Future Directions From Past Experience: A Century of Prostate Radiotherapy

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Abstract

Prostate cancer is the most commonly diagnosed noncutaneous malignancy in men, yet 100 years ago it was considered a rare disease. Over the past century, radiation therapy has evolved from a radium source placed in the urethra to today's advanced proton therapy delivered by only a few specialized centers. As techniques in radiation have evolved, the treatment of localized prostate cancer has become one of the most debated topics in oncology. Today, patients with prostate cancer must often make a difficult decision between multiple treatment modalities, each with the risk of permanent sequelae, without robust randomized data to compare every treatment option. Meanwhile, opinions of urologists and radiation oncologists about the risks and benefits involved with each modality vary widely. Further complicating the issue is rapidly advancing technology which often outpaces clinical data. This article represents a complete description of the evolution of prostate cancer radiation therapy with the goal of illuminating the historical basis for current challenges facing oncologists and their patients.

Clinical Genitourinary Cancer, Vol. 12, No. 1, 13-20
Keywords: Brachytherapy, History of medicine, IMRT, Proton therapy, Treatment planning

Background

Radiation therapy can trace its roots to some peculiar findings first described in 1895 by Wilhelm Röntgen, professor of physics at the University of Würzberg.[1] He described these findings along with photographs of the bony structures of the hand and was awarded the Nobel Prize in physics in 1901. The therapeutic effects of radiation were realized equally as early, first in treating severe skin diseases such as lupus. The marketability of radioactive materials was also quickly recognized and in 1905 the young Vice President of Tiffany & Co, George Kunz, was granted the first patent of radium's broad applications ranging from luminescence to its cytotoxic ability in "destroying germs, microbes, bacteria and the like"[2] In 1898 Marie Curie discovered radium and in 1935 her daughter Irène and partner Frédéric Joliot earned the Nobel Prize for describing the artificial creation of radioactive elements.[3]

In Röntgen's era, prostate carcinoma was thought to be a rare and insignificant disease. In 1893 the world literature on prostate cancer comprised only of 50 reported cases.[4] Today, prostate cancer is known to be the most common noncutaneous cancer in men and accounts for more than 700,000 cases a year.[5] In this article, interesting landmark advances in radiation therapy techniques will be highlighted with the goal of illuminating, clarifying, and inspiring future developments in prostate therapy.

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Submitted: Apr 26, 2013; Revised: Aug 16, 2013; Accepted: Aug 27, 2013; Epub: Oct 26, 2013

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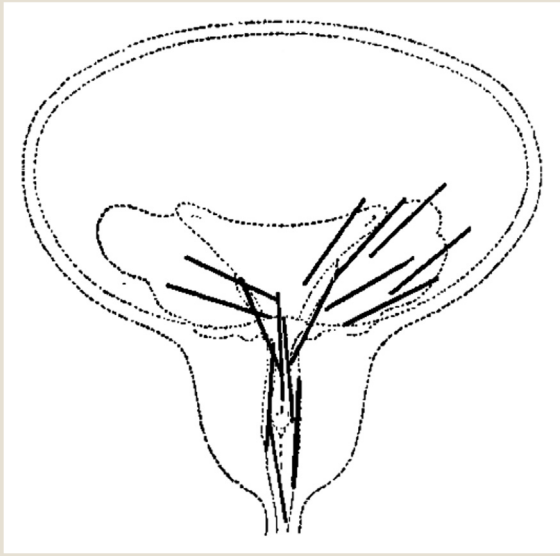
Brachytherapy (1911-Present)

Brachytherapy, or radioactive source implantation, dates back to 1911 when the French physician Octave Pasteau reported the therapeutic effects on prostate cancer with the insertion of radium catheters into the urethra.[6] Hugh Hampton Young, already the pioneer of the prostatectomy, experimented with revised methods and new instruments for brachytherapy through 1917.[7] During Dr Young's career, the radium sources were implanted using needles without any type of image guidance, making placement and dose planning unpredictable and bladder-wall implantation common (Fig. 1). Ultimately, the significant side effects attributed to poor planning caused brachytherapy to fall out of favor.

In 1952, Dr Rubin Flocks at the University of Iowa described his experience using an aqueous solution of ^{198}Au isotope.[8] The patients selected for this procedure were considered inoperable but without evidence of distant metastasis. Gold was selected over radium based on its reduced half-life and its ability to form a suspension. Unfortunately, significant injury to the rectal mucosa was reported in up to a third of cases. Gold ultimately lost popularity likely because of expense and a high complication rate, but the interest in brachytherapy remained.

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2013.08.003

Figure 1 Radium Needles Inserted by Hugh Hampton Young in 1917. Significant Toxicity Resulted From Seed Placement in the Bladder Wall During Early Brachytherapy Attempts



Between 1956 and 1971, Dr Willet Whitmore experimented with various isotopes, including ^{222}Radon, ^{192}Iridium, and ^{125}Iodine. Ultimately he reported a novel ^{125}I technique in which the source was sealed in titanium cylinders and implanted into the prostate using an open retropubic approach.[9] The procedure was considered "well tolerated" despite patients remaining hospitalized for up to 9 days after the open procedure. Dr Whitmore's work, however, was considered groundbreaking because of a low complication rate, with 19 of 26 patients reporting no complications. This represented a significant leap forward from earlier brachytherapy experiences and revitalized interest in brachytherapy as a feasible method of prostate cancer therapy.

Although the retropubic approach to seed implantation provided proof that when placed properly, radioactive seeds are well-tolerated, the open procedure had few advantages over a retropubic radical prostatectomy. It was not until percutaneous source placement could be guided that the true advantages of brachytherapy were realized. In 1983, Dr Holm from Denmark applied transrectal ultrasound to the guidance of ^{125}I seed placement.[10] This new technique allowed for accurate dose distribution, minimized the risk of injury to the nearby bladder or rectum, and spared the patient an open procedure, thus capitalizing on the advantages of low-dose rate (LDR) brachytherapy.

In the modern era, the Radiation Therapy Oncology Group (RTOG) 00-19 phase-II trial combined LDR brachytherapy with dose-reduced external beam in an attempt to achieve dose escalation by exploiting the dosimetric advantages of each technique.[11] In this study, the authors concluded that the grade 3 toxicity was elevated when compared with other RTOG studies using external beam radiation therapy (EBRT) or brachytherapy alone. However, in the absence of long-term randomized data, the exact benefit of this approach remains unclear. RTOG 0232 will provide the first phase III data investigating the combination of EBRT with LDR brachytherapy, therefore highlighting the importance of randomized trials in the evolution of radiation therapy techniques.

High-dose rate (HDR) brachytherapy was designed to further address planning challenges and was first described in a textbook report by Bertermann and Brix published in the Netherlands in 1990.[12] This technique employs a temporary ^{192}Iridium source rather than permanent ^{125}I seeds. The advantage to HDR brachytherapy is that the placement of the source is verified using computed tomography (CT) imaging before irradiation. Martinez et al at William Beaumont published the first phase I/II data documenting the procedure's feasibility in 1995, a study which was followed by multiple investigations into the potential use of HDR brachytherapy as a boost to external beam in intermediate- to high-risk patients.[13-16] In 1999, investigators began to consider the use of HDR treatments alone in low-risk prostate cancer patients.[17,18] There have been 2 single-institution phase III trials investigating the benefits of HDR boost to EBRT with each author concluding that there was a benefit to dose escalation.[19,20] Recently, the American Brachytherapy Society published a consensus statement regarding the use of HDR brachytherapy.[21] Although there is evidence for the role of HDR brachytherapy, in the absence of high-quality, multiinstitutional randomized data with patient-reported toxicity outcomes, the choice of technique remains the personal preference of the physician.

Early External Beam Radiation Therapy (1904-1960)

The evolution from kilovoltage radiation therapy through the development of modern megavoltage therapy defines the most significant development in the first 50 years of prostate therapy. External beam radiation was first used to treat prostate cancer by the French physicians Imbert and Imbert in 1904, seven years prior to the introduction of radium catheters.[22,23] Waters and Pierson provided the first report of palliative radiation for bone metastases from prostate cancer in 1923[24] but it was not until 1930 that Smith and Peirson reported on definitive local therapy. Despite the prostate residing deep within the pelvis, 200-kV Röntgen rays were used, given to an "erythema" dose from 1 anterior and 1 posterior field (Anteroposterior (AP)/Posteroanterior (PA) technique) with an occasional perineal field.[25] Although results showed an excellent relief of pain, external radiotherapy showed insufficient efficacy because of the superficial dose deposition of kilovoltage therapy and an inability to localize the prostate.[25,26] Indeed, as late as 1946 there were no reported cases of cure using radiation alone.[27] In 1941, when Huggins, Stevens, and Hodges reported the discovery of androgen deprivation, external radiation as a definitive cure lost popularity.[28]

In the mid-1950s, just as the limitations of androgen deprivation were realized, Flocks et al described the new ^{198}Au interstitial therapy, results which ignited a renewed interest in radiation as an adjunct therapy.[8] In the same year, Henry Kaplan and Edward Ginzton began attempts to build a new high-energy medical linear accelerator after hearing about a new "atom smasher" at a cocktail party. Determined to apply this technology to medicine, the first patient was treated in 1956. A child with retinoblastoma, having