Purpose: To determine if increasing the biologically equivalent dose (BED) via various radiation fractionation regimens is correlated with clinical outcomes or toxicities for prostate cancer.

Methods and materials: We performed a meta-analysis that included 12,756 prostate cancer patients from 55 studies published from 2003 to 2013 who were treated with non-dose-escalated conventionally fractionated external beam radiation therapy (non-DE-CFRT), DE-CFRT, hypofractionated RT, and high dose rate brachytherapy (HDR-BT; either mono or boost) with >5-year actuarial follow-up. BEDs were calculated based on the following formula: \( \text{BED}_{1.5} = \text{nd} \times \left(1 - e^{-\frac{d}{\alpha/\beta}}\right) \), where \( n \) is the number of fractions, and \( d \) is dose per fraction; assuming an \( \alpha/\beta \) of 1.5 for prostate cancer and 3.0 for late toxicities. Mixed effects meta-regression models were used to estimate weighted linear relationships between BED and the observed percentages of patients experiencing late toxicities or 5-year freedom from biochemical failure (FFBF).

Results: Increases in 10 Gy increments in BED (at \( \alpha/\beta \) of 1.5) from 140 to 200 Gy were associated with improved FFBF rates over DE-CFRT alone (median \( \text{BED}_{1.5} \) of 180–200 Gy), assuming an \( \alpha/\beta \) of 1.5. Further dose escalation is achievable using alternate fractionation (e.g. hypofractionated RT [HFRT]) and using brachytherapy (e.g. high dose rate BT [HDR-BT]) as a boost. HFRT and HDR-BT allow for \( \text{BED}_{1.5} \) escalation to 200–350 Gy to the prostate, while minimizing the dose delivered to surrounding normal tissues (BEDs at various \( \alpha/\beta \) ratios plotted in Fig. 1). However, there is currently no consensus regarding maximal dose using either of these approaches [8].

In certain cancers (e.g. lung), tumor control vs. BED curves have been shown to be sigmoidal [9–11]. In prostate cancer, multi-modality therapy with HDR-BT boost has been shown to have improved FFBF rates over DE-CFRT alone (median \( \text{BED}_{1.5} \) ~210 vs. 190 Gy), particularly for intermediate-risk patients [12]. Currently, the upper limit of the \( \text{BED}_{1.5} \) vs. tumor control curve is not well understood. Herein, we use a meta-analysis to determine if increasing the BED is associated with improved outcomes, as measured by PSA response or increased toxicity.

Methods and materials

Evidence acquisition

We defined inclusion criteria for the literature search using the Population, Intervention, Control, Outcome, Study Design (PICOS;
Table 1) approach. We conducted a systematic search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Fig. 2) in the literature selection process.

The meta-analysis included 12,756 prostate cancer patients (n) from 55 studies (N) published from 2003 to 2013, who were treated with non-DE-CFRT, DE-CFRT, HFRT, and HDR-BT (either boost or mono) with 5-year median and actuarial follow-up. Small (n < 150) and retrospective studies with HDR-BT were included to account for variability in fractionation schedules and BEDs, while other studies were larger and prospective.

For reference, the treatment characteristics, outcomes, and toxicities of studies using non-DE-CFRT, DE-CFRT, and HFRT are listed in the Supplementary Table 1 (including: prospective studies of non-DE-CFRT vs. DE-CFRT [1–7]); prospective studies of HFRT vs. CFRT [13–21]); prospective and retrospective studies of HDR-BT monotherapy in Supplementary Table 2 [22–31]; HDR-BT boost in Supplementary Table 3 (including: prospective studies [32–45]; retrospective studies [46–63]). Although SBRT may achieve BED1.5 > 200 Gy, studies using SBRT were not included as their follow-up times were limited.

Androgen deprivation therapy (ADT) was prescribed to nearly all high-risk patients, while it was not prescribed to low-risk patients. ADT was prescribed to select intermediate-risk patients, at the discretion of physicians among the studies; unfortunately, we cannot discern which intermediate-risk patients received ADT. Nonetheless, dose escalation studies of EBRT have demonstrated benefits of dose escalation up to ~180–200 Gy, among all risk types, with or without ADT [1–5].

Additionally, the inclusion of retrospective studies may skew the reported data, particularly since certain prospective [1–5,13–21] studies were specifically designed to evaluate BED escalation. Low-dose-rate (LDR)-BT boost was excluded because the dose delivered by a seed implant (to predict for FFBF and toxicity) could not be accurately captured by the BED calculation model used in fractionated approaches (described below).

**Statistical analysis**

BEDs were calculated for patients of various risk groups, at various α/β ratios, based on the following formula:

\[
\text{BED} = (nd + d) \left(1 + \frac{d}{(\alpha/\beta)}\right)
\]

For reference, a BED1.5 of 200 Gy is equivalent among the following fractionation schemes: 86 Gy in 43 fractions (2 Gy/fraction), 70.2 Gy in 26 fractions (2.7 Gy/fraction), or 32 Gy in 4 fractions (8 Gy/fraction).
To report outcomes, we calculated the BED\textsubscript{1.5} based on the RT fractionation regimen from each study (Supplementary Tables 1–3). For HDR-BT boost, the sum of the EBRT and HDR-BT components was added (Supplementary Table 3). We reported FFBF rates among low-, intermediate-, and high-risk group patients, as reported within each study (Table 2). We chose to use 5-year actuarial FFBF to include a large number of studies (since most do not have 10-year actuarial data) and still see an effect in treatment efficacy (e.g. instead of using 3-year FFBF).

We related the BED to the 5-year FFBF. The Phoenix (i.e. nadir + 2 ng/mL) definition was used for FFBF; if unavailable, but the study had at least 5 years of FU, then the ASTRO (i.e. 3 consecutive PSA rises) definition could be used. We used the Phoenix definition over the ASTRO definition because it is a better predictor of distant metastasis and cancer-specific survival. Studies with short follow-up (median of <5 years) that used only the ASTRO definition were excluded.

PSA is not a perfect test for recurrence; although more evidence of failure (e.g. positive biopsy, CT, MRI, bone scan) would have been preferred, these were not typically reported in the included studies. In perspective, certain tests (e.g. biopsy) are not routinely performed in other disease sites (e.g. lung) at time of recurrence.

To report late toxicity, we calculated the BED\textsubscript{3.0} based on the RT fractionation regimen from each study. Typically, late RTOG toxicity was reported at the latest follow-up time per patient within each study. The BED formula estimates the prescription dose to the tumor; we do not know which patients received 3D-CRT vs. IMRT, which may affect reported toxicities, since IMRT has lower GU/GI toxicity than 3D-CRT.

Mixed effects meta-regression models were used to estimate weighted linear relationships between BED and percentages with 5-year FFBF or the observed percentages of patients experiencing late toxicities. The weight applied to a given study’s published effect estimate was the ratio of the number of patients analyzed in that study divided by the total number of patients over all studies used for the meta-estimate of that effect. Separate meta-regression models were fitted for HDR-BT meta-estimates and for combined CFRT/HFRT meta-estimates of GU and GI.

### Table 2

<table>
<thead>
<tr>
<th>Study type</th>
<th>N (n)</th>
<th>BED (Gy) ranges at x/β</th>
<th>Risk group</th>
<th>5-year FFBFs at BED range with x/β of 1.5</th>
<th>Late RTOG grade 3–4 toxicity at BED range with x/β of 3.0</th>
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<td>Non-DE-CFRT; DE-CFRT; HFRT</td>
<td>140–200</td>
<td>98–133</td>
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<td>% Range</td>
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<td>I</td>
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<td>90–100</td>
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**Abbreviations:** BED: biologically equivalent dose; BT: brachytherapy; CFRT: conventionally fractionated radiation therapy; DE: dose-escalated; FFBF: freedom from biochemical failure; GI: gastrointestinal; GU: genitourinary; HDR: high dose rate; HFRT: hypofractionated radiation therapy; H: high-risk; I: intermediate-risk; L: low-risk; N: studies; n: patients; RTOG: Radiation Therapy Oncology Group

\textsuperscript{1} Denotes p-value < 0.001.

\textsuperscript{2} Denotes expected difference in percentage per 10-unit difference in BED.

\textsuperscript{3} Denotes insufficient data reported.
toxicities. The 5-year FFBF models were further stratified by low-, intermediate-, and high-risk groups. Results were summarized by slopes representing expected changes in 5-year FFBF or late toxicity percentages per 10-Gy change in BED. BEDs at which the plotted dose–response curves began to plateau were selected by the investigators. HDR-BT models were used to estimate the expected 5-year FFBF and toxicity percentages at these selected BEDs along with 95% confidence intervals (CIs). Statistical analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Study characteristics

There were 5385 patients treated with external beam radiation alone from 16 studies (Supplementary Table 1). The total number of fractions ranged from 26 to 44; the dose per fraction ranged from 1.8 to 2.75 Gy. BEDs$_{1.5}$ ranged from 144 to 197 Gy (median: 173 Gy).

There were 7371 patients treated with HDR-BT mono or boost from 39 studies (Supplementary Table 2). HDR-BT monotherapy was typically delivered in two to eight fractions, each at 6–12 Gy, to a total dose of 30–50 Gy. The lowest number of fractions used was two, at 12–13.5 Gy per fraction [31]; the highest number of fractions was nine, at 6 Gy per fraction [29,30]. BEDs$_{1.5}$ ranged from 208 to 299 (median: 270 Gy). Few HDR-BT monotherapy studies included high-risk patients [26,29,30].

For HDR-BT boost, the delivery of dose varied among institutions (Supplementary Table 3). Generally, EBRT was delivered to a total dose of 36–54 Gy in 1.8–2.0 Gy fractions; and HDR-BT was delivered to a total dose of 12–30 Gy in one to four fractions. Among all HDR-BT boost studies, the BEDs$_{1.5}$ ranged from 154 Gy to 307 Gy (median: 207 Gy).

Outcomes

Weighted meta-regression slope coefficients for 5-year FFBF and late RTOG GU and GI toxicity percentages related to BED for low-, intermediate-, and high-risk patients are shown in Table 2 and Fig. 3. Increases in 10 Gy increments in BED (at $z/b$ of 1.5) from 140 to 200 Gy were associated with 5-unit improvements in percent FFBF, consistent with the upslope of the dose–response sigmoidal curve seen in other disease sites [9–11].

For low-risk patients, 5-year FFBF increased from 75% to 95%, with BED escalation up to 200 Gy; FFBF plateaued at 95.7% (95% CI: 94.3%, 97.1%) above 200 Gy (Fig. 3, left upper panel). For intermediate-risk patients, 5-year FFBFs increased from 55% to 91%, with BED escalation to 200 Gy; FFBF plateaued at 89.4% (95% CI: 81.2%, 97.6%) above 200 Gy (Fig. 3, upper right panel). For high-risk patients, 5-year FFBF increased from 55% to 79%, with BED escalation to 200 Gy; FFBF plateaued at 81.0% (95% CI: 66.5%, 95.5%) above 200 Gy (Fig. 3, lower left panel). BED escalation above 200 Gy was not associated with improved 5-year FFBF among any risk group: the meta-regression slope coefficients demonstrated insignificant ($p$-value > 0.05), near-zero unit improvement in FFBF per 10 Gy increment in BED (slopes listed in Table 2: -0.11 for low-risk; 0.31 for intermediate-risk; 0.42 for high-risk), consistent with the plateau of the dose–response sigmoidal curve.

Toxicity

Increases in 10-Gy increment in BED (at $z/b$ of 3.0) from 98 Gy to 133 Gy was associated with a 0.81% increase in RTOG Grade 3–4 GI toxicity, but this was not statistically significant. Above a BED of 133 Gy, the late RTOG Grade 3–4 GU and GI toxicities plateaued at 7.2% (95% CI: 2.8%, 11.6%) and 0.7% (95% CI: 0.3%, 1.2%), respectively (Fig. 3, lower right panel). The meta-regression slope coefficients demonstrated insignificant ($p$-value > 0.05), near-zero unit change in late RTOG toxicity per 10 Gy increment in BED >133 Gy (slopes listed in Table 2: 0.01 for GU toxicity; 0.13 for GI toxicity).

Discussion

Dose escalation with CFRT to a BED of 180–200 Gy (at an $z/b$ of 1.5) has been shown to improve rates of tumor control (i.e., FFBF) over non-DE-CFRT in randomized controlled trials [1–5], representing the upslope and plateauing of the dose–response sigmoidal curve. We evaluated the effectiveness of further dose escalation (primarily with HDR-BT monotherapy or boost) to BEDs >200. We found that BED escalation >200 Gy had no additional clinical benefit. 5-year FFBFs for low-, intermediate-, and high-risk patients plateaued at 95.7% (95% CI: 94.3%, 97.1%), 89.4% (81.2%, 97.6%), and 81.0% (66.5%, 95.5%), meaning that tumor control no longer correlated with BED once a BED of 200 Gy was reached. We also evaluated late toxicity from dose escalation to BEDs >133 Gy (at an $z/b$ of 3.0). We found that late RTOG Grade 3–4 GU and GI toxicities plateaued at 7.2% (95% CI: 2.8%, 11.6%) and 0.7% (0.3%, 1.2%), respectively.

For tumor control, we used an $z/b$ of 1.5 because in 2001 hypothesis-generating reports indicated that prostate cancer cells had an $z/b$ ratio significantly lower than surrounding tissues, implying that the cells were more sensitive to large fraction doses. If the $z/b$ ratio for the tumor is lower than that for the normal tissues (i.e., 3–5; for connective tissue, bladder/rectal mucosa), increasing the dose per fraction would increase the therapeutic ratio [64]. There has been controversy in calculating the accurate $z/b$ ratio for prostate cancer [65], with most studies suggesting values between 1 and 3.

Nonetheless, if we had used different $z/b$ values, we would have arrived at the same conclusion, with a BED that would correspond to a particular $z/b$ value, and the same RT fractionation cutoffs. For example, in lung cancer [10,11], the plateau of the dose–response sigmoidal curve appears to begin at a BED for ~100 Gy (at an $z/b$ ratio of 10), which corresponds to a BED of ~200 Gy (at an $z/b$ ratio of 1.5) (Fig. 1). Thus, if we had used an $z/b$ ratio between 1.5 and 5, we would have similarly described the upslope and plateau of the dose–response sigmoidal curve. Once the plateau of the dose–response sigmoidal curve is reached, further dose escalation is likely not warranted.

Although the radiobiology of disease is different from low- to high-risk patients in terms of propensity to develop FFBF, there was no difference in terms of dose escalation benefit, which was surprising. For low-risk patients, outcomes are generally excellent, and we did not expect to see a benefit to dose escalation. We know that high-risk patients benefit from ADT, which specifically affects FFBF, the primary outcome measure. While all dose escalation trials of further dose escalation (i.e., >200 Gy) have shown improvement in FFBF, they have not shown benefit for overall survival [1–5]; on the other hand, trials using ADT have shown overall survival and FFBF benefit for ADT. The use of a radiation sensitivity index (e.g., using microarrays to detect expression of RbAp48, RGS19, and RSP1A) will help to further personalize dose recommendations to individual patients [66].

Our results have clinical implications. First, initiation of clinical trials of further dose escalation (i.e., >200 Gy) is not likely to additionally improve clinical outcomes, as the plateau of the dose–response sigmoidal curve has been reached. Second, the use of radiosensitizers with high BEDs would likely not have clinical benefits for patients; instead, patients may benefit from multimodal therapies that include novel anti-androgens, androgen synthesis inhibitors, gene therapy [67], anti-oxygen deprivation therapy
transcription/translation blockers, and immuno-modulators. Third, since the dose-response sigmoidal curve is similar to what has been reported in lung cancer, we suspect other disease sites would also exhibit this phenomenon.

There are likely a few reasons why late toxicities were not correlated to BED escalation. First, the side-effect profiles of HDR-BT (mono or boost) are different than those of EBRT alone. Moreover, studies using a high BED (i.e. with HDR-BT) tended to be retrospective and single-institutional; the reported toxicities may have been higher if the studies were prospective and multi-institutional. Second, a worrisome toxicity of prostate RT (particularly BT) is urethral stricture, which has previously been reported to occur in up to 8% of patients receiving HDR-BT. Among the HDR-BT monotherapy and boost studies analyzed, less than 6% of patients had Grade 3–4 GI or GU toxicity, though most of the toxicities reported among individual studies were due to stricture. Moreover, the rate of stricture was significantly higher when using a multimodal approach (i.e. boost). The median time of stricture formation following HDR-BT monotherapy has not yet been reported; notably, however, the rate of stricture increases with longer follow-up time. Although we reported 5-year actuarial follow-up time for FFBF, the median follow-up time for studies using HDR-BT monotherapy was only at 2.9 years, compared to HDR-BT boost at 4.5 years; and EBRT at 5.4 years. Thus, the studies using high BEDs may have increased reports of toxicity with longer follow-up.

Third, there are other more important predictive factors for toxicity besides BED alone. Among studies HDR-BT monotherapy or boost, non-dosimetric patient and treatment characteristics predicting late toxicity included older age (>65 years) [51,54], ADT use [54], initial presence of symptoms [54], prior trans-urethral resection of the prostate [72,73], hypertension [72], and increasing the dose-per-fraction of HDR-BT [72].

Finally, the RTOG toxicity scores are physician (i.e. non-patient)-reported, do not include the evaluation of anorectal symptoms such as urgency of defecation and fecal incontinence, and they have few discrete values (i.e. Grades 0–5). Most patients tend to have minor toxicities (i.e. Grade 1–2); detecting significant differences between these two values may not be possible, particularly because most studies included in this analysis typically only report severe (i.e. Grade ≥ 3) toxicities. The studies in this analysis generally did not use patient-reported quality of life (QOL) measures.

This meta-analysis has other limitations. For example, risk stratification methods varied: most EBRT patients were stratified with the National Comprehensive Cancer Network (NCCN) system, while HDR-BT monotherapy and boost patients, were stratified using the NCCN system, number of risk factors, American Joint Committee on Cancer (AJCC) system, and others. Currently, the NCCN model is superior to the AJCC in risk-stratification [74]. Finally, cancer cells treated with high doses per fraction are hypothesized to die by means (e.g. lipid membrane phosphorylation) that are not explained by typical radiobiological models [64]. Thus, although we would have seen an upslope-and-plateau effect of tumor control at any α/β ratio we used (between 1.5 and 5), it is unclear if extremely hypofractionated regimens would have similar outcomes and toxicities.

Additionally, we excluded LDR-BT studies in this analysis. The equation to calculate the BED of LDR-BT is different than the BED equation that is used for fractionated regimens [75], and BEDs (even at a constant α/β ratio) are not easily compared. Moreover, the LDR-BT BED equation is not suitable for comparing BEDs at a
wide range of x/b ratios (e.g. from 1.5 to 10); thus, we would not be able to compare the FFBF and toxicity of studies using LDR-BT to those that use fractionated RT (i.e. EBRT, HDR-BT). Given these differences in BED calculation, we did not feel it was appropriate to include studies using LDR-BT in this analysis. Nonetheless, we acknowledge that studies of LDR-BT BED escalation have shown a similar trend of improved FFBF with higher BED: for example, the Mount Sinai and Memorial Sloan Kettering experiences reveal that a BED (at an x/b of 2)>150 [76] and >200 [75,77] are associated with improved FFBF.

Additionally, the findings that there is no further dose response above 200 Gy is almost entirely dependent on the HDR-BT data. While it is possible that this is indeed a dose effect, there may be other factors contributing to the results [e.g. improved dosimetry, decreased prostate movement with HDR-BT]. We cannot comment on outcomes of BED escalation above 200 Gy with EBRT (e.g. with SBRT), since those studies were excluded from this report due to their limited (i.e. typically <5 year) follow-up.

Finally, we refrain from practice-limiting recommendations. The data presented are not suitable for the identification of “optimal” treatments or excluding treatment schemes and protocols. Our findings are limited to HDR-BT monotherapy and boost regimens. HDR-BT is characterized by extreme intratumoral dose heterogeneity, which differentiates this method from homogeneous EBRT techniques, which is not captured by the BED formula used in this analysis. Our data cannot replace the strong necessity for clinical trials comparing escalated dose schemes in order to confirm the conclusions of this analysis.

This study suggests that prostate cancer control with dose escalation with RT follows a sigmoidal dose–response curve. An increase in BED to 200 Gy (at x/b of 1.5) was associated with increased disease control, while doses above 200 Gy did not result in improved additional clinical benefit. Despite the current controversy in the literature regarding the exact x/b ratio of prostate cancer, the sigmoidal phenomenon which we have characterized, would still hold.

Conclusion

For prostate cancer RT, an increase in the BED to 200 Gy (at x/b of 1.5) was associated with increased prostate cancer control. Doses above 200 Gy did not result in additional clinical benefit.

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Approval/disclosures

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Conflicts of interest

We have no conflicts of interests.

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None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.05.011.

References