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A history of prostate cancer treatment

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Abstract

The increased incidence of prostate cancer has led to remarkable changes in diagnosis and treatment over the past century. What were the first ways in which prostate cancer was treated, and how did these evolve into the variety of therapeutic strategies from which patients have to choose today?

In 1853, J. Adams, a surgeon at The London Hospital, described the first case of prostate cancer, which he discovered by histological examination[1]. Adams noted in his report that this condition was “a very rare disease”. Remarkably, 150 years later, prostate cancer has become a significant health problem. In the United States, it is the most commonly diagnosed cancer in men, with 180,000 new cases and about 31,000 deaths occurring annually[2]. This dramatic increase in the number of prostate cancer cases can be attributed to several causes. First, prostate cancer was not differentiated from other types of urinary obstruction until the early 1900s. Second, the incidence of prostate cancer increases more rapidly with age than any other cancer type[2]. The number of cases has risen as the average life expectancy has increased over the past century. Third, the increased incidence seems to be, in some way, related to the ‘Western’ lifestyle: the incidence of clinical prostate cancer is significantly lower in Asian populations, compared with Western populations[3], and it

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DATABASES
The following terms in this article are linked online to:
Cancer.gov: http://www.cancer.gov/cancer_information/prostate cancer
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Medscape DrugInfo:
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bicalutamide | cetrorelix | cytoxan | docetaxel | doxorubicin | estramustine | etoposide | finasteride | 5-fluorouracil | flutamide | goserelin | ketoconazole | leuprolide | mitoxantrone | nafarelin | nilutamide | paclitaxel | vincristine

FURTHER INFORMATION
Andrew Schally - Nobel Prize:
http://www.nobel.se/medicine/laureates/1977/
The Brady Urological Institute at Johns Hopkins University: http://urology.jhu.edu/
Charles Huggins - Nobel Prize:
http://www.nobel.se/medicine/laureates/1966/
The Prostate Cancer Research Institute:
http://www.prostate-cancer.org/
The University of Pennsylvania's Oncolink site for prostate cancer:
http://oncolink.upenn.edu/templates/types/section.cfm?c=16&s=57

increases in men who have emigrated to Western nations, indicating some type of environmental or dietary effect[3].

This increased incidence has led to remarkable changes in the diagnosis and treatment of prostate cancer over the past century. Fifty years ago, the typical patient was a man in his early seventies who was diagnosed with metastases to the bone and/or soft tissues. Characteristically, these lesions were bulky and histologically poorly differentiated. Diagnosis at such an advanced disease status was a death sentence, with patients dying within 1–2 years. In the 1940s, Charles Huggins (FIG. 1a) found that metastatic prostate cancer responds to androgen-ablation therapy, which heralded the beginning of a new era of prostate cancer therapy[4]. Remarkably, medical castration with oral oestrogens became the first effective systemic treatment for any cancer, and, to this day, androgen ablation remains the most generally useful prostate cancer therapy.

Androgen-ablation therapy

The concept of androgen ablation to control prostate disease goes back to 1786, when the surgeon John Hunter described seasonal variations in the size of the testicles and prostate gland in animals. He later concluded — on the basis of the effects of castration — that there was a direct connection between the testes and secondary sex organs,[5]. Later, in the nineteenth century, a number of reports describing a link between the testes and prostate gland were also published[6]. In 1893, the Philadelphia surgeon W. White measured changes in the size of the prostate gland in dogs after castration, reporting atrophy of glandular elements and a decrease in prostate weight[7]. He advocated castration as a treatment for urinary obstruction disorders. Numerous reports on the efficacy of castration therapy followed, with mixed results that might have been due to the lack of distinction between cancer and benign prostatic hyperplasia[6].

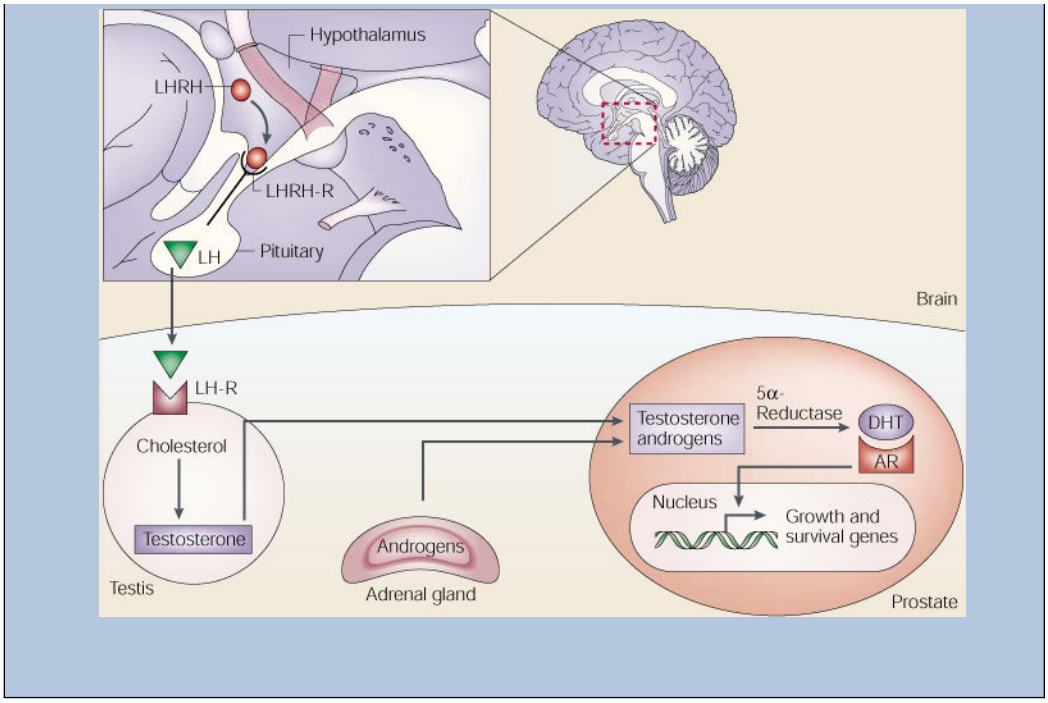
At the beginning of the twentieth century, experiments in animals established the relationships between the pituitary, testes and prostate gland (BOX 1). In 1935, Clyde Deming's group at Yale reported that in primates, castration caused a decrease in the size of the normal prostate gland, but had no effect on benign prostatic hyperplasia in humans[8]. A few years later, Robert Moore and Allister Mclellan found that oestrogen injections produced atrophic changes in the prostate epithelium, but, again, had no effect on benign prostate hyperplasia[9].

Box 1

Androgen production and action

In the hypothalamus, androgens bind to the androgen receptor (AR) to stimulate production of luteinizing hormone (LH)-releasing hormone (LHRH). LHRH travels to the pituitary where it interacts with LHRH receptors (LHRH-Rs). This interaction stimulates the release of LH. LH that is released by the pituitary binds to LH receptors (LH-R) in the testes, inducing production of testosterone, which is synthesized from cholesterol. Testosterone enters prostate cells, where it is converted to dihydrotestosterone (DHT) by the enzyme 5α reductase. DHT binds tightly to AR, enters

the cytoplasm, and the complex translocates to the nucleus where it activates transcription of genes that regulate cell growth and survival. Increased testosterone levels can also decrease LHRH and LH production through negative feedback loops, thereby maintaining serum testosterone at physiological levels. The adrenal gland can also produce androgens.



In the late 1930s, Ethel Gutman and Alexander Gutman reported that serum acid-phosphatase levels increased in patients with metastatic prostate cancer[10,11]. Around this time, Charles Huggins (FIG. 1a) established a method to measure the effect of various hormonal manipulations on prostatic function[12]. He found that castration or oestrogen administration resulted in glandular atrophy, which could be reversed by readministration of androgen. He also showed, in dogs, that acid-phosphatase production decreased following androgen ablation. He then determined that castration or oestrogen administration resulted in rapid shrinkage of the enlarged prostate of older dogs. Subsequently, he studied the effects of castration on men with benign prostatic hyperplasia and found a reduction in levels of prostate epithelial-cell replication[13].

The beneficial effect of androgen ablation on metastatic prostate cancer was not realized until 1941, when Huggins and Clarence Hodges treated these patients by either castration or oestrogen therapy. To monitor prostate size and therapeutic efficacy, they measured serum acid-phosphatase levels. Huggins and Hodges concluded that “Prostatic cancer is influenced by androgenic activity in the body. At least with respect to serum phosphatases, disseminated carcinoma of the prostate is inhibited by eliminating androgens, through castration or neutralization of their activity by oestrogen injection”[14].

That same year, Huggins *et al.* published a second paper describing the effects of treating advanced prostate cancer patients by surgical or medical castration by means of oral oestrogen (stilbesterol) administration[4]. Huggins, therefore, was the first to use a systemic approach to treat prostate cancer. Castration resulted in appreciable increases in weight, appetite and haematocrit and, most notably, patients experienced less pain. To acknowledge the importance of these findings, Charles Huggins was awarded the Nobel Prize in Physiology and Medicine in 1966.

The discovery of the beneficial effects of androgen ablation led to larger clinical studies that assessed castration in men with advanced prostate cancer. One of the most important was a randomized study that began in the 1960s and was organized by the Veterans Administration Cooperative Urologic Research Group (VACURG). This study compared the effects of treating prostate cancer patients with the oral oestrogen diethylstilbesterol (DES)[15], and concluded that DES treatment was as effective as orchiectomy in treating prostate cancer.

In the 1960s, two main problems associated with systemic hormonal therapy became evident. The first was related to findings, such as the VACURG study, which revealed that lowering serum testosterone levels with oral oestrogen caused significant cardiovascular and thromboembolic toxicity. In addition, it became evident that androgen ablation, by means of castration or oestrogen administration, was not sufficient to completely cure patients with advanced prostate cancer. Even Huggins, in the conclusion of his first paper describing androgen ablation, noted, “It is certain that, in many cases, regression of the neoplasm is not complete”[4].

Knowing that, in addition to the testes, the adrenal gland also produces low levels of androgen (BOX 1), Huggins and W.W. Scott determined that bilateral adrenalectomy in men who no longer responded to castration therapy could slow cancer growth, but that tumours eventually began to grow again[16]. Others showed similar effects following hypophysectomy. Although adrenalectomy or hypophysectomy were shown to have transient palliative effects in patients who failed medical or surgical castration, these approaches were not widely used, due to the inherent complexity of the surgical approach.

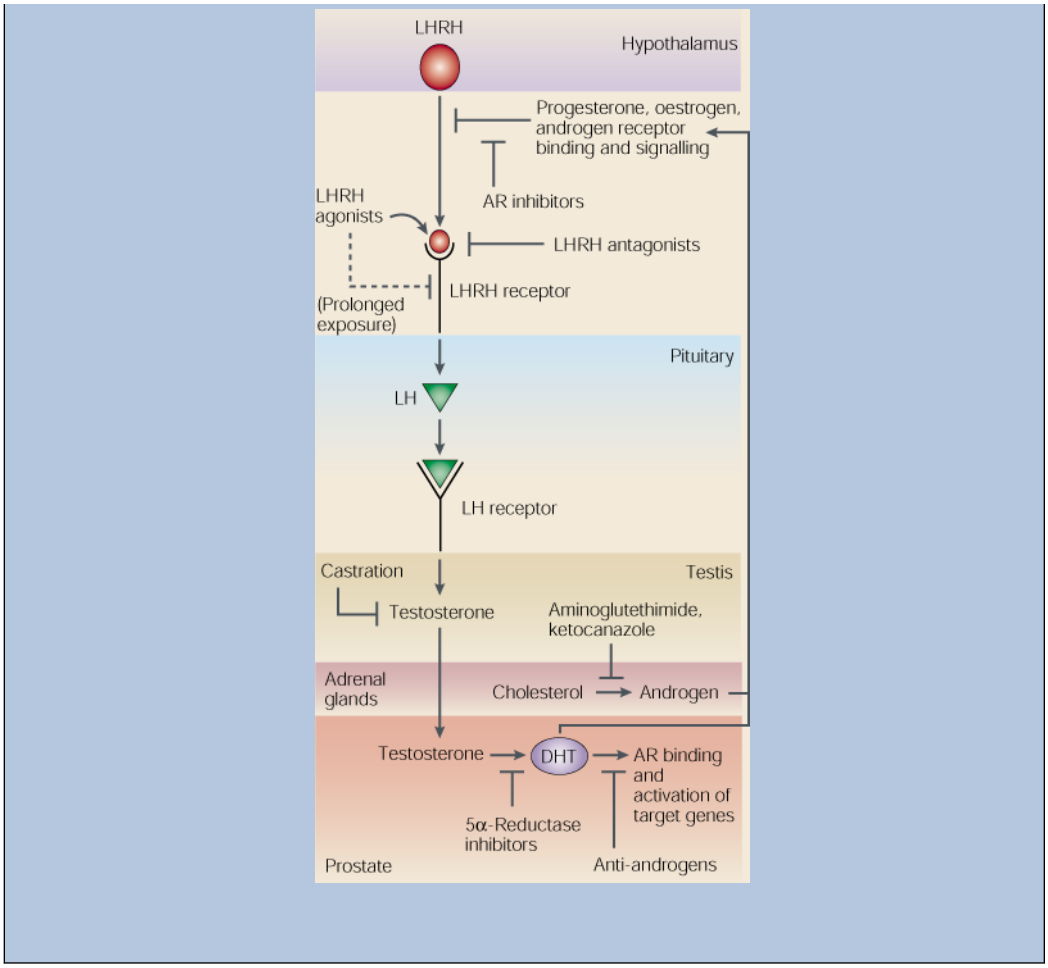
New approaches were developed during the 1960s–1980s that involved the development of hormone treatments to either block adrenal androgen production or inhibit androgen interaction within the target tissue (BOX 2). Two years before the publication of the initial results of the VACURG study, Andrew Schally (FIG. 1b) had determined the structure of the hypothalamic hormone known as luteinizing hormone (LH)-releasing hormone (LHRH; also know as gonadotropin-releasing hormone) and developed the means to synthesize it[17]. Hypothalamic release of LHRH induces the pituitary to produce LH. LH binds to a receptor on the testes, activating testosterone production. Schally investigated ways to manipulate this system, developing synthetic peptide agonists of LHRH[18].

Box 2

Multiple ways to regulate androgen production

Hypothalamic production of luteinizing hormone (LH)-releasing hormone (LHRH) induces production of LH by the pituitary. LHRH production is inhibited when ligands bind to the progesterone receptor, the oestrogen receptor and the androgen receptor (AR), which binds dihydrotestosterone (DHT) and testosterone. Androgen receptor inhibitors (anti-androgens) block the negative feedback of androgens to stimulate LHRH and LH release. Anti androgens therefore eventually increase the levels of serum testosterone by disrupting normal negative feedback loops. LHRH agonists, such as leuprolide, goserelin, buserelin and nafarelin, bind to LHRH receptors in the pituitary and initially stimulate LH release, which leads to increased testosterone production (the ‘testosterone flare’).

Prolonged exposure to LHRH agonists, however, downregulates the LHRH receptor, decreasing LH release and inhibiting testosterone production. LHRH antagonists, such as cetrorelix, abarelix and orgalutran, directly inhibit the LHRH receptor, leading to decreased production of LH and testosterone. Surgical castration also decreases testosterone levels by removing the source of production (testes). In the adrenal glands, cholesterol is converted to adrenal androgen. Adrenal androgen production can be inhibited by drugs such as aminoglutethimide and ketoconazole. 5α Reductase inhibitors (finasteride) block the conversion of testosterone to DHT. As well as their main effects on LHRH and LH production, anti androgens such as cyproterone, flutamide, bicalutamide and nilutamide are direct competitive inhibitors of DHT, binding to AR in the normal and cancerous prostate cancer cells.



Administration of LHRH agonists was found to produce a transient increase in serum testosterone levels — known as a ‘testosterone flare’ — which caused pain and obstructive symptoms. Schally and others, however, noted that chronic administration of these LHRH agonists (BOX 2) produced inhibitory effects, downregulating pituitary receptors for LHRH, leading to a suppression of circulating levels of follicle-stimulating hormone (FSH) and LH[19,20]. This resulted in lowered serum testosterone levels — equal to those caused by castration. LHRH peptide agonists were found to suppress tumour growth in rats with hormone-responsive prostate cancers[19]. Schally and colleagues showed that advanced prostate cancer patients who were treated with daily doses of the LHRH agonists experienced a 75% decrease in serum testosterone levels, a decrease or normalization of plasma acid-phosphatase levels, and, most importantly, a marked reduction in cancer-associated bone pain[21]. In 1977, Schally received the Nobel Prize in Physiology and Medicine for this exciting work.

Several additional synthetic LHRH agonists were subsequently developed for clinical use[18]. These included leuprolide (Lupron),goserelin (Zoladex), buserelin and nafarelin. LHRH agonists were found to be as effective as DES in treating prostate cancer[22]. Like other approaches to lowering serum testosterone, treatment with LHRH agonists causes significant side effects, such as hot flushes, loss of libido and impotence. These agents, however, do not

lead to the increased thromboembolic events that are associated with oestrogen therapy[22]. Subsequently, long-acting microcapsulated delivery systems for these agonists were developed that were designed to release a controlled dose of the peptide over several months. These agonists have been tested in a large number of randomized trials that compared the various approaches to androgen-ablative therapies (such as orchiectomy, oestrogen administration and LHRH agonists)[23]. These studies revealed that all approaches are equally effective, reducing tumour growth in 70–80% of symptomatic patients[23]. On the basis of these studies, LHRH agonists have become the preferred method for androgen-ablative therapy in many countries, particularly the United States.

LHRH antagonists, which directly inhibit the LHRH receptor, have also been developed as prostate cancer therapeutics. These antagonists were initially developed for contraceptive purposes[18,23]. Several of these antagonists, such as cetrorelix (Cetrotide), abarelix and orgalutran (Ganirelix) have been tested in clinical trials as treatment for men with advanced prostate cancer. Preliminary data indicates that these agents are as effective as the LHRH agonists in lowering serum testosterone, but do not cause the testosterone flare that is associated with LHRH-agonist therapy.

While these studies were underway to develop alternative methods of ‘medical castration’, a number of investigators were working to develop medical alternatives to adrenylectomy. Compounds that suppress adrenal steroidogenesis and, subsequently, androgen production were identified. These initially included drugs such as aminoglutethimide and, later, the antifungal agent ketoconazole[24,25]. Ketoconazole is less toxic than aminoglutethimide and is now used as a second-line hormone therapy in combination with low-dose corticosteroid treatment in patients who fail androgen ablation and LHRH-agonist therapy[23].

In the late 1960s, the androgen receptor was discovered and characterized by three independent groups — those of S. Liao, N. Bruchovsky and I. Mainwaring[26–28]. Screening of chemical libraries for androgen-receptor blockers led to the discovery of cyproterone — a ‘pure’ steroidal anti-androgen that competitively inhibits the binding of dihydrotestosterone (DHT) or testosterone to the androgen receptor[29] (BOX 2). As cyproterone binds not only to androgen receptors that are expressed by prostate cancer cells, but also to the androgen receptors that are expressed in the hypothalamus and pituitary, it blocks the negative feedback of androgens at the hypothalamic-pituitary level. So, treatment with cyproterone can eventually increase the level of LH released into the circulation[29], leading to increases in the serum testosterone level, ultimately diminishing the ability of cyproterone to compete for androgen-receptor binding and to block androgenic stimulation. Pure anti-androgens are therefore poor choices for monotherapy of prostate cancer.

To overcome this problem, an acetate group was added to cyproterone, creating cyproterone acetate. Cyproterone acetate retains its androgen antagonistic ability to directly compete with DHT for binding to the androgen receptor, but is also a progesterone agonist that binds progesterone receptors in the pituitary, inhibiting the release of LH[30]. This drug, therefore, functions to indirectly decrease serum testosterone levels and also acts directly as an anti-androgen in prostate cancer cells[30]. This ‘combined modality’ monotherapy has been shown to be as equally effective as medical castration with DES in treating prostate cancer[31].

At the time, the perceived limitation of cyproterone acetate was its central effects on androgen secretion, with subsequent loss of libido and sexual potency. In addition, there were several reports stating that cyproterone acetate caused liver hyperplasia. Pharmaceutical companies began to search for alternative non-steroidal 'pure' anti-androgens that would not have these side effects, and, in the 1970s, discovered flutamide. Flutamide became the first such non-steroidal antiandrogen to be tested clinically and was approved in 1989 by the United States Food and Drug Administration (FDA) for use in treating prostate cancer (REE 32). Additional pure non-steroidal anti-androgens were developed later, and include bicalutamide and nilutamide[23] (BOX 1). The presumed advantage of these agents was that they did not affect libido or potency like the other centrally acting agents under development (that is, cyproterone acetate and LHRH agonists). Later, it became clear that these agents, like cyproterone, eventually crossed the blood-brain barrier, and so increased the levels of LH released into the circulation, leading to a subsequent increase in serum testosterone. The effects of pure anti-androgen treatment have been compared to those of medical or surgical castration in randomized trials in men with metastatic prostate cancer. Although these drugs seem to be better tolerated, they are inferior therapies in terms of overall and progression-free survival[33,34].

As these new agents were being developed, it became clear that none of these approaches (orchiectomy, LHRH agonists or anti-androgens) were by themselves able to cure patients with advanced prostate cancer[28]. The next logical step, therefore, was to combine androgen-ablative therapy directed at both reducing the amount of testosterone released from the testes (orchiectomy or LHRH agonist) and at neutralizing androgens produced by the adrenal glands with anti-androgens that act directly within prostate cancer cells. The idea that combined androgen therapy might be more effective than either agent alone was proposed by Ferdinand Labrie and colleagues[35,36]. Combined androgen blockade also overcame the problems of the testosterone flare that was associated with administration of LHRH agonists, and the gradual increase of serum testosterone associated with pure anti-androgen monotherapy. It did not, of course, overcome the problem of the androgen-independent cells that are present in tumours, even at early stages.

Regardless of this, a large number of randomized clinical trials were undertaken that compared combined androgen blockade with monotherapy[23]. One of the earliest of these, published by David Crawford *et al.* in 1989 (REF. 37), reported that the combination of leuprolide and flutamide produced a slightly longer progression-free survival. This study resulted in a significant shift in treatment philosophy, and led many physicians in the United States to use combined androgen blockade as initial therapy for advanced prostate cancer. Subsequently, a total of 27 randomized Phase III trials using various combinations of androgen deprivation were performed, of which only three showed a statistically significant benefit for complete androgen blockade[38]. These trials have now been subjected to five separate meta-analyses[38,39]. The conclusion of these meta-analyses overall was that the trials do not show a significant or substantial survival benefit from combined androgen blockade.

The ultimate conclusion of these numerous studies is that although androgen ablation provides significant palliative therapy for most patients, it is never curative. These results

are consistent with the fact that prostate cancers are composed of a heterogeneous collection of androgen-dependent and -independent cells. Androgen-ablative therapy, no matter how completely or early it is given, does not eliminate the androgen-independent cell type. This realization has led to alternative treatment strategies that attempt to minimize the duration of androgen ablation either by delaying therapy until patients have clear evidence of metastases or by giving therapy on an intermittent basis[23].

The realization that androgen ablation is never curative has led to two alternative approaches to the treatment of prostate cancer. The first has been an attempt to develop better treatments for systemic disease. The second has been to successfully develop methods to aggressively screen for cancers that are still confined to the prostate and so are potentially treatable by definitive local therapy. So, as we have entered the twenty-first century, the characteristics of the typical prostate cancer patients have changed dramatically. At present, most patients are diagnosed in their sixties with localized — not metastatic — disease.

Prostatectomy

During the past several decades, there have also been significant improvements in the surgical and radiological techniques that are used to treat localized prostate cancer. Historically, surgery for prostate cancer was initially performed to relieve symptoms of urinary obstruction[6]. Before the twentieth century, there were sporadic reported cases of surgical removal of obstructive prostatic masses[6]. There was, however, no systematic technique for removal of the prostate until the pioneering work of Hugh Hampton Young, who, in 1904, at the Johns Hopkins Hospital, performed the first radical perineal prostatectomy[40] (see TIMELINE). This technique became the standard method for prostatectomy for the next 40 years.

Initially, the procedure was performed primarily as palliative therapy, but was later used in an attempt to achieve curative resection. Several decades later, transurethral prostatic resection (TURP) became available as the preferred therapy for the relief of obstructive prostate cancer. The next surgical advance came in 1945 when Terrence Millin introduced the retropubic approach for prostate enucleation[41]. This approach offered significant advantage over the perineal approach because it was easier to learn and allowed access to the pelvic lymph nodes, which is useful for tumour staging. Although minor improvements in technique were made over the next 40 years, prostatectomy was not commonly performed because almost all patients were left impotent by the procedure. The next significant advance occurred in 1983 when Patrick Walsh (FIG. 1c) developed a modified technique for radical retropubic prostatectomy — on the basis of an anatomical approach — to enhance control of bleeding. This approach avoided injury to the neurovascular bundles that innervated the corpora cavernosa of the penis[42], thereby allowing erectile function and sexual potency to be maintained without compromising the adequacy of surgical margins.

Around the time of the development of this new surgical technique, prostate-specific antigen (PSA) was discovered[43] and reported to be a potentially useful serum marker for prostate cancer[43–45]. The FDA soon approved measurement of PSA levels to monitor prostate cancer progression and response to therapy, and later approved the test for prostate cancer

screening. Additionally, in the late 1980s, the ultrasound-guided 'biopsy' device allowed for several high-quality core biopsies to be obtained[46]. These new diagnostic tests were coupled with the improved surgical technique, and this led to a dramatic increase in the number of prostate cancer patients who were treated by prostatectomy. For example, between 1974 and 1993, the number of patients who were treated by radical prostatectomy or radiation therapy for prostate cancer tripled[2]. Early detection methods have been so effective that, between 1990 and 1995, the prostate cancer death rate in the United States for men younger than 75 years of age fell for the first time in decades[2].

Radiation therapy

The first reports on the use of radiation to treat localized prostate cancer appeared at the beginning of the twentieth century and were limited to the introduction of radium sources into the urethra and rectum as a palliative alternative to surgery[47–49]. Eventually, prostate tumour growth was slowed by the insertion of radium-containing needles into the prostate gland itself, via the perineum, the rectum or the open bladder. These techniques, however, were difficult to perform and uncomfortable for the patient. Real interest in brachytherapy did not occur until the 1970s, when Willet Whitmore described an open implant technique using the ^{125}I radioisotope of iodine (REF. 50). The isotope was sealed in miniature titanium cylinders and inserted into the prostate without the aid of any imaging device. Although the technique had great appeal, it frequently resulted in inconsistent dose distributions, with some areas receiving too much and others too little irradiation. This led to serious complications and a high rate of local failure. The use of brachytherapy declined until 1983, when H. Holm reported a technique of implanting the prostate with radioactive 'seeds'[51] under the guidance of transrectal ultrasonography. Recent studies have characterized the safety and utility of brachytherapy and defined subsets of patients with localized disease who are most likely to benefit from it. Brachytherapy has now emerged as a commonly used approach for treating localized prostate cancer[52].

External Beam Radiotherapy was initially used only as an adjunct to interstitial radium because the kilovoltage delivery systems were not adequate to allow definitive treatment of most deep-seated neoplasms such as prostate cancer. With the discovery of androgen-ablation therapy in the early 1940s, radiation therapy lost popularity as a treatment for prostate cancer. Renewed interest in radiation therapy returned in the 1950s when higher-energy cobalt machines that could penetrate to deeper levels became available. The first reported series of prostate cancer patients who were treated with ^{60}Co (cobalt) therapy focused on patients with unresectable disease[53]. Soon after, Juan Del Regato reported on a small number of patients who were apparently cured following ^{60}Co therapy[54]. In the late 1950s, pioneering work by Malcolm Bagshaw (FIG. 1d) and others revealed the possibility of radiation curability of prostate cancer[55,56].

Over the ensuing decades, higher-energy accelerators and new types of radiation were developed. Improved radiographic and data-processing capabilities, such as computerized tomography, resulted in three-dimensional conformal treatment plans that allowed the prostate to be treated with a high dose of radiation, while sparing more of the surrounding normal tissues[57]. As early as the 1960s, cytoreductive hormonal therapy was added to

radiation therapy to reduce tumour burden and provide a more favourable geometry for external irradiation[57]. Recently, three separate randomized trials have shown the beneficial effects of combining androgen-ablation therapy with radiation, improving times of relapse-free and overall survival[58–60]; also, the incorporation of androgen ablation before, during and after external-beam radiation has become the standard of care.

Cytotoxic chemotherapy

Many patients initially respond to androgen-ablative therapy but, with time, develop fatal androgen-independent disease[61]. This realization led investigators to test cytotoxic chemotherapy as treatment for hormone-refractory prostate cancer. Small studies using alkylating agents were reported in the 1950s and 1960s (REF. 62), but were poorly documented and used subjective response criteria. In 1972, the National Prostatic Cancer Project (NPCP), under the leadership of Gerald Murphy (FIG. 1e), began a programme to evaluate the efficacy of chemotherapy in patients with hormone-refractory prostate cancer[63]. In 1975, the programme reported subjective improvement and minimal toxicity in the first national randomized study of 5-fluorouracil versus cytoxan versus standard therapy[64]. Further randomized trials followed, but results were difficult to evaluate because of small sample size and the response criteria used[65].

Subsequently, a large number of singleagent Phase II studies were conducted in which numerous chemotherapies were tested in patients with advanced prostate cancer. In general, response rates of <10% were observed in these single-agent studies, after the category of ‘stable disease’ was excluded from the evaluation[66]. More recent studies have relied on a fall in serum PSA as the main indicator of response. Using this criteria, a number of chemotherapy combinations resulted in a >50% decline in serum PSA levels in a significant proportion of patients. After palliative responses were seen in two randomized studies that involved mitoxantrone and corticosteroid, this became the only FDA-approved chemotherapeutic combination for metastatic prostate cancer[67,68]. Other combination therapies have included agents such as estramustine, vincristine, etoposide, doxorubicin, and the taxanes paclitaxel and docetaxel[69–73]. Emerging clinical data indicate a survival advantage in patients treated with these newer chemotherapy combinations who have a significant fall (that is, >50–75%) in serum PSA[74]. These exciting preliminary results await confirmation in ongoing large randomized studies.

Future directions

There is now a genetic and biochemical framework for understanding the process of both sporadic and inherited forms of prostate cancer[75]. This process involves interactions between diet, environmental exposure, inherited susceptibility and ageing[76]. On the basis of this knowledge, there are now rational approaches for targeting and preventing the development of life-altering or life-threatening prostate cancer. These include dietary and chemoprevention approaches to lower the risk of clinical prostate cancer development[77]. In addition, owing to the use of serum PSA screening and improved biopsy techniques, most men will be diagnosed with prostate cancer at a stage that is potentially curable by surgical

and/or radiological approaches. So, the good news is that the diagnosis of prostate cancer is no longer automatically a death sentence.

Although results from recent trials with systemic therapy for metastatic disease have been encouraging, significant progress is still needed in the area of non-androgen-ablative approaches, which could be used to treat androgen-independent prostate cancer. Previous studies have shown that the proliferative growth fraction of human metastatic prostate cancers is usually less than 10% (REFS 78,79). A new approach is therefore to develop agents that induce apoptosis in androgen-independent prostate cancer cells, in a proliferation-independent manner. Several of these agents are under preclinical development, and include PSA-activated prodrugs[80,81] and targeted anti-angiogenic agents[82]. Several are also in early clinical trials. These include gene-therapy vectors that contain prostate-specific promoters to drive the expression of lytic virus specifically in prostate cells[83]. A targeted gene-therapy approach is also being developed to activate the immune system to recognize prostate cancer cells[84]. These types of approaches might provide the next generation of prostate cancer therapies.

Glossary

BILATERAL ADRENALECTOMY	Surgical removal of both adrenal glands to eliminate production of adrenal androgens
BRACHYTHERAPY	Radiation therapy applied inside the patient by means of radioactive seeds that are implanted into the prostate gland. These seeds deliver radiation over a very short distance, thereby minimizing the amount of radiation that is delivered to normal tissue
EXTERNAL BEAM RADIOTHERAPY	Radiation therapy applied from outside of the patient to a defined area of the body (such as the prostate gland)
GLEASON GRADING SYSTEM	The ‘gold standard’ for grading prostate cancer, used by pathologists worldwide. This system involves assessing both the predominant and secondary pattern of gland formation within a prostate sample. The sample is scored to create a Gleason ‘sum’, ranging from 2 to 10, with the highest number indicating the most aggressive cancer. Patients with a Gleason sum of less than 6 typically respond well to therapy, whereas patients with a Gleason sum greater than 7 usually have poor outcomes
HAEMATOCRIT	Percentage of the blood that is red blood cells, normally between 40–52% in men and 36–46% in women
HYPOPHYSECTOMY	Surgical removal of the pituitary gland. The pituitary gland produces hormones that stimulate the secretion of several hormones that include cortisol, thyroid hormone and testosterone

ORCHIECTOMY	Surgical removal of the testicles
RADICAL PERINEAL PROSTATECTOMY	Surgical removal of the prostate by means of a perineal approach. The perineum is the area between the base of the penis and the anus
RADICAL RETROPUBIC PROSTATECTOMY	Surgical removal of the prostate by means of a retropubic approach in which the surgeon enters the pelvis above the pubic bone in front of the bladder to visualize the prostate and remove it
TRANSURETHRAL PROSTATIC RESECTION (TURP).	Removal of prostatic tissue by means of the urethra under direct visualization using electrocautery to relieve symptoms of urinary outflow obstruction

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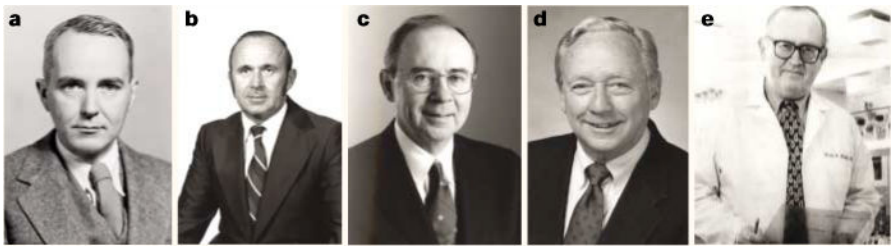
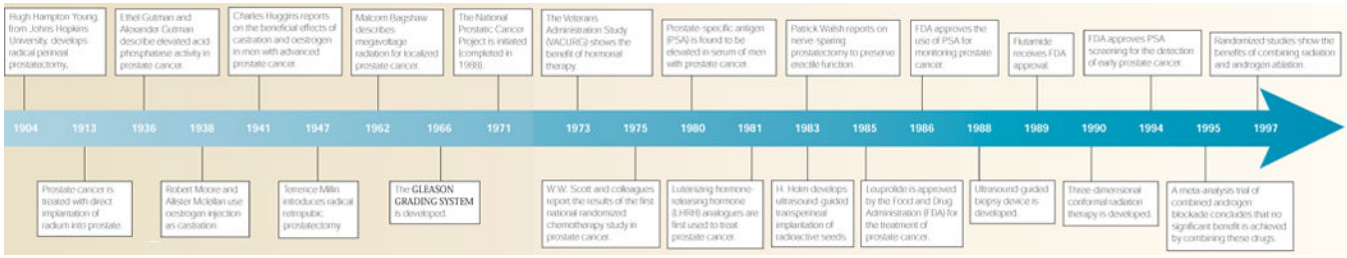


Figure 1. Prostate cancer research pioneers

a | Charles Huggins discovered that prostate cancers respond to androgen therapy. **b** | Andrew Schally determined the structure of luteinizing hormone-releasing hormone and developed the means to synthesize it. **c** | Patrick Walsh developed a modified technique for radical retropubic prostatectomy. **d** | Malcolm Bagshaw investigated the use of radiation therapy for prostate cancer. **e** | Gerald Murphy evaluated the efficacy of chemotherapy in patients with hormone-refractory prostate cancer, and his lab discovered prostate-specific antigen.



Timeline.
A century of prostate cancer therapy