Comparisons of External Beam Radiation Therapy, Brachytherapy, and Combination Therapy in the Treatment of Prostate Cancer

Blakely Dueitt

Introduction

Cancer is caused by a group of uncontrollably dividing cells (American Cancer Society 2001). The rapid cell divisions cause excess tissue mass (a tumor), which causes compression of surrounding organs and glands, resulting in damage to the normal tissue cells. Advanced cancer cells can break off from the original tumor, travel through the body via the blood, and start a secondary tumor called a metastasis (National Institute of Health 1990, 1996). Different cancers may behave quite differently. Here, prostate cancer and treatment methods will be reviewed.

Prostate cancer is the most common non-skin form of cancer found in men. The American Cancer Society has estimated that 198,000 new cases of prostate cancer will appear in 2001, mainly in men over the age of 50. Prostate cancer appears twice as often in African American men than in any other race and more often in US, Canada, and northwestern Europe than any other countries.

The affected gland, the prostate, is found at the base of the penis, inferior to the bladder and anterior to the rectum. It is about the size of a walnut and covers the urethra. The prostate functions in producing a fluid in semen and is involved in erections (American Cancer Society 2001). There are certain symptoms associated with prostate cancer. These symptoms result from the swelling of the prostate and the compression caused by the enlarged tissue mass. Since the prostate gland encompasses the urethra, men can experience frequent urination, weak or interrupted urine flow, pain or burning with urination, blood in urine, or the inability to urinate. However, a diagnosis cannot be made on these symptoms; a pathologic analysis must be the diagnostic factor (National Institute of Health 1990).

There are many different treatment options for prostate cancer. The method of treatment is dependent on many factors, including the stage of the cancer and the age of the patient. There are six major courses of treatment from which a patient and his physicians may choose: surgery, radiation therapy, hormone therapy, chemotherapy, watchful-waiting, and palliation. Surgery involves the removal of the prostate (prostatectomy) or the removal of cancer tissue in the prostate (transurethral resection of the prostate, TURP). Radiation therapy uses high-energy rays or seeds to destroy tissue. Hormone therapy, used for spreading cancers, works by decreasing androgen production; it is often used in conjunction with other treatment methods. The watchful-waiting method is typically used on older patients that may not physically be able to handle other treatments. Palliative treatments are used when the cancer has progressed beyond the scope of cure. In palliation, the pain is treated with medicine or external beam radiation.

Three types of radiation therapy are reviewed below. Each treatment option has its advantages and its disadvantages, and different goals and purposes which can be individualized for each patient. Research and debates about these radiation therapy methods are occurring constantly in hopes that improvements can be made so that the confidence in each treatment may be raised.

Basics in Radiotherapy

The hopes of radiation exist with "repairing" patients to "good, sound or healthy conditions (Bedford 2001)." Radiation causes chromosomes to break, exposing part of the DNA. The bases of the exposed DNA are damaged, causing the DNA to split. After the DNA breaks, the cancer cells cannot repair themselves. The DNA of cells is only vulnerable to breakage in certain stages of the mitotic process. Repeated doses of radiation are given to the patients so that all cells can be in the vulnerable stage at one point (Bedford 2001).

External Beam Radiation Therapy

External beam radiation therapy (EBRT) is the one of the oldest techniques used to treat prostate cancer. With external radiation, electrons of high-energy electromagnetic waves are accelerated so that they hit a metallic target and yield photons. The photons interact with surrounding tissues producing high-speed electrons that are able to split water molecules. The split water molecules yield a hydroxy radical, which causes damage to the DNA of rapidly dividing cells, including tumor cells. Normal cells do not experience as much of a deadly result as tumor cells do because normal cells are not dividing as rapidly and normal cells have the ability to repair the damaged DNA. Tissue cell death is partly measured by the lack of oxygen in the tissue (hypoxia) and the fraction of dividing cells compared to the number of non-dividing cells (Wolfson 1999).

There are two main goals that can be achieved with external radiation therapy, palliative and curative. In patients with low-grade prostate tumors, low-grade beams should be used so that the cancer can be controlled, while at the same time be slowly reduced. However, with some medium-grade tumors, high-energy beams should be used so that the cancer cells may be destroyed more quickly. In both of these cases, a cure is the goal (Lattanzi et al. 2000). Use of adjuvant external radiation therapy is suggested mainly for patients under age 75 with localized tumors (Hazra 1978). Although external beam radiation therapy may be used for curative purposes, it is often regarded as a palliative treatment method.

There is much to consider while administering external beam radiation therapy. This includes the pre-planning, the administration of the beams, the chemistry behind the therapy, and the current research being performed. In the planning procedure, patients should have an evaluation similar to a diagnostic evaluation. After the evaluation, physicians perform bone scans to test for metastases and CT scans of the abdomen and pelvis, which aid in defining the prostate area and area of normal tissue. The prostate area is further defined using an urethrogram with a bladder contrast and a rectal marker (Vicini et al. 2000). Physicians use the evaluation and the diagnostic tests and scans to prescribe the dosage, since the dosage is based on the initial tumor stage and tumor size. While prescribing the dosage, doctors must consider the tolerance of the normal tissues; strong doses may be too high for normal tissue recovery (Wolfson 1999). Once the planning is finished, the actual treatment may begin. Most often, a four-field technique is used, which covers the prostate, the seminal vesicles, the pelvic lymph nodes, and a 1.0-cm margin around the three fields (Lattanzi et al. 2000). Each field is treated daily with approximately 200 rads ("radiation absorbed doses") for 5 to 6 weeks, with an additional treatment "boost" of 1,500 rads to the prostate at the end of treatment (Hazra 1978). Each daily treatment is given within a few minutes, allowing the radiation to reach the cells, but not actually affect the cells until later. The brief exposures, with time in between each dose, allow the normal cells some recovery time (Bidmead 2001).

One of the major problems in external beam radiation methodology results from the necessity of daily dose treatments, each of which requires realignment of the beams according to the original CT scans. In the past, studies have shown unnecessary damage to normal tissue because of alignment errors. In a particular study reported by Lattanzi et al., 189 alignment errors were recorded for 54 patients. Over half of the time there were 5 mm or greater alignment errors in the anterior-posterior plane; a third of the time there were errors in the lateral, as well as in the superior-inferior plane. To help prevent these errors, research is being performed on the use of ultrasounds combined with CT scans in the alignment process. CT scans from the planning are used in conjunction with real-time images provided by an ultrasound at each treatment to create sagittal and transverse planes which can redefine the cancerous areas (which have shrunk over the treatments). With redefined areas, the centers of each field and dosages can be adjusted so that the optimal radiation levels and positions are used (Lattanzi et al. 2000).

External beam radiation therapy carries some positives and negatives that must be considered. Two great advantages exist: patients experience no pain with the actual procedure and the clinical failure rate is quite low (15% when measured after 2.5 years) (National Institute of Health 2000). However, the list of negatives is longer than the list of positives. On a superficial level, daily hospital visits for 5 to 6 weeks is a great inconvenience to many and usually interferes with work and other daily activities (Korb 2000). On a health level, patients may experience no improvement in pain, and may experience hemorrhoids, diarrhea due to inflammation of the rectum, frequency in urination due to inflammation of the bladder, fatigue and perhaps impotency (Monga et al. 1999).

Brachytherapy

Brachytherapy, an intraoperative procedure that places radioactive materials within the tumor, has developed greatly over a century. The United Kingdom's Saint Bartholomew's Hospital first used radium brachytherapy in 1906 (Aird 2001). In 1913, doctors treated prostate tumors with brachytherapy for the first time. Nevertheless, the results of the prostate brachytherapy were not favorable, and too many complications existed (Nori and Moni 1997). Changes were made to the first isotopes used because bones were being unhealthily affected by the radiation, the specific activities of the isotopes were low, and the actual gamma rays emitted were too high. Scientists searched for appropriate radiation sources, and found that for an isotope to be a good source, it should have a high specific activity, have a half-life appropriate for the type of treatment (long half-life for permanent implantation and short half-life for temporary implantation), have a medium to low photon energy for protective reasons, have a non-powder form (so that it may be more easily handled), and should not evaporate. Good isotopes include Cesium-137, Iridium-192, Iodine-125, and Palladium-103 (Aird 2001). Even with all of the brachytherapy research occurring, the use of brachytherapy to treat prostate cancer declined until the 1970's when doctors began using Iodine-125. Brachytherapy treatment for prostate cancer was not used often because of the rare number of successes; successes only occurred when there was good seed placement and appropriate dosage, both of which were hard to do because of the lack of visual knowledge and guidance techniques.

The advances and acceptance of prostate brachytherapy seemed to parallel the advances in imaging (i.e. CT scans and ultrasounds); with the ultrasound and the perineal approach, brachytherapy began its climb to worldwide acceptance and usage (Nori and Moni 1997, Radge and Korb 2000). In the 1990's, a brachytherapy seed shortage occurred. Factory production of the seeds followed the shortage so that there could be certainty that a second shortage would never again occur. Since then, brachytherapy has become commonplace with its simple procedure and short recovery time (Radge and Korb 2000).

The practices and procedures of brachytherapy are important in establishing a basic understanding and view of the therapy. Foremost, there must be teamwork between the oncologist and the surgeon before and during the procedure so as to assure the utmost quality, accuracy, and safety of the implantation (Hu and Harrison 2000). Prior to the surgery, a patient is placed on a clear liquid diet without any oral antibiotics, is asked to have an enema, and is involved in a preplanning procedure. Three basic steps in planning include assessing the prostate volume, determining the optimal and minimum dosages, and determining the appropriate placing of the radioactive seeds. Usually, local anesthesia is used, however physicians may use general anesthesia if need be (Nori and Moni 1997). The patient is placed on his back so that the ultrasound probe can be inserted into his rectum. With the probe, doctors can link the prostate with the external equipment used for inserting the radiation seeds. The ultrasound images are compared to the images used during planning, on which the placement of the seeds is determined. Through the use of both of these images, a physician is able to insert the needles loaded with the seeds (Nori and Moni 1997, Radge and Korb 2000). After seed implantation, the accuracy of the seed positioning is observed through a double imaging technique including ultrasound and fluoroscopy. Seeds may be added if a portion of the prostate appears bare (Radge and Korb 2000). Physicians may also use computer programs to analyze an implant and the effective doses distributed to the gland and the surrounding tissue. The program can give optimal doses of radiation for each area of the prostate.

Comparisons before and after implantations are very easily performed with the computer (van der Laarse and Luthmann 2001). Only after all observations are complete and the surgeon feels comfortable with the procedure is the procedure finished. Most patients are given an antibiotic, an anti-inflammatory, and an alpha-blocker to help urine flow after surgery. With the help of these medications, patients are able to return to normal activity within one or two days (Radge and Korb 2000).

Currently, there are two main isotopes that are used for permanent brachytherapy, I-125 and Pd-103. There have not been any clinical trials that compare the benefits and problems of the two isotopes mainly because the patients selected for each source are quite different; however, comparisons can be made between the isotopes by observing data for complications and successes for each isotope (Peschel et al. 1999). The isotopes have many differences, as well as advantages and disadvantages. Both are capsulated in titanium on a 4 mm by 0.8 mm diameter silver rod (Aird 2001). The main difference is present in the half-lives of the isotopes; Pd-103 has a half-life of 17 days and has lower photon energy, whereas I-125 has a half-life of approximately 60 days and higher photon energy. With a shorter half-life, the original dose of Pd-103 is higher, meaning that Pd-103 is better for more quickly growing tumors. Iodine-125 is usually used on patients with low-grade tumors. Studies comparing I-125 and Pd-103 on rat cells support the use of iodine for slow growing tumors and palladium for more quickly growing tumors. However, studies at Yale and Blasko have compared the side effects of the two isotopes, suggesting that Pd-103 is the better isotope (Peschel et al. 1999). Yale and Blasko studies have shown that complications with I-125 are greater than with Pd-103. At Yale, 18 percent of patients experienced side effects with I-125 and patients treated with Pd-103 experienced no side effects. Similar data was observed at Blasko (Peschel et al. 1999).

Two different doses are available for brachytherapy, low dose and high dose. Each is used for different treatment purposes. Low-dose rate brachytherapy is beneficial because it allows time for the normal tissue cells to recover (Brenner et al. 2001). High-dose rate brachytherapy is used on localized prostate tumors to improve control without losing normal tissue. However, with high-dose rate, there is a remedial loss because it is challenging to deliver an effectively safe dose (Hoskins 2001).

Low-dose rate and high-dose rate often factor into decisions concerning the use of temporary or permanent brachytherapy. Temporary brachytherapy uses Iridium-192 and can be done in a single visit or in multiple visits. With a single visit, the low-dose seeds are implanted and the patient must stay in the hospital for a few days, with the seeds being removed on the last day. The major disadvantage of single-visit, temporary brachytherapy is the potential danger to the medical staff. With multiple visits, high-dose seeds are implanted and removed in the same surgical sitting (Nori and Moni 1997). Permanent brachytherapy involves a single hospital visit with low-dose seeds, which continually, for either 6 months (Pd-103) or 12 months (I-125), deliver radiation Permanent seeds are placed closely together because of the low dosage that is administered (Radge and Korb 2000). Permanent brachytherapy is the patient-preferred form because of its outpatient opportunity, consequently making permanent brachytherapy the most widely used form of brachytherapy by doctors (Nori and Moni 1997).

There are many advantages and disadvantages associated with brachytherapy. For most patients, the advantages far outweigh the disadvantages. Complications of brachytherapy are measured using the "Radiation Therapy Oncology Group grading system (grade I: minor symptoms requiring no treatment; grade II: symptoms requiring simple out-patient management but not affecting lifestyle; grade III: distressing symptoms altering lifestyle and requiring minor surgical intervention or hospitalization; grade IV: major symptoms requiring major surgical intervention or prolonged hospitalization; grade V: mortality) (Peschel et al. 1999)." Most of the negative effects of brachytherapy are in the short term. One study reported that only 8.8% of the patients experienced grade III or grade IV complications (Peschel et al. 1999). Most commonly, patients experience urinary tract infections due to the swelling of the prostate, pain, fatigue, and proctitis (Nori and Moni 1997; Arterbery 1997). One of the major disadvantages of brachytherapy is the chance of damaging normal tissue with an escaped radioactive seed; however, with pre-planning, unexpected normal tissue damage is rare (Hu and Harrison 2000). Also, brachytherapy is not the best treatment option for higher-grade tumors because seeds only radiate within a small radius of the prostate and do not reach metastases outside of the prostate area (Nori and Moni 1997).

Brachytherapy is a great treatment for many men because of its outstanding quality of life. Foremost, because brachytherapy is extremely localized, it is easier for doctors to spare surrounding normal tissue (considering all seeds stay in the planned space). Also, brachytherapy patients experience simple hospital schedules, with most being outpatients (Nori and Moni 1997). After being released from the hospital, patients are usually able to return to work within 3 days, making it an average of 8 total days missed, including the preplanning, the hospitalization, and the recovery days. Few patients showed reduced interest in sexual activity and/or lack of enjoyment of sex. On a whole, 100% of the brachytherapy patients would recommend the procedure to their friends, and 98% would choose the procedure again if they had the chance (Arterbery 1997).

Combination Therapy

In some cases, oncologists feel that combination therapy is the optimal treatment. Combination therapy involves external beam radiation therapy and brachytherapy (Radge and Korb 2000). It seems that the initial combination of the two treatments was perhaps a way of introducing brachytherapy without losing confidence in a treatment plan. However, throughout the decades, confidence in brachytherapy has increased and the use of combination therapy has decreased (Radge et al. 2000).

The combination of external beam radiation therapy and brachytherapy is not the best method for all patients. Actually, men with grade II tumors, which are palpable yet confined to the prostate, are the best candidates for joint treatment. The external radiation therapy is administered first so that it may shrink the tumor and treat any possible lymph node metastases (Wolfson 1999). Approximately one to three days after the initial external radiation treatment, patients receive the first brachytherapy treatment; patients receive a total of two or three implants with I-125, Pd-103, or Cs-137. The implants are performed seven to ten days apart. External radiation and brachytherapy are never administered on the same day, and the overall treatment period is finished within six weeks (Han et al. 1999, Radge and Korb 2000, Sakurai 2000).

The success and acceptance of combination treatment is debatable. Radge et al believe that there is not enough evidence to support the addition of external radiation therapy to brachytherapy for all patients (money and side effects were compared to higher success rates); they believe that the combination treatment is only good for high-risk patients (2000). On the other hand, some physicians believe that by combining the two treatments it is possible to increase the dosage without harming more normal tissues and thereby increase the actual survival rate (compared to either treatment administered alone) (Nori and Moni 1997). More studies are currently being performed so that a common view concerning the use of the combination treatment may be achieved.

Conclusion

Although external beam radiation therapy is the older technique, research suggests that brachytherapy is the best treatment of today's prostate cancer. The term "today's" cancer is used because cancer has changed due to the advances in screening techniques. Many times, prostate cancer can now be detected while it is still localized, therefore supporting the patient requirements for brachytherapy. As reviewed, brachytherapy is a great option for localized prostate cancer because of its convenience, excellent maintenance of quality of life, and few side effects. Brachytherapy is appealing to older men that are not physically able to withstand a complicated surgical prostatectomy, as well as for younger men that wish to maintain a normal life-style. As one may expect, the use of brachytherapy has increased with the increased number of localized tumors, while the use of external beam radiation therapy has decreased with the increased number of confined prostate tumors. Positive studies showing the long-term success of brachytherapy have also contributed to its increased use. It appears that through continual advances in brachytherapy and diagnostic techniques, the brachytherapy treatment method may become one of the best, most assuring and successful options for men affected with prostate cancer.

References

Aird E. 2001. Sources in Brachytherapy. In: Joslin CA, Flynn A, Hall EJ, editors. Principles and Practices of Brachytherapy. New York: Oxford University Press Inc. p 3-10.

[ACS] American Cancer Society. 2001 Oct. 1. ACS home page. <http://www.cancer.org>. Accessed 2001 Oct. 1.

Arterbery VE, Frazier A, Dalmia P, Siefer J, Lutz M, Porter A. 1997. Quality of Life After Permanent Prostate Implant. Serminars in Surgical Oncology 13:461-64.

Bedford JS. 2001. The Radiobiology of Low-dose-rate and Fractionated Irradiation. In: Joslin CA, Flynn A, Hall EJ, editors. Principles and Practices of Brachytherapy. New York: Oxford University Press Inc. p 180-185.

Bidmead AM. 2001. Dose-rate Effects with Human Cells. In: Joslin CA, Flynn A, Hall EJ, editors. Principles and Practices of Brachytherapy. New York: Oxford University Press Inc. p 180-88.

Brenner PA, Dale R, Orton C, Fowler J. 2001. Radiobiology of HDR, LDR, and PDR Brachytherapy. In: Joslin CA, Flynn A, Hall EJ, editors. Principles and Practices of Brachytherapy. New York: Oxford University Press Inc. p 189-204.

Campbell T, Blasko J, Crawford ED, Forman J, Hanks G, Kuban D, Montie J, Moul J, Pollack A, Raghavan D, et al. 2001. Clinical Staging of Prostate Cancer: Reproducibility and Clarification of Issues. Int. J. Cancer 96:198-209.

Gao X, Porter A, Grignon DJ, Pontes JE, Honn KV. 1997. Diagnostic and Prognostic Markers for Human Prostate Cancer. The Prostate 31:264-81.

Han I, Orton C, Shamsa F, Hart K, Strowbridge A, Deppe G, Porter A, Chuba PJ. 1999. Combined Low-Dose-Rate Brachytherapy and External Beam Radiation for Cervical Cancer: Experience Over Ten Years. Radiation Oncology Investigations 7:289-96.

Hazra TA. 1978. Radiation Therapy in Carcinoma of Prostate: Past Achievements

and Future Progress. Prog. Clinical Biol. Res. 25:99-104.
Hoskins PJ. 2001. High-dose-rate Afterloading Brachytherapy for Prostate Cancer. In: Joslin CA, Flynn A, Hall EJ, editors. Principles and Practices of Brachytherapy. New York: Oxford University Press Inc. p 257-65.
Hu KS, Harrison LB. 2000. Results and Complications of Surgery Combined with Intra-operative Radiation Therapy for the Treatment of Locally Advanced or Recurrent Cancers in the Pelvis. Seminars in Surgical Oncology 18:269-78. King CR. Patterns of Prostate Cancer Biopsy Grading: Trends and Clinical Implications. 2000. Int. J. Cancer 90:305-11.
Korb L. 2000. Radiotherapy for the Palliation of Prostate Cancer. Seminars in Surgical Oncology 18:75-79.
Lattanzi J, McNeeley S, Donnelly S, PalacioE, Hanlon A, Schultheiss TE, Hanks GE. 2000. Ultrasound-Based Stereotactic Guidance in Prostate Cancer: Quantification of Organ Motion and Set-Up Errors in External Beam Radiation Therapy. Computer Aided Surgery 5:289-95.
Mongra U, Kerrigan AJ, Thronby J, Monga TN. 1999. Prospective Study of Fatigue in Localized Prostate Cancer Patients Undergoing Radiotherapy. Radiation Oncology Investigations 7:178-85.
[NIH] National Institute of Health. 2000. Understanding Treatment Choices for Prostate Cancer. US Department of Health and Human Services; 44 p.
[NIH] National Institute of Health. 1996. What You Need To Know About Prostate Cacner. US Department of Health and Human Services; 33 p.
[NIH] National Institute of Health. 1990. Cancer of the Prostate: Research Report. US Department of Health and Human Services; 21 p.
[NIH] National Institute of Health. 1980. Science and Cancer. US Department of Health and Human Services; 109 p.
Neulander EZ, Duncan RC, Tiguert R, Posey JT, Soloway MS. Deferred treatment of localized prostate cancer in the elderly: the impact of the age and stage at the time of diagnosis on the treatment decision. 2000. BJU International 85:699-704.
Nori D, Moni J. 1997. Current Issues in Techniques of Prostate Brachytherapy. Seminars in Surgical Oncology 13:444-53.
Peschel RE, Chen Z, Roberts K, Nath R. 1999. Long-Term Complications with Prostate Implants: Iodine-12 vs. Palladium 103. Radiation Oncology Investigations 7:278-88.
Radge H, Korb L. 2000. Brachytherapy for Clinically Localized Prostate Cancer. Seminars in Surgical Oncology 18:45-51.
Radge H, Korb LJ, Elgamal A, Grado GL, Nadir BS. 2000. Modern Prostate Brachytherapy: Prostate Specific Antigen Results in 219 Patients with up to 12 Years of Observed Follow-Up. Cancer 89:135-41.
Sakurai H, Mitsuhashi N, Takahashi M, Yamakawa M, Akimoto T, Hayakawa K, Niibe H. 2000. Radiation Therapy for Elderly Patient with Squamous Cell Carcinoma of the Uterine Cervix. Gynecologic Oncology 77:116-20.
van der Laarse R, Luhmann RW. 2001. Computers in Brachytherapy Dosimetry. In: Joslin CA, Flynn A, Hall EJ, editors. Principles and Practices of Brachytherapy. New York: Oxford University Press Inc. p 48-80.
Wolfson AH. 1999. Conventional Radiation Therapy of Cervical Cancer. Seminars in Surgical Oncology 16:242-46.

Blakely Dueitt is a senior majoring in Biology from Louisville, KY. She was a Reader's Digest Fellow at New York University Medical Center in the Radiation Oncology Department.