The Utilization of HDR Brachytherapy in Prostate Cancer Treatment

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**Abstract**

**Background:** HDR brachytherapy for the treatment of prostate cancer has many known benefits and advantages. Despite its value, there has been a decrease in the utilization of the treatment technique over the last decade. However, there has been increased interest in recent years to incorporate HDR brachytherapy for prostate cancer into treatment options.

**Objectives:** To assess the current application and potential increased usage of HDR brachytherapy for prostate cancer.

**Methods:** A literature review was conducted to gain knowledge about HDR brachytherapy for prostate cancer. All sources were used to understand the process, benefits, risks, usefulness, and costs of treatment.

**Results:** HDR brachytherapy for prostate cancer has been around for many years and has evolved over time. HDR brachytherapy has been proven to be useful in treating prostate cancer based off a variety of patient results and factors.

**Conclusions:** Despite the benefits and clinical applications of HDR prostate brachytherapy, there has been underutilization of the procedure. The patient outcomes and treatment related side effects may alter the current views on HDR brachytherapy for prostate cancer treatment. More research needs to be completed to attract its use as a primary treatment for prostate cancer.

**Introduction**

 According to the American Cancer Society,1 “prostate cancer is the most common type of cancer and the second leading cause of cancer death in men”. It is reported that one in eight men will be diagnosed with prostate cancer in their lifetime.1 Radiation therapists are accustomed to the treatment of prostate cancer. Over time, there has been an increase in the techniques and modalities in which radiation can be used to treat prostate cancer. These treatments include traditional external beam radiation therapy (EBRT), stereotactic body radiation therapy (SBRT), low dose rate (LDR) brachytherapy, and high dose rate (HDR) brachytherapy. High dose rate brachytherapy for the treatment of prostate cancer can be completed as a monotherapy or as boost in combination with EBRT.

Although the usage of HDR brachytherapy for the treatment of prostate cancer has been decreasing since its peak in 2002, there has been a renewed interest in the therapy in recent years.2,3 High dose rate brachytherapy for prostate cancer is a treatment technique that therapists participate in. It is important for radiation therapists to know it’s process, patient eligibility, benefits, and how it compares to other treatment options readily available. It is also critical for therapists to be aware of the reasons why HDR brachytherapy may not be utilized for prostate cancer patients. Due to the renewed interest in the technique, the usage of HDR brachytherapy for prostate cancer may be increased.2,3

**Methods**

 A literature review was conducted to assess the current use of HDR brachytherapy for the treatment of prostate cancer. Patient selection, fractionation schemes, cost, side effects, and quality of life were researched and compared between various treatment modalities to evaluate the benefits, advantages, risks, and reasons for utilizing HDR brachytherapy for the treatment of prostate cancer. Multiple data bases including PubMed, MedLine, and EBSCOhost, and others were searched for “HDR brachytherapy”, “prostate”, “EBRT”, “benefits”, and “toxicities”. In addition, many studies were viewed, including original research, which reported varying benefits and uses for HDR brachytherapy in the treatment of prostate cancer. An effort was made to compare the use of HDR brachytherapy to existing methods of radiation treatment to the prostate.

**Literature Review**

 **How HDR Brachytherapy is Completed**

 Brachytherapy is a radiation treatment technique utilized for many types of cancers.3 The word “brachy” means “short distance” and the word “therapy” refers to “treatment”.3 Unlike other forms of radiation therapy, this technique uses live radioactive sources at a close distance to the target structures.3 Brachytherapy is often completed through a HDR type treatment meaning that a large dose of radiation is given during a short amount of time. High dose rate brachytherapy has many potential benefits including fewer treatment sessions, higher doses given to target structures, lower doses delivered to surrounding critical structures, and decreased side effects as compared to EBRT alone.3-10 Along with these benefits, HDR brachytherapy can be completed on an outpatient basis as a monotherapy or as an additional boost to EBRT. This treatment technique may have high potential benefit for prostate cancer as compared to other available treatment options as prostate cancers respond very well to hypofractionated treatment regimens.4

Regardless of whether a prostate cancer patient receives HDR brachytherapy as a monotherapy or as an additional boost to their EBRT, they must meet specific patient criteria. The patient must first be able to withstand surgery.5 Secondly, a patient’s stage of disease largely determines their eligibility.5 High dose rate brachytherapy as a monotherapy means that it is the only form of radiation the patient will receive for their treatment. High dose rate monotherapy generally has a dosing of 27 Gy in two fractions.4 To be eligible for this, a patient must have low-risk or favorable intermediate-risk prostate cancer.5 According to Ouhib et al5, specifically having “clinical stage II, T1c or T2a, prostate specific antigen (PSA) ≤ 10 ng/mL, and Gleason score of ≤ 6”. If a patient has HDR brachytherapy as a boost to EBRT, the patient will be treated to 37.5 Gy with EBRT then have one fraction of 15 Gy as the boost.4 To be eligible for this, a patient will have high-risk or very high-risk prostate cancer.5 According to Ouhib et al5, specifically having “clinical stage ≥ T2b, pretreatment PSA ≥ 10, and Gleason score ≥ 7”.

 High dose rate brachytherapy requires a patient to maintain a dorsal lithotomy position and be put to sleep using general anesthesia for the duration of the procedure and treatment.6 Several needles, between 16 and 20, are placed into the patient’s prostate.5 This is most commonly achieved using transurethral ultrasound (TRUS) and in some cases using magnetic resonance imaging (MRI) as image guidance.4,6 Multiple needles are required to deliver a uniform dose to the target structures as well as to give multiple options when creating the treatment plan.4-6 These needles are held in place by a square shaped template attached to the patient’s perineum.4-6 The template also allows for needles to be denoted and mapped out for treatment planning.4-6

After the needles are placed in the prostate, an image must be acquired in some fashion for the treatment planning to take place.4-6 These images are acquired using one of the following technologies, computed tomography (CT)-based, ultrasound (US)-based intraoperative, or MRI-based planning.4,6 Computed tomography-based treatment planning uses a CT scan to localize the needles in the prostate for treatment planning.4,6 Ultrasound-based intraoperative treatment planning acquires a three-dimensional image using the same modality that was used to place the needles, TRUS.4,6 Magnetic resonance imaging can be utilized in a variety of ways for HDR prostate brachytherapy treatment.4-6 An MRI can be taken prior to the procedure and fused with planning images, used as image guidance for needle insertion, and/or a planning image is taken after the needles are placed.4,6

Regardless of what image planning technique is used, it is imperative that the needles do not move inside the patient’s prostate after they have been placed.4-6 Each of the imaging modalities has their pros and cons. Computed tomography-based treatment planning runs a risk of the needles moving since the patient must be brought from the operating room to a room that has a CT scanner.4,6 However, it is quite common for radiation oncology departments to have CT scanners and brachytherapy sources located in the same room. Magnetic resonance imaging-based treatment planning has the most difficulties, all treatment accessories must be MR compatible, the workflow is quite different due to the limited size of the machine bore, and the patient will most likely need to be transported to the treatment room.4,6 However, MRI gives an excellent picture of the prostate since it is soft tissue. Ultrasound-based treatment planning provides the best solution as everything is completed in the operating room, hence there is no risk that the needles will move when transporting the patient.4,6 However, it can be difficult to identify the needles when using a three-dimensional TRUS images.6

After needles are properly placed in the prostate and planning images are acquired using any of the various methods, treatment planning can begin. The target structures and organs at risk are identified and outlined.4 The urethra and rectum are of particular concern when using HDR brachytherapy for the prostate.4 Needles are reconstructed using the treatment planning system.4 A treatment plan is developed using anatomy-based inverse planning.4 The dose distribution is based on how long the source will reside in the needle and its position in the needle.4 The afterloader positions are generally equidistant within the needles, the treatment planning system then determines the amount of time the source will be in each needle.4 When using HDR to treat the prostate, the whole prostate will be included in the clinical target volume (CTV), if there is macroscopic extracapsular extension or seminal vesicles involvement a three-millimeter margin will be added to the CTV.4 Once treatment planning is complete, catheters are connected from the HDR unit to the needles to allow the live sources to enter the prostate.3 The actual delivery of the radiation is short compared to all the other steps in the treatment process.

**HDR Brachytherapy Benefits**

There are many benefits to the use of HDR brachytherapy in the treatment of prostate cancer. Many studies have found that HDR brachytherapy as a boost provides increased results compared to EBRT alone.3 Prostate cancers have been shown to have a high responsiveness to hypofractionated treatment schemes such as HDR brachytherapy.9 High dose rate brachytherapy allows for a dose escalation to occur, this is also true with the use of EBRT intensity modulated radiation therapy (IMRT). However, HDR brachytherapy allows for a greater dose to be delivered just to the target structure rather than surrounding critical organs.3 This allows for lower toxicities, less treatment related side effects, lower incidences of local recurrence, less metastases, and increased treatment results.7-10

The use of HDR brachytherapy as a boost to EBRT has been shown to provide better results than EBRT alone.3,7,9 A study was completed by Hoskin et al7 in which a total of 218 prostate cancer patients were randomized to receive either EBRT alone or EBRT with HDR brachytherapy boost. Four years post treatment, the 106 EBRT patients and 110 EBRT + HDR brachytherapy boost patients were analyzed for relapse free survival (RFS), overall survival (OS), and toxicities.7 It was found that patients who were treated with EBRT + HDR brachytherapy boost had a higher RFS than those treated with EBRT alone.7 With a relapse rate of about 137 months for EBRT + HDR brachytherapy boost versus 82 months for EBRT alone.7 Each treatment scheme was also given a six and 12-year RFS with EBRT + HDR brachytherapy boost being 71 percent and 48 percent, and EBRT alone being 55 percent and 27 percent.7 The study7 found no difference between OS, biochemical relapse, and metastasis free survival when comparing the two treatment types. Both treatment options showed relatively similar incidences of genitourinary (GU), urethral strictures, and gastrointestinal (GI) events six- and eight-years post treatment.7 However, Hoskin et al7 did find that there was a higher incidence of severe grade 3 urinary events with EBRT + HDR brachytherapy boost than with EBRT alone within the first year of the first EBRT fraction.7

Another study8 was completed on 79 prostate patients who received two fractions of HDR brachytherapy one week prior to their 28 fractions of EBRT. Each patient was evaluated one, three, and five years post treatment for early and late toxicities, metastases, local recurrence, and PSA value. Of all 79 patients in the study, 84.81 percent of them reported no treatment related side effects.8 Of the 15.19 percent of patients that did report side effects, all of them were grade one toxicities. The most common reported side effects included anal pain, symptomatic proctitis, diarrhea, high urinary frequency, and urgency, each occurring at very low rates.8 During this study8, only one patient died due to progressive disease and bone metastasis. It was also found that PSA at the time of diagnosis, during the first HDR brachytherapy treatment, and at the first follow-up was a significant predictor of local recurrence.8 Meaning the higher the PSA level at each stage, the more likely the cancer would return.8 The evidence provided from Ecke et al8 contributed to the already available evidence that HDR brachytherapy with EBRT improves the overall survival of prostate cancer.3,7,9

**Quality of Life of HDR Brachytherapy Patients**

To assess the validity in the use of HDR brachytherapy as compared to other treatment techniques, it is important to analyze the quality of life for patients treated with this modality. A health-related quality of life (HRQOL) survey was completed by 37 patients treated with 3-dimentional conformal (3-DC) boost and 38 patients treated with HDR brachytherapy boost.9 The HRQOL survey was mailed out to both groups of patients after their treatments had been completed. The questionnaire was based on the European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) which is used to measure the quality of life in cancer patients.9 This type of questionnaire contains 30 items and covers a variety of factors that affect quality of life, physical, cognitive, social, physical symptoms, financial difficulties, and more.9 A prostate-specific module (PR25) was used in conjunction with EORTC QLQ-C30 to assess prostate specific treatment related side effects.9 Vordermark et al9 found that there were no significant differences in quality of life (QOL) post-treatment between the two groups studied. The insomnia and diarrhea scores from the EORTC QLQ-C30 survey were significantly higher for the 3-DC group as compared to the HDR boost group.9 There were no significant differences between the two groups concerning urinary and bowel side effects.9 It was also revealed that erectile problems were more frequently reported amongst the HDR boost group than the 3-DC boost group.9 This reveals a possible risk associated with the use of HDR brachytherapy when treating the prostate. Erectile problems can have a significant effect on one’s quality of life. Therefore, it is important to take this into consideration when choosing a treatment option.

The quality of life of prostate cancer patients receiving HDR brachytherapy as a monotreatment were also studied alongside physician reported toxicities to assess the timing of fractions in relation to toxicities. The study10 included 122 patients that were given two fractions of HDR brachytherapy, 63 of them with one week and 59 with two weeks between treatments. Between the two treatment groups, there were no significant differences in QOL scores, or physician reported toxicities.10 This signifies that physicians do not need to be concerned about the timing between fractions having a negative impact on toxicities. For both treatment groups, there were decreased GU, GI, and sexual QOL scores immediately following treatment.10 Overtime the GU and GI QOL scores increased, returning to baseline.10 However, the sexual QOL scores did not return to baseline.10 Physicians mainly reported patients having grade two GU toxicities, grade one GI toxicities, and grade two sexual toxicities.10 Grade three GU and sexual toxicities were reported at one percent and no grade three GI toxicities were reported.10 This study10 shows that HDR brachytherapy has little to no negative impact on a patient’s QOL, making it an excellent option for the treatment of prostate cancer.

**Cost of Care**

 When assessing the benefits of HDR brachytherapy in the treatment of prostate cancer, it is essential to understand the various costs of treatment techniques. Each treatment option for prostate cancer has their own benefit, reasons for use, and associated cost. A study by Laviana et al11 was done in which prostate cancer treatment options were calculated using the cost analysis model, time-driven activity-based costing (TDABC). The TDABC calculation depends on the resources used for the medical service, the fraction of time the resource was used, and the cost of each resource per unit time.11 The model allows for personnel, equipment, facility, and support costs to be factored into the total cost.11 The studiers followed localized, low-risk prostate patients for each treatment modality from their initial visit through five years follow-up to calculate the cost of care for robotic-assisted laparoscopic prostatectomy (RALP), HDR, LDR, IMRT, SBRT, active surveillance (AS), and cryotherapy.11

It was found that IMRT and SBRT were two of the most expensive treatment options.11 The cost of a single session of IMRT is $297.84 and SBRT is $479.31, a single fraction of SBRT is almost double that of an IMRT treatment.11 However, the number of fractions must be considered to get the total cost. With SBRT having five fractions and IMRT having 45 fractions, the total cost for IMRT is in turn higher than SBRT with a cost of $23,565 and $11,665 accordingly.11 Next it is important to talk about both LDR and HDR at the same time. The large difference between the cost of these treatment modalities is due to the number of treatments, procedure time, cost per session, disposable costs, and the largest contribution to the total cost.11 Low dose rate treatments occur once, last for 99.5 minutes, have a cost per session of $3,888, with a disposable cost of $1.921, and the permanent Iodine-125 seeds account for 75.6 percent of the total cost.11 Conversely, HDR treatments occur twice, last for 150.7 minutes, have a cost per session of $4,000 for the first and $3,956 for the second, with a disposable cost of $2,296, and the flexi needles account for 20% of the total cost.11 Using this model, the cost of a typical EBRT + HDR brachytherapy boost would cost $8,467.60. This shows the significant cost reduction hospitals would have using this treatment technique, a possible reason for the increased interest in HDR brachytherapy.3

**Underutilization of HDR Brachytherapy**

With the declined use of HDR brachytherapy for prostate cancer patients, it is important to understand why the modality is underutilized despite all the benefits it is found to have.2 A study12 completed in Victoria, Australia was conducted to assess the use of both EBRT and HDR brachytherapy for prostate cancer. Using the Prostate Cancer Outcome Registry Victoria (PROC-Vic), it was found that 1,806 men were treated with EBRT for their prostate cancer, and only 124 of them were documented to have HDR brachytherapy in addition to their EBRT.12 Based on the PROC-Vic, the patients who did receive the HDR brachytherapy boost were younger, considered high-risk, being treated at a public institution, and being treated at a metropolitan center.12

Some reasons for the underutilization of HDR brachytherapy in Victoria, Australia can be applied to hospitals in the United States. The decrease may be due to the use of IMRT EBRT.12 Intensity modulated radiation therapy allows for higher doses of radiation to be delivered to target structures, sparing of normal organs, and dose escalations, hence eliminating the need for HDR brachytherapy boosts.12 External beam radiation therapy also allows for the treatment technique of SBRT which provides a hypofractionated, large dose treatments like that of HDR brachytherapy.13 Another reason could be that there are a limited number of radiation oncologists performing HDR brachytherapy.12 According to 2015 data, 30 percent of United States medical students are unaware of the use of HDR brachytherapy in the treatment of prostate cancer, and 10 percent do not believe it to be a definitive treatment option.14,15 Many medical residents also report not performing this treatment as part of their learning, so there is a lack of awareness and experience.16-21 In addition, there are also a limited number of oncology institutions in Victoria.12 For this reason, patients may be declining the therapy due to a need for traveling or they may not be offered the treatment. Government funding of equipment may also play a large factor in HDR brachytherapy underutilization.12 There are many reasons ranging from other therapy techniques to a lack of education on the procedure that contribute to the limited use of HDR prostate brachytherapy in hospitals.

**Conclusion**

 HDR brachytherapy as a monotreatment and as a boost to EBRT for prostate cancer has many known benefits. These include a significant reduction in the number of times a patient must come for treatment, little to no GU or GI toxicities once treatment is completed, a higher incidence of relapse free survival rates, and a significant decrease hospital costs as compared to similar dose escalation treatments like IMRT and SBRT.7-11 Despite all these advantages, there has been an overall decrease in its use over the past decade.3 Some causes may include limited locations completing the procedure, the number of residents learning and preforming HDR brachytherapy, and similar treatment options readily available at hospitals.12-21 However, there has been increasing interests in its use in recent years.2 This may be due to the increased studies being completed on its effectiveness in treating prostate cancer, especially using HDR brachytherapy as a boost when treating high-risk patients.4,7-10 More research must be completed to properly educated radiation oncologists, medical physicists, dosimetrists, and radiation therapists about the benefits of using HDR brachytherapy as a monotherapy or as a boost to EBRT.

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