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Scientific Article

Individualized Dose-Escalation of HDR Prostate Brachytherapy Implant to Decrease Required External Beam Radiation Dose: A Retrospective Feasibility Study

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Abstract

Purpose: High-dose-rate brachytherapy (HDR-BT) is commonly combined with external beam radiation therapy (EBRT) for the treatment of localized prostate cancer. Escalating the HDR-BT dose as far as organ-at-risk (OAR) constraints allow, on a personalized basis, would allow for a reduction in EBRT dose while achieving similar total biologic equivalence. The primary objective of this study was to determine the dosimetric feasibility of escalating the HDR-BT dose from 15 Gy to 16 or 17 Gy while continuing to meet OAR constraints from the original 15 Gy plan on an individualized basis.

Methods and materials: A total of 53 consecutive HDR-BT plans were retrospectively assessed to determine what percentage of plans could be reoptimized to deliver a dose of 16 Gy or 17 Gy, while meeting defined 15-Gy OAR constraints. Factors independently associated with dose escalation were examined.

Results: Thirty-nine plans (74%) and 2 plans (4%) were successfully escalated to a dose of 16 Gy and 17 Gy, respectively. Rectum V80 and urethra D_{max} were independently predictive of the ability to dose escalate to 16 Gy.

Conclusions: Individualized HDR-BT dose escalation beyond 15 Gy without compromising OAR constraints is dosimetrically feasible. This approach could allow for a corresponding reduction of EBRT fractions (ie, from 15 to 12 fractions) and would be beneficial in terms of resource savings for departments, convenience for patients, and potentially better tolerance of treatment with the expected reduction in biologically equivalent doses to OARs. A clinical trial is being developed to

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investigate the efficacy and tolerance of personalized HDR-BT/EBRT dose fractionation for localized intracapsular prostate cancer.

Introduction

An estimated 1 in 7 Canadian men will be diagnosed with prostate cancer.[1] Patients with localized prostate cancer are typically presented with treatment options that can include surgery, radiation, hormone treatment, active surveillance, or a combination of these treatments. When patients are treated with radiation, treatment may consist of external beam radiation therapy (EBRT) alone, low-dose-rate brachytherapy (LDR-BT), high-dose-rate brachytherapy (HDR-BT) monotherapy, or HDR-BT combined with EBRT. HDR-BT monotherapy has been investigated for patients with intermediate- or high-risk prostate cancer but is typically used in combination with EBRT.[2–5]

HDR-BT allows for a highly conformal radiation dose to be delivered to the prostate while sparing normal tissues, such as the rectum and urethra, owing to rapid dose fall-off. HDR-BT has advantages over LDR-BT in terms of cost, avoidance of postimplant radiation protection procedures, and lower dose to critical structures, which appears to reduce acute toxicity.[6,7] HDR-BT combined with EBRT appears to be superior in terms of efficacy and tolerance to EBRT alone for patients with intermediate- and high-risk prostate cancer.[5,8,9] A study of intermediate-risk patients showed a 5-year biochemical control rate of 92% versus 81% in favor of HDR-BT plus EBRT over EBRT alone.[10] In a group of high-risk patients, a 90% 10-year distant metastasis-free rate in the HDR-BT plus EBRT group was observed compared with 67% in the EBRT-alone group.[11]

Many EBRT component dose fractionation regimens have been used, including 40 Gy in 20 fractions, 44 Gy in 22 fractions, 45 Gy in 25 fractions, 36 Gy in 12 fractions, and 37.5 Gy in 15 fractions.[12] In addition, HDR-BT dose fractionation has also varied, including 18 to 19.5 Gy in 3 fractions, 19 to 21 Gy in 2 fractions, and 15 Gy in 1 fraction.[12] The total biological equivalent dose (BED) can be calculated using $(nd\,[1+d/(\alpha/\beta)])$, where n is the number of fractions, and d is the dose per fraction, using an α/β of 1.5.[13] Higher BEDs (>260 Gy) have been shown to be correlated with improved biochemical control at 5 years.[14]

A common treatment regime is 15 Gy in 1 HDR-BT fraction, followed by 37.5 Gy in 15 fractions of EBRT (total BED: 265 Gy), which has been shown to be efficacious and cause low rates of late urinary and gastrointestinal toxicity.[15–17] HDR-BT as monotherapy (without EBRT), at doses as high as 19 Gy (BED: 260 Gy) has been shown to be tolerated well by patients with low- to intermediate-risk prostate cancer.[18] Therefore, it is reasonable to presume that increasing the HDR-BT dose slightly above 15 Gy would be well tolerated as well. This could allow for a decrease in the required EBRT dose and therefore fewer EBRT treatments in patients receiving combination therapy. For example, dose escalating the HDR-BT boost to 16 Gy could allow for a decrease of 3 fractions of EBRT (to 30 Gy in 12 fractions) to achieve the same radiobiologic effect (total BED: 267 Gy) if continuing to use an EBRT fraction size of 2.5 Gy. Dose escalating to 17 Gy could allow for a decrease of 6 fractions (to 22.5 Gy in 9 fractions; total BED: 270 Gy). This algorithm is shown in Figure 1.

Our experience is that HDR-BRT plans are heterogeneous in terms of the ease in meeting dose constraints for the prostate and for organs at risk (OARs). For plans with little difficulty achieving the dose constraints at a prescription dose of 15 Gy, an individualized escalation to a higher dose level may be reasonable to consider. Shortening the course of EBRT after HDR-BT could lead to better quality of life for patients with prostate cancer treated with radiation and would decrease the demand on EBRT services. Of note, fractionated therapy may be preferred from a radiobiologic point of view compared with single-fraction HDR-BT monotherapy, and combination HDR-BT with EBRT has resource advantages over multifraction HDR-BT because there is no need to hospitalize patients between fractions or schedule multiple operative procedures.[2]

The primary objective of this study was to determine the feasibility of escalating the dose from 15 Gy to 16 or 17 Gy in a retrospective series of individual HDR-BT cases while continuing to meet the OAR constraints from the original plan. The secondary objective was to determine what factors, if any, predicted successful dose escalation. If dose escalation is determined to be feasible, this study will guide the execution of a prospective clinical trial to assess the efficacy and tolerance of personalized HDR-BT/EBRT dose fractionation for localized intracapsular prostate cancer.

Methods and Materials

After local research ethics board approval, archived treatment plans from 53 consecutive HDR-BT patients between June 2017 and May 2018 were accessed. All
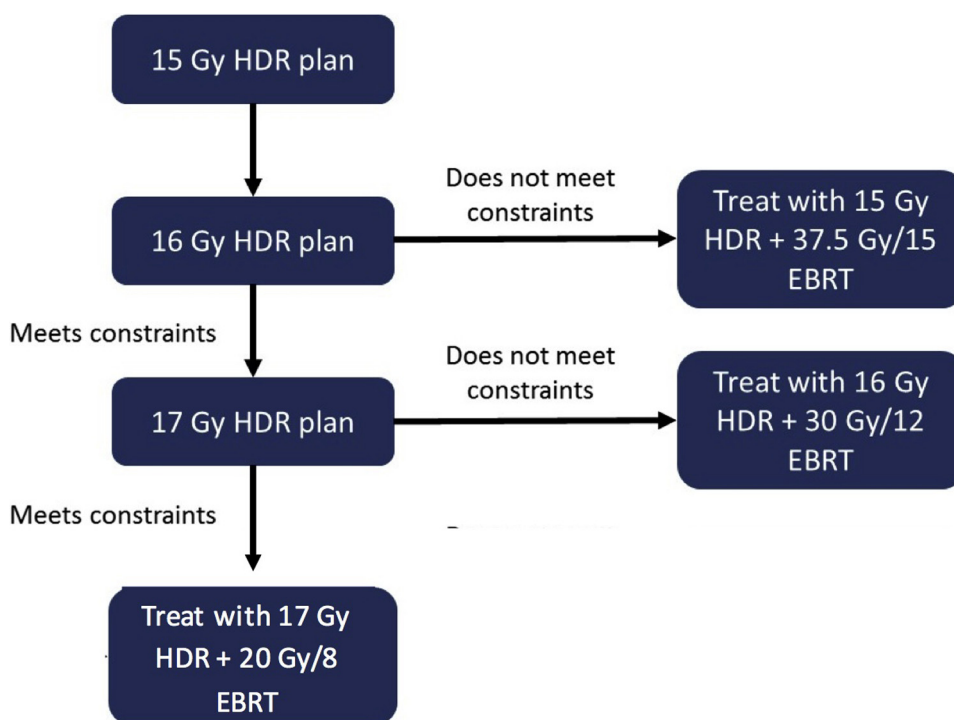
Figure 1   High-dose-rate brachytherapy dose-escalation algorithm.

patients were treated with a 15 Gy HDR-BT implant, followed by 37.5 Gy in 15 fractions to the prostate. No patients received pelvic lymph node irradiation. A chart review was performed to extract demographic information, androgen therapy treatment details, and prostate cancer tumor characteristics. The plan dosimetric parameters (prostate D90, V100, V150, and V200; urethra maximum point dose [D_{max}] and D10; rectum V80 and D_{max}), contoured prostate volume, and number of needles inserted were extracted from the original 15 Gy plan using the Oncentra Prostate software package. Plan parameter nomenclature is standardized, such that D90 refers to the minimum dose received by 90% of the volume, and V100 refers to the volume receiving at least 100% of the prescription dose.

Brachytherapy and contouring methods

Implants were placed by 2 local radiation oncologists with patients under general anesthesia. Plastic needles with solid metal obturators were placed through a perineal template under live transrectal ultrasound guidance with patients in the dorsal lithotomy position. Planning ultrasound images were collected using a continuous acquisition of transverse images, in 1 mm slices. The treatment plan was designed to cover the contoured prostate only with no additional clinical or planning target volume margins. A separate planning structure was generated around the prostate with a 3 mm margin in all dimensions, except for 0 mm superior and posterior to exclude the

rectum. This planning structure was used to identify areas where catheter dwell positions could be activated and was not considered in the plan evaluation. The urethra was contoured using a 3.5 mm radius structure, centered around the Foley catheter (2.8 mm radius) and extending just above and just below the aforementioned planning structure. The entire visualized rectal wall was contoured. Treatment was delivered using an HDR Iridium-192 source. Patients were treated with the rectal ultrasound probe fully inserted.

Plan optimization methods

The optimization parameters were then changed to escalate the plan dose to 16 or 17 Gy. The constraints for urethra (urethra D_{max} <18.75 Gy [125% of 15 Gy] and urethra D10 <17.7 Gy [118% of 15 Gy]) and rectum (rectal $V_{12\ Gy}$ <0.5cc [80% of 15 Gy]) from the 15 Gy plan were maintained. These constraints were chosen because they are the standard set of parameters used for planning at our center and have been used in other published series.[15,16] The constraint for prostate V_{100} (of the prescription dose) was maintained at >95%.

The literature was examined to determine reasonable prostate V_{150} ($V_{22.5\ Gy}$) and V_{200} ($V_{30\ Gy}$) constraints. Studies using 19 Gy as a single implant show acceptable toxicity data with V_{150} (or $V_{28.5\ Gy}$) of 18% to 35%.[3,18,19] This means that 18% to 35% of the prostate received 28.5 Gy. This dose is comparable to the V_{200} dose (30 Gy) for a 15 Gy treatment. Therefore, the $V_{30\ Gy}$ can

be assumed to safely be increased to around 15% to 30%. A prostate $V_{30\ Gy}$ constraint of 30% was used for this study. Studies using a 15 Gy implant use a V_{150} (or $V_{22.5\ Gy}$) dose constraint of up to 40%.[20,21] However, when interpolating the dose constraints from a 19 Gy plan, using the $V_{19\ Gy}$, $V_{28.5\ Gy}$, and $V_{38\ Gy}$ constraints, $V_{22.5\ Gy}$ can be estimated at around 61% (this value is not published but is calculated using interpolation of known dose constraints).[19] Therefore, $V_{22.5\ Gy}$ can likely be safely increased to 40% to 55%. A prostate $V_{22.5\ Gy}$ constraint of 55% was used for this study.

Using these OAR and target volume constraints, an automatic dose optimization was performed to attempt to obtain an acceptable dose-escalated plan. If the automatic optimization was unable to meet the outlined criteria, a manual optimization was performed. The manual optimization allowed for changes to the dose delivered per catheter dwell position. New dwell positions were not activated. Manual optimization was performed by 2 separate authors, and concordance was verified for the initial 10 plans. Top priority was set to achieve a prostate V_{100} >95% of the target dose. Plans were rejected if, after automatic and manual optimization, they did not meet the defined constraints: prostate V_{100} >95%, prostate $V_{22.5\ Gy}$ <55%, prostate $V_{30\ Gy}$ <30%, rectum $V_{12\ Gy}$ <0.5cc (80% of 15 Gy), urethra D_{max} <18.75 Gy (125% of 15 Gy), and urethra D_{10} <17.7 Gy (118% of 15 Gy). If a plan was successfully escalated to 16 Gy, an escalation to 17 Gy was attempted.

Analytic approach

The analysis of the data included both descriptive and regression modeling. Statistical significance for all analysis was set at a 2-sided alpha level of $P < .05$. The statistical analysis was completed using the software statistical package STATA, version 12SE.

A bivariate regression analysis was used to determine the strength of association of each predictor variable to the dose-escalation level outcome measure (ie, 16 Gy and 17 Gy). Predictor variables with statistically significant associations with the outcomes of interest were included in the multivariate regression analysis. We assessed for multicollinearity among predictor variables using the variance inflation factor. We then determined the most parsimonious multivariate model to explain the relationship between predictors and outcomes of interest.

Results

The baseline characteristics of the 53 consecutive HDR-BT patients are shown in Table 1. The majority of patients (81%) had intermediate-risk disease. Table 2 shows the plan parameters from the original plans. Thirty-one plans (58%) had minor deviations in dose

Table 1 Patient characteristics (n = 53)

Patient characteristics	Mean (standard deviation)	n (%)
Age (y)	68.2 (5.9)	
T stage		
T1c		18 (34)
T2a		15 (28)
T2b		10 (19)
T2c		5 (9)
T3a		2 (4)
N+		2 (4)
Gleason grade group		
1 (3 + 3)		4 (8)
2 (3 + 4)		26 (49)
3 (4 + 3)		20 (38)
4 (4 + 4)		2 (4)
5 (4 + 5)		1 (2)
Prostate-specific antigen level* (ng/mL)	11.3 (6.1)	
<10		27 (51)
10-20		21 (40)
>20		5 (9)
Risk group		
Intermediate		43 (81)
High		10 (19)
International Prostate Symptom Score*	5.5 (4.3)	
ADT before HDR-BT		29 (55)
Length of ADT, if given (mo)	4.0 (1.5)	
No. of biopsy cores taken ≥12		43 (81)
Percent positive cores	44.9 (19.2)	
Total tissue involved (%)	18.6 (14.3)	
Prostate volume on ultrasound (cm³)	32.9 (9.2)	
Contoured prostate volume (cm³)	37.2 (10.1)	
Number of HDR-BT needles inserted	15.1 (2.0; range, 11-18)	

Abbreviations: ADT = androgen deprivation therapy; HDR-BT = high-dose-rate brachytherapy.

  * International Prostate Symptom Score: 0-7 = mildly symptomatic; 8-19 = moderately symptomatic; 20-35 = severely symptomatic

parameters outside of the predefined targets but were still deemed clinically acceptable (Table 2 shows the predefined targets). Thirty-nine plans (74%) and 2 plans (4%) were successfully escalated to a dose of 16 Gy and 17 Gy, respectively, while strictly meeting all defined study limits. Thirteen of the 14 plans that were not successfully elevated to 16 Gy had minor deviations from the original plan, indicating that an original plan with no minor deviations had a high chance of being escalated to 16 Gy

Table 2 Original 15 Gy high-dose-rate brachytherapy plan parameters

Plan parameter	Mean	Standard deviation	Range	Target
Prostate D_{90}	107.70%	2.4	100.5-112.4	
Prostate V_{100}	96.30%	1.5	90.6-99.03	>95%
Prostate V_{150}	34.30%	3.1	26.39-45.78	<35%
Prostate V_{200}	10.20%	1.7	7.4-15.32	<11%
Urethra D_{max}	122.73%	3.9	116.2-135.3	<125%
Urethra D_{10}	113.60%	2	108.7-117.9	<118%
Rectum V_{80}	0.15cc	0.15	0-0.49	<0.5cc
Rectum D_{max}	91.17%	9.6	76.3-120.07	

Table 4 Parsimonious multivariate regression model of 16 Gy dose escalation on predictor variables

Variable	Odds ratio (95% Confidence interval)
Rectum V_{80}	0.975 (0.96-0.99)*
Urethra D_{max}	0.466 (0.24-0.91)*
Rectum D_{max}	1.00 (0.90-1.12)
Prostate V_{200}	0.471 (0.22-1.02)

  * $P < .05$.

(93%). Of all plans with minor deviations, 18 (58%) could still be escalated to 16 Gy.

In bivariate regression models, prostate D_{90}, prostate V_{100}, prostate V_{200}, urethra D_{max}, urethra D_{10}, rectum V_{80}, and rectum D_{max} were significantly associated with the ability to dose escalate to 16 Gy (Table 3). The bivariate regression models for the 17 Gy dose escalation outcome did not yield any significantly associated variables. The parsimonious multivariate model for the 16 Gy dose escalation was statistically significant (Table 4). The variance inflation factor was 32. Rectum V_{80} and urethra D_{max} were independently predictive of the ability to dose escalate to 16 Gy.

The 2 plans that were successfully escalated to 17 Gy are shown in Figure 2 in comparison with the 2 selected plans that could not be escalated to 16 Gy.

Discussion

This retrospective feasibility study showed that 74% of 15 Gy HDR-BT plans were successfully escalated to 16 Gy while meeting all dose constraints. Only 4% of the

Table 3 Bivariate regression of 16 Gy dose escalation on predictor variables

Variable	Odds ratio (95% confidence interval)
Prostate volume (ultrasound) Contoured prostate volume	1.00 (0.94-1.07)
Androgen deprivation therapy use	0.58 (0.17-2.06)
Number of needles used	1.09 (0.80-1.49)
Prostate D_{90}	2.08 (1.24-3.47)*
Prostate V_{100}	4.27 (1.52-11.94)*
Prostate V_{150}	0.94 (0.77-1.14)
Prostate V_{200}	0.54 (0.34-0.89)*
Urethra D_{max}	0.74 (0.60-0.92)*
Urethra D_{10}	0.58 (0.37-0.90)*
Rectum V_{80}	0.98 (0.98-0.99)*
Rectum D_{max}	0.89 (0.82-0.97)*

  * $P < .05$.

plans (2 of 53) could be escalated to 17 Gy using the existing needle arrangement. We have demonstrated the feasibility of BT dose escalation without compromising dose to the urethra and rectum and believe this approach is worthy of evaluation in a clinical trial because an escalation of the HDR-BT dose to 16 Gy and subsequent decrease in EBRT prescription (from 37.5 Gy in 15 fractions to 30 Gy in 12 fractions) would be more convenient for patients and lead to cost savings for departments and could potentially be better tolerated because of the lower cumulative dose to OARs.

Many dosimetric variables emerged as univariately predictive of successful dose escalation. As expected, there was significant collinearity (as demonstrated by a variance inflation factor of 32) between dosimetric variables such as urethra D_{max} and D_{10}, rectum D_{max} and V_{80}, and prostate V_{150} and V_{200}. A hot plan would tend to have higher dosimetric variable values than a cool plan; therefore, these variables were not strictly independent. The parsimonious model that minimized collinearity showed that rectum V_{80} and urethra D_{max} were independently associated with successful dose escalation to 16 Gy. Therefore, a 15 Gy plan with a high rectal V_{80} or urethra D_{max} is less likely to be successfully escalated to 16 Gy. However, these variables are not entirely predictive, and when this approach is tested in a clinical trial, dose escalation should be attempted in all plans and not only those selected based on dosimetry. The additional optimization time is on the order of 5 minutes and will not lead to a clinically significant prolongation of HDR-BT cases.

There could have been an even higher rate of successful dose escalation if we had been less conservative in terms of OAR dose constraints. For example, Gomez-Iturriaga et al performed 19 Gy HDR-BT treatments and allowed 1 cm^3 of the rectum to get 60% of the dose (11.4 Gy), whereas we limited 0.5 cm^3 of the rectum to a comparable 80% of the 15 Gy dose (12 Gy).[18] Another 19 Gy HDR-BT study, which was reported as well tolerated, allowed a urethra D_{max} of 120% (22.8 Gy), equivalent to a 152% dose in a 15 Gy plan, whereas we used a limit of 18.75 Gy (125% dose in a 15 Gy plan).[21] Of course, these comparisons must consider the addition of OAR toxicity due to the EBRT fractions in our study population. Therefore, it was deemed safest to only extrapolate escalated dose limits for prostate V_{150} and
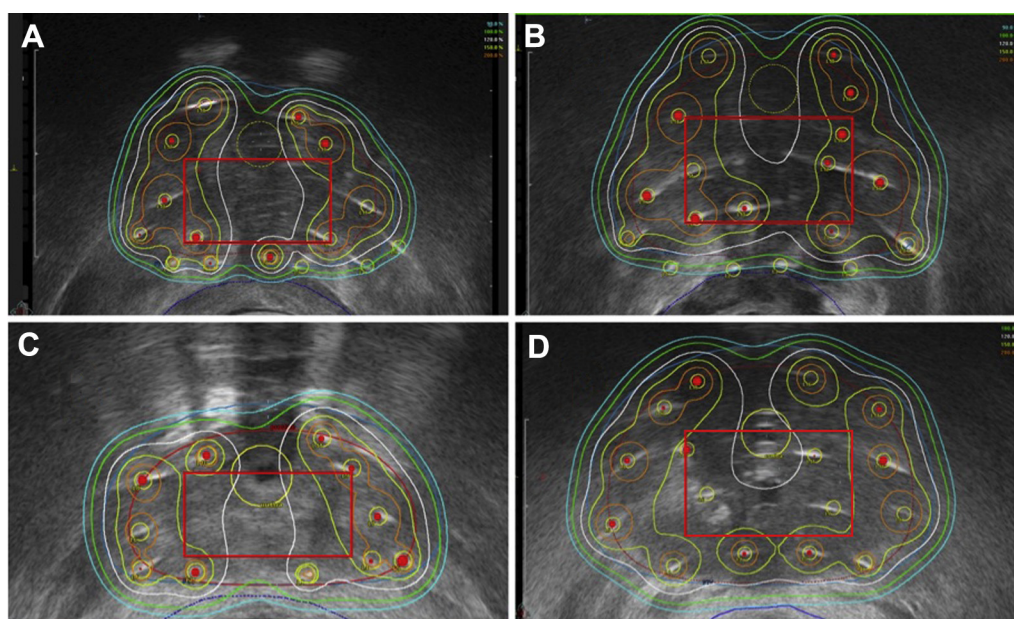
Figure 2   Comparison of selected plans that could not be escalated to 16 Gy (A, B) with the 2 plans that were successfully escalated to 17 Gy (C, D). Red box highlights density of central needles: 0-1 for A and B, and 4-5 for C and D.

V_{200} from the literature and maintain the known safe OAR limits for this feasibility study. It could be hypothesized that, by escalating the HDR-BT dose while maintaining the same OAR constraints for the rectum and urethra and decreasing the number of EBRT fractions delivered (to 30 Gy in 12 fractions), there may be less toxicity than with the conventional treatment approach of 15 Gy HDR-BT with 37.5 Gy of EBRT in 15 fractions.

None of the clinical, pathologic, or technical features were associated with ability to escalate the dose. Subjectively the main determinant of the ability to dose escalate appeared to be needle geometry (eg, needle separation, distance from OARs). Plans that resembled the plans included in Figure 2 (relatively higher density of catheters located centrally) seemed to be easily escalated to 16 Gy. A higher density of centrally located needles allowed for adequate dose coverage centrally without needing to rely on pushing dose from peripheral needles (closer to OARs). This suggests that the radiation oncologist could consider inserting more needles or optimizing the needle distribution in other ways to attempt to achieve dose escalation if this technique were to be attempted prospectively. A more detailed study of needle geometry may be worthwhile.

The goal of this study was to determine the feasibility of dose escalating HDR-BT to decrease the number of EBRT fractions required after HDR-BT, but is EBRT after HDR-BT required at all? The Radiation Therapy Oncology Group study 0232 showed equivalent progression-free survival with LDR-BT alone and LDR-BT plus EBRT in low-tier, intermediate-risk patients with prostate cancer.[22] However, these data should not be

extrapolated to patients with higher-risk disease or those who are treated with HDR-BT considering the radiobiologic differences between LDR-BT and HDR-BT single-fraction monotherapy. For example, a study of patients with low- and intermediate-risk prostate cancer showed a higher rate of local failure in patients treated with 19 Gy in 1 fraction HDR-BT monotherapy versus 27 Gy in 2 fractions HDR-BT monotherapy.[2] In addition, Prada et al and Siddiqui et al observed a lower-than-expected rate of biochemical control in a series of patients treated with 19 Gy HDR-BT monotherapy.[3,23] These studies suggest that the equivalent dose of HDR-BT monotherapy is overestimated with classical models and that this may in part be due to the lack of tumor reoxygenation and/or cellular reassortment when treating with a single fraction. Currently, there is no evidence to support treatment of patients with intermediate- or high-risk prostate cancer with single-fraction HDR-BT monotherapy outside of clinical trials.

For patients with extracapsular extension or those in whom pelvic nodal irradiation is desired (noting that the role for pelvis irradiation is still unclear),[24-27] a lower EBRT dose may affect the effective treatment of extraprostatic disease. Therefore, these patients may need to be excluded from studies looking to minimize EBRT dose by increasing HDR-BT dose. The incorporation of magnetic resonance imaging into patient evaluation and treatment planning may mitigate possible concerns about underdosing in the tumor for lesions near the urethra and rectum.

There are several limitations and assumptions with this study. This feasibility study has a relatively low sample

size, and external validity could have been improved by assessing more cases and including cases from other institution. There are inherent limitations to a retrospective study design in terms of generalizability and confounding variables. In addition, this feasibility study did not actually deliver the escalated dose to patients; therefore, clinical data with regard to toxicity and local control are not available. These limitations will be addressed by the planned prospective clinical trial assessing the safety and efficacy of individualized HDR-BT dose escalation and EBRT dose reduction.

Another, albeit unavoidable, limitation of this study was the significant collinearity of dosimetric variables, which affected the authors' ability to draw conclusions with regard to the independent correlation of dosimetric variables with the ability to dose escalate. This study relied on radiobiologic calculations using the linear quadratic model, which may not be as applicable or reliable when using a high dose per fraction. However, studies highlighting this issue report that this is due in part to the lack of tumor reoxygenation and/or cellular reassortment when using a single fraction, which is an issue that may be somewhat mitigated with our proposed schedule that still includes fractionated treatments.[23] Therefore, the expected tolerance and efficacy equivalence of this alternate fractionation should be confirmed clinically. One also must consider uncertainties in estimating the alpha/beta ratio for prostate cancer when developing alternative EBRT dose-fractionation schedules if individualized HDR-BT escalation with EBRT de-escalation is to be performed clinically.

Conclusions

This retrospective feasibility study found that 74% of 15 Gy HDR-BT plans could be escalated to 16 Gy while still respecting the 15 Gy dose constraints for OARs, with a smaller percentage of patients (4%) being successfully escalated to 17 Gy. Individualized HDR-BT dose escalation with a corresponding reduction of EBRT dose may be clinically feasible and advantageous in terms of resource savings for radiation therapy departments, increased convenience for patients, and potentially better tolerance of treatment. This feasibility study will guide the design and implementation of a clinical trial to investigate the safety and efficacy of individualized HDR-BT dose escalation and EBRT dose reduction in patients with localized intracapsular prostate cancer.

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