Radiotherapy for localized prostate cancer

Thomas J. Eichler, MD

Thomas Johns Cancer Center, Richmond, Virginia, USA

EICHLER TJ. Radiotherapy for localized prostate cancer. The Canadian Journal of Urology. 2007;14(Supplement 1):19-23.

Over 200000 cases of prostate cancer will be diagnosed in the United States in 2007. Management of this common malignancy is controversial with essentially equal long-term survival and local control with either surgery or radiation therapy stage for stage in the setting of localized disease. Factors that can affect treatment recommendations include stage and grade of disease, the pre-treatment PSA, physician bias and patient choice. This paper examines several of the radiotherapeutic options for the treatment of prostate cancer, and will also discuss evolving modalities that may offer additional treatment choices in the future.

Key Words: radiation, radiotherapy, external beam, EBRT, 3D CRT, IMRT, IGRT, brachytherapy, protons, hypofractionation

Introduction

Radiation has been an important modality for the treatment of cancer since shortly after the discovery of x-rays by Wilhelm Roentgen in November 1895. The role of therapeutic radiation in the management of cancer has evolved over the past century into a distinct medical specialty devoted to the research and treatment of a variety of neoplastic processes, including prostate cancer.

The American Cancer Society estimates that there will be over 219000 cases of prostate cancer diagnosed in the United States in 2007 with a projected 27000 deaths. African American men and Jamaican men of African descent have the highest incidence of prostate cancer in the world. As daunting as these figures might appear, however, the number of deaths from lung cancer dwarfs that of prostate cancer with nearly 90000 men expected to die in 2007.[1]

Multiple treatment options exist for the management of localized prostate cancer and depend on a variety of factors, most notably the stage and grade of the disease and the pretreatment prostate specific antigen (PSA) level. Surgical options include a standard radical retropubic prostatectomy, a transperineal prostatectomy, a laparoscopic prostatectomy or a robotic procedure. Radiotherapy options are equally varied with a choice of either some form of external beam radiation therapy (EBRT) or brachytherapy. External beam options include three-dimensional conformal radiotherapy (3D CRT) or the more technically sophisticated formats including intensity modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT). Low-dose-rate (LDR) prostate brachytherapy is an increasingly popular option for many men. Combined modality therapy using LDR or high-dose-rate (HDR) brachytherapy and some form of EBRT may also be offered for intermediate and high-risk prostate cancers. Androgen deprivation may be a useful adjunct for surgery or radiotherapy. Cryotherapy is another choice for treating prostate cancer although many centers prefer to reserve cryotherapy for salvage of radiotherapy failures. Active surveillance and watchful waiting may be offered to selected men depending on stage, grade, PSA and a variety of additional co-factors.

Address correspondence to Dr. Thomas J. Eichler, 1401 Johnston-Willis Drive, Richmond, VA 23235, Richmond, Virginia, USA

Defining biochemical failure after radiation therapy

The normal range for PSA is 0 ng/ml-4 ng/ml with variation according to patient age. Settling on a definition for what constituted biochemical failure following treatment with radiation, however, proved to be a more difficult task. An American Society of Therapeutic Radiology and Oncology (ASTRO) consensus conference met in 1996 and agreed that patients with three consecutive rises in their PSA value post radiotherapy would be considered a treatment failure.[2] Multiple problems with this definition soon became evident: it was restricted to EBRT monotherapy, a sensitivity to length of follow-up, the potential for false positives due to benign PSA bounces and the lack of correlation with clinical progression of disease. In addition, there was the issue of the actual date of failure which was put at the midpoint between the end of treatment and the first PSA rise, creating a possible backdating artifact.

ASTRO recognized these problems and convened a second conference in Phoenix in 2005 leading to a new definition, PSA nadir + 2 ng/ml (or more) with failure "at call", i.e., no backdating.[3] The so called Phoenix Definition has supplanted the earlier ASTRO definition, although this earlier value still has merit when looking at the older literature.

External beam radiation therapy

Beginning in the early 1960's, the standard field arrangement for treating prostate cancer was a simple anterior-to-posterior/posterior-to-anterior (AP/PA) set-up to deliver 6000 rads to 6500 rads (radiation absorbed dose) with significant GI and GU toxicity consisting of diarrhea, urinary frequency, nocturia and dysuria. This evolved to a 4-field technique that added right and left parallel opposed fields to the AP/PA design with a modest decrease in morbidity and a slightly higher dose in the range of 6840 rads (or centiGray, cGy), delivered at 180 cGy/day in 38 fractions, Monday through Friday. The final 2340 cGy was often delivered using a smaller set of fields arranged as right and left 120 degree arcs designed to spare portions of the rectum and bladder. This technique remained popular until the mid 1990's when CT simulation, coupled with improvements in computer software, led to the development of three-dimensional reconstruction of anatomic structures. This was a major step in better understanding the true relationship between the target volume and the surrounding normal tissues, thus permitting tighter blocking schemes and subsequently leading to the safe escalation of the radiation dose. Three-dimensional CRT was initially performed with standard, bulky mounted cerrobend blocks, a fairly cumbersome arrangement given block shifts in millimeter increments that were often necessary for fine-tuning a 3D CRT set-up. This eventually gave way to the advent of multileaf collimation whereby motorized, computer-controlled leaves in the head of the linear accelerator were used to tightly shape a prospective radiotherapy treatment field with a higher degree of reproducible precision. A typical 3D CRT set up consists of six coplanar fields, usually with 10 mm-15 mm margins around the prostate.

At the same time, major academic institutions were evaluating an innovative technique for irradiating tissue with unparalleled accuracy by modifying the radiation dose as it was being delivered. The genesis of this revolutionary treatment was the aforementioned multileaf collimation that was now being used to temper the dose of radiation in real time, permitting increasingly tighter margins to be employed with similarly escalating doses. This breakthrough, known as intensity modulated radiation therapy or IMRT, is arguably the most important advance in the delivery of therapeutic radiation since the introduction of the linear accelerator in the early 1950's. Dozens of computer-controlled leaves move in and out of the radiation beam during daily treatments to attenuate the beam in such a way to provide sharp edges around the target volume, thereby sparing more normal tissue. Doses quickly escalated from 6840 cGy to 7200 cGy then to a relatively standard dose of 7560 cGy at 180 cGy x 42 fractions. Set-up typically consisted of 5-7 non-coplanar fields with an anterior margin of 7 mm-10 mm and a posterior margin of 5 mm-7 mm. Treatment usually was delivered in approximately 15 minutes. IMRT has been rightfully hailed as a significant advance in the radiotherapeutic management of prostate cancer and, with its' predecessor 3D CRT, has become the standard of care.

It was (and continues to be) universally accepted that the accuracy of radiotherapy is only as good as the daily reproducibility of the treatment field. Weekly port films have been performed for decades as a standard quality assurance measure in an attempt to document this struggle to achieve perfection. The words "image guidance", however, crept into the radiation oncologist's lexicon nearly 10 years ago when the daily use of abdominal ultrasound was employed to improve the accuracy of 3D CRT and IMRT prostate set-ups, marking the beginning of the age of image-guided radiation therapy, better known today as IGRT. On Board Imaging (OBI) is also being used with cone beam CT scans or

kV/mV films of the patient in the treatment position with images acquired daily. These images are superimposed on the original simulation film to compare the two set-ups, with positioning adjustments made in near-real time, resulting in a new paradigm in radiotherapy precision. All of the major manufacturers, including Varian (Trilogy), Siemens (Primatom) and Elekta (Synergy) have equipment capable of performing IGRT, as well as other companies such as TomoTherapy, Inc. (Tomotherapy), Novalis Brain Lab (ExacTrac) and Accuray (CyberKnife).

Prostate IGRT can be accomplished in a number of different ways but the most popular method appears to be using OBI with or without implanted fiducial markers. These markers, consisting of three gold seeds, are inserted into the prostate gland under ultrasound guidance by the urologist. CT simulation films are then obtained with daily OBI to corroborate set-up accuracy. Not everyone, however, may be an appropriate candidate for implantation of fiducial markers, nor are they absolutely necessary for employing OBI. Normal structures, i.e., bony anatomy, offer as very reasonable alternative to fiducials with little drop off in accuracy to the trained eye. The radiation treatment itself can be delivered using either an IMRT or 3D CRT technique.

The use of image-guidance with IMRT has not only permitted safer dose escalation but has also resulted in a significant improvement in treatment-related morbidity. Most patients experience some increase in urinary frequency and nocturia, often accompanied by dysuria of varying degrees. Bowel movements may also increase in frequency, rarely progressing to frank diarrhea. Potential long-term side effects include hematochezia and hematuria, both of which are uncommon.

Brachytherapy

Low-dose-rate prostate brachytherapy has grown incrementally over the past 15 years. Brachytherapy can deliver a large dose of radiation to the prostate and proximal seminal vesicles while maintaining safe doses to the bladder, rectum and urethra. So-called "open" procedures with poor dosimetry have been supplanted by ultrasound techniques with excellent coverage of the prostate gland. There are two prevailing philosophies regarding implant technique, preplanned versus real time.

Preplanned implants rely on a preoperative volume study with the number and location of the needles and seeds determined in advance. In this method, the bulk of the work is done before the actual implant with the expectation that the volume study at the time of the procedure will precisely match the plan. Real time implants, on the other hand, are designed in the operating room at the time of the procedure with needle and seed placement determined by the live volume study. There is minimal preoperative labor with this type of implant although the procedure itself usually takes longer. A well-executed preplanned implant can be done in 20-45 minutes while a real time procedure can take from 45-90 minutes. Implants are usually done under general anesthesia but spinal anesthesia and even techniques using local anesthesia may be employed. Most implants are still done in the hospital operating room although the ambulatory surgery center setting has become increasingly popular in the United States for economic reasons. Patients usually go home a couple of hours after the procedure with a 3-7 day recovery time.

The two most popular isotopes for brachytherapy are ^{125}I and ^{103}Pd. From a therapeutic standpoint, there is no significant difference between these two isotopes; they both effectively treat prostate cancer.[4] The principal difference lies in their half-lives. All isotopes require six half-lives to decay from 100% activity down to ~1% (100-50-25 etc.). The half-life of ^{125}I is 60 days, meaning that it takes nearly a full year, 360 days, for an ^{125}I implant to deliver its full dose. The half-life of ^{103}Pd, on the other hand, is only 17days with an active life of ~3 and a half months or 102 days. ^{125}I is most often used for patients with low-intermediate risk disease whereas ^{103}Pd is frequently implanted in higher risk patients. These seeds are available from a number of manufacturers and may be "loose" or "stranded". Small studies have concluded that there is no dosimetric advantage to one over the other but that the rate of seed embolization is significantly lower with stranded seeds.[5-7] Bard Urologic has developed a device called the Quicklink which uses loose seeds to custom design stranded seeds in real time for implant.

LDR brachytherapy may be used as the sole treatment for patients with low and intermediate risk disease or in combination with some form or external beam radiotherapy for patients with high risk prostate cancer, i.e., stage T2c or higher, Gleason score ≥ 8 or PSA > 20. In the high risk setting, the implant dose is reduced by one-third with the addition of an external beam dose of 4500 cGy. The rationale for combined modality treatment rests on the fact that seeds alone cannot adequately treat disease that may extend beyond the prostate capsule or into the seminal vesicles. The external beam field is designed to cover the seminal vesicles in their entirety as well as providing a margin around the prostate to accommodate the risk of extracapsular extension. The sequencing of the procedures does not appear to be

critical although patient compliance may be better with EBRT followed by implant. When a partial implant is done at the outset, EBRT usually follows after a 2-month interval.

HDR brachytherapy using a ^{192}Ir source may also be used in combination with EBRT for management of localized prostate cancer. The most common protocol is to perform two or three HDR implants following a dose of approximately 4500 cGy with EBRT. There is also growing institutional experience looking at HDR brachytherapy alone, similar to the more common LDR brachytherapy implant.

The side effects from brachytherapy are similar to what is often noted during external beam radiotherapy. Patients will usually experience an increase in urinary frequency with some urgency and dysuria. The urinary stream may also be slower. Most men, however, note little change in their bowel habits. These acute effects resolve over a period of several weeks to months. Long-term side effects include the potential for hematuria and hematochezia of varying degrees, urethral stricture and the remote chance of a urethrorectal fistula.

A look into the future

As healthcare costs continue to skyrocket, two very different treatment paradigms will take center stage for the radiotherapeutic management of prostate cancer. One, proton therapy, is technically feasible but expensive with limited availability. The other involves manipulating the radiobiology of the prostate and surrounding normal structures to devise a plan that uses conventional radiotherapy but with fewer, higher dose fractions, known as hypofractionation, with the caveat that it is demonstrably less expensive than protons and, potentially, more effective.

Protons have, literally, been around since the beginning of time. Their use in the management of cancer had been largely limited to the treatment of certain eye tumors, spine and base of skull lesions. The attraction of protons has been the deposition of energy at depth, the so-called Bragg Peak, with relative sparing of the superficial structures. Special filters are now applied to spread out the Bragg peak to conform to the tumor with a sharp dose drop off. Studies dating back into the '70's from Shipley, et al, at Massachusetts General Hospital (MGH) have demonstrated the potential for using protons as a boost for treating prostate cancer.[8] Recent data from MGH suggests that a high dose proton boost to the prostate may improve the duration of biochemical control in low and intermediate risk men but offer no discernable advantage for high risk patients with no significant difference in toxicity.[9]

Despite the lack of data to support their use in the majority of malignancies, proton centers are popping up around the US. The science of medicine suggests that there may be a role for protons in the future. The business of medicine, however, will attempt to take advantage of lucrative reimbursement for proton therapy, a situation that, in a time of diminishing resources, almost certainly will not last. Unless there are well-designed clinical trials that clearly establish the superiority of protons over photons, the future of this expensive but exciting technology may be in jeopardy.

Another school of thought is looking at the radiobiology of prostate cancer in an attempt to exploit differences in the response of the prostate and the surrounding normal structures to fewer but larger doses of radiation. This theory of hypofractionation examines the dose rate for treating prostate cancer, in particular the concept that the prostate may be more sensitive to the dose rate than the surrounding normal structures, the bladder and the rectum. It is beyond the scope of this paper to describe the nuances of the α/β ratio and the linear quadratic model but simply stated, a lower ratio suggests greater sensitivity to radiation. Several authors have postulated that the α/β ratio for the prostate is between 1 and 3 with a ratio for the rectum of 6. It is this difference that Fowler et al at the University of Wisconsin used to create their model that suggested that 10 large fractions delivered over no less than 5 weeks could yield a 15%-20% improvement in biochemical (PSA) control rates.[10]

MD Anderson treated 100 consecutive patients to 7000 cGy at 250 cGy x 28 fractions over 5 and a half weeks with a median follow-up of 66 months.[11] Using either of the definitions for evaluating biochemical failure following radiation, the results from this trial are very encouraging: overall 5-year bRFS was 97%, 88% and 70% for low, intermediate and high risk disease using the original ASTRO definition, with the Phoenix Definition giving results of 97%, 93% and 75%. Grade 3 rectal toxicity was 3% with only 1% grade 3 urinary toxicity.

Fox Chase Cancer Center in Philadelphia has also evaluated hypofractionation for prostate cancer and concluded that 270 cGy x 26 to 7020 cGy was well tolerated with acceptable acute toxicity.[12]

Building on these studies, the RTOG is currently accruing patients for a phase III randomized trial (RTOG 0415) looking at conventional doses of radiation (180 cGy x 41 fractions to 7380 cGy) versus hypofractionation (250

cGy x 28 fractions to 7000 cGy).[13] In addition, the phase III OCOG PROFIT study is accruing intermediate risk patients and will compare 78 Gy in 39 fractions versus a hypofractionation arm of 60 Gy and 20 fractions.[14] The results of these trials may provide the necessary impetus for changing the way we treat prostate cancer with EBRT using fewer, larger fractions with a potential cost savings.

Conclusion

Prostate cancer continues to be a frequently diagnosed malignancy in American men. External beam radiotherapy and brachytherapy are excellent modalities for treating this disease with acceptable morbidity. The use of protons continues to grow but hypofractionation may ultimately become the standard for EBRT with shorter treatment times and the potential for significant cost savings.

Disclosure

None □

References

1. American Cancer Society. Estimated New Cancer Cases and Deaths by Sex for All Sites, US, 2007. In: Cancer Facts and Figures 2007. Atlanta: American Cancer Society; 2007.
2. Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997 15;37(5):1035-1041.
3. Roach M 3rd, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;15;65(4):965-974.
4. Cha CM et al. Isotope selection for patients undergoing prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1999;45(2):391-395.
5. Kaplan ID et al. A comparison of the precision of seeds deposited as loose seeds versus suture embedded seeds: a randomized trial. *Brachytherapy* 2004;3(1):7-9.
6. Spadinger I et al. Prostate brachytherapy postimplant dosimetry: a comparison of suture-embedded and loose seed implants. *Brachytherapy* 2006;5(3):165-173.
7. Reed DR et al. A prospective randomized comparison of stranded vs. loose 125I seeds for prostate brachytherapy. *Brachytherapy* 2007;6(2):129-134.
8. Shipley WU et al. Proton radiation as boost therapy for localized prostatic carcinoma. *JAMA* 1979;241(18):1912-1915.
9. Zietman AL et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;294(10):1233-1239.
10. Fowler JF et al. What hypofractionated protocols should be tested for prostate cancer? *Int J Radiat Oncol Biol Phys* 2003;56(4):1093-1104.
11. Kupelian PA et al Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: long-term outcomes. *Int J Radiat Oncol Biol Phys* 2005;63(5):1463-1468.
12. Pollack A et al. Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. *Int J Radiat Oncol Biol Phys* 2006;64(2):518-526.
13. RTOG website http://rtog.org/members/protocols/0415/0415.pdf
14. ClinicalTrials.gov website http://clinicaltrials.gov/show/NCT00304759