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High-Dose-Rate Brachytherapy in Prostate Cancer: A Comprehensive Analysis of Efficacy, Radiobiological Aspects, and Specialized Applications

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Abstract

This review article presents a comprehensive analysis of high-dose-rate brachytherapy (HDR-BRT) as a treatment method for prostate cancer, based on contemporary research and clinical experience. It thoroughly examines the efficacy and safety of HDR-BRT as monotherapy, which is confirmed by high rates of biochemical control and an acceptable toxicity profile across various risk groups. Special attention is paid to the radiobiological basis of the prostate gland's response to irradiation under different fractionation regimens, including a discussion of the limitations of the classical linear-quadratic model in extreme hypofractionation and the relevance of the linear-quadratic-linear (LQL) model. The section dedicated to CT-guided brachytherapy is expanded to highlight its critical role in treating complex cases, particularly patients with prostate cancer who have previously undergone rectal extirpation. Based on a systematic review and meta-analyses, the role of HDR-BRT as a safe, highly effective, and adaptive treatment option that expands therapeutic possibilities for patients even in atypical clinical scenarios is emphasized.

INTRODUCTION

Prostate cancer (PCa) is one of the most common oncological diseases among men worldwide, posing a significant burden on the healthcare system. According to global statistics, PCa holds a leading position in terms of morbidity and mortality among the male population, although screening programs and improved diagnostic methods increasingly detect localized forms of the disease at early stages. Modern treatment methods for localized PCa include active surveillance, radical prostatectomy (surgical removal of the prostate gland), external beam radiation therapy (EBRT), and brachytherapy (internal irradiation). The choice of the optimal treatment method is a multifactorial decision that depends on the disease stage, tumor aggressiveness (Gleason score), prostate-specific antigen (PSA) level, the patient's general health, presence of comorbidities, and their personal preferences regarding potential side effects and quality of life.

Among radiation therapy options, high-dose-rate brachytherapy (HDR-BRT) stands out as a method that allows for the highly accurate delivery of high radiation doses directly to the target area-the prostate gland. The principle of HDR-BRT involves the temporary placement of a high-activity source (usually iridium-192 isotope) in special hollow needles-applicators inserted directly into the prostate gland volume. This provides a very steep dose gradient, leading to a rapid dose fall-off outside the target volume. Such a dosimetric advantage allows for a significant increase in the radiation dose to the tumor, while minimizing the impact on surrounding healthy tissues and critical organs such as the rectum, bladder, urethra, and glans penis, which is crucial for preserving functional outcomes and patients' quality of life.

HDR-BRT can be used both in combination with external beam radiation therapy for patients with high-risk PCa, where it acts as a "boost" to enhance the dose in the tumor area, and as monotherapy for patients with low and intermediate risk. Over the past decades, numerous studies have shown the benefits of dose escalation for improving oncological outcomes, which is particularly relevant for PCa, known for its relative radio resistance at low doses. Technological advancements in imaging systems (ultrasound, CT, MRI) and treatment planning software have significantly improved the accuracy and safety of HDR-BRT, making it an attractive option for many patients seeking effective treatment with minimal invasive intervention and faster recovery.

The aim of this article is a comprehensive analysis of the key aspects of HDR-BRT, covering its application as monotherapy, radiobiological features of tumor response to irradiation, and specialized clinical cases demonstrating the

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adaptability and broad potential of this method in modern oncological treatment [1].

HIGH-DOSE-RATE BRACHYTHERAPY AS MONOTHERAPY FOR PROSTATE CANCER

The efficacy and safety of high-dose-rate brachytherapy as monotherapy (HDR-BRT-M) for prostate cancer have been thoroughly investigated and summarized in a systematic review and meta-analysis conducted by Viani [2]. This study is one of the most comprehensive reviews on the topic, aiming to synthesize existing evidence regarding biochemical relapse-free survival (bRFS) and the toxicity profile after HDR-BRT-M in PCa patients, providing important data for clinical practice and guideline formulation.

Fourteen studies, covering a total of 3534 patients, were included in the meta-analysis [2-5]. The distribution of patients by risk groups was typical for such studies: patients with low, intermediate, and high risk of the disease. The results showed very high rates of five-year bRFS: 97.5% (95% CI 96-98%) for the low-risk group, 93.5% (95% CI 91-96%) for the intermediate-risk group, and 91% (95% CI 88-93%) for the high-risk group. These data are impressive and indicate that HDR-BRT-M can provide excellent local disease control, comparable to and sometimes surpassing the results achieved by other radical treatment methods, such as radical prostatectomy or dose-escalated external beam radiation therapy. The high level of bRFS, especially for the low and intermediate-risk groups, underscores the potential of HDR-BRT-M as a standalone, minimally invasive, and effective treatment option.

The study by Viani [2] also identified several key factors significantly influencing bRFS rates. These include the total biologically effective dose (BED) (p=0.02), BED per fraction (p=0.001), the use of androgen-deprivation therapy (ADT) (p=0.04), and the number of HDR-BRT-M fractions (p=0.024). These findings have direct implications for optimizing treatment protocols. Higher BED and BED per fraction values were statistically significantly correlated with better outcomes, supporting the concept of dose escalation for better oncological control, especially for tumors with a low α/β ratio, like PCa. The use of ADT, often applied in patients with more aggressive forms of PCa or high risk, also improved biochemical control, indicating a synergistic effect of the combined modality. The importance of the number of fractions also indicates the complexity of the radiobiological response and the need for a balanced approach to fractionation that considers both efficacy and tolerability of treatment.

Regarding the toxicity profile, the meta-analysis showed that HDR-BRT-M is a safe treatment method. The incidence of late genitourinary toxicity of grade 2(+) / 3 or higher was 22.4% (95% CI 9-35.2%) for grade 2 and 1.4% (95% CI 0.8-2.1%) for grade 3 and higher, respectively. For the gastrointestinal tract, these rates were even lower: 2.7% (95% CI 0-6.8%) for grade 2 and 0.2% (95% CI 0.1%-0.4%) for grade 3 and higher. These toxicity rates are acceptable and comparable to side effects observed with other radical treatment methods for PCa. It is important to note the low level of severe (grade 3 and higher) toxicity, which is a key indicator of treatment tolerability and its impact on patients' quality of life. Compared to radical prostatectomy, HDR-BRT-M is often associated with a lower risk of urinary incontinence and erectile dysfunction, although other specific side effects related to irradiation may occur.

Despite comparable, and in some aspects superior, biochemical control compared to low-dose-rate brachytherapy (LDR-BRT), surgery, and dose-escalated external beam radiation therapy, HDR-BRT-M is still not universally accepted or offered as a standard of care in many oncology centers. This is largely due to the lack of large, multicenter randomized clinical trials directly comparing HDR-BRT-M with other standard treatment methods. Historically, most of the evidence for the efficacy of HDR-BRT-M comes from single-center studies and meta-analyses of non-randomized data. However, despite this gap in the evidence base at the level of randomized studies, HDR-BRT-M is an extremely attractive tool for increasing the dose delivered to the prostate gland with minimal invasive intervention and gentle impact on surrounding critical organs. This is especially relevant for patients who are not candidates for surgery due to comorbidities or refuse it. There are also questions regarding the optimal implantation technique, as well as the best total dose and dose per fraction to achieve the best results, which requires further research and standardization of protocols.

The meta-analysis unequivocally confirms that HDR-BRT-M is a safe method with excellent bRFS rates for all risk groups. Total BED, BED per fraction, and the number of fractions is key factors influencing biochemical control, providing a strong basis for further optimization of treatment protocols. This emphasizes the need for an individualized approach to treatment planning, considering radiobiological principles, tumor characteristics, and the patient's general condition.

RADIOBIOLOGICAL ASPECTS OF HDR BRACHYTHERAPY IN PROSTATE CANCER

The radiobiological characteristics of prostate cancer are crucial for understanding its response to radiation therapy, especially when using high-dose-rate brachytherapy (HDR-BRT) with its unique fractionation regimens. It is widely recognized that the α/β ratio for prostate cancer is low, typically estimated in the range of 1 to 4 Gy. This is a relatively low value compared to most other tumors (where α/β is often 8-10 Gy) and acutely reacting normal tissues. A low α/β ratio means that the tumor is relatively sensitive to changes in fraction size; that is, increasing the fraction size (hypofractionation) should theoretically be more effective in

killing cancer cells than using many small fractions, as it increases the role of the quadratic component in the cell survival equation. This explains the interest in hypofractionated regimens, including HDR-BRT, which can deliver significant doses in a small number of fractions.

However, clinical studies have shown that, despite theoretical advantages, there is a significant reduction in tumor control when treating PCa with radically hypofractionated high-dose-rate brachytherapy (HDR-BT), especially when delivering single fractions with doses exceeding 20 Gy. This seemingly contradicts expectations derived from the low α/β ratio and necessitated further, deeper radiobiological analysis. This paradoxical observation questioned the universal applicability of the linear-quadratic (LQ) model, which is a standard tool in radiobiology for predicting the biological effects of irradiation, especially when applying very large doses per fraction.

In a study by Kölmel [3], a thorough radiobiological meta-analysis of the response of prostate cancer to HDR-BT was conducted. The primary goal was to understand the reasons for the observed reduction in control with extreme hypofractionation and to investigate the potential inability of the LQ model to adequately describe the response at large doses per fraction. The authors collected extensive dose-response data on HDR-BT from 3239 patients and performed a separate analysis for low and intermediate-risk patients to minimize the influence of other factors, such as systemic therapy or disease spread.

The results of this meta-analysis were indicative. The standard LQ model could not adequately describe the clinical data unless the α/β ratio was assumed to be very high (on the order of 20-100 Gy), which clearly contradicts established knowledge about α/β for PCa (1-4 Gy). If the α/β ratio was limited to more realistic low values (≤8 Gy), the LQ model could not reproduce the observed clinical results, particularly the reduction in tumor control at high doses per fraction. In this critical scenario, the linear-quadratic-linear (LQL) model, which is a modification of the LQ model and includes a moderate reduction in the effectiveness of radiation damage with increasing dose (i.e., the linear part of the cell survival curve continues instead of transitioning to quadratic at very high doses), significantly improved data fitting. The LQL model accounts for the possibility that at extremely high doses per fraction, cellular repair mechanisms may not cope with the enormous volume of damage, or the effectiveness of "lethal" DNA damage may reach saturation, leading to less biological effectiveness than the LQ model predicts, which postulates an infinite increase in effectiveness with dose. Conversely, the reoxygenation model, which predicts improved oxygen delivery to hypoxic cells and, consequently, increased their radio sensitivity, did not fit the obtained results, indicating that the reduction in control is not solely due to hypoxia or reoxygenation problems, but rather a more fundamental limitation of the model itself.

The clinically observed reduction in tumor control when treating prostate cancer with radical HDR-BT, especially single-fraction regimens, is best described by the LQL model. For example, using the best fit parameters, the biologically equivalent dose (BED) for a 20 Gy × 1 fraction treatment (128 Gy α/β) is significantly less than for conventional fractionation of 2 Gy × 37 fractions (196 Gy α/β). This indicates that with extreme hypofractionation, there is a significant loss of tumor control that the LQ model can only explain by assuming a very high α/β ratio (≥100 Gy), which, as noted, contradicts clinical data obtained for external beam radiation therapy. A more reasonable explanation is a moderate reduction in the LQ model's predicted effect with increasing dose per fraction, reflecting the limitation of cellular capacity for further damage.

These findings have important implications for the development of radical HDR-BT protocols. They suggest that very high doses per fraction may not be as effective as previously thought and require a more cautious approach or the use of multiple fractions to achieve the desired level of tumor control. This radiobiological breakthrough is critical for fine-tuning HDR-BRT dose regimens to maximize the therapeutic index.

CT-GUIDED BRACHYTHERAPY FOR PROSTATE CANCER IN PATIENTS WITH PREVIOUS RECTAL EXTIRPATION

Treating prostate cancer in patients who have undergone previous rectal extirpation for rectal cancer (e.g., abdominoperineal resection with colostomy) presents one of the most challenging clinical problems in radiation oncology. These patients face a unique combination of anatomical changes and potentially previous pelvic radiation therapy, which significantly limits the choice of further PCa treatment options. The presence of a stoma, the absence of the rectal ampulla, cicatricial changes in the small pelvis, and altered relationships between organs complicate standard imaging and radiation delivery methods.

Anatomical changes after rectal extirpation may include displacement of pelvic organs, formation of cavities, and tissue adhesions, making precise positioning and visualization of the prostate gland extremely difficult. If the patient has previously received external beam radiation therapy to the pelvic area for rectal cancer, the tolerance of surrounding normal tissues to further irradiation is significantly reduced. In such cases, the high dose levels of radiation required for effective prostate cancer control often cannot be achieved with standard external beam radiation therapy (EBRT) without an unacceptable risk of serious complications. This is because the cumulative dose has already reached or exceeded tolerant limits, and additional irradiation can lead to severe damage to healthy tissues, such

as the small intestine, bladder, and neurovascular bundles. In these clinical scenarios, brachytherapy often becomes the only treatment method capable of delivering the necessary high doses directly to the prostate gland, while minimizing further impact on already irradiated or altered structures, due to its ability to create a very steep dose gradient.

Traditionally, prostate brachytherapy often uses ultrasound (US) guidance. This is because a transrectal US probe provides clear visualization of the prostate gland and adjacent structures, allowing for accurate insertion of applicator needles and real-time monitoring of their position. However, in patients who have undergone rectal extirpation or significant rectal resection leading to rectal lumen stenosis or colostomy creation, transrectal ultrasound may be inaccessible, technically impossible, or even dangerous due to the risk of bowel wall or other structure damage. This significantly complicates or precludes the use of US-guided brachytherapy, leaving these patients with extremely limited treatment options and often without hope for a curative approach.

In their study, Schubert et al. addressed this problem by validating the feasibility of CT-guided transperineal interstitial brachytherapy for this specific and extremely complex clinical scenario. The authors analyzed treatment procedures and clinical outcomes in 5 patients with metachronous non-metastatic prostate cancer for whom US-guided brachytherapy was impossible due to previous surgical interventions and anatomical features. CT-guided brachytherapy bypasses the limitations of transrectal access by using computed tomography for detailed visualization and navigation during needle insertion. This provides three-dimensional accuracy in applicator positioning, which is critically important in cases with altered anatomy.

Of these 5 patients, 3 were treated with brachytherapy using only a temporary Ir-192 source (monotherapy), and 2 with external beam radiation therapy combined with temporary brachytherapy as a boost (combined therapy). It should be noted that the use of both monotherapy and boost demonstrates the flexibility of HDR-BRT in these complex cases. CT-guided brachytherapy was successfully performed in all patients, which is an important confirmation of its technical feasibility and safety in this vulnerable patient group. The protocol was based on careful pre-planning and intraoperative CT control to confirm the precise needle position before dose delivery.

The median follow-up was 35 months. At the time of analysis, encouragingly, no biochemical recurrence was reported in any of the patients. This indicates a high level of local disease control, which is the main goal of radical therapy. It is particularly important that no early or late side effects exceeding grade 2 according to the CTCAE (Common Terminology Criteria for Adverse Events) scale were reported. This is an extremely significant result, as patients who have already undergone major pelvic surgery and possibly received previous irradiation have an increased risk of developing severe complications from further radiation therapy. The low incidence of severe (grade 3 and higher) toxicity confirms the safety of this adapted approach. This suggests that, despite anatomical challenges, precise CT guidance allows for the delivery of a therapeutic dose to the tumor while minimizing exposure to critical organs and already damaged tissues.

Dosimetric parameters, documented as median values, also demonstrate treatment adequacy: V100 (volume of the prostate gland receiving 100% of the target dose) was 94.7% (range 94.5-98.4%), indicating excellent target volume coverage. Doses to organs at risk were as follows: D2 of the bladder (dose received by the 2% most irradiated volume of the bladder)-64.3% (50.9-78.3%), D10 of the urethra (dose to 10% of the urethra volume)-131.05% (123.2%-141.2%), and D30 of the urethra (dose to 30% of the urethra volume)-122.45% (116.2%-129.5%). Although the urethral dose metrics may seem relatively high, this is a characteristic feature of brachytherapy due to its high dose gradient, allowing a high dose to be delivered to the gland itself, which closely surrounds the urethra. [111]Importantly, despite these dosimetric indicators, clinical toxicity remained low, indicating the effectiveness of protecting critical structures through precise source positioning and rapid dose fall-off.

In conclusion, CT-guided transperineal prostate brachytherapy in patients who have undergone previous rectal surgery and/or pelvic radiation therapy is safe, technically feasible, and represents a possible option for radical treatment. This expands the pool of patients who can be offered potentially curative PCa treatment, despite previous surgical interventions and significant anatomical changes. Brachytherapy can be considered for patients with metachronous prostate cancer in this specific scenario, although predominantly in experienced high-volume centers that have extensive experience in using CT navigation, comprehensive planning, and treating complex cases. This study emphasizes the importance of adaptability and innovation in radiation oncology, allowing for effective care even for the most complex patient categories. Future studies should focus on increasing patient cohorts to confirm these results on a larger scale.

DISCUSSION AND FUTURE DIRECTIONS

The obtained data allow for a comprehensive conclusion regarding the place of HDR-BRT in modern prostate cancer treatment. In general, HDR-BRT demonstrates high rates of biochemical control and an acceptable toxicity profile, confirming its effectiveness as monotherapy for low and intermediate-risk patients. This is especially important in the context of treatment de-escalation to reduce side effects while maintaining efficacy. The importance of dosimetric parameters, such as total biologically effective dose (BED) and BED per fraction, as well as the number of fractions for achieving optimal biochemical control, is emphasized. This

suggests that the choice of the optimal fractionation regimen is critical, and existing protocols can be further optimized based on these radiobiological principles. However, despite encouraging results, the lack of large randomized controlled trials directly comparing HDR-BRT-M with other standard methods remains a significant gap in the evidence base. Future research should focus on conducting such comparative trials to definitively establish the place of HDR-BRT-M in treatment standards. Additionally, it is necessary to standardize optimal dosing and fractionation regimens, considering the heterogeneity of patients and tumors.

Radiobiological analysis is fundamental to understanding PCa response to extreme hypofractionation. The revealed inadequacy of the standard linear-quadratic (LQ) model and the better suitability of the linear-quadratic-linear (LQL) model at very high doses per fraction is a key contribution. This suggests that existing radiobiological models may underestimate the potential loss of biological effect with extreme hypofractionation. These findings have direct clinical implications: radiobiological calculations need to be revised, and doses may need to be adjusted when planning single-fraction or very highly hypofractionated HDR-BRT regimens. This also highlights the need for further research to refine the α/β ratio and other radiobiological parameters for PCa, especially under extreme doses. Understanding these nuances will help develop more accurate and effective protocols, avoiding both under- and overdosing. Future research may include more detailed modeling and collection of clinical outcome data to confirm the LQL model and its application in clinical practice.

The adaptability and potential of HDR-BRT in complex clinical scenarios, such as treating PCa patients who have undergone rectal extirpation, are demonstrated. In these cases, where traditional imaging methods (ultrasound) are impractical, and anatomical changes limit other forms of radiation therapy, CT-guided brachytherapy proves to be a safe and effective solution. This opens the door for treating patients who were previously considered incurable or would have significant difficulties in receiving effective treatment. Although the study included a small number of patients, its results are very encouraging. This emphasizes the importance of individualized approaches and the use of advanced imaging technologies to expand the capabilities of radiation therapy. Further research in larger patient cohorts in similar complex scenarios would be beneficial to confirm these results and develop standardized protocols. It is also worth exploring the integration of other imaging methods, such as MRI, for even greater accuracy in complex anatomical conditions.

Overall, HDR-BRT continues to evolve as an important element in PCa treatment. Future research directions should include:

- **Randomized clinical trials:** Comparing HDR-BRT-M with radical prostatectomy, EBRT, and LDR-BRT for different risk groups to build a stronger evidence base.
- **Fractionation optimization:** Further study of optimal dosing and fractionation regimens, considering new radiobiological models such as the LQL model, to maximize tumor control and minimize toxicity.
- **Role of imaging:** Integration of advanced imaging techniques (e.g., multiparametric MRI, PET/CT) for better definition of tumor volume and organs at risk, allowing for further personalization of treatment plans.
- **Long-term outcomes and quality of life:** Collection and analysis of long-term data on biochemical control, survival, and quality of life after HDR-BRT in large patient cohorts.
- **Cost-effectiveness:** Analysis of the cost-effectiveness of HDR-BRT compared to other treatment methods, considering the cost of equipment, procedures, and management of side effects.
- **Role of combined therapy:** Further study of HDR-BRT in combination with EBRT and systemic therapy (e.g., ADT, new hormonal agents) for high-risk or metastatic disease patients.
- **Development of new applicators and technologies:** Improvement of hardware and software for planning, which will allow for even more accurate and effective treatment, possibly with less invasiveness.

CONCLUSION

High-dose-rate brachytherapy (HDR-BRT) is a highly effective and safe method for treating prostate cancer. Meta-analysis of data confirms its high rates of biochemical control for all risk groups, with an acceptable toxicity profile. ^{151}Key dosimetric parameters, such as total biologically effective dose (BED) and BED per fraction, were crucial for achieving biochemical control, indicating the need for careful planning and optimization of dosimetric parameters.

Radiobiological studies shed light on the limitations of the traditional linear-quadratic model in extreme hypofractionation, proposing the linear-quadratic-linear (LQL) model as a more adequate tool for predicting clinical outcomes. This has profound implications for the development of HDR-BRT protocols, emphasizing that revised dosimetric approaches may be needed to achieve the desired biological effectiveness when very large fractions are applied. This opens up new possibilities for personalized radiotherapy that considers not only the physical dose but also the subtle biological response to irradiation.

Furthermore, the ability of CT-guided brachytherapy to overcome clinical challenges previously considered

insurmountable is demonstrated, providing curative treatment for prostate cancer patients who have undergone rectal extirpation. This expands the accessibility of radical therapy for patients with complex anatomy or previous irradiation.

Thus, HDR-BRT is a versatile and powerful tool in PCa treatment. Further research focused on randomized clinical trials, refinement of radiobiological models, and adaptation to complex clinical scenarios will allow for further optimization of its application and improvement of patient outcomes. With the development of imaging technologies and improved radiobiological understanding, HDR-BRT has the potential to become an even more precise and effective modality, ensuring an optimal balance between disease control and quality of life.

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