarter and much less intensively.”

Peter T. Scardino, MD, FACS
Chair, Department of Surgery; David H. Koch Chair
Memorial Sloan-Kettering Cancer Center

As Chairman of the Department of Surgery, Dr. Scardino oversees a department widely recognized for its expertise and innovation in cancer surgery. In addition to his administrative responsibilities, he is a surgeon specializing in prostate cancer. His expertise is in early detection, prognosis, and surgical treatment of prostate cancer. Radical prostatectomy—complete removal of the prostate—can cure many men with prostate cancer. His team has developed surgical techniques to preserve urinary and sexual function after prostatectomy, and they continue to seek ways to improve...
quality of life for patients after treatment.

Not all prostate cancers progress in the same way. Many cancers pose little or no threat to life and health, while others grow aggressively and are resistant to treatment. He and his colleagues have pioneered the use of statistical models to predict both the natural progression of prostate cancer and how it will respond to treatment. These predictive tools (nomograms) help them tailor treatment for individual men according to the specific characteristics of their cancer. Today, nomograms are being used to help physicians and patients make medical decisions regarding a variety of other cancers as well, including pancreatic, lung, and breast cancer.

In 2001, he received an NIH grant to establish an ongoing Specialized Program of Research Excellence (SPORE) in prostate cancer at Memorial Sloan-Kettering Cancer Center. His SPORE has an ambitious research program focused on developing therapies appropriate for patients with different types of prostate cancer at different stages of development. The group hopes to achieve this by using molecular and genetic data to improve their prediction models for prostate cancer, identifying the critical mechanisms by which prostate cancer grows and spreads, and developing drugs and immunological techniques for treatment-resistant metastatic cancers.

His position at Memorial Sloan-Kettering includes appointments as head of the Prostate Cancer Program, member in the Sloan-Kettering Institute’s Molecular Pharmacology and Chemistry Program; and the incumbent of the David H. Koch Chair. He is also a professor in the Department of Urology at Weill Cornell Medical College and at SUNY Downstate Medical Center.

He has written many articles and book chapters and edited the Comprehensive Textbook of Genitourinary Oncology. In 2005, with Judith Kelman, he wrote Dr. Peter Scardino’s Prostate Book, a guide to prostate cancer, prostateitis, and benign prostate hyperplasia (BPH). He serves as editor-in-chief of Nature Clinical Practice Urology, and is an editorial board member and reviewer for several peer-reviewed journals. He is an active member of the National Academies’ Institute of Medicine and of the American Urological Association.

Dr. Catalona joined the Northwestern faculty in 2003. He is known for having been the first to show that the PSA test is a simply and accurate method for detecting prostate cancer, and developed the “free” PSA test as a means of improving the accuracy of prostate cancer screening. He currently conducts research focusing on the genetics of prostate cancer and specializes in prostate cancer surgery, noted for his expertise in performing “nerve-sparing” radical prostatectomy that can preserve sexual potency.

Dr. William Catalona fielded many questions from the media on behalf of the AUA and urologic groups who all maintain a united front that PSA testing should not be eliminated as a screening test for prostate cancer.

“The reaction among urologists is an overwhelming majority feel this was unwise, unfounded, and really misinformed,” said Dr. Catalona. “Many believe the USPSTF has overestimated the harms of screening and underestimated the benefits of screening. The question is, do the harms exceed the benefits or do the benefits exceed the harms?”

In a paper (Abstract 416) presented at AUA meeting by New York University researchers, they evaluated the tweets from the USPSTF announcement for 20 hours after. Of all the tweets analyzed, 90% expressed no opinion. Of the 10% with an opinion, approximately 3 to 1 favor screening.

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What do physicians tell their patients? “The great consensus among urologists is the patients should be allowed to make a decision for themselves. It is highly desirable to discussing the potential risks and benefits of screening and if the patient wishes to proceed, then a PSA test should be given along with a digital rectal examination. I hope the task force recommendation will not affect health care insurance coverage for patients. A lack of coverage would adversely affect the poor, including
many African American men who have a 50% higher risk for
developing prostate cancer and a 200% higher death rate from
prostate cancer.”

Dr. Catalona was encouraged that last year President Obama,
for his annual physical, did request a PSA test and said that the
government would not discontinue insurance coverage for PSA
testing.

Existing studies will mature and there will be more evidence
on this issue, “I recommend physicians follow the research
and stay in close dialog.” There is no alternative to screening
with PSA—it is the only thing out there to allow us to detect
prostate cancer in its early form. Dr. Catalona believes without
it, prostate cancer deaths would increase dramatically. “Then
we would go back to a time when prostate cancer patients
presented with metastatic disease from the beginning. We
don’t want to go back there—no one wants to go back there.”

View the video statement from Dr. Catalona at http://www.
urotoday.com/index.php?option=com_content&Itemid=190&ca
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the Harrison Department of Surgical Research. He has been
certified and recertified by the American Board of Urology. He
was awarded an honorary Ph.D. from the University of Patras,
Greece in September 2005. The U.S. Preventive Services Task
Force’s recent announcement with respect to the evaluation
of routine PSA screening was a very interesting one to me.

From the standpoint of physicians who actually take care of
these patients, and recognizing that oncologists certainly share
in the treatment of patients in the late stages of the disease,
my own personal philosophy can be spelled out quite simply.

Certain facts are irrefutable:

- The mortality from prostate cancer has decreased coincident
  with the use of PSA screening.
- There has been a stage migration in diagnosis meaning
  that it is much less common to see patients presenting with
  metastatic or even extensive local disease.
- It is illogical to assume that late advanced disease is as
  easily cured or successfully managed as early stage disease.
- There is no question that there are some patients who are
  over treated.
- There is no question that some patients are not fully
  informed of the risks of various types of active management;
  further, some patients remain relatively uninformed
  regarding active surveillance.
- PSA screening cannot distinguish high-risk or aggressive
disease from low-risk or non-aggressive disease.

With these facts in mind, my personal philosophy is that in
general, patients with a life expectancy of less than 8-10 years
(and I do not cite a specific age because age is very often
unrelated to life expectancy) do no benefit from screening for
prostate cancer. Patients with a life expectancy of greater than
8-10 years need to be asked, “if you had prostate cancer would
you want to know about it, and would you want to participate
in decisions regarding the type of management?”

This assumes that the discussion would include the alternative
to active surveillance. If the answer to this question is “yes,” then I
think the patient deserves to be screened with PSA testing and
digital rectal exam (DRE). If the answer is “no,” then I think,
with proper documentation, one can omit PSA screening. I do,
however, believe a DRE should still be carried out since it checks
not only for prostate abnormalities but for abnormalities of the
rectum as well.

One point that bears mentioning is that it is generally not the
urologist who initiates PSA screening but rather the primary
care provider—whether a family physician, internist, nurse
practitioner, physician assistant, or medical subspecialist.

Finally, if a patient chooses not to be screened for prostate
cancer, there needs to be a prohibition disallowing him from
seeking legal sanctions under the accusation of “failure to
diagnose”—and the extensive ramifications that always go
along with this sort of lawsuit [1].

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BEYOND THE ABSTRACT - PROSTATE-CANCER MORTALITY AT 11 YEARS OF FOLLOW-UP, BY FRITZ H. SCHRÖDER, MD

Published on March 15, 2010

Written by Fritz H. Schröder, MD, as part of Beyond the Abstract on UroToday.com. This initiative offers a method of publishing for the professional urology community. Authors are given an opportunity to expand on the circumstances, limitations, etc., of their research by referencing the published abstract.


Fritz H Schröder is Professor of Urology in the Department of Urology at Erasmus University Medical Centre. Dr Schröder is a member of the American Urological Association (AUA), the American Association of Genitourinary Surgeons (AAGUS), the International Urological Society (SIU) and the Genitourinary Group of the European Organisation for Research and Treatment of Cancer (EORTC), among others. He is also on the editorial board of many journals, including The Prostate, World Journal of Urology, Der Urologe A, Current Opinion in Urology, Aktuelle Urologie, Urology, British Journal of Urology. Dr Schröder’s research group has been awarded several prizes, including the Marius-Tausk prize in 1986, the award of the Dutch Urological Society in 1984 and the Schöller-Jungmann prize in 1979. He became Professor of Urology in 1972, having completed his training in urology in the Department of Urology at the University of Hamburg/Saar. He had previously completed several residencies at different American universities. He obtained a PhD in 1967, having studied medicine at the University of Hamburg/Saar, from where he graduated in 1964.

The investigators were surprised to see only a very small increase in the relative reduction of prostate cancer mortality from 20% to 21% but were delighted that the level of evidence increased from 0.04 in 2009 to 0.001 in 2011.

Attempts are ongoing to try to explain the reasons why the mortality curves do not separate more during the added period of two years. Our data so far suggest that in spite of excluding prevalent prostate cancer prior to randomization, there are men who have rather advanced prostate cancer at the time of entry into the study and that we are witnessing an effect of the treated natural history of these cases which seem to die around this period of follow-up. Obviously, the group is very curious how further follow-up will change this situation.

The abstract cites a significant rate ratio of 0.62 for the time period 10-11. Obviously, this translates into a relative risk reduction during that time period of 38%. Again, the investigators were surprised about this finding. Even with a median follow-up of 11 years, follow-up must be assumed to be incomplete during the period immediately preceding the median. The effect of possible incomplete follow-up during this period cannot be excluded at this time. The data may change with more follow-up.

The abstract reports that 1,055 men needed to be invited for screening and 37 cancers needed to be diagnosed and treated in order to prevent one death from prostate cancer. These data are based on a population with follow-up restricted to 11 years. On page 985 of the manuscript we state that if we consider all follow-up in a non-truncated analysis the number needed to invite (NNS in the previous publication) and to diagnose (NNT in the previous publication) is 936 and 33. These figures show a marked improvement compared to the NNS of 1,410 and the NNT of 48 in the 2009 publication, which amounts to 31% for the NNT figures.

Obviously, our manuscript does not address the downsides of screening except for showing a large difference in incidence between the screen and control arm, suggesting overdiagnosis. The difference between 6,963 PC diagnosed in screening and 5,396 diagnosed in the control arm amounts to 22.5%. Obviously, it remains unclear what proportion of this difference can be earmarked as overdiagnosis. As in previous publications and comments, I have to state that the analysis of quality of life and quality of life adjusted life years is still pending. Our manuscript is under review.

Finally, I should like to address a remark made in the editorial comment which is also brought forward by a number of other prominent comments on our study: ERSPC does not show a difference in overall mortality. Our study has not been designed for this purpose. In our power calculation, which is cited in all our reports, the endpoint and the resulting power are clearly determined. Our study group wishes to contribute to the understanding of screening with respect to saving lives by reducing the proportion of prostate cancer deaths. This is what we are doing. In this way we are contributing to a common goal of all public health services in most western countries, the decrease of the proportion of prostate cancer deaths contributing to overall mortality.
A publication with 10 years follow-up is pending, but currently the data is embargoed. Professor Schroeder reviewed the Rotterdam data to some extent as well as the Swedish data. In their 11-year data, 34,833 men were screened and 2,028 CaP cases were diagnosed in the screening arm, which translates to a 29% relative risk reduction. The NNI and NNM are 616 and 39.9 to save one life. The Göteborg trial began in 1994 and joined the ERSPC in 1996. They randomized 20,000 men and Dr. Jonas Hugosson reported that the CaP mortality absolute risk reduction was 0.40%. The rate ratio of CaP death was 0.56, meaning that the risk reduction of CaP death is 44%. The NNS is 293, and the NNT is 12. This data may predict the longer-term outcome of ERSPC, he said. Sweden has the highest incidence and CaP mortality rates in Europe.

They also evaluated metastatic disease and the effect that screening has on it. A metastatic lesion needed to be radiographically documented or was assumed with a PSA >100ng/ml. In the screened arm there are 256 M+ patients, compared with 416 in the control arm, roughly a 30% difference. There is a 52% relative risk reduction for having CaP metastasis at the time of diagnosis. This decreases and reverses so that the screened patients actually have a higher likelihood of metastasis over the follow-up period. Most of the metastatic cases are detected in the first screening round, but this needs further evaluation regarding the implications.

With respect to overdiagnosis and overtreatment, overdiagnosis is inherent in screening, but it is high at 54% in the ERSPC. The ERSPC 8-year detection rate was 8.3%, compared to an incidental rate of 20% and 21.9% in the PCPT control arm. To minimize overdiagnosis and over treatment he advised to use risk modifiers as decision tools and develop multiplex tools to assess patients and their cancers.

Reported for UroToday by Christopher P. Evans, MD, FACS, Professor and Chairman, Department of Urology, University of California, Davis, School of Medicine.