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Original article

What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation

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ABSTRACT

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 $\geqslant$5-year actuarial follow-up. BEDs were calculated based on the following formula: $(nd[1 + d/(\alpha/\beta)])$, where n is the number of fractions, and d is dose per fraction; assuming an α/β 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 α/β of 1.5) from 140 to 200 Gy were associated with 5-unit improvements in percent FFBF. Dose escalation of BED above 200 Gy was not correlated with FFBF. Increasing BED (at α/β of 3.0) from 98 to 133 Gy was associated with increased gastrointestinal toxicity. Dose escalation above 133 Gy was not correlated with toxicity.

Conclusions: An increase in the BED to 200 Gy (at α/β of 1.5) was associated with increased disease control. Doses above 200 Gy did not result in additional clinical benefit.

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Prostate cancer is the second most prevalent solid tumor diagnosed in men of the United States and Western Europe. Treatment options for localized prostate cancer include radical prostatectomy (RP) and radiation therapy, which is delivered either as external beam radiation therapy (EBRT) or brachytherapy (BT).

There has been an improvement in freedom from biochemical failure (FFBF) rates with dose-escalated conventionally fractionated radiation therapy (DE-CFRT) up to 76–80 Gy in 2 Gy fractions [1–7], which is a biologically equivalent dose ($BED_{1.5}$) of 180–200 Gy, assuming an α/β 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 $BED_{1.5}$ escalation to 200–350 Gy to the prostate, while minimizing the dose delivered to surrounding normal tissues (BEDs at various α/β 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 $BED_{1.5}$ ~210 vs. 190 Gy), particularly for intermediate-risk patients [12]. Currently, the upper limit of the $BED_{1.5}$ 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;

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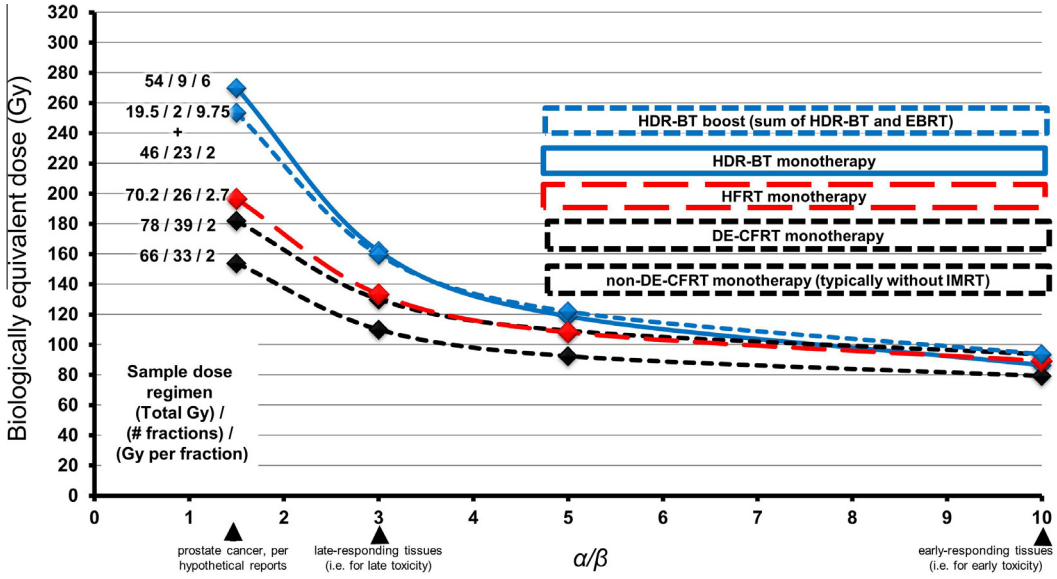

Fig. 1. A plot of BED curves for α/β ratios of 1.5–10 for several radiotherapy schedules. Radiotherapy dose escalation and alternate fractionation techniques (e.g. HFRT, HDR-BT) have enabled delivery of a high BED to the prostate while minimizing the dose to the normal tissues, thereby increasing the therapeutic ratio. This plot compares BED curves for α/β ratios of 1.5–10 Gy for some of the non-DE-CFRT, CFRT, HFRT, HDR-BT monotherapy, and HDR-BT boost regimens included in this meta-analysis (listed in Supplementary Tables 1–3).

Table 1
Population, Intervention, Control, Outcome, Study Design (PICOS) inclusion criteria.

Population	Men with localized (T1-T2, N0-Nx, M0) and locally advanced (T3-T4, N0-Nx, M0) prostate cancer	
Intervention	Non-DE-CFRT; DE-CFRT; HFRT	HDR-BT mono and/or boost
Control	Either no control group (i.e. intervention as a monotherapy); or a multi-arm study that contains the intervention	
Outcomes		
Efficacy	Actuarial FFBF @ 5-year actuarial FU, stratified by risk groups • Phoenix definition preferred • ASTRO definition may only be used if there is ⩾5 year median FU	
Safety	Late RTOG toxicities, GI and GU	
Study design		
Efficacy, safety	Large (n > 150), prospective	Small, retrospective studies included to account for variability in fractionation schedules and BEDs

Abbreviations: ASTRO: American Society for Radiation Oncology (3 consecutive rises); BED: biologically equivalent dose; BT: brachytherapy; CFRT: conventionally fractionated radiation therapy; DE: dose-escalated; FFBF: freedom from biochemical failure; FU: follow-up; GI: gastrointestinal; GU: genitourinary; HDR: high dose rate; HFRT: hypofractionated radiation therapy; RTOG: Radiation Therapy Oncology Group.

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 $BEDs_{1.5}$ > 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:

$$BED = (nd[1 + d/(\alpha/\beta)])$$

For reference, a $BED_{1.5}$ 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).

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