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Current Advances in Prostate Brachytherapy

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CURRENT ADVANCES IN PROSTATE BRACHYTHERAPY

STATEMENT OF OBJECTIVES

The purpose of this continuing education lesson is to provide an overview of the role of brachytherapy in the management of prostate cancer. This lesson describes the benefits of brachytherapy when compared with other forms of treatment such as surgery and external beam radiotherapy. To develop an appreciation of the role of brachytherapy in a disease such as prostate cancer, the lesson can be considered to be in two parts.

The first part describes the etiology, physiology and pathology of prostate cancer. This information is necessary to provide the reader with knowledge vital to develop an understanding and appreciation of the rationale of brachytherapy and its application in prostate cancer.

The second part of the lesson describes brachytherapy in detail, focusing on the modalities available. The reader should be able to describe the appropriate brachytherapy modality based on criteria such tumor stage, grade and pathology characteristics.

Specifically, this unit will address the resurgence of interest in this therapeutic modality that has occurred because of ongoing improvements in medical imaging, computerized treatment planning software, and remote afterloading technology.

Upon completion of this continuing education module, the reader should be able to:

1. Define the term “brachytherapy” and describe the principles of dose conformity and dose minimization.

2. Summarize the advances in technology which have resulted in renewed interest in brachytherapy as a key treatment modality in prostate cancer therapy.

3. Identify the anatomy of the prostate and describe how the anatomical architecture impacts on treatment.

4. Describe the value of diagnostic screening in brachytherapy management decisions.

5. Outline the most common isotopes used in prostate brachytherapy and describe the properties that determine suitability for use in brachytherapy.

6. Describe other treatment modalities used for the management of prostate cancer.

7. Describe the rationale of dose rate in the management of prostate cancer.

8. Identify relevant applications for both high dose and low dose rate brachytherapy in terms of tumor stage and histology.

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INTRODUCTION

The discovery of radium by the Curies in 1898 was promptly followed by its clinical application in the treatment of cancer, initiating the medical discipline known today as brachytherapy. The name "brachys," derived from the Greek language meaning short, implies brachytherapy occurs when sealed sources of radioactive material are used to deliver radiation at very short distances by placing the sources within cavities, lumens, tissues or on the surface of tumors. The physical benefits of this mode of treatment is that very high doses of radiation can be delivered directly or almost directly to malignant tumors with a very rapid fall off of dose to surrounding normal tissues. This lesson describes the application of brachytherapy in the management of prostate cancer, which continues to be most common cause of death in men from cancer in the United States.

In early prostate cancer, brachytherapy can successfully control local disease in approximately 80% of cases and achieve 10-year survival rates similar to the results obtained with other forms of treatment such as surgery or external beam radiotherapy, with decreased urinary and bowel morbidity and sexual dysfunction. Prostate brachytherapy, offered either as a sole modality therapy or in conjunction with moderate dose external beam radiotherapy, is challenging surgery as the treatment of choice for localized prostate cancer. Current advances in prostate brachytherapy are continuing to offer men with prostate cancer excellent treatment outcomes in terms of improved tumor control and quality of life.

PROSTATE BRACHYTHERAPY – A RESURGENCE OF INTEREST

Prostate cancer is essentially a disease of elderly men. Almost half of all men over the age of 80 have evidence of prostate cancer. Unfortunately by the time most men display symptoms of prostate cancer such as urinary hesitancy, urgency, nocturia or impotence, it is often too late to offer curative therapy. With the lifetime risk of developing prostate cancer being 1 in 6, attempts at early diagnosis continued to be the mainstay of research for many years[1] .

The introduction of prostate specific antigen (PSA) and transrectal ultrasonography (TRUS) in the 1980s led to an increase in the absolute incidence of prostate cancers and to an increase in the detection of early stage disease[2] . Renewed interest in low risk curative therapies soon emerged, as the treatment paradigm shifted from a palliative to curative setting. The roles of watchful waiting (observation), radical prostatectomy (surgery), radical external beam radiotherapy and interstitial brachytherapy (where the brachytherapy source is directly implanted into the prostate tissue) became the topic of active debate across the globe.

In addition to the detection of early stage disease, PSA also became significant in demonstrating the effectiveness of standard therapies. As a surrogate tumor marker, PSA elevation became associated with disease progression. Biochemical surveillance by PSA assays demonstrated that the standard therapies of radical prostatectomy and external beam radiotherapy were not as effective as initially thought in the management of more advanced disease[3] . PSA surveillance re-established the therapeutic boundaries for advanced disease, challenging clinicians to deliver more aggressive therapy in the local setting, in the belief that PSA levels, and hence active disease, would remain under control. Within the discipline of external beam radiotherapy, PSA control and treatment failure was associated with volume and dose considerations. Escalating the dose within the tumor and reducing the irradiated volume of normal tissues were two concurrent

strategies that were identified as being significant in improving tumor control[4]. These strategies became significant in the management of both early and late stage prostate cancer.

Brachytherapy, dismissed in the early 1970s as a viable treatment option, underwent a significant revival of interest in the late 1980s. Concurrent developments in imaging technology, computer dose modeling and delivery apparatus underpinned this interest and realized the potential to deliver higher uniform doses to the target area, while minimizing the dose to surrounding structures. This resurgence of interest was evident across the world, as clinicians attempted to provide alternatives to the standard radical prostatectomy and radical external beam radiation therapies.

By the late 1980s high and low dose rate brachytherapy techniques were gaining acceptance as safe, effective and viable treatment options for both early and advanced disease. Both techniques demonstrated significant improvements in control with minimal acute and chronic morbidity[5]. The direct placement of the radioactive source within the tumor facilitated precise shaping of the radiation dose around the prostate gland and significantly lower dose to surrounding bladder and rectal structures. Improved tumor control and lower toxicity (side effects) is predicated on escalating the dose to the target area (the tumor with a small margin) beyond conventional levels while minimizing the dose to adjacent normal tissue structures. This resurgence of interest in brachytherapy continues today, as clinicians attempt to improve control in both early and advanced stage disease through the combined strategies of tumor dose escalation and normal tissue dose and volume minimization.

PROSTATE CANCER

The etiology of prostate cancer is unknown, however there is a strong hereditary predisposition. A number of genetic events appear to be required for the development of clinically significant prostate cancer, although it is not known if other contributing environmental or hereditary factors exist. In humans, aberrant expression of the p53 gene appears to be a biomarker that may be able to predict previously undiagnosed and recurrent tumors in patients with clinically localized prostate cancer. These data suggest that tumor suppressor genes involved in cell cycle regulation are not only critical to the pathogenesis and progression of the cancer, but may be potential therapeutic targets.[6]

Several human studies have suggested a link between diet and an increased risk of prostate cancer. Diets low in fat and high in soy protein have been previously suggested to reduce the risk of cancer. Some researchers have also identified race as a significant risk factor in the predisposition towards prostate cancer, however the data are unconvincing. It is fair to say that the role of race as a prognostic feature in men with prostate cancer remains controversial[7].

Anatomy

The prostate is a male sex gland resembling a walnut in shape and weighing about 20 gm. Located immediately inferior to the bladder and anterior to the rectum, it is transversed by the urethra (the portion of the urethra passing though the prostate is called the prostatic urethra). The seminal vesicles lie superior and posterior to the prostate. The prostate is divided into five histologically distinct zones[8]:

1. the anterior zone;
2. the peripheral zone, accounting for 75% of prostatic volume and the area in which prostate cancer tends to be localized. 70% of cancers originate in the peripheral zone;

3. the central zone, where up to 20% of cancers are noted to arise;
4. the preprostatic urethra; and
5. the transitional zone, where 10% of cancers arise.

The functions of the prostate gland are not well understood. It consists of approximately 30 to 50 tubuloalveolar glands that open into the prostatic urethra through 15 to 30 ducts arranged in a radial pattern with a stroma of fibromuscular connective tissue, blood vessels, lymphatics, and nerves. The gland produces an acidic fluid (pH 6.5) that constitutes approximately 30% of seminal fluid ejaculate, containing calcium, zinc, acid, phosphatase, a clotting enzyme and profibrinolysin.[9]

The natural history of prostate cancer is highly variable. The majority of cancers of the prostate arise in the peripheral zone and do not affect the periurethral areas until the cancer has spread, explaining the lack of symptoms in patients in the early stages of prostate cancer. In fact, symptoms generally do not appear until the cancer has spread beyond the prostate and affected other organs, all but reducing the impact of curative therapies. Prostatic cancers can be separated into cancers of acinar (which accounts for 98% of all cancers of the prostate) and proximal duct origin or of distal duct origin.

It is interesting to note that the prostate itself is rarely associated with metastases from other tumors. Prostate cancer is considered a slow growing tumor and its prognosis is relatively good.

Tumor Grade

Tumor stage and tumor grade remain the most important prognostic indicators of prostate cancer. After a clinical diagnosis of prostate cancer has been established, a staging workup must be completed to determine the grade (degree of cellular differentiation between cancerous cells and normal cells) and stage (extent to which the disease is present and has spread). Prognosis and treatment are determined according to the grade and stage of the cancer. Staging systems are also used to determine the biologic potential of the cancer. In general, small tumors tend to be well differentiated and slow growing, whereas most poorly differentiated tumors tend to be larger, more aggressive, and associated with a poorer prognosis. Patients with tumors confined to the prostate gland have a better prognosis than do patients with tumors that have spread beyond the prostatic capsule[10]. Extracapsular spread is indicative of a more aggressive type of tumor.

Several grading systems have been proposed to facilitate the diagnosis of distinct histological patterns based on the degree of cellular differentiation. Donald Gleason introduced the system of histopathological averaging in which the final score is the average of two patterns. The first pattern, (x) is from the more dominant areas and the second (y) from the less dominant areas.[11] The Gleason score is:

$$x + y = z.$$

The lowest possible score is 2, indicating a well-differentiated tumor and the highest possible score is 10, indicating a very poorly differentiated tumor. In general, well-differentiated tumors (Gleason grades 2 to 5) are slow growing and associated with a low mortality rate. Patients with poorly differentiated tumors (Gleason grades 7 to 10) have a much higher probability of dying from prostate cancer.[12]

An analysis of data pooled from six studies that used deferred treatment in patients with clinically localized prostate cancer support a difference in survival based on the level of tumor differentiation. In this

collective group of 828 men, the disease-specific survival rate at 10 years was 87% in patients with well or moderately differentiated tumors, whereas patients with poorly differentiated tumor had a 10-year disease-specific survival rate of only 34%. In this same series, metastasis-free survival was 81% for patients with well-differentiated tumors, 58% for patients with moderately differentiated tumors, and 26% for patients with poorly differentiated tumors.[13]

Tumor Volume

Tumor volume is also an important prognosticator. Tumors with volumes less than 0.5 cc are rarely associated with extracapsular spread, whereas extracapsular spread is common in tumors reaching 1.0 cc or more. Seminal vesicle invasion is common in tumors greater than 3.0 cc. However, overt metastases rarely occur in tumors less than 4.0 cc in size. Nodal involvement is another prognostic factor, with the risk of dying directly related to the extent of nodal involvement.[14]

Tumor Staging

Tumor staging is important to determine if, and to what extent, a cancer has spread from its point of origin. Proper staging is critical in establishing a prognosis and in selecting an appropriate treatment protocol. Although there are several staging systems in use, the American Joint Committee for Cancer TNM (tumor, node, metastases) system continues to gain favor and is the system referred to in this article.

T1 tumors are generally localized, with little or no presenting complaints. Detection is often incidental, following routine PSA screening. In general, patients with incidentally detected prostate cancer have a good prognosis, although overall survival rates at 10 years vary from 30% to 85% in the literature. This variation is believed to be due to the presenting PSA, grade and volume of the tumor, with high grade, high volume tumors associated with a poorer prognosis. Patients with low volume disease generally have a better prognosis.[15]

T2 tumors generally are confined to one lobe of the prostate; characterized by the presence of moderately to poorly differentiated cells; and a tumor volume of less than 1.5 cc. Patients often present with obstructed flow symptoms, however, it is not uncommon for there to be no symptoms at all. On examination the tumor can be palpated and appears on TRUS as a hypoechoic lesion. PSA is generally elevated. The overall 10-year survival for patients with T2 tumors ranges between 34% and 71%.[16, 17]

T3 tumors display extension beyond the capsule but not involving other pelvic organs (except T3c tumors which invade the seminal vesicles). Presenting symptoms include acute urinary retention, pelvic pain and bleeding. Detection is via examination (DRE – Digital Rectal Examination), imaging (TRUS, CT, MRI) and PSA. 10-year disease free survival rates have been reported to approach 55%.[18] T4 tumors extend through the prostate capsule and invade other pelvic organs such as the bladder or rectum. Presenting symptoms are similar to those for T3 tumors. Survival is comparatively poor, the mean survival being around 4 years.[19] Survival is not impacted greatly by choice of treatment. Treatment is palliative, to alleviate symptoms and improve quality of life.

Incidence of Prostate Cancer

Each year in Australia over 12,000 men are diagnosed with prostate cancer.[20] In the United States, during 1999, it is anticipated that nearly 180,000 new cases of prostate cancer will be identified.[21] During this same year in the United States, prostate cancer is expected to claim the lives of 37,000 men. Death rates from prostate cancer will continue to climb due in part to the increasing proportion of

elderly men in society along with reduced mortality from other causes such as circulatory and cardiac diseases.[22]

The incidence of prostate cancer in the United States continues to be highest in African American men, followed by white men, Hispanic men, Asians and American Indians. For all races, the 5-year survival rates have climbed from 67% in the period 1974-76 to 93% in 1989-94.[23]

Diagnostic Screening

The intent of screening clearly is to detect early stage disease and therefore attempt to alter prognosis. The three most common prostate cancer screening techniques are digital rectal examination (DRE), transrectal ultrasonography (TRUS) and prostatic specific antigen assay (PSA). All three techniques have contributed to the increased survival rates described previously.

DRE is commonly used to assess the contour, texture and symmetry of the gland. Experienced clinicians can also determine the degree of induration of the seminal vesicles and whether extracapsular components reach the pelvic sidewall. In less experienced hands, the value of DRE can be suspect.[24] TRUS examination of the prostate is a valuable test in addition to DRE. It provides information about the echo pattern and facilitates accurate needle placement for core biopsies from specific areas (base, mid and apex) as well as any suspicious palpable or hypoechoic areas. TRUS is also used routinely in the brachytherapy treatment process.

PSA is secreted from the acini into the ducts and can be measured in the serum. PSA rises more quickly with prostate cancer than with other causes such as ageing, infection or inflammation. PSA levels however can vary substantially in different patients, as PSA leakage from cancerous blood vessels is highly variable. PSA variation with tumor bulk (stage) and histological differentiation (grade) can also be unpredictable. Some studies suggest values greater than 4ng/ml are indicative of early stage disease (T1-T2), 10ng/ml are indicative of non–organ confined disease (stage T3). Levels greater than 20ng/ml have been associated with bone metastases (stage T4).[25]

The reported predictive value of PSA in screening studies however is the topic of ongoing debate. Reported predictive accuracy rates have been demonstrated to be in the range 28% to 35%.[26] That is to say, only one third of men with elevated PSA levels (greater than 4ng/ml) will be found to have prostate cancer on biopsy and two thirds will not (false positive). False positive elevation occurs with inflammation, infection and instrumentation, and returns to normal if the gland does not contain cancerous cells. Combining DRE with PSA increases the positive predictive value to 49% if both are considered positive.[27] The addition of TRUS examination lifts the predictive value to over 65%.[28]

The question of whether mass PSA screening improves outcome still remains unanswered. Various clinical trials are yet to conclusively demonstrate a reduction in mortality with PSA screening. Nevertheless, the proportion of men diagnosed with metastatic disease (stage T4) in the USA, Europe and Australia has been steadily falling in the past decade,[29] as more men present with T1, T2 and T3 disease. While this debate continues, the challenge in the clinic remains to offer low risk curative therapy to all presenting candidates, be it early stage or later stage disease.

MANAGEMENT OPTIONS

Prior to determining the appropriate treatment strategy, it is vital that a complete staging workup be undertaken. This will impact on the protocol selected and should include:

1. a complete history and physical examination;
2. DRE;
3. pathological and histological evaluation;
4. PSA, full blood workup, biochemistry and liver function tests, and
5. Imaging, comprising of chest x-ray, bone scan, Computerized Tomography (CT) and or Magnetic Resonance Imaging (MRI) abdomen and pelvic scan and Transrectal Ultrasound (TRUS) (including core biopsies).

Surgery

Radical prostatectomy — the complete resection of the prostate has been the current standard therapy for selected patients with localized, organ-confined disease (T1 or T2) for more than three decades. Where life expectancy is considered to be greater than 15 years and the Gleason score is reported as 6 or less, surgery has been the gold standard in treatment.[30] However, despite ongoing technical advances in surgical technique, morbidity, particularly impotence and incontinence, remains a concern to clinicians and patients.[31] Complications and quality of life considerations following surgery is assuming greater importance in the selection of the appropriate treatment strategy. Advances in imaging, dose modeling, and treatment apparatus in the brachytherapy field offer an attractive alternative to surgery, which offers similar tumor control rates, but potentially lower complications.

Radical External Beam Radiotherapy

This treatment option is usually recommended for selected patients with organ-confined disease (T2 and T3). Many series have been reported for external beam radiotherapy demonstrating results comparable to both surgery and brachytherapy.[32]

Patients with limited extra organ disease (T3c) with a life expectancy of greater than 10 years are also suitable for radical external beam radiotherapy. Radical external beam radiotherapy can produce acceptable results in these patients, particularly where the presenting PSA is less than 15mg/ml. However, to produce similar results in patients where the presenting PSA is greater than 15mg/ml, combined treatment strategies involving hormonal therapy are required.[33] In addition, the external beam strategy may involve higher doses and larger irradiated volumes.[34] Intensity Modulated Radiation Therapy (IMRT) and 3-Dimensional Conformal Radiation Therapy (3D CRT) strategies that facilitate this dose and volume escalation whilst limiting the dose to normal structures have been demonstrated to produce results in these groups of patients that are comparable to published surgical series[35] . The opportunity to escalate the dose while minimizing the volume of normal tissue and potentially the incidence of complications is a feature of both IMRT and 3-D CRT that is not possible with conventional external beam radiotherapy.

Hormonal Therapies

As described in the previous section, hormonal therapy is offered in combination with external beam radiotherapy to reduce the tumor bulk thereby limiting the volume requiring irradiation (or implantation with brachytherapy strategies). Numerous studies have demonstrated a disease free survival benefit for T2 and T3 (in addition to the T3c tumors previously discussed).[36]

Hormonal therapy is also offered to patients presenting with disseminated disease (T4) and those who have failed other forms of treatment. Prostate cancer survives under the stimulus of androgens, and cancer progression can be temporarily reversed by androgen suppression.[37] Androgen suppression may take the form of estrogens (tablets or injections), LHRH analogues (lutinising hormone

releasing hormones – injections) or bilateral orcidectomy (surgical removal of both testes). Remission during hormonal manipulation can last on average 1-2 years. Common side effects include weight gain, hot flashing, osteoporosis and loss of libido.

Brachytherapy

The genesis of interstitial brachytherapy can be traced back to 1901 when Pierre Curie filled a small tube with radium and suggested to French dermatologist Henri Danlos that he insert the tube into a tumor in an attempt to eradicate it. The first recorded prostate brachytherapy treatment was conducted in 1917 when Barringer inserted stainless steel radium needles through the perineum (trans-perineal) and into the prostate, guided by a finger in the rectum.[38] .The theory, although not explicit at the time, involved moving the source of radiation close to the target cancerous cells, and away from surrounding normal tissues.

These treatments continued sparingly until the 1930s, when fears associated with radiation protection prevented further investigation into the use of isotopes in cancer therapy. Concurrent developments with external beam radiotherapy and the use of hormonal therapies at this time further curtailed ongoing research into the discipline known as brachytherapy.[39]

Results from long term follow-up of locally advanced prostate cancer, however, remained only moderate; numerous researchers began to re-explore the potential benefits of brachytherapy. In 1972, Whitmore inserted radioactive Iodine 125 sources directly into the prostate through an open pelvic surgical approach.[40] Sources in the form of individual 1mm x 5mm seeds were deposited throughout the entire gland. Whitmore postulated brachytherapy would offer higher doses of radiation to the prostate while reducing the radiation dose and hence side effects and morbidity to the bladder and rectum. Analysis of the results from the Whitmore series was extremely discouraging. Many patients returned with active disease still present in the prostate despite what was thought to be higher than conventional doses. Examination of the radiation source distribution pattern within the prostate demonstrated significant problems; most implants were haphazard, with the ^{125}I seeds unevenly deposited throughout the gland. Problems with visualization and access at the time of implantation contributed to the unacceptable loading pattern. Subsequent dose calculations demonstrated substantial regions of the prostate to be significantly underdosed, contributing to treatment failure. Once again brachytherapy was relegated down the list of potential therapies, with surgery promoted as the gold standard.

In 1983, Holm and colleagues demonstrated that transrectal ultrasonography could be used to more accurately implant the prostate. Coupled with a trans-perineal implant approach, radioactive ^{125}I seeds were directed into the prostate through the perineal region directly anterior to the anus and posterior to the scrotum; the procedure was only minimal invasive and relatively simple to perform. Using a template attached to the perineum assisted in the uniform spacing and loading of the seeds. Interest in interstitial seed brachytherapy quickly developed from the work of Holm; early results demonstrated comparable results with those achieved with surgery, but with greater patient tolerance and potentially lower risk of normal tissue toxicity.

STATE-OF-THE-ART BRACHYTHERAPY FOR PROSTATE CANCER

The work of Holm became the foundation for ongoing interest and improvement in interstitial prostate brachytherapy all over the

world. During the 1990s prostate brachytherapy challenged surgery and radical external beam radiotherapy as an efficacious treatment option in the management of both early (T1/T2) and advanced (T2/T3/T3c) stage disease. High and low dose rate techniques developed synchronously that shared fundamental similarities built on the discovery of researchers such as Curie, Whitmore and Holm. Each technique provides the ability to accurately define the implant and target volume, and deliver treatment in a far more exacting and reproducible manner than the methods of the past.[41]

Benefits of Brachytherapy — Preferential Dose Deposition

Radiation can injure cells either directly or indirectly. With direct damage, a photon of ionizing radiation causes direct injury to DNA by altering its structure. However, a photon is more likely to indirectly damage the DNA molecule by producing free radicals after incidental collision with neighboring water molecules. These free radicals ultimately interact and damage the DNA molecule.[42] By ensuring that these events predominantly occur within the tumor, the highly localized doses delivered using brachytherapy can minimize damage to surrounding normal tissues. Compared with radical external beam

Table 1

Commonly used isotopes in brachytherapy[43]

Isotope	Emission	Half-life	Average Energy
Iodine-125[ZA]	x-ray	60 days	28 keV
Palladium-103[*]	x-ray	17 days	21 keV
Iridium-192[G†]	gamma	74 days	380keV
Caesium-137	gamma	30 years	662 keV
Gold-198[‡]	gamma	2.7 days	412 keV
Strontium-89	beta	51 days	0.583 MeV (average)
Strontium-90	beta	29years	0.196 MeV (average)
Phosphorous-32	beta	14 days	0.695 MeV (average)

[*]Used in low dose rate (LDR) brachytherapy of the prostate.

[†]Used in high dose rate (HDR) brachytherapy of the prostate.

[‡]Not commonly used in prostate brachytherapy due to short half-life and unacceptably high levels of radiation exposure to treatment staff.

radiotherapy, significant benefits should be realized as no radiation need traverse normal structures in reaching the target region. The benefit of brachytherapy is realized with this preferential delivery of dose within the tumor.

Isotopes in Brachytherapy

Selection of isotope is therefore essential if direct and indirect ionizing events are to be maximized within the tumor or target environment. Table 1 details the commonly used isotopes in brachytherapy.

^{25}I and ^{103}Pd are exclusively used for low dose rate (LDR) brachytherapy, whereas ^{192}Ir is used for high dose rate (HDR) brachytherapy. Gamma sources are clearly the isotopes of choice in the prostate, where dose deposition of up to 0.5 cm is often required from the source. This physical characteristic enables sources to be placed at approximately 0.5 cm to 1.0 cm intervals throughout the volume, ensuring the implantation process is relatively efficient and minimally invasive. Using beta sources in this application would require many more sources spaced at approximately 0.1 cm to 0.2 cm intervals. Clearly this would require excessive time and trauma in producing a uniform source and dose pattern. Further details regarding source properties and selection will be described in the relevant low dose rate and high dose rate sections.

Low Dose Rate (LDR) Permanent Seed Brachytherapy

LDR brachytherapy implants using ^{125}I and ^{103}Pd are characterized by dose rates within the implant field of 8cGy/hour and 24cGy/hour respectively. At these dose rates, normal cells within the irradiation matrix (and beyond) maintain continuous cell repair potential; repairing DNA damage as it is sustained. Malignant cells, however, have less potential to repair this damage, and therapeutic gain is achieved by this repair-damage phenomena at low dose rates. The seeds, which are approximately 5mm in length and 1mm in diameter and encapsulated by an outer stainless steel sheath, remain in-situ permanently. With a half-life of 60 days for ^{125}I, approximately 30% of the dose is delivered in the first 4 to 6 weeks following implantation.

The most common application of LDR permanent seed brachytherapy is for early stage (T1/T2) disease, where the implant alone is the sole therapy. Offered as an alternative to both surgery and radical external beam radiotherapy, this monotherapy is gaining wide acceptance as being efficacious, cost effective, minimally invasive and highly appealing to patients. For later stage disease (T2/T3/T3c), LDR brachytherapy may be offered as an adjunct to moderate dose external beam therapy. This combined approach is capable of irradiating periprostatic tissues more effectively than monotherapy brachytherapy and is able to deliver a significantly higher intraprostatic dose than is possible with radical external beam therapy alone[44] . The addition of external beam radiotherapy is warranted on the grounds that the brachytherapy alone will not adequately irradiate the malignant tissues outside the prostate.

Clinical Advantages

The advantage of permanent seed brachytherapy is largely derived from the availability and selection of low energy isotopes. The low energy photons of reactor produced ^{125}I and ^{103}Pd, 28 keV and 21 keV respectively, are significantly attenuated in tissue resulting in a favorable dose deposition pattern. The low energy effectively confines the high dose region to the prostate, affording lower doses in the surrounding tissues. As nuclear research continues, the window of therapeutic advantage could be widened as new isotopes are discovered.

These low energy photons also facilitate relatively simple radioprotection practices, requiring no elaborate shielding in the operating room (OR). Occupational exposure to radiation amongst medical, paramedical and nursing staff is minimal; with monitoring and strategic rotation of staff in the OR, no staff member should exceed annual acceptable dose limits.

In terms of the procedure, there is high patient and physician acceptance. For patients, the procedure is performed as an outpatient case with little discomfort. For monotherapy cases, this single treatment is highly appealing. Physicians find the procedure relatively simple to perform; the current technique (to be described later) ensures low morbidity in the appropriately selected patient. When viewed with encouraging results, monotherapy permanent seed implants are gaining favor as the treatment of choice for selected T1 cases.[45]

Clinical Disadvantages

A significant disadvantage of permanent seed brachytherapy relates to the unforgiving nature of placement errors associated with the low energy source. Source placement errors can result in unacceptable areas of underdosage or overdosage, which are unable to be modified once the implant is complete. Source placement errors can occur at the time of implant or at any time thereafter.

Irregularities within the prostate or movement of the gland during implantation can result in source position errors. Seed migration can occur up to one month post implantation; initial gland swelling and subsequent resolution can effect the position of each individual seed. The dosimetric (dose deposition pattern) success of the implant is highly dependant on the prostate tissues maintaining the seed matrix. The brachytherapy technique described by Whitmore in the 1970s failed to control localized prostate cancer. Radiographs of these implants demonstrated the wide variability of seed placement. The lack of uniform dosimetry was associated with the treatment failure[46] . Fortunately the techniques employed today result in more exact implant patterns and hence better outcomes.

The rate at which treatment is delivered is also a significant concern within the brachytherapy community. Generally, radical external beam and high dose rate temporary implants deliver the radiation at rates up to hundreds of cGy/hour. Permanent low dose rate implants using ^{125}I and ^{103}Pd are characterized by dose rates of 8cGy/hour and 24cGy/hour respectively.[47] The work of eminent radiobiologists such as Hall[48] in cell and animal lines suggests that dose rate may impact on the ability of radiation to impart cellular DNA damage. This is particularly relevant when the cell line is rapidly dividing as in poorly differentiated cancers.[49] These findings question the use of low dose rate isotopes in the treatment of high grade tumors, particularly those demonstrating high Gleason scores. The significance of this work remains unclear in the clinic; more research is warranted and pending. However, most clinicians would avoid the use of ^{125}I in high grade, poorly differentiated tumors, choosing to use ^{103}Pd or high dose rate temporary implants. Nuclear research into isotopes with low energy photons and higher dose rates is continuing.

Selection Criteria for Therapeutic Advantage – Control Vs Morbidity

The recognition of factors that may increase complications from low dose rate brachytherapy is an important aspect of appropriate patient selection. Prostate volume is a significant factor. In general, prostate glands that are in excess of 50 cc to 60 cc, as determined by TRUS, are unacceptable for

implantation. As the prostate increases in size, brachytherapy become technically more difficult as uniform implantation becomes complicated. In addition to areas of underdosing where tumor clonogens may remain viable, overdosing in the central and preprostatic urethral zones may cause significant urethral toxicity such as strictures, fistula and obstruction.

As discussed previously, the use of concurrent hormonal therapies have been successful in reducing prostate volume. The use of LHRH analogues for 3 to 4 months can result in a 40% volume reduction, making implantation possible.[50] In this setting, patients that may have previously been considered incurable are now being offered state of the art brachytherapy. Clinicians need to be wary however of reducing the volume below 20 cc, where implantation again becomes extremely difficult. Ideal implant volumes are in the range of 20 cc to 50 cc.

Ensuring that tumor control is maximized and morbidity minimized is dependant on more than volume alone; other criteria to consider include grade, stage, Gleason score and presenting PSA. While research continues, the following guidelines could be considered relevant in selecting the appropriate treatment strategy.[51] These guidelines are an example of current clinical practice, but the author acknowledges that variations do occur. For example, many clinicians use hormonal therapy in all strategies:

Monotherapy (Low dose rate permanent implant alone)

- Stages – T1, T2a (early stage T2 disease)
- Gleason – 2 to 6
- Presenting PSA – less than 10

Combined Therapy (Low dose rate permanent implant + moderate dose external beam)

- Stages – T2b, T2c (later stage T2 disease), T3
- Gleason – 7 to 10
- Presenting PSA – greater than 10

Hormones and Combined Therapy (LHRH 3 to 4 month + implant + external beam)

- Stages – T3c
- Gleason – 7 to 10
- Presenting PSA – greater than 20
- Or in any case where the initial prostate volume as determined by TRUS exceeds 50cc

Technique Description

Low dose rate permanent seed implant is characterized by 3 distinct phases in the active treatment process: pre-planning, implantation and post-implant evaluation.

Pre-planning the implant is essential in order to maximize the therapeutic window. Most pre-planning involves either a TRUS or CT examination. These studies determine the target volume to be implanted, as well as visualizing the location of surrounding rectal, bladder and urethral structures. The implant team uses the data from the pre-plan study to determine the ideal seed locations as well as calculate the dose to the rectum, bladder and urethra.

The use of sophisticated dose modeling software enables multiple interactive calculations to be made, allowing the team to alter the pattern in order to achieve the ideal dose distribution. As a general guide, the following doses are set as absolute constraints[52]:

- Tumor (mean peripheral gland dose) = 144Gy for ^{125}I (monotherapy)
- Tumor (mean peripheral gland dose) = 115Gy for ^{103}Pd (monotherapy)

- Tumor (mean peripheral gland dose)= 108Gy for ^{125}I (combined)
- Tumor (mean peripheral gland dose)= 90Gy for ^{103}Pd (combined)
- Rectum (anterior rectal wall)= 70%-75% of tumor dose (all cases)
- Urethra (periprostatic urethra)= 115%-130% of tumor dose (all cases)

Current software algorithms use sophisticated dose calculation algorithms that take into account the source geometry, as well as attenuation and scatter of radiation both within the radioactive source and the patient. These developments have significantly advanced understanding and confidence in planning the ideal implant based on all key patient and tumor characteristics.

The implant procedure used today is derived from the approach pioneered by Holm. The procedure is routinely performed in the outpatient setting, and is well tolerated by most patients. Following spinal anesthesia, the patient is placed in the lithotomy position. Under direct transrectal ultrasound guidance, the sources are implanted into the prostate via the perineum. The sources are commonly pre-loaded into implant needles that allow the sources to be deposited within the prostate as the needle is withdrawn (see Figure 1).

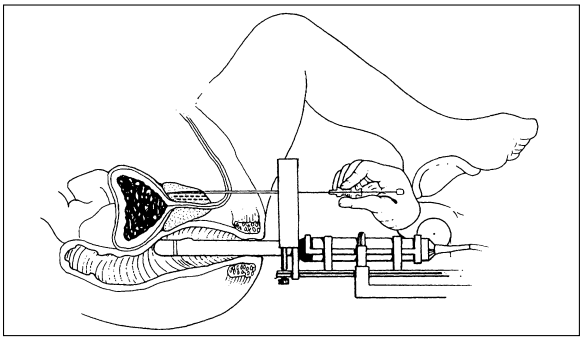

Figure 1. Modern transperineal seed implantation (Reprinted from Grimm PD, Blasko JC, Ragde H, et al. Does brachytherapy have a role in the treatment of prostate cancer? *Hematol Oncol Clin North Am.* 1996; 10:653.)

Recent developments in bi-planar scanning technology enable the clinician to view needle/source placement in simultaneous axial and sagittal planes, facilitating precise needle placement and identification of surrounding structures. Fluoroscopy and cystoscopy is also employed to ensure sources are loaded according to the pre-plan matrix. Perineal templates sutured to the perineum assist in accurate needle and source placement. Between 90 and 120 sources are deposited in the average implant. Most procedures are completed in less than one hour.

Post-implant evaluation occurs approximately 4 weeks following implantation. At this time prostate swelling as a result of the trauma associated with the implant should have resolved, and no further migration of seeds should be seen. Generally, CT is used for this evaluation. Thin CT slices facilitate accurate identification of each seed, which can be difficult when the number of seeds exceeds 100. The actual dose distribution throughout the tumor and normal tissues are generated. This final step is important in order to correlate clinical outcomes with the delivered dose distribution. Only by undertaking this evaluation can ongoing refinement and progress be achieved.

Results

To date, low dose rate brachytherapy has not been subjected to prospective randomized trials; therefore, most data is largely retrospective and single-institution derived. Monotherapy results generated from the Seattle[53] experience indicates 5-year local control rates of 97%, which appear equivalent to those of radical prostatectomy and radical external beam radiotherapy. 10-year disease free survival data from the same institution confirms similar results to published surgical series.[54] Morbidity such as rectal injury (bleeding, ulceration, stricture), incontinence and impotence also appear acceptable when

compared to other treatment modalities such as surgery. Rectal injury rates as reported in the Seattle[55] series were consistently below 2%. Incontinence rates in the same series demonstrated an actuarial incontinence rate of 48% at six years for those patients undergoing this treatment following previous surgical trans-urethral resection of the prostate. Incontinence rates for those cases who had not undergone this procedure were in the order of 0.5%. These data therefore impact significantly in the selection of patients for this form of treatment. Potency maintenance rates vary with age; for men over the age of 70 the data suggest total impotence rates of 30% and partial impotence rates of 20%.

Low dose rate permanent seed brachytherapy is challenging other treatment modalities. For early stage, low volume, low Gleason score cases, monotherapy is now recommended as the treatment of choice by many clinicians. In advanced disease, brachytherapy as a boost dose in a combined regimen is offering comparable if not better opportunities for tumor control and significantly lower morbidity and toxicity in the appropriately selected patient.

High Dose Rate Temporary Needle Brachytherapy

HDR temporary brachytherapy implants using ^{192}Ir are characterized by dose rates in excess of 100Gy/hour. At these dose rates, normal cells within the high dose region (and beyond) do not have the capacity to repair radiation damage when the total dose approaches the clinical threshold dose for tumor control. To maximize the therapeutic window and exploit differential cell repair kinetics within normal and malignant cells, HDR treatments are fractionated (the total clinical dose is divided into 3 or 4 equal fractions). Fractionation allows multiple sub-lethal doses to be delivered with a refractory period of between 6 and 8 hours between fractions. The refractory period is sufficient for normal cells to begin to repair sub-lethal damage before the next dose of radiation. As previously described, repair in malignant cells is not as efficient or effective, and the damage becomes cumulative. Over the course of 3 to 4 fractions, the therapeutic window is achieved as malignant cell kill exceeds that of normal cells.

The clinical application of HDR temporary needle brachytherapy is very similar to that described for the LDR permanent technique. While LDR monotherapy is offered for early stage (T1/T2) disease, the main application for HDR temporary brachytherapy is in the combined and combined/hormonal approaches for later stage disease (T2/T3/T3c). These combined strategies are gaining favor as clinicians attempt to escalate the absolute dose within the prostate to higher levels than previously achievable.

Interest in high dose rate temporary needle brachytherapy grew from ongoing concern and criticism associated with the suspect dosimetry inherent in the low dose rate permanent implant technique. Despite ongoing technical refinements, many clinicians remain concerned that inadequate dose throughout the gland as a result of source placement variability and migration may have an adverse clinical outcome.

Clinical Advantages

High dose rate temporary needle brachytherapy theoretically remedies the inadequacies of permanent seed implants by utilizing plan optimization functions associated with the stepping source dosimetry function. Temporary hollow needles become the conduit for the high activity ^{192}Ir source (> 10 Ci), which is remotely driven and loaded into each needle. This small source, approximately 1mm in diameter and 5mm in

length, progresses along the needle in predetermined steps (stepping source dosimetry). The treatment unit, known as a remote afterloader, advances the single high activity source into and through each treatment needle according to the calculation model. Movement of the source within each needle is driven by the unit to set positions (known as dwell positions) and for predetermined times (known as dwell times). A combination of dwell position and dwell time within each implant needle results in a highly conformal dose matrix. Recent developments with sophisticated modeling software have enabled the brachytherapy team (Radiation Oncologist, Urologist, Radiation Therapist, Physicist) to construct customized dose distributions, cognizant of all normal tissue constraints. High dose rate brachytherapy is delivered only after the implant needles are in-situ and all modeling is complete.

The ability to plan and deliver treatment in a controlled environment has several advantages over LDR seed implantation. First, treatment planning and modeling occurs immediately following needle placement; dose variation throughout the gland is controlled. No part of the gland need be under or overdosed. Secondly, the optimizing functions enable the team to generate a unique dose distribution, which tightly conforms to the shape of the external prostate contour. This conformal dose distribution minimizes dose to surrounding structures. Thirdly, the ability to differentially deliver dose, such as higher doses to peripherally located bulky tumor, or lower doses to the central prostatic urethra makes HDR brachytherapy even more advantageous.[56]

Advances in stepping source technology not only supports the precise placement of the source within the implant matrix, it also greatly reduces occupational exposure to radiation. No source handling occurs with HDR brachytherapy; source movement is controlled remotely, and treatment occurs in a shielded environment. This is significantly different from the situation with LDR permanent implants, where the sources are manually inserted and some degree of occupational exposure to radiation occurs. Despite significant infrastructure costs associated with building and capital equipment works, which can exceed millions of dollars, the benefits of HDR remote afterloading brachytherapy in terms of reduced occupational exposure to radiation are well documented.

In addition to the benefits of source placement accuracy and remote afterloading, the physical property of the ^{192}Ir source overcomes significant concerns regarding the effect of dose rate on cell viability. Dose rates in excess of 100Gy/hr with HDR treatments are well above the threshold described by Hall for radiation damage repair. High Gleason score tumors therefore remain eminently suitable for a HDR approach.

Clinical Disadvantages

While the dose rate effect described above can provide advantages in the clinical setting, clinicians must be mindful of high dose rate effects on adjacent normal tissues. The risk of damage to normal tissues is related to the amount of dose delivered at any one session, the number of sessions per day and the inter-session interval (refractory period). With LDR brachytherapy, normal tissues immediately adjacent to the conformal dose distribution display some radiation repair responses. Sub-lethal damage in these cells can be simultaneously repaired in the presence of ongoing irradiation. With HDR brachytherapy this repair is not possible, so treatment must be delivered in finite calibrated doses which must not exceed the

repair threshold of normal cells. For this reason, HDR brachytherapy must be fractionated; the total dose must be delivered in small equal fractions allowing sub-lethal repair in normal tissues.

Single LDR permanent implants commonly translate into approximately three to six separate HDR treatments if tumor control and normal tissue toxicity is equated. Clearly then, HDR brachytherapy becomes significantly more labor intensive and less appealing to patient and clinician alike. The prospect of four repeated HDR temporary implant procedures could have condemned HDR brachytherapy to an early departure from the clinical arena. Fortunately, ongoing clinical research in the radiobiological sciences indicated that multiple treatments could be delivered per day. Analysis of cell repair kinetics suggested that sub-lethal repair in normal cells in the near high dose region should be complete within 6 hours. This theory is evident in HDR protocols today, where typically four HDR prostate brachytherapy sessions are conducted over two consecutive days, with the interval between fractions being no less than six hours. This regimen involves only one surgical, imaging and dose calculation procedure and four relatively simple and quick treatments over 36 hours (needles are left in-situ between treatments).

Selection Criteria for Therapeutic Advantage – Control Vs Morbidity

The recognition of factors that apply for LDR brachytherapy equally applies in the HDR brachytherapy setting; disease stage, volume, grade, Gleason score and presenting PSA readily impact on protocol design. While HDR monotherapy is offered by some clinicians, the overwhelming application is in the combined strategies where biochemical control in advanced disease is the predominant aim.

Technique Description

The HDR temporary implant technique bears many similarities to those described in the LDR section. Generally however, sophisticated pre-planning is not required as implant quality is assured by both hardware and software applications.

The implant phase occurs in the Operarting Room (OR), where closed-end hollow needles are introduced trans-perineally into the prostate under direct ultrasound control. Usually 11-18, 20cm, 1.9mm diameter needles are required to adequately implant the prostate. Templates are used to assist with accurate and expeditious needle placement. Concurrent imaging with fluoroscopy and cystoscopy ensures the prostate is adequately implanted (see figure 2).

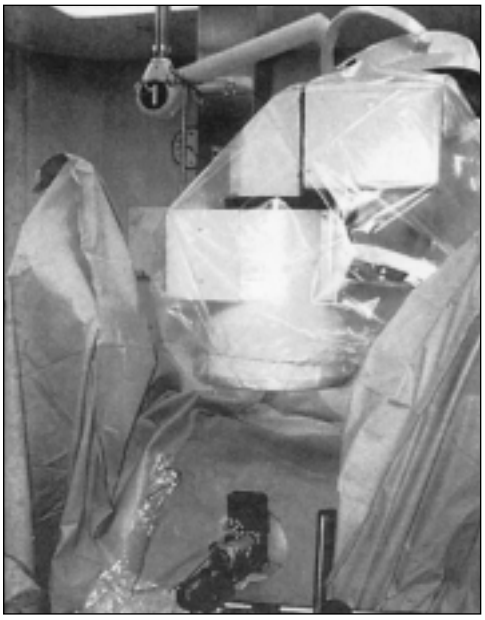

Figure 2. Setup in the OR with the patient draped in the litothomy position, with fluoroscopy unit and transrectal ultrasound probe in the rectum attached to the perineal template. (Reprinted with permission from Nag S, Pak V, Blasko J, Grimm PD. Brachytherapy for prostate cancer. In Nag S, ed. *Principles and Practice of Brachytherapy*. Armonk, NY: Futura Publishing Company Inc, 1997:425.)

Postoperative CT and or ultrasound imaging is used to identify needle positions as well as the prostate capsule, rectum, bladder and urethra (see figure 3).

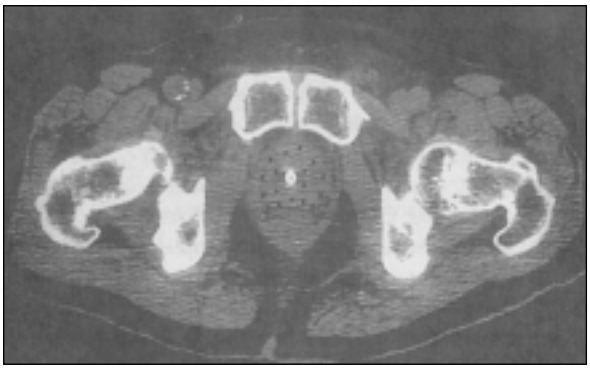

Figure 3. CT Image showing trochars (black dots) placed by TRUS guidance. (Reprinted with permission from Rodriguez RR, Demanes J, Alteri GA. High dose rate brachytherapy in the treatment of prostate cancer. *Hematol Oncol Clin North Am.*

These data are used in the implant optimization process, the benefits of which have been described. In the optimization process, software algorithms perform iterative calculations throughout the identified target volume, to achieve the desired dose matrix. Using stepping source technology, the system builds highly conformal dose patterns that attempt to satisfy all set criteria. Typical criteria[57] for the HDR brachytherapy phase alone includes

- Tumor (mean peripheral gland dose) = 4 fractions of 4Gy to 5Gy over two consecutive days, minimum inter-fraction interval of 6 hours. Martinez at the William Beaumont Hospital employs 3 HDR fractions of 5.5Gy.[58]
- Rectum (anterior rectal wall)= 70-75% of tumor dose
- Urethra (periprostatic urethra)= 115–130% of tumor dose

Moderate beam external beam radiotherapy either precedes or follows the brachytherapy. Typical external beam regimens deliver between 45Gy and 50Gy in 25 to 30 daily treatments. Martinez uses an external beam dose of 45.6Gy to compliment the 3 HDR brachytherapy fractions.

Results

High dose rate brachytherapy as a boost in conjunction with moderate dose external beam radiotherapy to the prostate is challenging conventional stand alone surgical and radical external beam therapies. Mate[59] describes comparable results to surgery for low volume tumors presenting with initial PSAs of less than 10 ng/ml. For bulkier tumors indicated with initial PSAs of 10-20 ng/ml, the results appear significantly superior to radical external beam radiotherapy. European data confirms these results, indicating that combined HDR temporary prostate brachytherapy is well tolerated and very effective as a definitive treatment for prostate cancer.[60]

CONCLUSION

Brachytherapy is an effective treatment for localized prostate cancer. Reducing the volume of normal tissue irradiated to a high dose permits further escalation of the dose within the prostate. In this setting, brachytherapy offers an equivalent or improved opportunity for biochemical tumor control with a well tolerated cost effective treatment possessing a lower risk of incontinence, impotence and rectal injury in the appropriately selected patient.

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QUESTIONS

1. The lifetime risk of developing prostate cancer is
   a. 1 in 4.
   b. 1 in 6.
   c. 1 in 8.
   d. 1 in 10.

2. Brachytherapy was rediscovered as a viable treatment option for prostate cancer in the
   a. 1950s.
   b. 1970s.
   c. 1980s.
   d. 1990s.

3. Prostate brachytherapy involves the placement of radioactive sources
   a. Around the tumor.
   b. Within the tumor.
   c. Into the circulatory system.
   d. Onto the perineum.

4. Brachytherapy has gained clinical interest because
   a. The tumor is irradiated to higher doses than is conventionally possible.
   b. The tumor is irradiated to higher doses and normal tissues completely protected.
   c. The tumor receives a uniform dose.
   d. The tumor is irradiated to higher doses and normal tissue is preferentially protected.

5. Which anatomical structure traverses the prostate?
   a. The prostatic urethra
   b. The seminal vesicles
   c. The bladder
   d. The rectum

6. The percentage of tumors occurring within the peripheral zone of the prostate is
   a. 75%.
   b. 70%.
   c. 50%.
   d. 20%.

7. In general, well differentiated prostate tumors are recognized as
   a. Rapidly dividing with a Gleason score of 7-10.
   b. Rapidly dividing with a Gleason score of 2-5.
   c. Slowly dividing with a Gleason score of 2-5.
   d. Slowly dividing with a Gleason score of 7-10.

8. The reported predictive accuracy rate of PSA screening alone is approximately
   a. 10%.
   b. 20%.
   c. 30%.
   d. 40%.

9. When DRE is added to PSA, the predictive accuracy rate is approximately
   a. 20%.
   b. 30%.
   c. 40%.
   d. 50%.

10. The work of Holm in the 1980s laid the foundation for brachytherapy today because of developments with
    a. Transrectal ultrasound and CT imaging.
    b. Better sepsis control in the operating room.
    c. Discovery of the ^{125}I isotope.
    d. Transperineal surgical techniques and transrectal ultrasound.

11. The isotope most commonly used in LDR brachytherapy is
    a. ^{125}I.
    b. ^{192}Ir.
    c. ^{198}AU.
    d. all of the above.

12. Occupational exposure to LDR brachytherapy is
    a. Minimal because of the use of shielding.
    b. Negligible because of remote afterloading.
    c. Excessive and of concern.
    d. Minimal because of the use of low energy isotopes.

13. The dose rate effect in LDR brachytherapy is a concern because
    a. Patients remain radioactive for longer periods
    b. Rapidly dividing tumor cells display synchronous radiation damage repair
    c. Of questionable ability to impart damage to rapidly dividing tumor cells
    d. Normal cells are unable to repair cellar damage

14. ^{103}Pd is used to counter the dose rate effect because
    a. the dose rate within the matrix is higher by a factor of approximately 3.
    b. the average energy is lower (21KeV).
    c. the half life is shorter (17days).
    d. the prescribed dose to the implant matrix is lower.

15. LDR monotherapy is best indicated for which type of prostate cancer?
    a. Stage T2, Gleason score = 2, PSA = 5
    b. Stage T1, Gleason score = 4, PSA = 10
    c. Stage T2, Gleason score = 6, PSA = 5
    d. Stage T1, Gleason score = 4, PSA = 5

16. LDR post implant evaluation is necessary because
    a. Seeds migrate and the actual dose pattern must be calculated
    b. The actual dose pattern can be correlated with clinical findings
    c. Correlations lead to ongoing technical improvements
    d. All of the above

17. Interest in HDR brachytherapy grew from
    a. Concern over suspect dosimetry with LDR applications.
    b. Occupational exposure to radiation.
    c. The interest in treating later stage disease in combination with external beam radiotherapy.
    d. All of the above.

18. HDR brachytherapy addresses the concerns of source placement variability by utilizing
    a. Stepping source dosimetry.
    b. Remote afterloading.
    c. Higher activity source.
    d. None of the above.

19. Which factors have heralded the resurgence of interest in HDR prostate brachytherapy?
    a. Transrectal ultrasound, reactor produced isotopes, MRI and CT imaging.
    b. Transrectal ultrasound, perineal implantation, dose modeling software and remote afterloading hardware.
    c. Perineal implantation, higher dose rate isotopes and dose modeling software.
    d. Transrectal ultrasound, dose modeling software and remote afterloading hardware.

20. What is the role of fractionation in HDR brachytherapy?
    a. To increase the likelihood of tumor control and greater survival.
    b. To enable treatments to be modified as the tumor responds to each radiation dose.
    c. To allow normal tissues to repair sub-lethal radiation damage between fractions.
    d. To fit in with other treatments such as external beam radiotherapy.

21. HDR brachytherapy is predominantly indicated as a
    a. Monotherapy.
    b. Combined therapy.
    c. Alternative to surgery for elderly patients with a life expectancy greater than 10 years.
    d. All of the above.

22. Rectal dose in both LDR and HDR brachytherapy is ideally limited to 75% of the gland dose because
    a. Tumor control is likely to be acceptable as 70% of cancers occur in the peripheral zone.
    b. Historical data indicates that this dose is acceptable.
    c. The risk of toxicity such as bleeding, ulceration and stricture is clinically acceptable.
    d. Tumor control is likely to be acceptable as 20% of cancers arise in the central zone.

23. Results from monotherapy LDR brachytherapy studies indicate
    a. Similar results to surgery for early stage disease.
    b. Similar results to surgery for late stage disease.
    c. Superior results to surgery as toxicity is less.
    d. Inferior results to surgery as toxicity is greater.

24. Results from combined HDR brachytherapy studies indicate
    a. Similar results to external beam radiotherapy (based on IMRT & 3D CRT) for early stage disease.
    b. Similar results to external beam radiotherapy for later stage disease.
    c. Superior results to external beam radiotherapy as toxicity is less.
    d. Inferior results to external beam radiotherapy as toxicity is greater.

25. A patient presents with a T2a tumor. Analysis reveals a Gleason score of 4 and presenting PSA of 8. TRUS examination reveals a well defined hypo-echoic lesion in the peripheral aspect of a gland which measures 65cc in volume. What would be the appropriate management strategy?
    a. Surgery
    b. LDR monotherapy brachytherapy
    c. HDR combined brachytherapy
    d. HDR or LDR combined therapy in association with hormones