Ten Years of Progress in Prostate Cancer

In the 1980s, 2 milestones for treating prostate cancer occurred. The first was the development, by T. Ming Chu and his colleagues at Roswell Park Cancer Institute, of prostate-specific antigen (PSA) testing for monitoring treatment (FDA-approved 1986) and then for early detection (FDA-approved 1994). The second was the development, by Patrick Walsh and his colleagues at Johns Hopkins Hospital, of anatomic radical prostatectomy that made surgical treatment of clinically localized prostate cancer safe. The 1990s saw the development of—and demonstration of a survival benefit from—taxotere-based chemotherapy for advanced prostate cancer and the development of conformal external beam radiation therapy that allows safer delivery of doses of sufficient intensity to generate meaningful control of clinically localized prostate cancer. Progress in these 2 decades set the table for an explosion of progress over the past 10 years.

Early Detection of Prostate Cancer

The decrease in the death rate from prostate cancer in America began in 1992 and has now reached 40%, largely because of the acceptance by men of the need for routine digital rectal examination and PSA measurement for early detection. Confidence in the value of early detection of prostate cancer, however, has been shaken by publication of the American1 and European2 PSA screening trials, and then by the recent draft recommendation by the U.S. Preventative Services Task Force against the use of PSA in asymptomatic men regardless of age, race, or family history.3

Before the introduction of PSA testing, most men with prostate cancer presented with incurable disease that had already spread beyond the prostate, and too often to bones. Now, such widespread disease at diagnosis is unusual. Of all men treated for prostate cancer, 70% to 90% have no evident disease and an undetectable PSA level 10 years later, and those who receive radiation therapy or surgery are unlikely to die of prostate cancer. PSA testing will perform better if used more often in men at higher risk of prostate cancer death and less often in men at lower risk. Men with a father—or, even more problematic, a brother—diagnosed with prostate cancer have a higher risk of prostate cancer death and less often in men at lower risk. Men with a father—or, even more problematic, a brother—diagnosed with prostate cancer have a more than twofold increased risk of developing the disease. African-Americans are approximately 1.5 times as likely to be diagnosed with prostate cancer and, if they get it, 2.3 times as likely to die of it compared with European-Americans.

About one-fourth of American men older than 85 years have had PSA tests performed in the past year.4 The urologic community has been criticized for overuse of PSA in men older than 80 years, when life expectancy has fallen to 8 years and the chance of dying of prostate cancer, if it is detected by PSA, is less than 1%. Many people believe that this overuse of PSA testing is guided by greed. However, in the VA Medical System, where financial gain is of less concern, the frequency of PSA measurement in older men was similar.5 Thus, overuse of PSA and overdetection of autopsy-type prostate cancer is a problem of education of both men and physicians.

The American and European studies showed no decline and 15% decline, respectively, in mortality using PSA for early detection of prostate cancer. Both studies have been criticized for many reasons. The 2 population-based studies performed in Goteborg, Sweden (part of the European study),6 and Tyrol, Austria,7 were better conducted and more relevant to the PSA debate. They showed declines in prostate cancer–related mortality of 40% and 54%, respectively. If PSA is used intelligently for early detection, and intelligent decisions are made regarding treatment, deaths from prostate cancer in America should continue to decrease.8

The ideas and viewpoints expressed in this editorial are those of the author and do not necessarily represent any policy, position, or program of NCCN.

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Clinically Localized Prostate Cancer

Radical prostatectomy and radiation therapy have improved greatly in the past 10 years. The first robotic radical prostatectomy was performed in November 2000. An estimated 80% of all radical prostatectomies performed today in America are performed robotically. Robotic surgery offers a safer operation with less blood loss, shorter hospital stays, and more rapid recovery of activities of daily living and urinary control. The surgery usually requires only an overnight hospital stay, and postoperative blood transfusion need is a rare event. Although the initial hope was that robotic prostatectomy would produce better long-term outcomes, it is now apparent that robotic and open prostatectomy produce similar rates of cancer control and preservation of urinary control and erectile function. Robotic surgery is more expensive but the hope is that the cost of robotic surgery will decline as competitors enter the market place and robotic surgery use expands in other areas.

A similar technologic explosion has improved radiation therapy. Intensity modulated radiation therapy (IMRT) using daily image guidance (IGRT) provides more focused therapy, which has allowed the delivery of higher doses of radiation therapy with less dose to surrounding tissues. IMRT/IGRT should improve long-term outcomes, although a minimum of 10 years of follow-up will be required to evaluate cancer control and side-effect profiles.

Reimbursement cost structures and patient anxiety about a cancer diagnosis have created a uniquely American problem that has become well recognized in the past several years. It is estimated that at least 40% of men in America are overtreated for prostate cancer. Overtreatment derives from the difference between autopsy-incidental and aggressive-lethal cancer. A man's chance of having prostate cancer on autopsy is roughly equivalent to his age. If prostate biopsies are performed after elevated PSA or abnormal prostate examination results or because of participation in clinical studies, approximately half of those autopsy cancers will be discovered. Obviously, as men age and undergo prostate biopsy for any reason, the likelihood of uncovering an autopsy cancer becomes greater. To help physicians counsel individual patients, the NCI-funded Early Detection Research Network developed a nomogram that estimates the chance of uncovering prostate cancer on biopsy and the chance of uncovering aggressive prostate cancer on biopsy. In similar fashion, the need for intervention can be guided by several nomograms that help men and their health care providers evaluate the potential benefit of treatment.

This information and a growing appreciation by both patients and clinicians of the problems of overtreatment have spawned new interest in active surveillance as an option for the management of clinically localized prostate cancer. In 2009, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer were the first cancer guidelines to recommend active surveillance as treatment; active surveillance is the only recommendation for men who have very low-risk prostate cancer and a life expectancy of less than 20 years, or low-risk prostate cancer and a life expectancy less than 10 years. This change was considered controversial at the time. Fortunately, experiences at Johns Hopkins, the University of California San Francisco (UCSF) and Toronto show active surveillance to be a continually more attractive alternative for men with very low-risk and low-risk prostate cancer. The evolution of active surveillance as an appropriate treatment for many men with prostate cancer should continue as the criteria for safe conduct of active surveillance are refined and experience continues to suggest that a period of active surveillance followed by intervention when appropriate does not diminish the chance of cure.
Advanced Prostate Cancer

Developments in the treatment of advanced prostate cancer have come so frequently over the past 2 years that updates to the NCCN Guidelines have been required as often as 3 times annually to accommodate practice-changing developments. Perhaps the most significant development in advanced prostate cancer is the realization that the androgen receptor (AR) and the expression of androgen-regulated genes remain central to the recurrence and progression of prostate cancer during androgen deprivation therapy (ADT). Previously, prostate cancer was thought to recur as an “androgen-independent” tumor. However, the AR remains expressed and hypersensitized to what were thought to be low levels of tissue androgens.

However, prostate cancer develops the ability to produce dihydrotestosterone (DHT), the preferred ligand for the AR, through intracrine metabolism, probably from weak adrenal androgens or even cholesterol. The recognition of the importance of the AR and intracrine metabolism of testicular androgens has led to renewed interest in the development of secondary ADT, which has been shown to extend survival in men with castration-recurrent prostate cancer, and offers hope that ADT can be improved on when first instituted. The importance of ketoconazole (CYP17A1) for backdoor metabolism of adrenal androgens to DHT led to the redevelopment of abiraterone acetate. Abiraterone acetate can be administered safely, perhaps with prednisone coadministration, to reduce tissue levels of testicular androgens. In addition, currently available anti-androgens have limitations that cause them to compete ineffectively at the AR ligand-binding domain for testosterone and DHT. Medivation and Aragon have developed better anti-androgens, and MDV3100 has been reported to extend survival in men with castration-recurrent prostate cancer.

The adverse effects of ADT have also been addressed. First, trials continue to show that intermittent ADT does not change survival and offers improved quality of life compared with continuous ADT. In addition, Smith et al. focused attention on the adverse effects of ADT on bone health and diseases that constitute the metabolic syndrome. Preemptive management of metabolic syndrome may decrease the cardiovascular and diabetic side effects associated with ADT. In addition, new agents have been shown to reduce the risk of skeletal-related events (zoledronic acid and denosumab). Finally, men who develop castration-recurrent prostate cancer have new opportunities for therapy that extend beyond secondary ADT. Sipuleucel-T was shown to extend life expectancy in men with castration-recurrent and chemotherapy-relapsed prostate cancer. Sipuleucel-T provides proof of principle that advanced prostate cancer is susceptible to immunomodulation. Other immunotherapies are being developed and tested and should become available soon. In addition, the dose and dosing interval of sipuleucel-T should be improved as knowledge increases through interrogation of data acquired from immunomonitoring. Finally, life expectancy has been shown to be extended by cabazitaxel in men in whom docetaxel failed.

The Next 10 Years

It is apparent that early detection of prostate cancer is not enough; researchers must develop a biomarker/molecular fingerprint of the aggressive (lethal) phenotype. Until the differences between autopsy and lethal prostate cancer are identified, the use of PSA testing for early detection of prostate cancer will have controversies, because patients who need treatment cannot be reliably distinguished from those who do not.

However, ongoing studies suggest that when intelligent physicians use appropriate guidelines to select men for active surveillance, they are good at it. Johns Hopkins and UCSF reported no prostate deaths in their active surveillance programs, and Toronto reported no prostate cancer deaths since their guidelines were changed to exclude
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men with Gleason grade 3 + 4 = 7. At the same time, patients require the greatest safety possible, and safety can be improved through further study of criteria for active surveillance and appropriate means of monitoring men who select active surveillance.

In addition, many of the issues regarding overtreatment would diminish if the adverse effects of treatment were lessened. Treatment that ablates the prostate without the need for surgery or radiation should be possible if prostate-specific targets can be identified. ADT should be made prostate-specific and possibly even prostate cancer–specific and complete, in which case ADT would be converted from palliative to curative.

Finally, several forces in play have produced exaggerated concern about the financial and quality-of-life costs associated with the 40% decline in prostate cancer mortality. First, PSA is overused because of medicolegal concern about failure to diagnose prostate cancer while curable. Second, obtaining PSA levels when men are asymptomatic and digital rectal examination results are normal in those older than 75 years has a high likelihood of leading to prostate biopsy; as many as 40% of these men will have prostate cancer detected that will threaten the life of fewer than 1%. The detection of very low-risk or low-risk prostate cancer leads to even greater harm if these men—who did not require treatment in the first place—undergo surgery or radiation.

Increases in the detection of prostate cancer and subsequent treatment with radiation therapy has occurred in states where radiation therapy units have been moved outside the hospital setting and are owned by urologists through an inappropriate expansion of the Stark Law’s in-office exception. The NCCN Guidelines for Prostate Cancer Early Detection and those for prostate cancer treatment can be used to standardize practice, educate patients and physicians about controversies, reduce overtreatment while enhancing the detection of potentially lethal prostate cancer, and curb the purveyors of excessive early detection and care. This excess can diminish the performance of PSA testing for early detection and impair quality of life, especially of older men who disproportionately experience erectile dysfunction and loss of urinary control as a result of bladder and periprostatic tissue injury from treatment they did not need. Patients, physicians, insurers, and governmental agencies should embrace the NCCN Guidelines to maintain and even improve on the 40% reduction in prostate cancer deaths while avoiding overdiagnosis and overtreatment of autopsy cancer.

References


