Radiation dose escalation for early prostate cancer: reigniting the FLAME? Reply

Kerkmeijer, L.G.W.; Pos, F.J.; Haustermans, K.; Heide, U.A. van der

Citation
Kerkmeijer, L. G. W., Pos, F. J., Haustermans, K., & Heide, U. A. van der. (2021). Radiation dose escalation for early prostate cancer: reigniting the FLAME? Reply, *39*(27), 3086-+. doi:10.1200/JCO.21.00789

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Reply to I. R. Vogelius et al

Vogelius et al[1] added the results of the FLAME trial[2] to their previous meta-analysis of prostate cancer radiotherapy trials.[3] Showing that the FLAME focal boost arm cracked the alleged ceiling for dose escalation, it is now more plausible that the fractionation sensitivity of prostate cancer decreases with increasing fraction size.

By incorporating the nominally prescribed dose for the boost of 95 Gy in the model, the effect of boosting is, however, underestimated. The actual focal boost dose in the study arm of the trial was often lower, as we strictly adhered to prespecified dose constraints to organs at risk, compromising the focal boost dose if necessary. This was a deliberate choice to avoid additional toxicity as long as the benefit of focal boosting was unproven. It resulted in a range of applied boost doses, with a median of 84.7 Gy.[4] This corresponds to a median equivalent dose in 2-Gy fractions (EQD2) of 94.5 Gy (Fig 1). With a biochemical relapse-free rate of 92%, this exactly matches the meta-analysis of Vogelius et al.[1]

The meta-analysis shows a decreasing relative biologic effect with increasing fraction size when moving beyond moderate hypofractionation. This should in our view not lead to the conclusion that ultrahypofractionation should not be pursued for high-risk prostate cancer. Instead, the focal boost concept should be integrated with ultrahypofractionation, taking this decreasing biologic effect into account. In the hypo-FLAME trial, we tested a schedule of 35 Gy with an integrated boost up to 50 Gy, in five fractions. This boost dose would correspond to an EQD2 of 160 Gy, but likely has a smaller effect. However, again to limit toxicity, the boost dose in the trial was compromised, leading to a median dose of only 40.3 Gy (range, 36.2-50.8 Gy).[5]

The predicted probability of biochemical failure as a function of achieved boost dose in the FLAME trial demonstrates that when an absolute boost dose of > 90 Gy is indeed reached, the biochemical failure rate decreases to a few percent.[2] The route toward improved outcome is now clear. The challenge has become a technical one: how to reach such a high boost dose safely. The recent improvements in radiotherapy techniques offer a solution. Modern (magnetic resonance) image guidance and online adaptive treatment techniques improve the capacity to boost the tumor by external beam radiotherapy without increasing the dose to the surrounding organs at risk.[6-8] Rectal spacer gels, injected to put some distance between the rectal wall and the prostate, may be appropriate in some cases.[9] The TARGET trial showed that a focal boost to the tumor can be deposited safely with high-dose rate brachytherapy.[10]

Linda G. W. Kerkmeijer, MD, PhD
Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, the Netherlands
Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, the Netherlands

Floris J. Pos, MD, PhD
Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands

Karin Haustermans, MD, PhD
Department of Radiation Oncology, University Hospitals Leuven, Leuven, Belgium

Uulke A. van der Heide, PhD
Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands

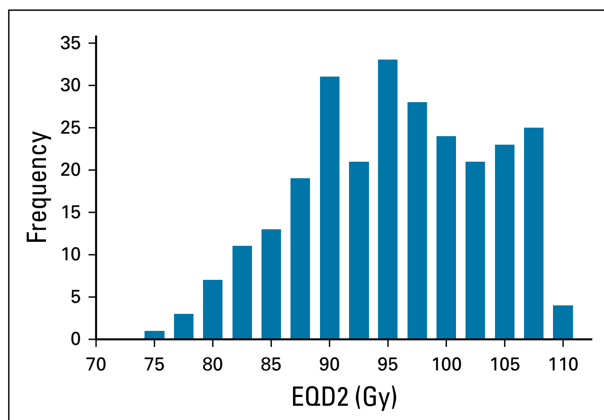

FIG 1. Histogram of EQD2 of the near-minimum dose to the tumor in the focal boost arm of the FLAME trial. As in the study by Vogelius et al,[1] we apply $\alpha/\beta = 1.62$ Gy. EQD2, equivalent dose in 2-Gy fractions.

SUPPORT

Supported by the Dutch Cancer Society (Grant No. KWF 10088).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.00789.

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DOI: https://doi.org/10.1200/JCO.21.00789; Published at ascopubs.org/journal/jco on June 4, 2021.

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