

Clinical Investigation

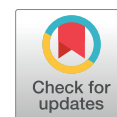
Diminishing Returns From Ultrahypofractionated Radiation Therapy for Prostate Cancer

Ivan R. Vogelius, PhD, DMSc,^{*,†,‡} and Søren M. Bentzen, PhD, DMSc^{‡,§}

^{*}Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;

[†]Department of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark;

[‡]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland; and [§]Division of Biostatistics and Bioinformatics, University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, Maryland



Received Oct 28, 2019, and in revised form Dec 30, 2019. Accepted for publication Jan 10, 2020.

Purpose: More than a decade of randomized controlled trials in prostate cancer has established a positive radiation dose response at moderate doses and a consistently low α/β ratio in the linear quadratic model for moderate hypofractionation. The recently published large randomized trial of ultrahypofractionated prostate cancer radiation therapy adds substantially to our current knowledge of dose response and fractionation sensitivity.

Methods and Materials: Randomized trials of dose escalation and hypofractionation of radiation therapy were meta-analyzed to yield the overall best estimate of the α/β ratio. Additionally, a putative saturation of dose effect previously reported at approximately 80 Gy EQD2 was investigated by mapping the relative effectiveness assessed at 5 years onto a single reference dose-response curve.

Results: Meta-analysis of 14 randomized trials including 13,384 patients yielded a best estimate of $\alpha/\beta = 1.6$ Gy (95% confidence interval, 1.3-2.0 Gy) but with highly significant heterogeneity ($I^2 = 70\%$, $P = .0005$). Further analysis indicated an association between increasing dose per fraction in the experimental arm and increasing α/β ratio (slope, 0.6 Gy increase in α/β per Gy increase in fraction size; $P = .017$). This deviation from the linear quadratic model could, however, also be explained by biochemical control maxing out at doses above approximately 80 Gy.

Conclusions: Biochemical control data from randomized controlled trials of dose-per-fraction escalation in prostate cancer radiation therapy are inconsistent with the presence of a constant fractionation sensitivity in the linear-quadratic model and/or a monotonic dose response for biochemical control beyond 80 Gy equivalent dose. These observations have a potential effect on the optimal doses in future trials and the interpretation of ongoing trials of ultrahypofractionation. © 2020 Elsevier Inc. All rights reserved.

Introduction

Evidence-based dose-time-fractionation regimens in radiation therapy (RT) for prostate cancer have been developed

substantially through a string of large randomized trials, first testing the effect of dose escalation¹⁻⁵ and subsequently testing hypofractionated regimens based on a putative high fractionation sensitivity of prostate cancer.⁶⁻¹⁴ The American

Corresponding author: Ivan R. Vogelius, PhD, DMSc; E-mail: ivan.richter.vogelius@regionh.dk

The authors acknowledge support from the Kirsten and Freddy Johansens award and National Cancer Institute (grant no. P30 CA 134274-04). S.M.B. was supported by funds through the Maryland Department of Health's Cigarette Restitution Fund Program.

Disclosures: I.R.V. reports institutional research grants from Varian Medical Systems and ViewRay.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Society for Radiation Oncology evidence-based guideline now supports the use of moderate hypofractionation in certain patient groups with good consensus and a high level of evidence, but it points to a lack of evidence behind ultrahypofractionated RT in the absence of data from randomized comparisons at the time the report was written.¹⁵

In light of the increased understanding of the complexity of tumor-host interactions and updated hallmarks of cancer, it may even be surprising that the linear-quadratic (LQ) model has provided such a good description of clinical data up until now. It has been questioned, however, whether the LQ model remains a reliable description of the time-dose-fractionation problem when moving beyond moderately hypofractionated regimens and toward ultrahypofractionated schedules or even stereotactic doses. Widmark et al⁶ pushed the experimental arm to 6.1 Gy times 7 over 1 to 2 weeks in a large trial that opened in 2005. Initially, the trial was designed to show superiority of the test arm over a control arm delivering 78 Gy in 2-Gy fractions. However, after a blinded interim analysis, the statistical analysis plan was revised to test for noninferiority of the test arm within a margin of 4%. The recent publication suggests that this margin of noninferior biochemical control was met with acceptable toxicity; this is indeed the first large randomized trial venturing beyond the widely accepted range of applicability of the LQ model. In the following, we will discuss the added insights from the Widmark trial compared with the existing body of clinical trials.

Methods and Materials

The previous search for randomized trials of prostate cancer RT¹⁶ was updated to October 2019. In short, trials were included if they enrolled patients with any-risk prostate cancer and if they randomized patients between 2 fractionation schedules delivered with external beam RT (EBRT) only. Finally, the trials had to report the outcome measures of overall survival and prostate-specific antigen control in sufficient detail to be included in the quantitative data synthesis. Studies of brachytherapy were excluded from the analysis. See the previous report for further details.¹⁶

A logistic dose-response function, $bNED = \frac{1}{1 + \exp\left(4\gamma_{50}\left(1 - \frac{EQD2}{D_{50}}\right)\right)}$, is assumed for the original dose-response

studies, and steepness was extracted from Vogelius and Bentzen¹⁶ to yield $\gamma_{50} = 0.62$ (95% confidence interval [CI], 0.37-0.87), assuming no effect of overall treatment time (no new data). Here, $EQD2$ is the fraction-size corrected prescribed radiation dose and D_{50} is the dose required for 50% biochemical control. Here we used the LQ model, $EQD2 = D\left(\frac{d+\alpha/\beta}{2+\alpha/\beta}\right)$ with D denoting the total prescribed physical dose and d the dose per fraction. Subsequently, the steepness of the dose response was used to estimate the α/β ratio for each included study, and these

were summarized in a forest plot using review manager.¹⁷ The heterogeneity of the observed α/β estimates was quantified by the I^2 statistics, which describe the percentage of variation that is not explained by random sampling.¹⁸

The observed α/β estimate in each study was plotted against dose per fraction in the experimental arm of the study to assess a possible systematic deviation indicating a potential limitation to the validity of the LQ model over the range of fraction doses applied in the trials. A linear regression of α/β estimate versus fraction dose was performed, and the P value for nonzero slope was used to test the dependence of α/β on fraction dose. The linear regression was weighted by the inverse variance of the study-specific α/β estimates (see Vogelius and Bentzen¹⁶ for details regarding derivation of the standard errors of the estimates).

Finally, we provided an estimate of an overall dose-response relationship for 5-year freedom from biochemical failure. As we have previously investigated, a simple plot of direct observed control probabilities on a single graph breaks the randomized comparisons in the trials and leads to exaggerated steepness of the dose-response relationship, probably owing to different case-mix and treatment support in newer series.¹⁹ Here, we assumed a logistic dose response as discussed previously, with $\gamma_{50} = 0.62$, and implemented a dose-modifying offset, δ Dose, estimated from the control arm in each trial to adjust for case mix, and so forth. In this way, all control-arm outcomes fall on a curve with $\gamma_{50} = 0.62$. D_{50} was adjusted until the mean value of δ Dose was zero to achieve a representative curve; this curve is illustrative only because the D_{50} of each study is assumed to differ according to case mix. Experimental arms were plotted on this curve with CIs using $bNED_{exp} = (bNED_{ctrl})^{HR}$, where $bNED_{ctrl}$ denotes the 5-year biochemical control in the control arm and HR is the reported hazard ratio between the arms of the study. The CI of HR was used to estimate the 95% confidence limits of $bNED_{exp}$. A linear fit weighted by the inverse variance of $bNED_{exp}$ estimates for observations with $EQD2 > 80$ Gy was performed to quantitatively discuss the previous hypothesis that the dose-response relationship flattens at such high doses.¹⁶

Results

The ultrafractionated study by Widmark et al⁶ is the only study added to the previous list of 13 randomized trials, yielding a total of 9 randomized trials of altered fractionation⁶⁻¹⁴ involving 9146 patients and 5 trials of dose escalation¹⁻⁵ involving 2238 patients.

The updated meta-analysis of the α/β ratio is still consistent with a low value and tight CI at $\alpha/\beta = 1.6$ Gy (95% CI, 1.3-2.0 Gy). Figure 1 shows the individual study estimates sorted by the inverse variance of each study. The heterogeneity is qualitatively visible; the P value for heterogeneity is $P < .001$, and I^2 is high at 70%. Random effects modeling yields slightly wider CIs at $\alpha/\beta = 1.6$ Gy

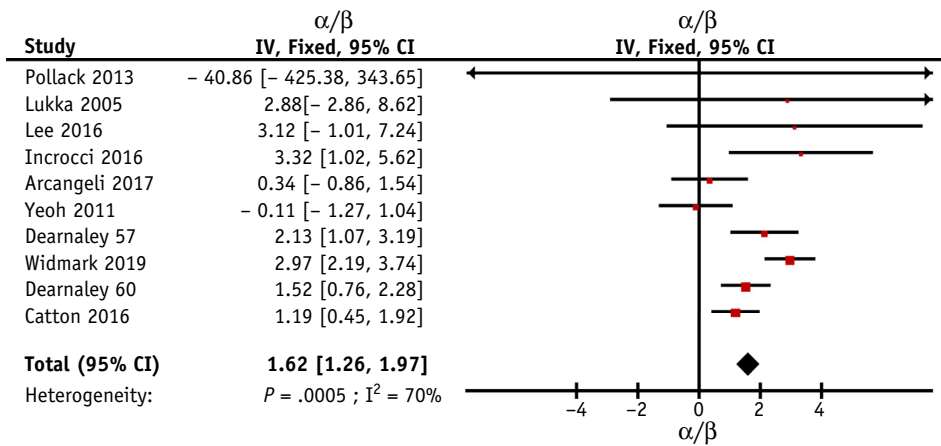


Fig. 1. Forest plot of estimated α/β value of the included studies with 95% confidence interval. Studies are ordered according to inverse variance (IV) of the estimate. Nine studies of altered fractionation are included. The 2 experimental arms by Dearnaley et al⁹ are included as individual studies and denoted by experimental arm dose rather than date of publication.

(95% CI, 0.8-2.4 Gy). The Widmark study, testing the only ultrafractionated schedule so far, yielded a higher α/β estimate than the remaining studies: $\alpha/\beta = 3$ Gy (2.2 Gy to 3.7 Gy) versus $\alpha/\beta = 1.3$ Gy (0.9-1.7 Gy), with a highly significant $P = .0001$ for difference between estimates.

The presence of heterogeneity might be interpreted as an indication that the linear quadratic fit to the entire range of fractionation schemes is not appropriate—in other words, that the effective dose is not well described by the single formula $EQD2 = D \left(\frac{d + \alpha/\beta}{2 + \alpha/\beta} \right)$ and constant α/β throughout the full range of studies. Figure 2 shows a replot of the individual study estimates of Figure 1, but as a function of the experimental arm fraction dose to explore this suggestion quantitatively. Linear regression shows a trend toward an increasing value of the study estimate of α/β with a slope of 0.57 Gy (of estimated α/β) per Gy increase in experimental arm fraction dose (95% CI, 0.2-0.9 Gy per Gy; $P = .02$). Figure 2 also illustrates the large information content of the Widmark trial in this context owing to the choice of the investigators to select a radically different fraction size.

Another possible cause of the heterogeneity in Figure 1 is the breakdown of the dose-response assumption, rather than the LQ fraction size correction. This hypothesis was discussed by Vogelius and Bentzen 2018,¹⁶ who found that the positive effect on the HR for dose escalation vanished when the experimental arm exceeded 80 Gy EQD2. Figure 3A shows the application of a dose-modifying offset, δ Dose, to each individual study control arm to arrange all studies on a representative dose-response curve in accordance with the overall best estimate of γ_{50} as derived from the 5 dose-escalation studies. Subsequently, Figure 3B shows the position of the experimental arms in relationship to the common dose-response curve after applying the same study-specific δ Dose. This maneuver allows visualization of a deviation from the sigmoid shape at doses exceeding ~ 80 Gy EQD2. Indeed, the data are

consistent with a flat dose response for all points exceeding 80 Gy EQD2 when fitted with a linear model (slope, 0.3% per Gy increase in EQD2; 95% CI, -0.5% to 1% per Gy EQD2; $P = .48$).

Discussion

Credit should go to Brenner and Hall²⁰ for first suggesting a high fractionation sensitivity of prostate cancer, with an estimated $\alpha/\beta = 1.5$ Gy (95% CI, 0.8-2.2 Gy) based on a fairly complex comparison of outcome after brachytherapy versus EBRT. Nevertheless, their α/β estimate is in remarkable agreement with the estimate presented here, which builds on the subsequent 20 years of systematic scientific effort to improve prostate cancer RT through dose escalation and hypofractionation in randomized controlled clinical trials.

In 2018 it was argued that the number of high-quality clinical trials of moderate hypofractionation was enough that the “question of the sensitivity of prostate cancer towards moderate hypofractionation was well elucidated”¹⁶ by the existing body of trials, with more than 10,000 patients. The question remained, however, of whether the low value of α/β would apply to regimens with more extreme hypofractionation. To this end, the ultrahypofractionated trial by Widmark et al is highly informative in terms of answering the question of sensitivity to fraction size beyond 3 Gy/fraction. Clearly, this also comes with the caution of only having a single data point, so further data from ongoing studies are still eagerly awaited.²¹ For example, the PACE-B trial, which recently reported early toxicity data,²² tests fraction doses of 7.3 Gy (cf, Fig. 2).

Figure 2 would seem to be in conflict with the presence of a constant (ie, dose-per-fraction-independent) value of α/β across the entire range of fraction sizes studied. In other words, a possible conclusion of the heterogeneous results presented here would be that at extreme hypofractionation, the effective doses are lower than expected (albeit not

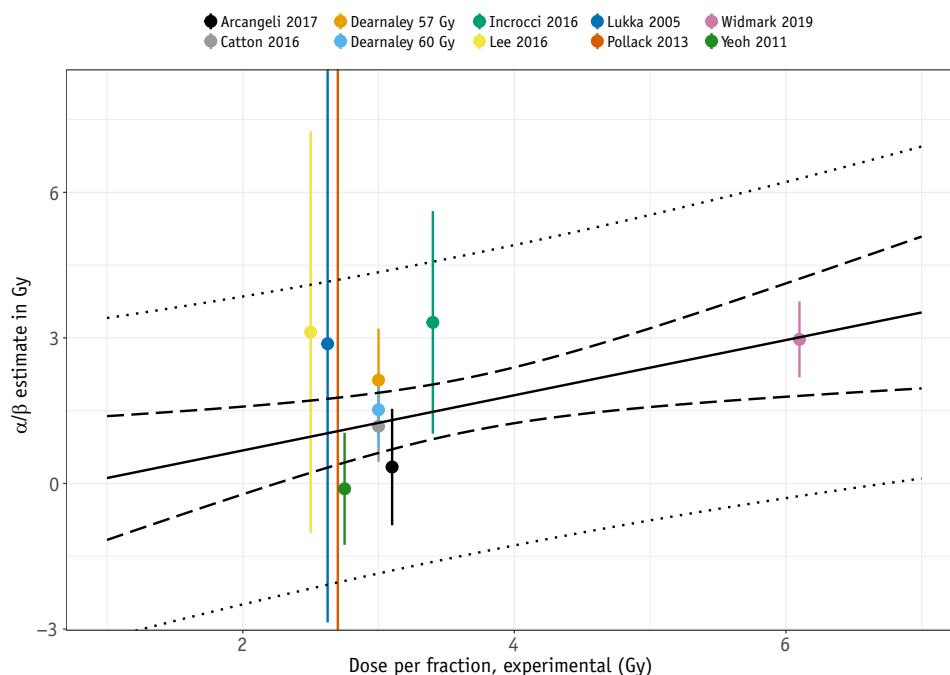


Fig. 2. Estimated α/β value and 95% confidence interval as function of experimental arm fraction size. Linear regression model with 95% confidence (dashed) and prediction (dotted) bounds are shown for the best fitting model with slope = 0.57 Gy/Gy (95% CI, 0.2-0.9 Gy per Gy; $P = .02$). The linear regression is weighted by the inverse variance of the individual α/β estimates from 9 included studies. The 2 experimental arms by Dearnaley et al⁹ are included as individual studies and denoted by experimental arm dose rather than date of publication.

catastrophically so). The experimental arm of the Widmark trial was dosed high enough, however, to maintain disease control, probably owing to heritage from an originally planned superiority design.

Figure 3 presents a different hypothesis, namely that the fraction size-corrected dose may be precise, but the biochemical control simply maxes out at or about the level of 87% biochemical control at 5 years/80 Gy EQD2. This would be analogous to, for example, the historical experience in Hodgkin lymphoma, where attempts to show a positive dose-response for tumor control above 30 Gy²³ were driven by the shape of the mathematical dose-response function rather than by the observed data points from published studies.²⁴ In Hodgkin lymphoma, subsequent studies have demonstrated the detriment to clinical outcome of further dose escalation.

If indeed the biochemical control is saturated at 80 Gy EQD2, the conclusion would be quite different with respect to the study by Widmark et al. In that case, the increased acute toxicity reported⁶ could possibly have been avoided by decreasing the dose to an effective 78 Gy to make the arms more balanced in intensity without a loss of biochemical control in the test arm.

Unfortunately, the coupling of dose intensification and hypofractionation in the current trials does not allow separation of the 2 hypotheses; the putative effect of nonconstant α/β versus saturation of disease control. However, in either case we conclude that superiority designs using dose

intensification above 78 to 80 Gy by means of extreme hypofractionation run a high risk of failure. That said, even if ultrahypofractionated therapy is not superior, but rather noninferior, it could be of value due to the impact on patient convenience and resources.

In terms of endpoints, it deserves mention that the endpoint of biochemical control has yet to be proven as a clinically relevant intermediate clinical endpoint,^{25,26} and previous attempts to couple effects on biochemical control to an effect on overall survival have failed.¹⁶ Furthermore, it may be argued that putative benefits of dose intensification may be delayed by the use of androgen deprivation therapy (ADT), but this would not affect the Widmark trial because ADT was not allowed.

The present analysis excluded studies of brachytherapy owing to the challenge of clearly defining dose-time-fractionation from literature reports as a result of the inhomogeneous dose. The recent Ascende-RT trial lends some support to the value of brachytherapy in improving biochemical control rates.²⁷ Unfortunately, the large number of patients treated on trials of EBRT is not matched by brachytherapy combinations, so definitive estimates are not available yet.

We now know that the overall treatment time affects toxicity by increasing the acute reactions if dose is delivered in very short schedules,²⁸ which may also affect the Widmark results. When we turn to disease control there are some suggestions of a moderate detrimental effect of

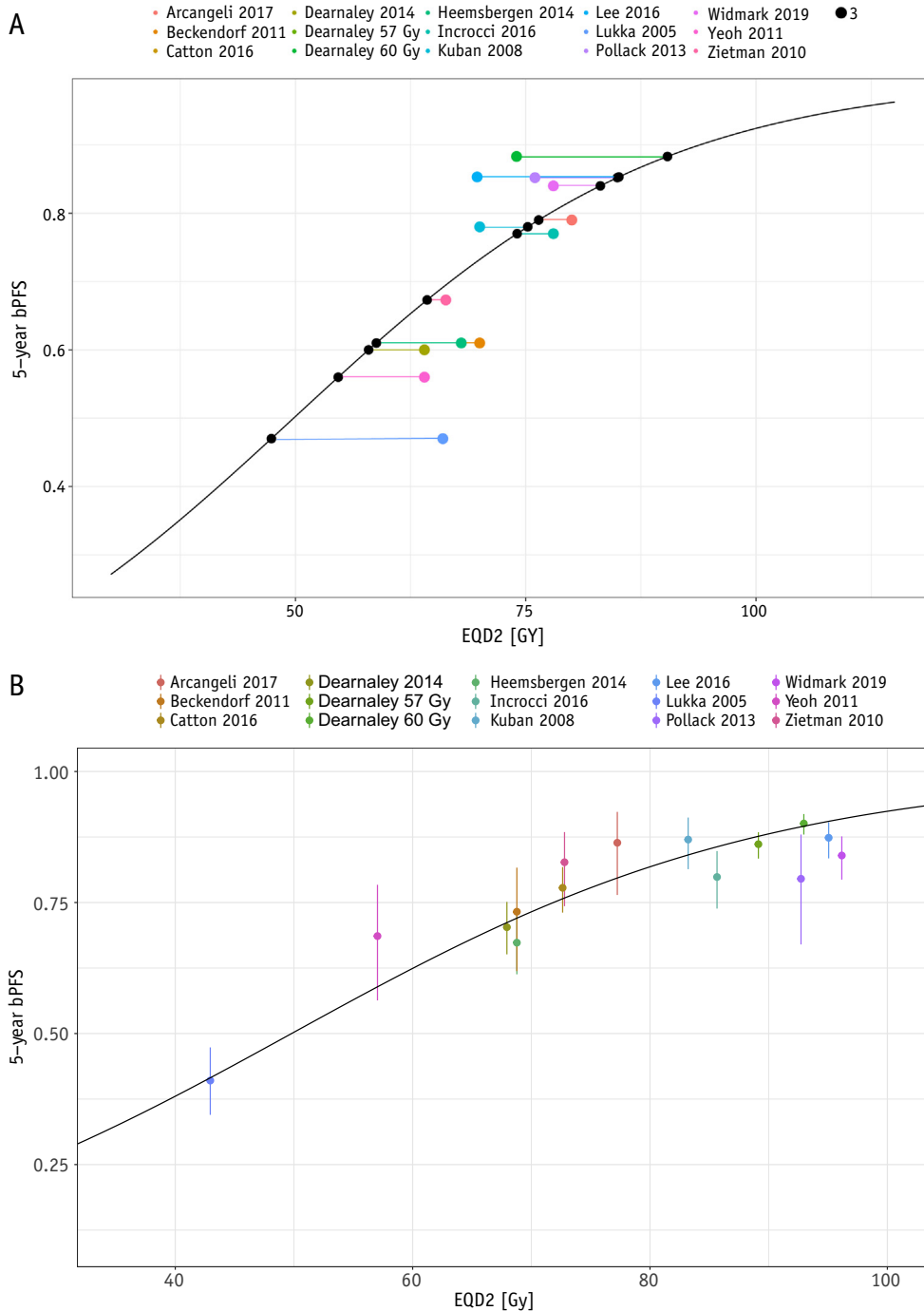


Fig. 3. (A) Illustration of the study-specific dose offset, δ Dose, required for the control arm outcome to fall on a reference sigmoid dose-response curve with the steepness defined by meta-analysis of the normofractionated randomized dose-escalation studies. (B) Experimental arm EQD2 and control probabilities after applying δ Dose. Note signs of systematic deviation from sigmoid shape at high doses. Error bars show 95% confidence interval of the biochemical progression free survival estimate as detailed in Methods and Materials. Nine studies of altered fractionation and 5 studies of dose escalation are included. The 2 experimental arms by Dearnaley et al⁹ are included as individual studies and denoted by experimental arm dose rather than date of publication.

protracting the overall treatment time,^{29,30} but it is unclear if such an effect would extend to the short schedules of ultrahyperfractionation. We therefore analyzed the current data without an assumed effect of overall treatment time. If the previously reported effect of overall treatment time is

included (data not shown), the Widmark study loses weight in the meta-analysis of α/β , but the study outcome is in agreement with the predicted effect from studies above 80 Gy EQD2 in the experimental arm of Vogelius and Bentzen.¹⁶

Conclusions

The addition of data from the ultrafractionated schedule tried in the Widmark trial adds to our knowledge of the fractionation biology of prostate cancer. The data appear to be in disagreement with the presence of a single, constant α/β ratio or a sigmoid dose-response curve with improved biochemical control from exceeding 80 Gy EQD2 prescriptions. It appears that either the validity of the LQ model is challenged when extended to the ultra-hypofractionated dose-per-fraction range or that the expectation of continued improvements in biochemical control with dose-per-fraction intensification is likely to be unfulfilled.

References

- Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV. Long-term results of the dutch randomized prostate cancer trial: Impact of dose-escalation on local, biochemical, clinical failure, and survival. *Radiother Oncol* 2014;110:104-109.
- Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: Long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2014;15:464-473.
- Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67-74.
- Beckendorf V, Guerif S, Le Prise E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys* 2011;80:1056-1063.
- Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. *JAMA* 2005;294:1233-1239.
- Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, noninferiority, phase 3 trial. *Lancet* 2019;394:385-395.
- Arcangeli G, Saracino B, Arcangeli S, et al. Moderate hypofractionation in high-risk, organ-confined prostate cancer: Final results of a phase III randomized trial. *J Clin Oncol* 2017;35:1891-1897.
- Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol* 2013;31:3860-3868.
- Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, noninferiority, phase 3 CHHIP trial. *Lancet Oncol* 2016;17:1047-1060.
- Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III non-inferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. *J Clin Oncol* 2016;34:2325-2332.
- Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): Final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2016;17:1061-1069.
- Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol* 2017;35:1884-1890.
- Lukka H, Hayter C, Julian JA, et al. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *J Clin Oncol* 2005;23:6132-6138.
- Yeoh EE, Botten RJ, Butters J, DiMatteo AC, Holloway RH, Fowler J. Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: Final results of phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2011;81:1271-1278.
- Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated radiation therapy for localized prostate cancer: Executive summary of an ASTRO, ASCO, and AUA evidence-based guideline. *Pract Radiat Oncol* 2018;8:354-360.
- Vogelius IR, Bentzen SM. Dose response and fractionation sensitivity of prostate cancer after external beam radiation therapy: A meta-analysis of randomized trials. *Int J Radiat Oncol Biol Phys* 2018;100:858-865.
- Review manager (revman) [computer program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2008.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.
- Diez P, Vogelius IS, Bentzen SM. A new method for synthesizing radiation dose-response data from multiple trials applied to prostate cancer. *Int J Radiat Oncol Biol Phys* 2010;77:1066-1071.
- Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999;43:1095-1101.
- Lukka HR, Pugh SL, Bruner DW, et al. Patient reported outcomes in NRG oncology RTOG 0938, evaluating two ultrahypofractionated regimens for prostate cancer. *Int J Radiat Oncol Biol Phys* 2018;102:287-295.
- Brand DH, Tree AC, Ostler P, et al. Intensity modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): Acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol* 2019;20:1531-1543.
- Vijayakumar S, Myriantopoulos LC. An updated dose-response analysis in Hodgkin's disease. *Radiother Oncol* 1992;24:1-13.
- Brincker H, Bentzen SM. A re-analysis of available dose-response and time-dose data in Hodgkin's disease. *Radiother Oncol* 1994;30:227-230.
- Williams S. Surrogate endpoints in early prostate cancer research. *Transl Androl Urol* 2018;7:472-482.
- Xie W, Regan MM, Buyse M, et al. Metastasis-free survival is a strong surrogate of overall survival in localized prostate cancer. *J Clin Oncol* 2017;35:3097-3104.
- Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT trial): An analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;98:275-285.
- Quon HC, Ong A, Cheung P, et al. Once-weekly versus every-other-day stereotactic body radiotherapy in patients with prostate cancer (PATRIOT): A phase 2 randomized trial. *Radiother Oncol* 2018;127:206-212.
- Vogelius IR, Bentzen SM. Meta-analysis of the alpha/beta ratio for prostate cancer in the presence of an overall time factor: Bad news, good news, or no news? *Int J Radiat Oncol Biol Phys* 2013;85:89-94.
- Thames HD, Kuban D, Levy LB, et al. The role of overall treatment time in the outcome of radiotherapy of prostate cancer: An analysis of biochemical failure in 4839 men treated between 1987 and 1995. *Radiother Oncol* 2010;96:6-12.