The Inexorable March of Prostate Cancer Research
Testosterone and Beyond

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KEYWORDS

• Prostate cancer • Discoveries • Treatments • Surgery • Radiation therapy • Hormonal therapy

KEY POINTS

- The relationship between testosterone and prostate cancer was described by Huggins in 1941.
- Multiple strategies can reduce serum testosterone to castrate levels.
- The observation that some prostate cancers can be observed and that treatment can be deferred was described by Klotz in 2002.
- Genetic testing is playing an increased role in prostate cancer screening and management.
- Immunotherapy and PARP inhibitors are new strategies being pursued for some advanced prostate cancers.

INTRODUCTION

Wikipedia defines a generation as being 20 to 30 years.[1] Although not strictly proven, it has been suggested that surgeons are at their peak from 35 to 55 years of age.[2,3] It therefore should come as no surprise that over the past century or so that, with some noticeable exceptions, major discoveries in prostate cancer treatment have occurred at 20-year intervals.

It can be theorized that each new generation of physicians, surgeons, and nonphysicians alike inherit the knowledge of those who have gone before them. Their own experience accrues, and by the time they reach their professional maturity in their fifties, they have contributed to and added to the knowledge of their field. With this as a construct, the author reviews the history of prostate cancer treatment discoveries over slightly more than the past hundred years.

THE SURGICAL FOUNDATION: HUGH HAMPTON YOUNG,1904

Although a British surgeon, J. Adams, described the first case of prostate cancer in 1853, Hugh Hampton Young[4] occupies his rightful place as the father of American urology and the father of radical surgery for prostate cancer. In his autobiography, he describes the evolution of his technique of the perineal approach to first remove benign obstruction of the prostate and then radical surgery for prostate cancer.

He performed the first perineal enucleation for benign prostatic obstruction on October 8. 1902. He continued to modify the surgical instruments to enable the perineal approach to prostate surgery, and on April 7, 1904, assisted by William S. Halsted, performed the first radical perineal prostatectomy.[5–8] Through Young's efforts, the perineal approach became the standard approach for radical surgical cure of prostate cancer for much of the remainder of the twentieth century.

THE BRITISH EMPIRE CANCER CAMPAIGN: 1923

Throughout most of the early years of the twentieth century, there was little evidence of collaborative cancer research across institutional lines in either the United States or Europe. A landmark event

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occurred in 1923 with the establishment of the British Empire Cancer Campaign, which was organized to "attack and defeat the disease of cancer in all its forms, to investigate its causes, distribution, symptoms, pathology and treatment and to promote its cure."

The formation of the British Empire Cancer Campaign provided the underpinning for collaborative science and presaged the formation of the National Cancer Institute by Congress in 1937. As the remainder of the twentieth century unfolded, organized medicine in North America and Europe became increasingly aware of the importance of cancer research.

Also, in the 1930s, Ethel and Alexander Gutman reported that serum acid phosphatase levels increased in patients with metastatic prostate cancer, which became the first and only biomarker for prostate cancer for the next several decades.

CHARLES HUGGINS: THE TESTOSTERONE-PROSTATE CANCER LINK: 1941

It is fair to say that Charles Huggins and the publication of his landmark article on the relationship between prostate cancer and androgens began the modern era of prostate cancer investigation and research.[9] More than 80 years later, androgen deprivation by a variety of means remains the underpinning of the treatment for advanced prostate cancer.[10] As a result of this work, Huggins was awarded the Nobel Prize in Physiology or Medicine in 1966.

THE VETERANS ADMINISTRATION COOPERATIVE UROLOGICAL RESEARCH GROUP STUDIES 1960-1975

Between 1960 and 1975, the Veterans Administration Cooperative Urological Research Group conducted 3 consecutive randomized trials comparing a variety of endocrine treatments for newly diagnosed prostate cancer. These studies, in aggregate, reported 6 major conclusions: (1) An increased hazard of cardiovascular deaths after therapy with 5 mg of diethylstilbestrol (DES); (2) Orchiectomy plus DES was no better than orchiectomy or DES alone; (3) Equivalent effects of 1.0 mg and 5.0 mg DES on prostate cancer; (4) Decreased cardiovascular hazard from therapy with 1.0 mg DES; (5) Premarin and Provera were no better than 1.0 mg DES at the doses studied; (6) Decisions about hormone treatment at diagnosis were dependent on patient characteristics, mainly age and Gleason grade.[11]

DONALD GLEASON: PATHOLOGIC SCORING OF PROSTATE CANCER: 1962

In 1962, Donald Gleason,[12] who was then a young pathologist at the Minneapolis Veterans Administration Hospital, devised the Gleason score, which was an objective, reproducible method to grade prostate cancer. In his obituary, it was mentioned, "The Gleason score has consistently been a key component of our predictive models. It is part of the backbone against which all newer predictive measures have come to be measured."[12]

THE IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGEN: 1970

In the 1960s and 1970s, many researchers were searching for new biomarkers that would facilitate the diagnosis and monitoring of a variety of malignancies.[13] In 1966, Mitsuo Hara[14] reported a partially characterized seminal protein, "gamma-seminoprotein," which was thought to be helpful in rape cases. In 1970, Tien Shun Li and S.J. Behrman,[15] while investigating male infertility, identified antigens in human semen, one of which was later shown to have the same amino acid sequence as prostate-specific antigen (PSA). Also in 1970, Richard Albin identified an antigen that was subsequently identified as PSA.[16] This identification of the association of PSA with prostate tissue, ultimately both benign and malignant, opened up a new era of prostate cancer diagnosis and management.

ANDREW SCHALLY: GONADOTROPIN-RELEASING HORMONE AGONIST ANALOGUES, 1972-1978

Andrew Schally demonstrated that the gonadotropin-releasing hormone (GnRH) agonistic analogue that he and his colleagues had developed between 1972 and 1978 inhibited the growth of prostate cancer in rats. Along with Dr George Tolis, Schally conducted the first clinical trial of GnRH agonists for patients with prostate cancer in 1982. They provided the foundation for this class of drugs to replace orchiectomy or estrogens to achieve castrate levels of serum testosterone. These drugs, as agonists, would initially cause a rise in serum testosterone or a "testosterone flare." Subsequently, GnRH antagonists were developed to obviate the transient testosterone flare. For his work on GnRH agonists, Schally was awarded the Nobel Prize in Physiology or Medicine in 1977.[16]

PATRICK C. WALSH: NERVE-SPARING RADICAL PROSTATECTOMY, 1982

Patrick C. Walsh performed the first nerve-sparing radical nephrectomy in a 52-year-old man at Johns Hopkins Hospital on April 26, 1982. The evolution of his thinking on the practicality of this technique was based on his experience with Pieter Doncker, MD, the outgoing chair of urology in Leiden, The Netherlands. That experience caused Walsh to recognize that the nerves leading to the corpora cavernosa were located outside the capsule and fascia of the prostate. The validation of the technique was confirmed when the patient reported 7 months postoperatively that he had regained potency. The early reports by Walsh ushered in the modern era of nerve-sparing radical prostatectomy as the surgical approach for prostate cancer.[17–19]

MALCOLM BAGSHAW AND RADIATION THERAPY FOR PROSTATE CANCER

Malcolm Bagshaw was the Chief of Radiation Therapy and then Chief of Radiation Oncology at Stanford University from 1960 to 1992. During that time, he introduced radiation therapy, primarily produced by radiation beams generated by a linear accelerator. He established external beam radiation therapy as a viable option for the treatment of localized prostate cancer.

WILLET F. WHITMORE AND INTERSTITIAL IMPLANTATION OF IODINE-125

Willet F. Whitmore is considered by many to be the "father of urologic oncology." Starting in 1970, he began utilizing the open implantation of radioactive iodine-125 seeds with pelvic lymphadenectomy at Memorial Sloan Kettering. Between February 1970 and April 1977, 300 patients with T1, T2, and T3 prostate cancer were treated. The 5-year survival rate for T1-T2 disease was 100% and for T3 was 65%.[20]

LAURENCE KLOTZ AND ACTIVE SURVEILLANCE OF PROSTATE CANCER

Laurence Klotz began enrolling patients with low-risk prostate cancer to an active surveillance protocol starting in 2002.[21] Because of encouraging early results, the enthusiasm for the selective use of active surveillance spread rapidly.

By 2018, Klotz reported that there had been 2400 publications on the topic of active surveillance in prostate cancer with more than 20,000 patients reported in the prospective series.[22] The use of active surveillance for management of prostate cancer has been increasing significantly. Using data from the Surveillance, Epidemiology, and End Results Program–Medicare, Liu and colleagues[23] reported that the use of active surveillance increased from 22% in 2004 to 2005 to 50% in 2014 to 2015 in patients with a Gleason score of 6 or below and increased from 9% in 2004 to 2005 to 13% in 2014 to 2015 for patients with a Gleason score of 7 or above.[23] The intensity of the surveillance, including biomarkers, imaging and biopsies, continues to evolve.[24]

LAPAROSCOPIC AND ROBOTIC PROSTATECTOMY

Laparoscopic prostatectomy was introduced in 1991 and began to become more widely utilized over the next decade.[25] However, it was not until 2008 when robotic prostatectomy began being introduced into urologic practice.[26] Tyson and colleagues[27] reviewed radical prostatectomy trends in the United States over a 14-year period. They found an overall decrease of 7% in the total number of prostatectomies during that period. That trend was likely due, at least in part, to an increased enthusiasm for active surveillance and a greater acceptance of radiation therapy with a lead in of androgen ablation.[24] It was significant that the number of open prostatectomies decreased by 70% during that time, and 18% of hospitals stopped performing open prostatectomies altogether.[26,27]

They further reported that from 2008 to 2011, the number of laparoscopic radical prostatectomies declined by 90%, and the number of open radical prostatectomies declined by 50%.[26,27] Similar trends were reported by Lowrance and colleagues[28] utilizing case logs from the American Board of Urology.

THE ANTIANDROGENS

As mentioned previously, the work of Huggins provided the initial foundation for the relationship between testosterone and prostate cancer. As research continued throughout the twentieth century, the key role of the androgen receptor came to be recognized and better understood.

A class of drugs known collectively as first-generation androgen receptor inhibitors, including flutamide, bicalutamide, and nilutamide, was introduced clinically in the last 2 decades of the twentieth century.[29] These drugs target androgen receptor translocation to the nucleus and prevent downstream signaling. Cyproterone acetate is another antiandrogen but has not been available in the United States. The second-generation

antiandrogens began with enzalutamide in 2012 and was followed by apalutamide and darolutamide, to improve on the mechanism. Abiraterone acetate prevents androgen biosynthesis.[30]

These drugs have been studied in a series of double-blind, placebo-controlled trials for efficacy and safety of these drugs in nonmetastatic castration-resistant prostate cancer. These trials revealed that enzalutamide (PROSPER Trial) and apalutamide (SPARTAN Trial) and darolutamide (ARAMIS Trial) improved survival in high-risk, nonmetastatic castration-resistant prostate cancer, and darolutamide may result in fewer adverse results.[31] This class of drugs is now part of the clinical armamentarium for treating selected patients with high-risk prostate cancer.

PROSTATE BIOPSY TECHNIQUES

The technique of prostate imaging and biopsy techniques has evolved and continues to undergo evolution. Over the past century, biopsy by digital palpation, ultrasound guidance, and MRI guidance have all been utilized by the urologic community. Controversy continues over the number of cores, antibiotic prophylaxis, and optimal imaging techniques. A detailed discussion of these issues is beyond the scope of this article, and the reader is referred to the current American Urological Association White Paper on the topic.[32]

GENETIC TESTING AND PROSTATE CANCER RISK

Over recent years, there have been increasing applications of genetic testing to evaluate prostate cancer risk. The Philadelphia Prostate Cancer Consensus Conference was convened to investigate this topic. At the conclusion of this conference, the following recommendations were made: Large, germline panels and somatic testing were recommended for metastatic prostate cancer. Reflex testing–initial testing of priority genes followed by expanded testing was suggested for multiple scenarios. Metastatic disease or family history suggestive of hereditary prostate cancer was recommended for germline testing. Priority genes to test for metastatic disease treatment included BRCA 2, BRCA 1, and mismatch repair genes with broader testing, such as ATM, for clinical trial eligibility. BRCA 2 was recommended for active surveillance discussions. Screening starting at age 40 years or 10 years before the youngest prostate cancer diagnosis in a family was recommended for BRCA 2 carriers, with consideration in HOXB13, BRCA2, ATM, and mismatch repair carriers.[33]

BIOMARKERS

Over the past several decades, there has been a panoply of prostate cancer biomarkers. These include serum, urine, and tissue biomarkers, which have been utilized for diagnosis, surveillance, and prognosis. This is beyond the scope of this article, but excellent recent reviews are available.[34,35]

IMMUNOTHERAPY AND PROSTATE CANCER

In 2018, James P. Allison and Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine for their discovery of cancer therapy by inhibition of negative immune regulation. The role of immunotherapy in the treatment of prostate cancer is still in its nascent, but exciting stage. Multiple treatment strategies are being pursued, including tumor infiltrating lymphocytes, vaccine-based therapies, CTLA-4 inhibition, PD-1, PDL-L1 inhibition, CTLA-4/PD-1 combination, bispecific T-cell engagers, and chimeric antigen receptor T-cell therapy.[36] There are now several phase III clinical trials underway that are evaluating the use of checkpoint inhibitors in a variety of prostate cancer circumstances. The next few years hold the promise of introducing an era of exciting new discoveries.

POLY(ADENOSINE DIPHOSPHATE-RIBOSE) POLYMERASE INHIBITORS AND PROSTATE CANCER

Germinal and/or somatic alterations of the DNA-damage response pathway genes were found in a substantial number of patients with advanced prostate cancers, mainly of poor prognosis. These alterations induce a dependency for single-strand break reparation through the poly(adenosine diphosphate-ribose) polymerase (PARP) system, which provided the rationale to develop PARP inhibitors.[37]

PARP is a family of 17 distinct proteins in which PARP 1 and 2 are involved in DNA repair. PARP 1 binds to damaged DNA gaps, and after conformational change, induces PARylation. PARP inhibitors are oral targeted therapies that competitively bind to NAD+ sites of PARP 1 and PARP 2, inducing a catalytic inhibition. Five different molecules are currently under development or recently approved: olaparib, rucaparib, niraparib, veliparib, and talazoparib. Their action inhibits the PARylation, and therefore, single-strand DNA break repair. These ongoing studies will provide important information about the role of PARP inhibitors in clinical medicine.

PROSTATE CANCER RESEARCH: THE MODERN ERA

It is fair to say that there have been several eras in prostate cancer research. The ground-breaking research of Huggins in the 1940s provided the underpinning for the understanding of the role of testosterone in the development of prostate cancer. The period from 1982 to 2002 may well be considered to be the Localized Prostate Cancer Era. The period from 2002 until now may be considered the Indolent Prostate Cancer Era. Now it would appear that we are entering the Prostate Cancer Genetics and Metastatic Prostate Cancer Era.

The next 20 years hold great promise for prostate cancer treatment. The collaborative research of urologists, radiation oncologists, medical oncologists, endocrinologists, and basic scientists will undoubtedly result in major clinical breakthroughs that will benefit our patients.

CLINICS CARE POINTS

- The role of serum and intraprostatic androgen levels continues to be a topic of intense investigation.
- Continued biomarker development, including genetic testing in selected patients, will aid both diagnosis and management of patients with prostate cancer.
- Selection of treatments for localized prostate cancer needs to be individualized according to the patient's characteristics, the tumor's characteristics, and the wishes of the patient and his family.

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