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HIGH-DOSE-RATE BRACHYTHERAPY FOR PROSTATE CANCER

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Summary of Literature Review

Introduction/Background

Over the last 2 decades, significant technical advancements have improved the delivery of prostate brachytherapy. The transrectal ultrasound-guided implant technique is the backbone of modern prostate brachytherapy. Whether it is permanent or temporary, ie, low-dose-rate (LDR) or high-dose-rate (HDR), respectively, both use similar image-guided techniques for inserting seed-bearing needles or afterloading catheters. This image-guided implant technique has improved the quality and reproducibility of prostate brachytherapy. In HDR brachytherapy, a computer-programmed remote afterloader is used to insert the radioactive source into the patient. This has several important practical advantages: (1) it is a reusable radioactive source, (2) there is no radiation exposure for hospital personnel, and (3) it offers flexible dosimetry. Our understanding of the radiobiology of hypofractionation, however, has changed the clinical application of HDR brachytherapy.

Early HDR prostate brachytherapy studies used brachytherapy in conjunction with external beam radiotherapy (EBRT). The rationale behind this approach was to take advantage of brachytherapy's dosimetry but use conventionally fractionated EBRT to counterbalance the potentially negative radiobiologic effect of hypofractionation. Dr. Brenner's 1999 seminal paper on prostate cancer radiobiology suggested that the prostate's alpha-beta ratio was much lower than previously believed [1]. This initiated a paradigm shift in the way we think about fractionation for prostate cancer. It also affected clinical trial design for both EBRT and brachytherapy.

Clinical Results of High-Dose-Rate Prostate Brachytherapy Boost

HDR prostate implants have been used as a boost in conjunction with EBRT. Typically, this involves 4-5 weeks (40-50 Gy) of EBRT treatment with one or more implants, which are sandwiched between, before or after EBRT. The older series used more implants (3 implants) compared with more recent series (1 implant). Older series also used more fractions (4 fractions) of HDR treatment compared with recent series (1 fraction).

Martinez et al [2-4], from the William Beaumont Hospital, reported on the first dose-escalation trial that used HDR brachytherapy as a boost. Multiple updates of these results have implemented dose escalation using increasingly larger fractions of HDR treatment, ranging from 5.5-6.5 Gy x 3 to 8.25-11.5 Gy x 2, combined with 46 Gy of EBRT. They have shown acceptable toxicity levels using 11.5 Gy x 2 treatments. Patients with prostate-specific antigen (PSA) levels ≥10, T ≥T2b, and Gleason scores ≥7 were selected for the trial. Despite a high frequency of poor prognostic factors, the actuarial biochemical control rate was 74% at 5 years using the American Society for Radiation Oncology definition. The 5-year actuarial rates of local failure and distant metastasis were 8% and 6%, respectively.

The RTOG® (0321) [5] reported the only prospective, multi-institutional phase II trial in HDR brachytherapy. It reported this study after achieving adequate follow-up for its primary endpoint. In the study, a combination of

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EBRT of 45 Gy in 25 fractions, in combination with HDR brachytherapy of 19 Gy in 2 fractions, was used to treat patients with locally confined stage T1c-T3b prostate cancer. The estimated rate of late grade 3 or greater genitourinary and gastrointestinal toxicity at 18 months was 2.56%.

The most recent hypofractionation HDR boost trial established that the HDR boost can be given as a single fraction of 15 Gy in combination with hypofractionated EBRT of 37.5 Gy in 15 fractions [6]. The full course of treatment was completed in 3 weeks. With a relatively short median follow-up of 1.14 years, the grade 3 genitourinary and gastrointestinal toxicity rate was 1.6%. A post hoc comparison of this trial with their own experience of EBRT 45 Gy and HDR boost of 10 Gy x 2 was done [7]. Based on a median follow-up of the single fraction trial at 45 months, it reported similar efficacy and toxicity between the 2 regimens.

Patients selected for the combination treatment are generally those at intermediate-to-high risk who may benefit from dose escalation [8]. Lower-risk patients, however, can also be treated with this approach. The potential advantage of HDR's delivery technology is demonstrated in difficult clinical cases, such as for patients who have (1) very large prostates, (2) extracapsular extension, and (3) post-transurethral resection of prostate (TURP). An HDR boost can be used to treat patients with very large prostates, including patients with prostates >60 cc [9]. Because the afterloading catheter can be placed in the prostate's periphery, HDR brachytherapy can be used to treat patients who have extracapsular extensions and seminal vesicle invasion [10]. Patients with prior TURP can be the most challenging cases for prostate brachytherapy; however, HDR brachytherapy has been shown to be successful in that setting [11].

HDR boost has also compared favorably against EBRT alone. From the only reported prospective randomized HDR trial, Hoskin et al [12] reported on 220 patients, randomized to EBRT alone 55 Gy/20 fractions or external radiotherapy of 35.75 Gy/13 fractions and HDR boost of 17 Gy/2 fractions. At a median follow-up of 30 months, there was significant improvement in biochemical relapse-free survival favoring the HDR boost group. There was also a lower incidence of acute rectal symptoms favoring the HDR boost group. The HDR boost group had a significantly better Functional Assessment of Cancer Therapy–Prostate score at 12 weeks. This trial was the first evidence of clinical benefit by dose escalation using HDR brachytherapy as compared to external beam boost. Unlike the result of dose escalation using EBRT, there was actually less toxicity with the HDR boost. One can reasonably conclude that the improved efficacy observed in these studies was due to the benefit of dose escalation in the brachytherapy arm. Similar gains in efficacy may be achieved using other dose-escalating EBRT techniques; however, the lack of increase or decrease in toxicity observed in the higher dose arm is unique to HDR brachytherapy. The results of this trial suggest that HDR brachytherapy boost may possibly be advantageous for dose escalation in prostate cancer. (See Variant 1.)

High-Dose-Rate Monotherapy

There had been interest in developing HDR monotherapy for patients with early-stage prostate cancer due to the technical advantages already listed. However, the large number of fractions required to deliver the full dose without EBRT created challenges for both the patient and physician. More fractions meant a longer hospital stay or more implant procedures. During multifractionated HDR treatment, catheter migration could cause degradation of dosimetry [13,14]. Various institutes had developed solutions to address this issue [15-18]; however, these solutions had limitations and required a significant amount of extra effort. Further exploration of hypofractionation is needed to determine a way to lower the number of fractions.

Clinical Results of High-Dose-Rate Monotherapy

Multiple studies have demonstrated the feasibility of this approach. Yoshioka et al [19,20] reported their results on patients treated with HDR monotherapy. The patient population included those with T1-T4 tumors. Higher-stage tumors were treated with adjuvant hormonal therapy and a higher implant dose. A total of 112 patients were treated with 8-9 twice-daily fractions of 6 Gy over 5 days. With a median follow-up of 5.4 years, the 5-year clinical local control rate was 97%, and the biochemical relapse-free rate was 83%. The late grade 3 toxicity reported was 3%.

Martinez et al [21] reported on the initial results from their ongoing prospective phase II monotherapy trial. Selection criteria included Gleason scores ≤7, PSA ≤10, and T ≤T2a. All patients were treated with 4 twice-daily fractions of 9.5 Gy over 2 days. Forty-one patients were treated per protocol, and all tolerated the treatment well.

Another prospective phase II monotherapy trial was conducted at Mount Vernon Cancer Center. Three dose levels were tested: 8.5 Gy x 4, 9 Gy x 4, and 10.5 x 3. At a 6-month follow-up, 2 patients showed grade 3 bladder

toxicity, 1 patient from each of the last 2 dose regimens. Early results suggest an excellent biochemical response and no difference in the acute and late toxicity between the three regimens [22].

Ghilezan et al [23] reported on an ongoing prospective HDR monotherapy trial delivering 2 HDR fractions with 1 implant. At a minimum follow-up of 6 months, 93 patients with a T stage ≤T2b, Gleason score 6-7 (3+4), and PSA ≤12 were treated with 2 different twice-daily fractionations of 12 Gy x 2 or 13.5 x 2 Gy. With a median follow-up of 17 months, there was no grade 3 toxicity; however 1 patient had grade 4 rectal bleeding.

Demanes et al [24] reported the largest series of HDR monotherapy. A combined experience of 2 centers, the series included 298 early-stage prostate cancer patients treated with HDR monotherapy and had a median follow-up time of 5.2 years. The groups were treated with 7 Gy x 6 and 9.5 Gy x 4. The 5- and 8-year biochemical control was 95% with 3% grade 3 genitourinary toxicity and <1% gastrointestinal toxicity.

More recently, Prada et al [25] reported the first single-fraction HDR monotherapy in which 40 consecutive patients who had favorable localized prostate cancer were treated with 19 Gy in single fraction. The authors used a transperineal injection of hyaluronic acid into perirectal fat to increase the distance between the prostate and rectum prior to the treatment [26].

Results showed no genitourinary or gastrointestinal toxicity of grade 2 or greater with a median follow-up of 19 months. This study represents the most hypofractionated brachytherapy for prostate cancer. The limited toxicity report from their preliminary experience is very encouraging for this approach.

Ongoing HDR monotherapy trials suggest that hypofractionated HDR brachytherapy is safe and effective. Future studies are likely to continue to push toward fewer highly hypofractionated treatments. These studies could help make HDR monotherapy more accurate and convenient for patients. (See Variant 2.)

Salvage High-Dose-Rate Brachytherapy

Patients with locally-recurrent prostate cancer following radiotherapy represent a special clinical challenge. Salvage surgical series using aggressive local therapy have demonstrated durable remission with a 5-year biochemical control range of 47%-82% [27]. Salvage surgery in this setting, however, is generally considered technically challenging and has a significant risk of toxicities, including urinary incontinence (0%-100%), strictures (0%-48%), and rectal injury (0%-19%) [27]. Alternative local salvage therapies, such as cryotherapy and high-intensity focused ultrasound, have also shown promising results with a 5-year biochemical control range from 50% to 95% [28,29]. As with the surgical approach, there is significant risk of toxicities, including urinary incontinence (4.4%-73%), urinary retention (0%-67%), and fistula (0%-3%) [28,29]. It is important to point out that there is no prospective comparative study of these treatments, and the published results vary greatly depending on patient selection.

LDR brachytherapy has been used to re-irradiate prostates previously treated with full-dose radiotherapy [30]. In a series with longer follow-ups, a 5-year biochemical control rate of 34% to 64.5% and grade 3+ toxicity of 0% to 47% was reported [31-34]. Lee et al also performed HDR salvage brachytherapy [34] in 21 consecutive patients treated with 36 Gy in 6 fractions using 2 implants. With a median follow-up of 18.7 months, the biochemical control rate was 89% with 14% grade 3 toxicity. The literature on salvage brachytherapy has shown encouraging results, and LDR brachytherapy is being tested in a prospective RTOG study. (See Variant 3.)

Summary

- In this article, we have reviewed the most common applications of HDR brachytherapy for prostate cancer.
- A review of the literature indicates a growing interest in shorter, more hypofractionated HDR approaches.
- Although the evidence for efficacy and safety of these hypofractionated treatments are better established in HDR boost, it is just beginning to emerge for HDR monotherapy.
- The ongoing prospective studies and updates on earlier studies will eventually settle these debates and establish the most efficient fractionation regimen.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **High-Dose-Rate Brachytherapy for Prostate Cancer**

Variant 1: **60-year-old man, stage T3b, Gleason score 7, adenocarcinoma. PSA 12 ng/mL, 65 cc prostate, 80% of biopsy cores were positive. There was perineural invasion and seminal vesicle invasion. Patient had TURP 5 years ago with IPSS 10/35. Patient agreed to have hormonal therapy and decided to undergo HDR brachytherapy boost.**

Treatment	Rating	Comments
EBRT 45 Gy + HDR brachytherapy 5.5-6.5 Gy x 3	7	
EBRT 45 Gy + HDR brachytherapy 8-11.5 Gy x 2	8	The panel felt the 2-fraction regimen has the best supporting evidence for this patient, who has a history of TURP and SV invasion.
EBRT 45 Gy + HDR brachytherapy 13-15 Gy x 1	5	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 2: **50-year-old man, stage T1c, Gleason score 3/3 adenocarcinoma. PSA 8 ng/mL, 60 cc prostate, 5% of biopsy cores were positive, negative diagnostic workup. Patient decided to undergo HDR monotherapy.**

Treatment	Rating	Comments
HDR Monotherapy 9.5 Gy x 4	7	Although there is a trend toward more hypofractionated monotherapy regimens, the panel felt the more fractionated regimens have a longer follow-up and stronger evidence for routine use.
HDR Monotherapy 10.5 Gy x 3	5	
HDR Monotherapy 13.5 Gy x 2	5	
HDR Monotherapy 19 Gy x 1	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 3: **50-year-old man with history of low-risk prostate cancer treated with 78 Gy with IMRT 5 years ago, now developed local recurrence. GS 7, PSA 5 ng/mL, PSA doubling time of 12 months, 30 cc prostate, 5% of biopsy cores were positive, negative diagnostic workup.**

Treatment	Rating	Comments
Hormonal therapy	5	The panel felt a definitive approach was more appropriate in this young patient.
Prostatectomy	6	
Cryotherapy	6	
Salvage Radiotherapy Modality		
LDR Brachytherapy	6	
HDR Brachytherapy	6	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		